

2014 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE



PART II: KEY DEVELOPMENTS IN THE FIELD OF RARE DISEASES IN EUROPE IN 2013

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

More information on the activities of the former European Union Committee of Experts on Rare Diseases and the EUCERD Joint Action can be found at www.eucerd.eu.

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ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG - Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area
EMA - European Medicines Agency
ERN - European reference network
EU - European Union
EUCERD - European Union Committee of Experts on Rare Diseases
EUROCAT - European surveillance of congenital anomalies
EUROPLAN - European Project for Rare Diseases National Plans Development
EURORDIS - European Organisation for Rare Diseases
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
IRDiRC – International Rare Diseases Research Consortium
JA - Joint Action
MA - Market Authorisation
MoH - Ministry of Health
MS - Member State
NBS - New born screening
NCA - National Competent Authorities
NHS - National Health System
PDCO - Paediatric Committee at EMA
RDTF - EC Rare Disease Task Force
WG - Working Group
WHO - World Health Organization

GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD) Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

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

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2013. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the Commission Expert Group on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2013

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Parts I – V also include a description of the methodology, sources and validation process of the entire report, and a selected bibliography and list of persons having contributed to the report.

Each year, there are around 15 000 downloads of the different sections of the report combined.

A. EUROPEAN COMMISSION ACTIVITIES

A.1. EUROPEAN COMMISSION ACTIVITIES RELATED TO RARE DISEASES IN THE FIELD OF PUBLIC HEALTH

1.1. Overview of European Commission Directorate General for Health and Consumers' activities in the field of rare diseases

1.1.1. Council Recommendation on an action in the field of rare diseases (8 June 2009)

On 8 June 2009, the Council approved a Council Recommendation on an action in the field of rare diseases¹. In early 2009, the European Parliament and the European Social and Economic Committee issued opinions on the Proposal for a Council Recommendation, overwhelmingly supporting the contents of the crucial document. The amendments issued during this process were incorporated into the final text adopted on 8 June 2009 by the European Council of Ministers - a body that serves to define the general political guidelines of the European Union and is the main decision-making agent. Every Council meeting is attended by one minister from each EU country. For the meeting on the rare disease Recommendation, it was typically the ministers of health who attended.

For an adequate follow-up of the Commission Communication and the Council Recommendation on an action in the field of rare diseases, the European Commission was to produce, by the end of 2013 and in order to allow proposals in any possible future programme of Community action in the field of health, an implementation report 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 and based on the information provided by the Member States, which should consider the extent to which the proposed measures are working effectively and the need for further action to improve the lives of patients affected by rare diseases and their families.

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

The European Commission Decision C(2009)9181 of 30 November 2009 formally established a European Union Committee of Experts on Rare Diseases. This new structure, evoked in Point 7 of the Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's Challenges, adopted on 11 November 2008, recommends that the European Commission be assisted by a European Union Advisory Committee on Rare Diseases:

"The preparation and implementation of Community activities in the field of rare diseases require close cooperation with the specialised bodies in Member States and with the interested parties. Therefore, a framework is required for the purpose of regular consultations with those bodies, with the managers of projects supported by the European Commission in the fields of research and public health action and with other relevant stakeholders acting in the field."

Thus, *"the Committee acting in the public interest shall assist the Commission in formulating and implementing the Community's activities in the field of rare diseases, and shall foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved"*.

Specifically, the European Union Committee of Experts on Rare Diseases was charged with the following responsibilities:

- assisting the Commission in the monitoring, evaluating and disseminating the results of measures taken at Community and national level in the field of rare diseases;

¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

- contributing to the implementation of Community actions in the field, in particular by analysing the results and suggesting improvements to the measures taken;
- contributing to the preparation of Commission reports on the implementation of the Commission Communication and the Council Recommendation;
- delivering opinions, recommendations or submit reports to the Commission either at the latter's request or on its own initiative;
- assisting the Commission in international cooperation on matters relating to rare diseases;
- assisting the Commission in drawing up guidelines, recommendations and any other action defined in the Commission Communication and in the Council Recommendation;
- providing an annual report of its activities to the Commission.

The European Union Committee of Experts on Rare Diseases replaced the European Commission's Rare Diseases Task Force (RDTF) established via Commission Decision 2004/192/EC of 25 February 2004 on the programme of Community action in the field of public health (2003 to 2008).

The Committee consisted of 51 members, including one representative from the ministries or government agencies responsible for rare diseases to be designated by the government of each Member State; four patient organisation representatives; four pharmaceutical industry representatives; nine representatives of ongoing and/or past Community projects in the field of rare diseases financed by the programmes of Community action in the field of health, including three members of the pilot European Reference Networks on rare diseases; six representatives of ongoing and/or past rare diseases projects financed by the Community Framework Programmes for Research and Technological Development; and one representative of the European Centre for Disease Prevention and Control. A call for expressions of interest was published at the end of 2009 for designating the representatives of patient organisations, industry, rare diseases research projects under Framework Programmes for Research and Technological Development, and rare diseases projects under Health Programmes representatives of the new Committee. Via the Commission Decision 2010/C 204/02 of 27 July 2010 the appointment of the members of the European Union Committee of Experts on Rare Diseases were adopted. The Committee met for the first time on 9-10 December 2010 in Luxembourg and elected Ségolène Aymé (Orphanet) as its Chair, with Kate Bushby (Treat-NMD), Yann Le Cam (EURORDIS) and Helena Kääriäinen (MS representative for Finland) as its three Vice-Chairs, with a two-year term of office. Observers from non EU countries were also issued invitations to the EUCERD's meetings. Until the 29 February 2012 the EUCERD was supported by the Joint Action for the support of the former RDTF/EUCERD Scientific Secretariat: from March 2012 until February 2015, the activities of the EUCERD are supported by a dedicated Joint Action².

Meetings and workshops

In 2013 a number of workshops were held with the support of the EUCERD Joint Action: Key indicators for national plans/strategies workshop (25 March 2013, Rome), Workshop on training of social service providers (10-11 October 2013, Copenhagen), and Workshop on registries for rare diseases and the European registry platform (22-23 April 2013, Luxembourg). The EUCERD held two meetings in 2013 in Luxembourg on 31 January – 1 February 2013³ and 5-6 June 2013⁴. A range of topics were discussed over the year including European Reference Networks, patient registries and databases for rare diseases National Plans and Strategies for Rare Diseases, the activities of the EUCERD Joint Action, Newborn Screening Practices in Europe, and ways to collaborate with other EU initiatives in the field.

To mark Rare Disease Day 2014, an editorial was published in Orphanet Journal of Rare Diseases highlighting the achievements of the EUCERD, entitled "The European Union Committee of Experts on Rare Diseases: three productive years at the service of the rare disease community"⁵.

Recommendations & Opinion

Three sets of recommendations were adopted by the EUCERD in 2013. The first set were the EUCERD Recommendations on European Reference Networks for Rare Diseases⁶. The recommendations were elaborated by the Committee to feed into the work of the Cross-Border Healthcare Expert Group. European Reference Networks (ERNs) are one of the structures foreseen by the Directive to share knowledge, facilitate the mobility of expertise, and to allow Member States to provide highly specialised services of high quality for

² See section on Joint Actions 1.2.1.

³ http://www.eucerd.eu/wp-content/uploads/2013/03/EUCERD7_ExecutiveSummary.pdf

⁴ http://www.eucerd.eu/wp-content/uploads/2013/07/8EUCERD_ExecutiveSummary.pdf

⁵ <http://www.ojrd.com/content/9/1/30>

⁶ http://www.eucerd.eu/?post_type=document&p=2207

patients where this would have been impossible without European networking, such as in the case of rare diseases. Member States are also encouraged in the Council Recommendation on an action in the field of rare diseases (8 June 2009) to help foster the participation of centres of expertise in these ERNs. The EUCERD has already elaborated recommendations concerning centres of expertise for rare diseases which describes how these centres could participate in such networks. The recommendation is addressed to the European Commission and the Member States and includes 21 individual recommendations covering a range of aspects including the mission, vision and scope of ERNs, their governance, their composition, their funding and evaluation, as well as their designation.

The second set of recommendations were the EUCERD's Core Recommendations on Rare Disease Patient Registration and Data Collection⁷. Rare disease registries are valuable instruments for increasing knowledge on rare diseases, and for supporting fundamental, clinical and epidemiological research, as well as for post-marketing surveillance of orphan medicinal products and medicines used off-label. This data is also crucial for the planning of healthcare services. The recommendation calls for the international operability of registries and databases and use of appropriate coding systems to enable the necessary pooling of data for public health and research purposes, gives advice concerning the establishment of registries and collection of data, highlights the various uses of patient data and how to best share this information, underlines the importance of adherence to good practice guidelines in the field, stresses the need for registries to be adaptable to meet future needs, and emphasises the importance of sustainability for the timespan of the registry's utility.

The third set of recommendations adopted was the EUCERD's Recommendation on Core Indicators for National Plans/Strategies for Rare Diseases⁸. This recommendation provides a list of 21 indicators which are intended to capture relevant data and information on the process of planning and implementing of these plans and strategies on a regular basis. These indicators would provide information notably to the European Commission on the implementation of the Council Recommendation on an Action in the field of Rare Diseases (June 2009) which encourages Member States to establish a national plan or strategy in the field by the end of 2013. They will also serve as a basis for the elaboration of indicators at national level tailored to the specific actions foreseen in the plans/strategies. This set of recommendations will be revised in the future to take into account the experiences of the Member States.

In addition to these three sets of recommendations, the EUCERD published an Opinion entitled "New Born Screening in Europe: Opinion of the EUCERD on Potential Areas for European Collaboration⁹". In the Council Recommendation of 8 June 2009 on an action in the field of rare diseases, it is recommended that Member States "Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences". The EUCERD was requested by the European Commission to examine the outputs of the tender within the EU Program of Community Action in Public Health (work plan 2009) for an "Evaluation of population newborn screening practices for rare disorders in Member States of the European Union¹⁰" and to issue their proposals for next steps. As a result of their discussions in this area, the EUCERD has agreed on 11 areas which respect the principle of subsidiarity, including actions to improve the quality and the efficiency of the screening process, while respecting the values of the Member States. These areas are not prioritised and are submitted to the European Member States, to the European Commission and to any third party involved for further consideration.

Report on State of the Art of Rare Disease activities in Europe

Each year the Scientific Secretariat of the European Union of Experts on Rare Diseases (EUCERD), supported by the EUCERD Joint Action (N° 2011 22 01) elaborates a comprehensive report covering the state of the art of rare diseases activities at European and Member State level.

The 2013 edition of the *Report on the State of the Art of Rare Disease Activities in Europe* published in July 2013 aimed to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2012.

The report is a comprehensive resource for the rare disease community and has been met with praise at both the EU and MS levels for providing valuable insight into understanding the current resources and

⁷ http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRRegistryDataCollection_adopted.pdf

⁸ http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

⁹ http://www.eucerd.eu/wp-content/uploads/2013/07/EUCERD_NBS_Opinion_Adopted.pdf

¹⁰ http://ec.europa.eu/eahc/documents/news/Executive_Report_to_EC_20120108_FINALE.pdf

activities in the field of rare diseases across Europe that will help determine future strategies to meet the needs of rare disease patients and their families in Europe and further afield.

The 2013 edition of the report is split into five parts this year:

- Part I: Overview of rare disease activities in Europe¹¹
- Part II: Key developments in the field of rare diseases in 2012¹²
- Part III: European Commission activities in the field of rare diseases¹³
- Part IV: European Medicines Agency activities and other European activities in the field of rare diseases¹⁴
- Part V: Activities in EU Member States and other European countries in the field of rare diseases¹⁵

Part I is a general overview, geared to a more general public, whilst Parts II, III, IV and V provide a more detailed report of the situation for stakeholders who wish to learn more about the situation at European or national level. In addition, an individual document for each country covered by the report, containing the extracted data from the report, have been produced for the first time this year in order to encourage the dissemination of this information at national level.

The 2013 edition of the report been elaborated with the collaboration of the members of the EUCERD in concertation with a wide range of stakeholders at national level. This report is a deliverable of the EUCERD Joint Action (EJA) : Working for Rare Diseases (N° 2011 22 01). All parts of the report are free to download from www.eucerd.eu.

The Scientific Secretariat of the EUCERD also produced individual reports for each European country containing an extraction of the data published in the *2013 EUCERD Report on the State of the Art of Rare Disease Activities in Europe* related to activities in that specific country. These country editions of the report provide both an overview of national activities up to the end of 2012, as well as a specific focus on the latest activities and developments in 2012. The reports are intended for use and dissemination at the national level, as an up-to-date source of information and support tool for stakeholders wishing to raise awareness of the field of rare diseases. These reports are available on the EUCERD website in the pages dedicated to other resources at the national level¹⁶.

OrphaNews

*OrphaNews*¹⁷ is the official newsletter of the rare disease community, supported by the EUCERD Joint Action. Twice a month, the newsletter delivers political and scientific news concerning the field of rare diseases and orphan medicinal products. The newsletter has around 15'000 registered readers from all over the world and representing all stakeholder groups. In 2010, a reader satisfaction survey¹⁸ was carried out with over 1000 responses from around 50 different countries. The overwhelming majority of readers were either 'satisfied' or 'very satisfied' with the newsletter. A new search engine feature, powered by Google Custom Search, was added to the archives in 2011, and a tool for the translation of the newsletter into other languages was developed. Italy identified national funding for these translations and the first edition of *OrphaNews* in Italian¹⁹ was launched in December 2011. The Newsletter is published in French as well since 2003.

1.1.3. European Commission Expert Group on Rare Diseases

The European Commission, recognising the valuable work carried out by EUCERD over its 3 year mandate and acknowledging a continuing need for a group of experts in this area, published on 30 July 2013 a Decision²⁰ to establish a Commission Expert Group on Rare Diseases taking into account the framework for Commission expert groups. The group has a similar range of missions and mode of functioning to the EUCERD, as it will provide the Commission with "*advice and expertise in formulating and implementing the Union's activities in the field of rare diseases and foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved*". The expert group will consist of representatives belonging to diverse stakeholder groups in the field of rare diseases as well as representatives from Member States.

¹¹ <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf>

¹² <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesII.pdf>

¹³ <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesIII.pdf>

¹⁴ <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesIV.pdf>

¹⁵ <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesV.pdf>

¹⁶ http://www.eucerd.eu/?page_id=154

¹⁷ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

¹⁸ http://www.orpha.net/orphacom/cahiers/docs/GB/Orphanews_survey2010.pdf

¹⁹ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=ItaliaNews>

²⁰ http://ec.europa.eu/health/rare_diseases/docs/dec_expert_group_2013_en.pdf

Members were selected via a call for expression of interest and the first meeting of the Committee, chaired by the EC, was held in Luxembourg on 11-12 February 2014.

1.1.4. European Commission work plans implementing the second programme of Community action in the field of health (2008-2013)

The annual work plan 2013²¹ for the health programme was adopted on 28 November 2012. €2 million was foreseen in the work plan to establish a sustainable platform to coordinate and maintain registries and networks on rare diseases, and financing is foreseen for a paediatric oncology pilot network in the context of the implementation of the Cross-Border Healthcare Directive.

1.2. Activities in the field of rare diseases funded by DG Health and Consumers

1.2.1. Joint Actions

Joint Action to support the European Surveillance on Congenital Anomalies (EUROCAT) network (2010-2013)

The Joint action supporting EUROCAT²², the European network of population-based registries for the epidemiologic surveillance of congenital anomalies, finished in 2013.

The main outcomes of the joint action include:

- Evaluation of the public health impact of congenital anomalies (CA) enabled by easily accessible and updated epidemiological information on the EUROCAT website (www.eurocat-network.eu).
- The detection, appropriate investigation and reporting of clusters and trends in congenital anomaly prevalence, including improving the capacity for rapid response through a newly established Task Force for Evaluation of Clusters in situations demanding immediate actions
- Assessment of the teratogenic impact of new or changing environmental exposures, including swine flu related exposures and maternal chronic diseases such as mental depression, obesity, epilepsy, diabetes and asthma.
- Evaluation of the potential for linkage between databases and electronic information systems on exposure, including European environmental pollution information systems and drug prescription databases in order to enable Europe-wide surveillance and etiological analyses of congenital anomaly risk in relation to such exposures
- Establishing strategic framework for primary prevention of CA to be implemented in the national plans for rare diseases
- Evaluation of progress in the prevention of neural tube defects in Europe by raising periconceptional folic acid status in women of childbearing age
- Evaluation of impact of delayed childbearing and changes in prenatal screening techniques and policy on Down Syndrome in Europe
- Contribute to the development of pharmacovigilance system in Europe (EUROmediCAT).
- Improved coding and classification of CA by training in coding and contribution of EUROCAT expertise to the revision of the International Classification of Diseases
- The addition of new registries to the network, and provision of guidelines and software to further interested regions/countries.
- Organisation of two European Symposia on the Prevention of Congenital Anomalies in order to bring together public health professionals, clinicians, scientists, patient organisations and governmental agencies and share the latest scientific and clinical results on the monitoring and prevention of congenital anomalies.

²¹ http://ec.europa.eu/health/programme/docs/wp2013_en.pdf

²² <http://www.eurocat-network.eu/>

Joint Action to support the Orphanet database (2011-2013⁴)

Orphanet²³ is the reference portal for information on rare diseases and orphan medicinal products in Europe. Orphanet, and was established in 1997 by the French Ministry of Health (*Direction Générale de la Santé*) and the INSERM (*Institut National de la Santé et de la Recherche Médicale*). Both agencies are still funding the core project.

The main achievements²⁴ of the Orphanet Joint Action in 2013 were:

- The Orphanet rare diseases ontology (ORDO) produced in collaboration with the EBI is now available on Bioportal (<http://purl.bioontology.org/ontology/OntoOrpha>). It represents a powerful research tool.
- The international website and the database have been translated into Dutch and since June 2013 all the information is accessible to users in Dutch.
- The encyclopaedia of rare diseases has been expanded and updated. As of 31 December 2013, some abstracts are available in Finnish, Polish, Greek and Slovak in addition to English, French, German, Italian, Spanish, Portuguese and Dutch. Emergency guidelines are available in Polish in addition to English, French, German, Italian, Spanish and Portuguese.
- A new collection of texts in the Orphanet Encyclopedia has been established. It is devoted to the disabilities associated with each rare disease and is addressed to the professionals in the field of disability as well as to the patients and their families.
- The directory of expert centres, medical laboratories, clinical trials, research projects, networks, registries and patient organisations has been expanded and updated.
- A new Orphanet Report Series was created about the European infrastructures useful to rare diseases.
- The list of rare diseases (in English and French) has been published as an Orphanet Report Series for more effective communication but also for easy retrieval of the Orpha codes by clinicians and coders.
- Most of the Orphanet Report Series have been updated (List of Rare Diseases, Prevalence of Rare Diseases, Lists of Orphan Drugs, Orphanet Activity Reports, and Satisfaction Surveys).
- An Orphanet mobile application was released for iPhone, iPad and Android, including the list of rare diseases, textual information and list of expert centres.
- The Orphanet Activity report 2012 has been translated into French, Italian and Spanish.
- The Orphanet Standard Operating Procedures, according to which Orphanet national teams agree to work, have been posted on the website.
- The Orphanet nomenclature has been included in several national health information systems; working groups and collaborations were set up in France, Germany, Belgium and Latvia. Collaborations are planned with Greece and Hungary.
- Germany has aligned the Orpha codes with its national extension and plans to add the missing codes in the next two years (up to 2016). DIMDI is developing a file for implementation in existing IT-systems which makes coding easier for coders and standardises coding results, if coded in both systems.
- The Orphanet online registration tool was launched in order to allow health professionals, patient organisations and researchers to submit or update their information related to rare diseases in Orphanet.

Orphadata is website, launched in the context of the Joint Action, to make Orphanet data available for re-use in research. Since January 2013, Orphadata products were downloaded more than 118,000 times, with an average of 9,880 times a month.

EUCERD Joint Action: Working for rare diseases (2012-2015)

A joint action between the European Commission and the EU Member States to support the EUCERD was approved in 2011 and started in March 2012. The Joint Action had its kick-off meeting in mid-March 2012 and will run through February 2015. Coordinated by Pr. Kate Bushby (Vice-Chair of the EUCERD, Joint Coordinator of TREAT-NMD, Newcastle University, UK) several work packages for the EUCERD Joint Action will support identified priority areas of the EUCERD's work. Specifically, this Joint Action will address the following priority areas of the Council Recommendation:

- Enhancing the visibility and recognition of RD;
- Contributing to the development and dissemination of knowledge on RD, from specialised research, through to the support of the healthcare professionals and the empowerment of patients;

²³ www.orpha.net

²⁴ <http://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2013.pdf>

- Contributing to improvements in access to quality services and care, from diagnosis, through to care and social support and innovative therapies.

In 2013 a number of workshops were held with the support of the EUCERD Joint Action: Key indicators for national plans/strategies workshop (25 March 2013, Rome), Workshop on training of social service providers (10-11 October 2013, Copenhagen), and Workshop on registries for rare diseases and the European registry platform (22-23 April 2013, Luxembourg). The annual report on the *State of the art of rare disease activities in Europe* was also published along with the *Orphanews* newsletter.

1.2.2. Project grants

Quality of Life in patients with Rare Diseases in Europe (BURQOL-RD) project (2010-2013)

There is a need for a better understanding of the costs that rare diseases represent for the health systems. The Quality of Life in patients with Rare Diseases in Europe (BURQOL-RD) project, which started in April 2010, was selected for this purpose. BURQOL-RD aimed to generate a model to quantify the socio-economic burden and HRQOL of people with rare diseases and their caregivers.

The main outcomes of the project were: a report on the socio-economic and health-related quality of life situation of patients and their carers affected by rare diseases in 8 European countries, and the preparation of integrated instruments that can be adapted to other rare diseases and countries in order to monitor the socio-economic burden and health-related quality of life of patients in Europe.

A BURQOL-RD metre has been developed as an on-line tool to facilitate the gathering of information from patients and carers through web-based questionnaires, automated calculation of the main outcomes through cross-matching the data obtained from patients with unit costs of resources, and presentation of the results on costs and health-related quality of life of patients with rare diseases across Europe in an interactive way.

The project has demonstrated that the health-care costs concerning rare diseases are substantial, and the social costs are higher. Knowledge of these costs is needed to aid the appropriate planning of health services. The tools produced by the project could be used to further update and monitor these results, and could be applied to other rare diseases for which no information on costs and health-related quality of life data is available.

Building consensus and synergies for the EU Registration of Rare Diseases Patients (EPIRARE) Project (2011-2014)

The general objective of this initiative which started in April 2011 is to build consensus and synergies to address regulatory, ethical and technical issues associated with the registration of rare diseases patients and to elaborate possible policy scenarios. The final outcomes of the project were published in 2014 online²⁵.

1.2.3. Call for Tenders

The aim of a call for tender is to purchase the provision of services, the execution of works, the supply of assets or to conclude building contracts. Two important calls for tenders have been launched in the field of rare diseases.

Call for Tender: Evaluation of population newborn screening practices for rare disorders in Member States of the European Union (2009-2011)

In July 2009 a call for tender was launched for an evaluation of the current situation of newborn screening (NBS) practices for rare disorders in the MS of the EU and was awarded to the Istituto Superiore di Sanità in Italy. The tender started on 30 December 2009 and ended on 29 July 2011.

There is a need to identify the current practices in the Member States, including: for which reasons the diseases to be screened are selected, how the decisions to expand the list of diseases are taken, what technologies are used and what organisation is in place to ensure comprehensive screening of all newborns and to evaluate the performance of the programmes.

This tender aimed to deliver: an extensive report on the practices of NBS for rare disorders implemented in all the Member States including number of centres, estimation of the number of infants screened and the number of disorders included in the NBS as well as reasons for the selection of these

²⁵ <http://www.epirare.eu/del.html>

disorders; the identification of types of medical management and follow-up implemented in the Member States; the establishment of a network of experts analysing the information and formulating a final opinion containing recommendations on best practices and recommending a core panel of NBS conditions that could be included in all MS practices; and the development of a decision-making matrix that could be used by Member States programs to systematically expand (or contract) screening mandates.

Two meetings of the EU network of experts on new born screening were held in 2010 to examine the criteria for implementing newborn screening and to discuss the analysis of the data collected by a survey of EU Member States, candidate Countries, EEA/EFTA and potential candidate countries concerning new born screening in each country. A consensus conference was organised in June 2011 to finalise the report on NBS practices²⁶ and the expert opinion²⁷ containing recommendations on best practices which were published in 2012. An executive report²⁸ to the EC was also issued. The EUCERD were presented with the results of the report in 2012 and the EC requested their opinion on areas in which EU-level collaboration could be envisaged in the future. The document was discussed by EUCERD members at their meetings in 2012 and an opinion on possible areas for European cooperation in the field was adopted in 2013²⁹.

Call for Tender: Creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines (2010-2011)

A call for tender³⁰ was launched in 2010 for the creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines (CAVOD). This call was awarded to Ernst and Young for a duration of 9 months. The study was published in late 2011³¹: it aims to identify and assess possible options for creating a mechanism for the exchange of knowledge between Member States (MS) and European authorities on the scientific assessment of the relative effectiveness of orphan medicines. The European Union Committee of Experts on Rare Diseases (EUCERD) is considering carefully the data provided by the CAVOD report and will issue a recommendation to the EC and MS on improving informed decisions based on the clinical added value of orphan medicinal products information flow in 2012 suggesting how to best coordinate and exchange information health technology assessment for orphan medicinal products, capitalising on mechanisms already in place at the MS level and at EU-level structures, such as the European Medicines Agency and the EUnetHTA network. Following the outcomes of this tender the EUCERD has elaborated a recommendation for the EC and Member States on improving the assessment of the Clinical Added Value of Orphan Medicinal Products encourages the creation of an Information Flow³².

1.2.4. Operational grants

Under the Health Programme, the European Union can offer support to finance some of the core operating costs for organisations that promote a health agenda in line with the EU Health Programme (2008-13). The purpose of an operating grant is to provide financial support towards the functioning of an organisation in its core activities, over a period that is equivalent to its accounting year, in order to carry out a set of activities.

An Operating Grants was awarded to EURORDIS (European Organisation for Rare Diseases) in 2013 to carry out its mission. EURORDIS is fully recognised as the main partner of patients in the field of rare diseases and the line of the European Commission has been always to recognise this central role in all the political affairs concerning the implementation of rare diseases policy. As a consequence the Commission has privileged the funding of EURORDIS and does not finance, nor has plans to finance, individually every patient organisation that exists in the EU.

²⁶ http://ec.europa.eu/eahc/documents/news/Report_NBS_Current_Practices_20120108_FINAL.pdf

²⁷ http://ec.europa.eu/eahc/documents/news/Expert_opinion_document_on_NBS_20120108_FINAL.pdf

²⁸ http://ec.europa.eu/eahc/documents/news/Executive_Report_to_EC_20120108_FINALE.pdf

²⁹ http://www.eucerd.eu/wp-content/uploads/2013/07/EUCERD_NBS_Opinion_Adopted.pdf

³⁰ http://ec.europa.eu/eahc/documents/health/tenders/2010/EN/EAHC_2010_05_tenderSpecifications_EN.pdf

³¹ http://ec.europa.eu/eahc/documents/news/CAVOD_Final%20Report_vf_corrected_281011.pdf

³² http://www.eucerd.eu/?post_type=document&p=1446

1.3. Joint activities of the European Commission DG Health and Consumers and the Joint Research Centre

European Platform for Rare Diseases Registration

Following the example of other areas where between Directorate for Health and Consumers and Joint Research Centre (JRC) are successfully working together (e.g. cancer registries, food safety, etc.), the services have agreed on the active involvement of JRC in the development of public health initiatives in the field of rare diseases. An administrative agreement between the Directorate for Health and Consumers and JRC was signed in December 2013.

According to Orphanet as of January 2014 there were 641 rare diseases registries distributed as follows: 40 European, 74 global, 446 national, 77 regional and 4 undefined. Most of the registries are established in public and academic institutions. A minority of them are managed by pharmaceutical or biotech companies, while others are being run by patient organisations. The lack of interoperability between rare diseases registries is severely jeopardising the registries' potential.

For this reason, the European Commission's Joint Research Centre is currently developing a European Platform on Rare Diseases Registration. The main objectives for this platform are to provide a central access point for information on rare diseases patients' registries for all stakeholders, to support new and existing registries in view of their interoperability, to provide IT tools to maintain data collection and to host activities of the surveillance networks.

The European Platform on Rare Diseases Registration platform will to coordinate activities of two surveillance networks: EUROCAT (European surveillance of congenital anomalies) and SCPE (Surveillance of Cerebral Palsy in Europe).

1.4. Activities of the European Commission DG Health and Consumers indirectly related to rare diseases

Directive 2011/24/EU OF on the application of patients' rights in cross-border healthcare (2011)

Directive 2011/24/EU adopted in March 2011 clarifies patients' rights to access safe and good quality treatment across EU borders, and be reimbursed for it. The Directive will provide a firm basis for increased cooperation between national health authorities through several actions. Some provisions are addressing the issue of rare diseases.

In particular Article 12 foresees enhanced cooperation of Member States in the area of European reference networks (ERN). It foresees that Commission is going to adopt through legal means (delegated and implementing acts) the criteria and conditions which the ERN and the healthcare providers must fulfil.

To prepare these acts, the Commission has led an extensive and exhaustive consultation process including the establishment of the Cross-Border Directive expert group which assisted the Commission on this task. In the case of the implementing acts the Commission was also assisted by the Committee on Cross-Border Healthcare composed of Member States representatives. Other consultation activities included a public consultation on the criteria for the ERN, visits to Member States, workshops and meetings with experts, medical societies, patients' organisations and other stakeholders

The main added value of the ERN and its Members is to facilitate improvements in access to diagnosis and delivery of high-quality, accessible and cost-effective healthcare in the case of patients who have a medical condition requiring a particular concentration of expertise or resources, particularly in medical domains where expertise is rare.

ERN could also be focal points for medical training and research, information dissemination and evaluation, especially for rare diseases. The Directive is not aiming to "create" new centres, but to identify already established centres at national level and to encourage voluntary participation of healthcare providers in the future ERN.

On 10 March 2014, two Decisions (a delegated³³ and an implementing³⁴) on the criteria for Networks and its Members and on the establishment and evaluation of European Reference Networks were adopted by the EC. Both legal measures will be published in the OJ and enter into force in May 2014.

Furthermore, Article 13 requires the Commission to support Member States in making health professionals more aware of diagnostic tools which may help rare disease patients, and in making patients more aware of the possibility of requesting a treatment abroad according and up to the entitlements they have in their Member State of affiliation. Article 8 also encourages Member States to seek the advice of experts when dealing with patients with rare diseases.

The transposition period came to an end in October 2013.

European Health Observatory Scoping Study (2013)

To analyse the current situation of reference networks and highly specialised centres in the different European Union countries and to possibly establish a logical, feasible and robust model, a scoping study was commissioned by the EC to the European Observatory on Health Systems and Policies (World Health Organisation). Details of this study are outlined in a document entitled “Building European Reference Networks in Health Care: Exploring concepts and national practices in the European Union³⁵” published in 2013. Although this study was performed within a short time and only provides a rough estimation of the existing networks in Member States, it is still a valuable analysis and provides ample help for building future models of European Reference Networks. This study assesses the historical context of how certain reference networks have been established in the European Member States. The document provides an examination of the medical conditions or interventions for which reference networks have been developed and the driving force for their establishment. The study also discusses the regulatory processes and the financial implications for establishing these networks. From the analysis, the study also proposes a road map for developing and synthesising reference networks in Europe, keeping in mind the heterogeneity and the needs of the Member States.

Adoption of the Commission Decision on criteria for European Reference Networks (2014)

On 10 March 2014, two Decisions on European Reference Networks (ERNs) were adopted by the European Commission. In the *Commission Delegated Decision setting out criteria and conditions that European Reference Networks and healthcare providers wishing to join a European Reference Network must fulfil*³⁶ the certain criteria that a European Reference Network should fulfil in order to efficiently deal with the needs of the patients are outlined. Overall, according to the criteria outlined by the European Commission, European Reference Network should:

- Have the knowledge and expertise to diagnose, follow-up and manage patients with evidence of good outcomes, as far as applicable;
- Follow a multi-disciplinary approach;
- Offer a high level of expertise and have the capacity to produce good practice guidelines and be able to implement outcome measures and quality control;
- Contribute towards research and development;
- Arrange teaching and training activities;
- Work in partnership with other centres of expertise and networks at national and international level.

The accompanying *Implementing Decision* lays down the procedure on how to establish and evaluate the ERNs. Both Decisions are expected to enter into force by the end of May 2014, at the expiry of the two-month period for possible objection to the Delegated Decision by the European Parliament and the Council.

2014 will also see the establishment of a European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment (EXPO-r-NeT) - has been recently funded under the EU Health Programme 2008-2013. This project will endeavour to establish a Paediatric Oncology European Reference Network (PO-ERN) “linking pre-existing reference centres inherent to the Cooperative PO- Clinical Trial Groups which may contribute high-level diagnostic and medical expertise to provide cross-border best care to rare childhood cancer populations”³⁷.

³³ <http://ec.europa.eu/transparency/regdoc/rep/3/2014/EN/3-2014-1408-EN-F1-1.Pdf>

³⁴ http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2014_147_R_0007

³⁵ <http://www.orpha.net/actor/EuropaNews/2013/doc/European-Reference-Networks.pdf>

³⁶ <http://ec.europa.eu/transparency/regdoc/rep/3/2014/EN/3-2014-1408-EN-F1-1.Pdf>

³⁷ <http://www.siope.eu/activities/eu-projects/expor-net/>

Revision of the Directive of the European Parliament and Council of 27 October 1998 on *in vitro* diagnostic medical devices

In September 2012, the European Commission issued a Communication³⁸ and proposed two Regulations³⁹ designed to revise current European Union legislation on medical devices and *in vitro* diagnostic medical devices. The proposed Regulations are in response to the Conclusions of the Council adopted on 6 June 2011 on innovation in the medical device sector as well as the European Parliament Resolution (on defective silicone breast implants) adopted on 14 June 2012. The proposed Regulations seek to adapt current legislation “*to the needs of tomorrow*” by creating a “*suitable, robust, transparent and sustainable regulatory framework*” that will serve to encourage the development of innovative medical devices and *in vitro* diagnostic medical devices that are safe, and effective. The European Parliament and Council need to adopt the Regulations in order for them to become law. There are a number of rare diseases that include medical devices as part of their clinical management, particularly in paediatric populations.

The proposed Regulation was debated in the Parliament and the Council in 2013.

³⁸ http://ec.europa.eu/health/medical-devices/files/revision_docs/com_2012_540_revision_en.pdf

³⁹ http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf and http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

A. 2. EUROPEAN COMMISSION ACTIVITIES RELATED TO RESEARCH IN THE FIELD OF RARE DISEASES

2.1. 7th Framework Programme for research, technological development and demonstration activities (2007-2013)

The Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7, 2007-2013⁴⁰) is composed of four main specific programmes – “Cooperation”, “Ideas”, “People” and “Capacities” – including cross-cutting issues such as support for SMEs, international cooperation, the contribution of research to EU policy, and societal considerations. Rare disease research specifically features under the heading of the Health theme, one of ten themes proposed under the specific programme on “Cooperation”. This specific programme is designed to gain or strengthen leadership in key scientific and technological areas by supporting trans-national cooperation between universities, industry, research centres, public authorities and stakeholders across the European Union and the rest of the world.

Specifically, the focus for rare diseases collaborative research in FP7 is on pan-European studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions. This sector includes rare Mendelian phenotypes of common diseases. Supported projects should help identify and mobilise the critical mass of expertise in order (i) to shed light on the course and/or mechanisms of rare diseases, or (ii) to test diagnostic, preventive and/or therapeutic approaches, to alleviate the negative impact of the disease on the quality of life of the patients and their families, as appropriate depending on the level of knowledge concerning the specific (group of) disease(s) under study.

The European Commission released on 10 July 2012 the content of a new Call for proposals⁴¹ based on the FP7 Health Work Programme 2013: this year, one specific rare disease topic is included: *Development of imaging technologies for therapeutic interventions in rare diseases*. Altogether 7 projects were funded in this topic with the overall EU contribution of €40 million. The Call included also a topic for *New methodologies for clinical trials for small population groups* which resulted in funding of 3 projects related to rare diseases with the total EU contribution of €8 million. For the period 2007–2013, close to 120 research projects related to rare diseases have been funded in FP7 Health Theme with an EU contribution of over €620 million.

2.2. Horizon 2020 (2013-2020)

Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. It is the biggest EU Research and Innovation programme with nearly €80 billion of funding available over 7 years (2014 to 2020) – in addition to the private investment that this money will attract. It promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market. Horizon 2020 is open to everyone, with a simple structure that reduces red tape and time so participants can focus on what is really important. This approach makes sure new projects get off the ground quickly – and achieve results faster.

Horizon 2020 has announced funding for many rare disease initiatives. The recently announced calls that is aimed to enhance research and development and build a knowledge structure in various areas of research including rare diseases research. The topics that address rare disease research are:

- ERA NET rare disease research implementing IRDiRC objectives⁴²: Aimed towards proposals that will coordinate national and regional programmes for research including rare disease research by

⁴⁰ http://cordis.europa.eu/fp7/home_en.html

⁴¹

http://ec.europa.eu/research/participants/portal/page/cooperation:efp7_SESSION_ID=m0pTRn7GxnWW8LynmvWxs9w6J1KJQC4ByLwcYvzJhm6GL0qNLQX11982354445?callIdentifier=FP7-HEALTH-2013-INNOVATION-1#wlp_call_FP7

⁴² <http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2216-hco-10-2014.html>

preparing and implementing a transnational call with EU co-funding, resulting in grants to third parties, with a view to implement IRDiRC objectives and identified priorities. Successful grants are expected to impact on national and transnational programmes and IRDiRC objectives as well as the leverage effect on European research and competitiveness, and should plan the development of key indicators for supporting this. Indicative budget for this ERA-NET is €5 million.

- New therapies for rare diseases⁴³: Altogether €60 million has been earmarked for successful proposals that address one or more of the following: development of new or improved therapeutic approaches, for repurposing of existing therapies, as well as for preclinical research, animal model development and good manufacturing practice (GMP) production. Proposed treatments to be developed may range from small molecule to gene or cell therapy. Selected proposals should contribute to the objectives of, and follow the guidelines and policies of the International Rare Diseases Research Consortium, IRDiRC.
- Support to integrate on European scale, and open up key national and regional research infrastructures to all European researchers, from both academia and industry, ensuring their optimal use and joint development, Horizon 2020 will award grants towards research activities that will help towards integrating and opening existing national and regional research infrastructures of European interest⁴⁴. Out of several research areas, building research infrastructures to support rare diseases research is one of areas that will be supported under this topic. This initiative will be recognised as a “starting community” which invites proposals requesting a contribution from the EU of up to €5 million to allow this topic to be addressed appropriately.

2.3. The International Rare Diseases Research Consortium (IRDiRC⁴⁵)

Governance

IRDiRC is governed by the Executive Committee, three Scientific Committees and twelve working groups⁴⁶. Until April 2013, IRDiRC was run by an Interim Executive Committee with representatives of all participating funding agencies. It was chaired by Dr Ruxandra Draghia-Akli, from the European Commission who handed over the Chairmanship to Paul Lasko in March 2013.

IRDiRC Policies and Guidelines

In April 2013, the IRDiRC’s policies and guidelines document was published⁴⁷. This document outlines the principles that the IRDiRC members agree to follow as well as the recommendations from the Scientific Committees. The general policies of the IRDiRC emphasise the collaboration in rare diseases research, the involvement of patients and their representatives in all relevant aspects of research, as well as the sharing of data and resources. Policies and guidelines are also defined for the following topics: ontologies, diagnostics, biomarkers, patient registries, biobanks, natural history, therapeutics, models, publication and intellectual property, and communication on IRDiRC.

EC support for IRDiRC activities

The EC announced its commitment to supporting the logistical organisation of IRDiRC activities through a dedicated support action topic in the FP7-HEALTH-2012-INNOVATION-1⁴⁸ call for proposals (Work Programme 2012). The project funded in this topic, SUPPORT-IRDiRC provides a Scientific Secretariat for the IRDiRC since its launch in October 2012. The Secretariat is located at the Rare Disease Platform in Paris, in the same structure housing the Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), pan-European rare disease and orphan drug information portal Orphanet, and the French Rare Disease Foundation. The contract for the SUPPORT-IRDiRC has been assigned to two partners: the INSERM (the French National Institute for Health and Medical Research) and the French Rare Disease Foundation. With this new resource, it is expected that the IRDiRC will have the means of achieving its ambitions.

⁴³ <http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2278-phc-14-2015.html>

⁴⁴ <http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/64-infraia-1-2014-2015.html>

⁴⁵ http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html

⁴⁶ http://ec.europa.eu/research/health/medical-research/rare-diseases/governance_en.html

⁴⁷ http://www.irdirc.org/wp-content/uploads/2013/06/IRDiRC_policies_24MayApr2013.pdf and http://www.irdirc.org/wp-content/uploads/2013/06/IRDiRC_Policies_Longversion_24May2013.pdf

⁴⁸ <http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-1> and <http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-2>

The Call FP7-HEALTH-2012-INNOVATION-1 resulted in the funding of a number of projects contributing directly to the IRDiRC objectives for a total of €95 million. Three large-scale integrating projects are being funded in the area of -Omics for rare diseases: EUReOmics will systematically apply -omics technologies for the molecular characterisation of rare kidney disorders in view of developing new diagnostics and treatments, NEUROMICS aims to use the most sophisticated -omics technologies to revolutionise diagnostics and develop pathomechanism-based treatments for large groups of rare neuromuscular and neurodegenerative diseases and RD-Connect will create an integrated platform connecting registries, biobanks and clinical bioinformatics for rare disease research into a central resource for researchers worldwide. The kick-off meetings of these projects were held in Barcelona on 25-27 January 2013. Also 10 new research projects were funded for preclinical and clinical development of orphan drugs with the major involvement of industry and small and medium sized enterprises.

Committed Members of the IRDiRC

The funding agencies now committed to the IRDiRC are from the following countries: Australia, Canada, China, Finland, Italy, France, Germany, Georgia, South Korea, the Netherlands, Spain, the United Kingdom, and the United States, in addition to the European Commission⁴⁹.

IRDiRC Conference (16-17 April 2013, Dublin)

The first IRDiRC conference was held on 16-17 April 2013 in Dublin, Ireland. Thought leaders from all over the world captured the audience with stimulating, inspirational and highly informative talks on the past, present and future of rare disease research. The IRDiRC was unanimously welcomed as needed at this time to advance the cause of rare disease research. IRDiRC promises to contribute in development of 200 therapies for rare disease and means to diagnose all of them by 2020. Rare disease stakeholders discussed the ways and means to help reach these goals. They provided examples of success stories as well as suggestions of the innovative ways in which stakeholders can come together to fulfil this goal.

This truly international conference was attended by more than 400 participants representing Europe, North America, Australia and Asia. It was recognised by one and all that expertise in rare disease, like the patients, are scattered across the globe. It is thus imperative for the global rare disease community to put their heads together to solve the great big jigsaw of rare disease, of which everyone holds a piece. This meeting boasted of attendance from policy makers, industry leaders, academicians as well as patient organisations from around the world. Representatives from regulatory bodies such as FDA, EMA, the Canadian and Australian regulatory agencies shared their expertise and pushed the need for more regulatory success for orphan drugs. Patient organisations such as Rare Voices Australia, Eurordis and Genetic Alliance US, gave an overview of the current need of patients and how coming together with a common agenda is urgent, but also achievable. Industry partners emphatically expressed the need to work with academicians, patient organisations and regulatory bodies to significantly increase the number and quality of drugs that is accessible to all. The buzz word was collaboration, collaboration, collaboration.

Mirroring the scientific committees of IRDiRC, the conference panels were divided into 3 tracks-therapies, diagnostic and interdisciplinary track-with experts in each area presenting the current outlook and the way forward. The therapies track addressed issues that deal with providing better treatment for patients such as drug repurposing, developing innovative therapies and ensuring an open dialogue with the regulatory bodies so that the treatments developed painstakingly see the light of day. The diagnostic track articulated the current projects that are underway to identify the causes of the rare diseases, the tremendous advancements in Next Generation Sequencing including the use of data generated from it and the crucial understanding of the Human Phenome. The speakers in the Interdisciplinary track highlighted the means by which successful collaborations can lead to successful treatments and diagnostics. They also endeavoured to delineate how future challenges in the extremely complex world of rare disease research can be overcome. Economic and ethical issues such as those that have cropped up due to recent advancements in technology, especially next generation sequencing, were also discussed at length.

The conference report is available online⁵⁰.

⁴⁹ http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members_en.html

⁵⁰ http://www.irdirc.org/wp-content/uploads/2013/06/IRDiRC_conference_report_April2013.pdf

2.4. Access to scientific information

Valuable information produced by researchers in many EU-funded projects will be shared freely as a result of a Pilot on Open Research Data in Horizon 2020⁵¹. Researchers in projects participating in the pilot are asked to make the underlying data needed to validate the results presented in scientific publications and other scientific information available for use by other researchers, innovative industries and citizens. This will lead to better and more efficient science and improved transparency for citizens and society. It will also contribute to economic growth through open innovation. For 2014-2015, topic areas participating in the Open Research Data Pilot will receive funding of around €3 billion.

Open access to scientific peer reviewed publications has been anchored as an underlying principle in the Horizon 2020 programme and is explained in the Regulation and the Rules of Participation as well as through the relevant provisions in the grant agreement. A fact-sheet⁵² explaining this approach has been published by the European Commission.

2.5. DG Research consultation on public-private partnership initiatives in health research

Public-private collaboration is considered crucial in the field of rare disease and orphan drug research, an area that suffers from a lack of resources and funding. Under the 7th Framework programme for research, technological development and demonstration activities (2007-2013) (FP7) the European Union (EU) entered into a Public Private Partnership (PPP) with the pharmaceutical industry, represented by its umbrella organisation European Federation of Pharmaceutical Industries and Associations (EFPIA). The Innovative Medicines Initiative (IMI) was established by Council regulation 73/2008 of 20.12.2007. Both partners contribute €1 billion each to implement IMI. With this funding IMI is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients – including rare disease medicinal products. Based on the success of IMI the European Commission is now exploring whether under Horizon 2020 a renewed PPP should be launched. The Commission proposal for Horizon 2020 foresees that the priority "societal challenges" is also implemented through PPPs. Selection of PPPs will be based on a set of clearly defined criteria, including the added value of action at the EU level, the scale of impact on industrial competitiveness, sustainable growth and socio-economic issues, and the long-term commitment from all partners based on a shared vision and clearly defined objectives. As part of this process a public consultation was conducted in 2012⁵³ seeking seeks key views relating to the launch of a PPP in the life sciences research area under Horizon 2020 and what areas should be addressed. The report⁵⁴ based on the responses was published in January 2013.

2.6. Reform of the EU Data Protection Directive

In January 2012, the European Commission proposed a comprehensive reform of the European Union's 1995 Data Protection Directive, seeking to update and modernise the legislation in view of the major technological advances made in recent years. The overhaul also aims to increase harmony between the 27 EU Member States which have implemented the current Data Protection Directive 95/46/EC differently, resulting in divergences in enforcement. The proposed Regulation will decrease the fragmentation by establishing a single set of rules valid across the EU. Specific provision on processing of personal data for health purposes and on historical, statistical and scientific research purposes will increase legal certainty and clarity on applicable rules

⁵¹ http://europa.eu/rapid/press-release_IP-13-1257_en.htm

⁵² https://ec.europa.eu/programmes/horizon2020/sites/horizon2020/files/FactSheet_Open_Access.pdf

⁵³ http://ec.europa.eu/research/consultations/life_science_h2020/consultation_en.htm

⁵⁴ http://ec.europa.eu/research/consultations/life_science_h2020/report_public_consultation.pdf

for data protection in health research. The Commission's proposal for the Regulation is currently being discussed in the European Parliament and the Council.

The European Parliament's rapporteur on the Data Protection Regulation published a draft report⁵⁵ in January 2013 endorsing that *"...processing of sensitive data for historical, statistical and scientific research purposes is not as urgent or compelling as public health or social protection."* Stakeholders in the rare disease community have expressed their concern as enacting it into law may make recruiting subjects for clinical research through registries extremely difficult. Eurordis published in 2013 a statement outlining the possible implications of the project for rare disease patients⁵⁶.

2.7. Revision of the EU Transparency Directive

European Member States according to Article 168(7) of the Treaty are responsible for the organisation of their healthcare systems and for the delivery of health services and medical care, including the allocation of resources assigned to them. Directive 89/105/EEC lays down a series of procedural requirements to ensure the transparency of pricing and reimbursement measures for medicinal products adopted by Member States. The directive has never been amended since its adoption. Therefore, the European Commission adopted in March 2012 the proposal for a *"Directive of the European Parliament and of the Council relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems"*⁵⁷. The overall objective of the proposal is to clarify the procedural obligations incumbent on Member States and to ensure the effectiveness of the Directive, both in avoiding delays in pricing and reimbursement decisions and in preventing barriers to pharmaceutical trade. In the context of rare diseases, to the proposal shall ensure that patients have equal and speedy access to medicines across Europe.

EURORDIS and Members of European Parliament Ms Antonia Parvanova (Bulgaria) and Mr Cristian Silviu Busoi (Romania) co-hosted a multi-stakeholder policy event in February 2013 *"to examine how different policy measures can help improve access to therapies for rare diseases"*. The meeting was attended by over 100 participants including several experts in the area of rare diseases. The co-host of this multi-stakeholder event, Rapporteur on the Transparency Directive Antonia Parvanova (Environment, Public Health and Food Safety Committee) said that, *"updated rules for a fair and transparent process on the pricing and reimbursement of medicines is to benefit all patients, and in particular the ones suffering from rare diseases. Availability and access to treatment is of crucial importance when we talk about rare diseases, and we should keep on upholding this principle throughout the upcoming legislative process. Our goal is to bring more transparency but also to support Member States for an efficient and evidence-based decision making process, which should ultimately support the sustainability of national healthcare systems, delivering for all."*

The European Parliament adopted its very supportive first reading position on 6 February 2013. As a result of the vote in Plenary and taking into consideration the position of the Member States in the Council, the European Commission adopted an amended proposal in March 2013, an encouraging step towards obtaining more transparency and wider access of medicinal products. Discussions on the amended draft proposal are ongoing.

⁵⁵ http://www.europarl.europa.eu/meetdocs/2009_2014/documents/libe/pr/922/922387/922387en.pdf

⁵⁶ http://www.orpha.net/actor/EuropaNews/2013/doc/Statement_Data_Prot_FINAL.pdf

⁵⁷ http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pricing-reimbursement/transparency/index_en.htm

A.3. EUROPEAN COMMISSION ACTIVITIES RELATED TO RARE DISEASES IN THE FIELD OF ORPHAN MEDICINAL PRODUCTS AND THERAPIES FOR RARE DISEASES

3.1. EU activities under Regulation (EC) No 141/2000 on orphan medicinal products

Orphan Medicinal Product Regulation (16 December 1999)

The regulation on orphan medicinal products (Regulation (EC) No 141/2000)⁵⁸ 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 placing on the market of medicinal products for the diagnosis, prevention or treatment of rare conditions, as without such incentives, it is unlikely that medicinal products would be developed for rare diseases. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides for incentives for products receiving an orphan designation. The incentives contained in the legislation aim to assist sponsors receiving orphan designations in the development of medicinal products with the ultimate goal of providing medicinal products for patients suffering from rare diseases.

The Commission adopts decisions on designation based on an opinion from the COMP. In 2013, the Commission granted 136 orphan designations. In addition, the Commission authorised 7 orphan medicinal products in 2013. In recent years, the number of designations has increased while the number of authorisations has remained stable (7 authorisations in 2013 versus 10 authorisations in 2012). Orphan medicinal products offer major benefits to patients suffering from rare diseases. For example, the active substance macitentan has been recently authorised for the treatment of pulmonary arterial hypertension and bosutinib for the treatment of chronic myeloid leukaemia. In 2013, the European Commission had also undertaken the revision of the EU guideline on the format and content of applications for designation as orphan medicinal products. The guideline, which was finally adopted in early 2014, has been reviewed to clarify how sponsors should define the medical plausibility of their product in relation to a disease and its significant benefit.

As of 2013, non-SMEs developing orphan medicinal products will have fewer benefits. Fee reductions for non-SME will now include a 40% reduction for non-paediatric protocol assistance (previously 75%) and no fee reductions for initial market-authorisation applications (previously 10%) and pre-authorisation inspections (previously 100%). Protocol assistance for paediatric-related medicines will continue to be free for non-SME.

3.2. European legislation and activities in the field of clinical trials

Revision of the EC Clinical Trials Directive

On 17 July 2012, the Commission adopted a "Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC"⁵⁹. The adoption was announced in a press release supported 'questions and answers' document⁶⁰ and was accompanied by an impact assessment report⁶¹. The proposal has been submitted to the European Parliament and the Council.

An agreement between Council and the European Parliament was reached in December 2013 and Regulation on Clinical Trials was formally adopted in April 2014.

⁵⁸ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

⁵⁹ http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

⁶⁰ http://ec.europa.eu/health/files/clinicaltrials/2012_07/press-releases/memo-12-566_en.pdf

⁶¹ http://ec.europa.eu/health/files/clinicaltrials/2012_07/impact_assessment_part1_en.pdf (Volume I) and http://ec.europa.eu/health/files/clinicaltrials/2012_07/impact_assessment_part2_en.pdf (Volume II)

The new Regulation introduces some significant measures which will contribute to boost clinical research in Europe while preserving the high level of patients' safety.

The main elements of the new legislative framework are the following:

- Streamlined application procedure via a single entry point, an EU Portal and Database. The Database and Portal are developed by the European Medicines Agency in cooperation with the Commission and the Member States. Additionally, the Regulation simplifies the application dossier requirements by setting a uniform list of documents to be submitted in the application for a clinical trial authorisation throughout the EU.
- Single authorisation procedure for all clinical trials. This procedure imposes a joint assessment by all the Member States concerned by the clinical trial of the part of the application dossier and a separate assessment by each Member State of other part of the dossier. The procedure ensures one single decision per Member State within clearly defined deadlines. It also extends the application of a tacit agreement principle to the whole authorisation process which, without compromising safety, will give sponsors, in particular SMEs and academics, increased legal certainty.
- Thirdly, it increases the transparency on the conduct and on the results of the clinical trials notably by requiring a publication of the clinical trials results, lay person summary of results and of a Clinical Study Report in case the marketing authorisation has been sought. The information stored in the EU Database is as well publically available but exceptions in particular for personal and commercially confidential information are provided for.
- Finally, the Regulation simplifies the reporting procedures which will spare sponsors from submitting broadly identical information separately to various bodies and different Member States.

The Regulation will facilitate the conduct of multinational trials which are essential for research on rare diseases. Furthermore, recitals 9 and 10 of the Regulation recognise the importance of the clinical trials for rare diseases and stress the particular importance of the rapid and in-depth assessment of the clinical trials application concerning rare medical conditions.

The Regulation will enter into application 6 months after publication in the Official Journal of a notice on the full functionality of the EU Clinical Trials Portal and EU Database, on a basis of a result of an independent audit.

B. EUROPEAN MEDICINES AGENCY ACTIVITIES IN 2013

1. The European Medicines Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases

Work programme

The European Medicines Agency's Management Board, at its meeting on 13 December 2012, adopted the Agency's work programme and budget for 2013⁶². The Agency's priorities will be to continue to ensure that assessment activities are conducted to the highest scientific levels, to increase efficiency in its activities, and to develop initiatives for greater transparency and communication with stakeholders. Further specific drivers include the continued implementation of the pharmacovigilance legislation and the new falsified-medicines legislation, and the planned revision of the veterinary medicines legislation. In 2013, the Agency expects a stable total number of applications for human medicines, with 100 applications in 2013. These include some 54 applications for new medicinal products (excluding designated orphan medicines), 20 new orphan medicines and 20 generic applications (2012: 52, 13 and 39 respectively). Some 10 applications for new veterinary medicines are expected, with 3 generic applications (2012: 9 and 3 respectively). The work programme is accompanied by a budget of €231.6 million, an increase of 4.1% over 2012, which includes fee revenue of €179.8 million (3.8% increase compared with 2012, this increase is mainly due to inflation) and a European Union (EU) contribution of €39.2 million.

During 2013 the Agency aimed at continuing to foster its approach to communication and transparency in order to strengthen public confidence in the Agency and the EU system of evaluation and supervision of medicines. The publication of the agendas and minutes of all scientific committees' meetings has already been put in place by the Committee for Orphan Medicinal Products since September 2012. Following the successful workshop in November 2012 on access to clinical-trial data and transparency, the Agency started a consultation with stakeholders at the beginning of 2013 in order to publish a policy on the release of data from clinical trials in early 2014. The EMA received more than 1,000 comments during the public consultation on its draft policy on publication and access to clinical-trial data.

In December 2014 the EMA adopted their 2014 work programme⁶³. In 2014, the Agency expects a slight general increase in its assessment activities for human medicines compared with 2013. Activities in the early stages of medicines development remain at a high level; these activities, which provide support to sponsors, include scientific advice on clinical development, orphan designation and support to micro-, small- or medium-sized enterprises. A 16% increase in the number of extensions of indication and variations applications is expected. A 12% decrease in the number of initial marketing-authorisation applications received is forecast, which is mainly due to a lower number of generic applications. The number of applications for new medicines containing a new active substance is expected to be stable. The road will also be cleared for the publication of the minutes of all scientific committees. The revision of the conflict of interests policy is also scheduled.

EMA annual reports

The EMA published in 2013 the annual concerning 2012⁶⁴. The report highlights the introduction of the new pharmacovigilance legislation which has led to the Pharmacovigilance Risk Assessment Committee (PRAC) and several changes in the structure of the agency. The agency has also endeavoured for an increased levels of transparency in their proceedings. The report has underscored the progress in bringing orphan medicinal products to the market. There was an 18% increase in application for orphan drug designation and a 36% increase in the number of Marketing Authorisation for OMP in 2012 compared to 2011. EMA also reported a 30% increase in the number of applications from micro, small and medium-size enterprises (SMEs), where 68%

⁶² http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/12/WC500136442.pdf

⁶³ http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001990.jsp&mid=WC0b01ac058004d5c1

⁶⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2013/04/WC500142077.pdf

of the applications submitted by SMEs were for OMP's. According to the report, "the Agency processed a total of nearly €7.5 million in fee reductions for designated orphan medicinal products" in 2012. The Agency's Committee for Advanced Therapies received 3 applications for Advanced-therapy medicinal products. They also adopted a draft opinion for Glybera, the first gene-therapy medicine approved in the EU, and a "second recommendation on certification on the quality data of a tissue-engineered product".

Reduced fees for designated orphan medicinal products

The EMA announced in 2013 greater fee reductions for large companies planning to market orphan drugs for rare diseases in the EU, thus further incentivising development of orphan medicinal products. The changes that will take effect in 2014, will offer reduced regulatory fees for larger companies and not just ones that are micro, small or medium-sized enterprises (SMEs). From 2014, non-SME companies submitting a marketing application for an orphan drug will be eligible for a 75 per cent fee reduction for non-paediatric-related initial and follow-up protocol assistance. Previously this reduction was only 40 per cent for larger firms. The EMA will also introduce a 10 per cent fee reduction for initial marketing-authorisation applications, where currently there is no reduction. There will also be a 100 per cent reduction for pre-authorisation inspections, updating the current situation where no fee reduction is offered. These incentives are intended to encourage more pharma companies to enter the growing rare disease market, which has tended to be off-putting for drug makers due to the limited customer base.

Incentives for SMEs in 2013

The European Medicines Agency (EMA) has continually provided incentives to micro, small and medium size enterprises to support them in the development of orphan medicines.

2. EMA Committee for Orphan Medicinal Products' (COMP) activities

EMA Committee for Orphan Medicinal Products (COMP)

Since 2000, there is a Committee for Orphan Medicinal Products⁶⁵ (COMP) at the European Medicines Agency (EMA). The COMP is comprised of health professionals representing each of the Member States, three patient representatives, and three other representatives nominated by the EC after recommendation from the EMA. The Committee meets once a month and it is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union. The Commission adopts decisions on designation based on an opinion from the COMP. The EMA maintains a searchable list of opinions on rare disease (orphan) designations⁶⁶. The fulfilment of the criteria for designation are reviewed by the COMP at the time of marketing authorisation, recommending to the Commission whether the medicinal product should enter the market as an orphan or a non-orphan product. The full list of orphan designations granted by the European Commission is available in the Community register of orphan medicinal products for human use held by the European Commission⁶⁷. The COMP is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU, and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products.

The development of orphan medicinal products is supported by incentives for development and placement on the market as provided for in the Orphan Regulation. The Scientific Advice Working Party in collaboration with the COMP offers protocol assistance to provide advice on the development of orphan medicinal products with regards to regulatory, quality, safety and efficacy issues. Protocol assistance activities have been increasing in number since its establishment.

⁶⁵This section reproduces information from <http://www.ema.europa.eu/htms/general/contacts/COMP/COMP.html>

⁶⁶http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&url=menus/medicines/medicines.jsp&id=WC0b01ac058001d12b

⁶⁷ <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>

The COMP is presently chaired by Bruno Sepodes (Portugal) and co-chaired by Lesley Greene (Patient Representative, UK). The COMP was a pioneer in including patient representatives as full members and the experience has illustrated the great added-value of this collaboration, which contributes to the quality of the opinions adopted for orphan designation.

Since its implementation⁶⁸, the Orphan Regulation has yielded more than 1234 positive opinions for orphan product designation, adopted from 1789 applications reviewed since 2000. To date, the distribution of the prevalence of conditions for which the designations have been adopted shows that the most frequently designated conditions have been those that affect between 1 and 3 in 10 000 patients, that is between approximately 50 000 and 150 000 people (receiving 50% of all orphan designations). Indeed, 48% of the orphan medicinal products having obtained market authorisation in the EU, are for the treatment of diseases affecting less than 1 in 10 000 patients.

The number of applications has increased steadily each year during the first decade of the Regulation with 201 applications received in 2013. Eighty-five designated products had received marketing authorisation by the end of 2013, of which oncology is by far the most common therapeutic area (40%). The average time span between designation and authorisation is 4.8 years.

The COMP has also granted orphan medicinal product designations to various innovative product types (i.e. fusion proteins, monoclonal antibodies, cell and gene therapy products, tissue-engineered products, oligonucleotides): at the end of 2013, the COMP had given more than 80 positive opinions for advanced therapy products out of a total of 1234 opinions for orphan medicinal product designation.

Positive opinions on orphan designations in 2013

The COMP adopted 136 positive opinions on orphan designations in 2013. The European Commission granted 136 orphan designations in 2013. Seven orphan medicinal products received marketing authorisation in 2013 covering 8 conditions (due to variations)⁶⁹.

3. EMA Committee on Human Medicinal Products (CHMP) activities

CHMP opinions in 2013 concerning orphan medicinal products

In 2013, the CHMP issued positive opinions for marketing authorisation applications for the following medicinal products with orphan designation: Bosulif for treatment of chronic myeloid leukaemia, Iclusig for the treatment of chronic myeloid leukaemia and the treatment of acute lymphoblastic leukemia, Pomalidomide for treatment of multiple myeloma, Procysbi for treatment of cystinosis, Orphacol for treatment of inborn errors in primary bile-acid synthesis, Defitelio for treatment of severe hepatic veno-occlusive disease, and Opsumit for treatment of pulmonary arterial hypertension.

CHMP guidelines on the clinical investigation of orphan medicinal products

In 2013 consultations on guidelines for the clinical investigation of medicinal products for Duchenne and Becker muscular dystrophies, and chronic primary immune thrombocytopenia were launched by the CHMP.

⁶⁸ Data provided by EMA

http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2014/01/WC500159429.pdf

⁶⁹ Data provided by EMA and

http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2013/03/WC500140633.pdf

4. EMA activities in the field of advanced therapies

Procedural advice on the provision of scientific recommendation on classification of advanced-therapy medicines (2013)

The EMA released a reflection paper⁷⁰ on the classification of advanced-therapy medicines for public consultation in 2013. The paper clarified the legal basis for the classification of medicines as advanced therapies and provides information on how these medicines are classified as gene therapy, somatic-cell therapy, tissue-engineered or combined medicines. The paper additionally discussed the information required for application for classification. In December 2013 the Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation (EC) No 1394/2007⁷¹ was published.

5. EMA activities in the field of medicinal products for paediatric use

Paediatric Committee (PDCO)

The Paediatric Committee (PDCO) has developed an inventory process aiming to identify areas in which further research and development specific to paediatric medicinal products are needed. Such an inventory could assist industry in identifying opportunities, provide a source of information for healthcare professionals and patients, and aid various PDCO assessment processes. The Agency published lists of medicines by therapeutic class progressively during 2012 and 2013. Each list was open for comments for two months after publication. The lists are available in online⁷³.

European Network of Paediatric Research – Enpr-EMA

The European Medicines Agency (EMA) announced in 2011 the publication of the first membership list of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)⁷⁴. Established to build a high-level network of existing research networks, investigators and centres with recognised expertise in performing clinical studies in children, the Enpr-EMA seeks to facilitate high-quality ethical research on medicines for use in children through networking and stakeholder collaboration with members from both within and outside the European Union as part of the EMA's accordance with European Paediatric Regulation (EC) No 1901/2006. Enpr-EMA's also aims to: coordinate studies relating to paediatric medicines and avoid unnecessary testing in children; build up scientific and administrative competence at a European level; help with the recruitment of patients for clinical trials; and promote European Commission framework programme applications. Enpr-EMA does not perform clinical trials or fund studies or research or decide on areas for paediatric research, as this is the responsibility of Member States, the European Commission or each individual network. The European Medicines Agency is responsible for ensuring collaboration within the network. The Enpr-EMA membership list⁷⁵ was compiled following a call for expressions of interest in 2010. Some 36 networks and centres have thus far applied for membership. Of these, 18 networks and centres have become members of Enpr-EMA. A second category of networks has been established for those “... *undergoing clarification before membership of Enpr-EMA*”. Networks grouped into a third category do not currently qualify for membership.

⁷⁰ [Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation \(EC\) No 1394/2007](#)

⁷¹ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf

⁷² http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf

⁷³ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000096.jsp&mid=WC0b01ac05800260a1

⁷⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a

⁷⁵ http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500100152

6. International cooperation between regulators in the field of orphan medicinal products

EU-USA collaboration in the field of orphan medicinal products⁷⁶

A workshop on orphan product designation and grants took place on 10 March 2014 at the EMA⁷⁷. Jointly organised by the EMA, the FDA and for the first time the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), this one day workshop was an effort towards bringing more treatments for rare disease patients faster. This one-of-a-kind workshop brought together the regulatory authorities from three large regions with legislation encouraging orphan medicinal product development: the United States, European Union and Japan. The agencies representing these areas, with contributions from Canada and Australia, have worked jointly over the years to improve the quality and number of orphan designations as well as encourage parallel submission for orphan medicinal designation. 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 by the FDA, MHLW/PMDA and EMA, 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. Finally the sponsors also had a chance to attend 40 minute face-to-face sessions with the 3 agencies to discuss their individual concerns or comments.

Joint work plan with EUnetHTA (2013)

The EMA has agreed a three-year joint work plan with EUnetHTA⁷⁸, which represents health technology assessment (HTA) bodies across Europe in an effort to harness its relationship with national bodies that assess cost-effectiveness of drugs. In this plan enhancement in collaboration was key, so that the work done by the EMA can assess the benefits and risks of a medicine for approval in the EU while at the same time addressing the needs of HTA organisations, which in turn assess the suitability of approved medicines for national reimbursement. However, the need for extended scientific advice and early dialogue between the EMA, HTA bodies and pharma companies was also commented in the plan. Also included in the plan is the exchange of ideas on the development of scientific and methodological guidelines to facilitate clinical-trial design that can generate data relevant to both parties. Additionally, collection of post-authorisation data once the drug is on the market and specific ways to share information on orphan drugs for rare diseases are also part of the plan. This publication is part of a collaborative effort between the EMA and EUnetHTA initiated in 2010 to address the recommendations made by the Pharmaceutical Forum – a group comprising members from Member States, EU institutions, industry, healthcare professionals and patients.

⁷⁶Information taken from the page

http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000228.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176e&jsenabled=true#section2 (accessed 22/04/2011).

⁷⁷http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/12/event_detail_000810.jsp&mid=WC0b01ac058004d5c3

⁷⁸ www.eunetha.eu

C. OTHER EUROPEAN ACTIVITIES IN 2013

1. E-Rare

The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis, few medicinal products and difficult access to care. That is why rare diseases are a prime example of a research area that strongly profits from coordination on a European scale. ERA-Net E-Rare was launched in 2006 and its second phase in 2010 (E-Rare-2, 2010 - 2014, FP7). The major goals of E-Rare are to foster systematic exchange of information and build a transnational research programme on rare diseases. The E-Rare Consortium gathers seventeen research-funding organisations from 13 European and Associated countries (Austria, Belgium, France, Greece, Germany, Hungary, Italy, Israel, Portugal, Romania, Spain, the Netherlands and Turkey) as well as Poland and Latvia, as observers. To continue and expand its activities in accelerating the development of new diagnostics and therapeutics for patients suffering from rare diseases in 2012 E-Rare joined the International Rare Diseases Research Consortium (IRDiRC). As a member of IRDiRC E-Rare strongly promotes transnational funding activities and facilitates the participation of a wide range of different funding organisations which might not have a strong RD research funding priority giving them the opportunity to participate in the shaping of the rare diseases research landscape and policies.

Since 2007 E-Rare has become one of the major contributors to transnational rare diseases research funding. The EC supports the coordination costs among the funding agencies. However, each national funding agency participating in the call funds the research carried out in their own countries once the projects have been selected.

The E-Rare Consortium has launched 6 joint transnational calls (2007, 2009, 2011, 2012, 2013 and 2014) for collaborative multidisciplinary research projects open for any rare disease (except rare cancers and rare infectious diseases), with a wide range of possible topics and approaches. A total of 640 multinational applications involving more than 2600 research groups from European and associated countries were submitted to the first 5 calls. Importantly, the 4th Joint Transnational Call (2012) was dedicated specifically to provide young, independent investigators the opportunity of building transnational collaborations in the field of rare disease research. The 6th Joint Transnational Call (JTC2014) is dedicated to development of innovative therapeutic approaches for rare diseases.

2. International Rare Disease Events in 2013

Rare Disease Day 2013 (28 February 2013)

The 6th edition of the annual Rare Disease Day 2013, organised by EURORDIS, was held on 28 February 2013. For Rare Disease Day 2013, which had as its theme *Rare Disorders without Borders*, thousands of activities took place in a 73 countries and regions. All around the world, rare disease stakeholders – including patients and patient alliances, health-care professionals, researchers, members of learned societies, policy makers, biopharmaceutical companies, media, and friends, turned out to help raise public and political awareness for the issues the rare disease community faces on a daily basis – a lack of knowledge and information, scarce and scattered resources, and a lack of medicines, treatments and services. New to the movement in 2013 were Bahrain, Iceland, Israel, Lebanon, Macedonia, Palestine, Saudi Arabia and Singapore.

In Brussels, EURORDIS co-hosted with Members of the European Parliament a Policy Discussion Meeting entitled “*Faster Access to Medicines for Rare Disease Patients*”, designed to move forward the process of improving access to treatment in the context of the revision of the EU Transparency Directive. The event was attended by 100 participants, and watched simultaneously by over 200 viewers from 10 countries through livestreaming.

Rare Disease Day was also the occasion to acknowledge the outstanding contributions of members of the rare disease community with the 2013 EURORDIS Awards⁷⁹.

⁷⁹ <http://www.eurordis.org/eurordis-awards>

The Internet and social media again proved successful in spreading the Rare Disease Day message and allowing the rare disease community to interact and share. The Rare Disease Day⁸⁰ website received over 20 000 visits on 28 February alone. In the months leading up to Rare Disease Day, visits topped 75 000. Hundreds of photos and videos were uploaded to the website's *Tell Your Story* section, including scores of images demonstrating the Rare Disease Day call to raise and join hands.

The official Rare Disease Day 2013 video, created to raise awareness for this year's theme of solidarity, and particularly international cooperation and collaboration, was translated into 15 languages and viewed over 60,000 times. The video was "liked" over 140,000 times on Facebook. Rare Disease Day also garnered plenty of "tweets" via Twitter. With some 28,000 tweets on 28 February (working out to about 17 tweets per minute), social media was a key tool for awareness raising.

From a Rare Disease Day Barbecue in Australia, to a scientific symposium in Bahrain, or a daylong event in Singapore based around the theme *Love is not Rare* the array of events on offer around the world was as diverse and original as the participants themselves. Painting classes, press conferences, policy events, petitions, fun runs, medical conferences were among the events that took place.

3. Other European activities in the field of rare diseases in 2013

ECRIN-ERIC

The European Clinical Research Infrastructures Network (ECRIN⁸¹) is a non-profit organisation that supports multinational academic clinical research projects in Europe which is "*hampered by the fragmentation of health and legislative systems in Europe*". ECRIN provides information, consulting and services to investigators and sponsors in the preparation and in the conduct of multinational clinical studies, for any category of clinical research and in any disease area. This is particularly relevant for investigator-initiated or academic clinical trials, and for clinical research on rare diseases where international cooperation is a key success factor. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.

On 29 November 2013, ECRIN was officially awarded the status of European Research Infrastructure Consortium (ERIC), a legal status designed to facilitate the joint establishment and operation of research infrastructures of European interest. Germany, Spain, France, Italy and Portugal are the founding members of ECRIN-ERIC, whose management office is located in the host country (France), in Paris.

In 2013, ECRIN organised a call for applications to allow multinational extension of trials already funded in the coordinating country in three specific areas: Nutrition, Medical Devices and Rare Diseases. Trials were proposed by public or private non-profit institutions, and to address important clinical questions. The evaluation process was based on the possible impact on the health of European citizens, the scientific merit and excellence, and the feasibility of each proposed trial. Project selection was carried-out by the ECRIN IA Scientific Board (which also includes patients representatives), supported by external peer-reviewers, each assessing one clinical trial in his/her specific field of competence, and three methodologists, each assessing all the trials pertaining to one of the clinical areas considered by the call. The ECRIN European Correspondents provided the Board with an estimation of the logistical feasibility and cost of the trials. Eight clinical trials, involving a total of 21 European countries, were recommended for free access to ECRIN services : 4 of the trials chosen are in the field of rare disease research.

⁸⁰ <http://www.rarediseaseday.org>

⁸¹ www.ecrin.org

D. EUROPEAN MEMBER STATES' ACTIVITIES IN 2013

D.1. AUSTRIA

National plan/strategy for rare diseases and related actions

In December 2013 the national plan for rare diseases including several annexes was in its final phase of development. The draft will be completed in the first months of 2014 and will then be revised by the Ministry of Health, the Ministry of Social Affairs and the Ministry of Science, Research and Economy, as well as other relevant stakeholders and authorities including the health sectors of the counties of Austria. This last revision process will probably be finalised in the second half of 2014. In its current draft format, the plan covers nine priority areas. No general budget will be allocated to the plan in advance. Instead, it is intended that the budget for each measure in each priority will be defined as soon as this measure will be implemented.

The main activities of the Coordination Centre for Rare Diseases (CCRD) in 2013 were the following:

- Acting as the main driving force in drawing the national plan for rare diseases until the end of 2013 through a participative process of discussing the nine priorities of the national plan with all representatives of the expert group as well as of the strategic platform;
- Continuous awareness raising among professionals / experts / doctors / patients on the topic of rare diseases through presentations and dissemination of information;
- Acting as the focal point for European activities in the field of rare diseases through active participation in EU-funded projects and initiatives such as Orphanet and EUCERD and the Cross Border Health Care Directive as well as other European initiatives in the area of Orphan Medical Products;
- Continuation of Orphanet activities:
 - Continuous updating of Austrian services in the Orphanet database;
 - Dissemination of information on Orphanet in Austria ;
- Acting as the communication hub between actors in the field, focusing on health care professionals and other stakeholders.

Centres of expertise

The development of a national designation process for centres of expertise is expected to start in the second half of 2014. It is intended that the developed criteria will be embedded in the Austrian health care structure plan, which might also specify the designation of future centres of expertise.

Registries

Apart from registries, Austria aims to fully integrate rare diseases into its diagnosis and activity documentation system (Diagnosen- und Leistungsdokumentation; DLD). To address this objective, a collaboration with Germany to introduce Orpha Codes into the health information system (for use in centres of expertise) is foreseen in the National Plan for Rare Diseases.

Neonatal screening policy

The screening for medium-chain acyl-CoA dehydrogenase deficiency was removed from the screening panel in 2013. In addition, the project to establish the screening for six different lysosomal storage disorders (e.g. Mucopolysaccharidosis (MPS) type 1, Gaucher, Fabry, Pompe, and Nieman-Pick Type A/B) concluded during 2013.

National alliances of patient organisations and patient representation

Pro Rare Austria, the national "Allianz für seltene Erkrankungen" was achieved the following milestones in 2013:

- Publications in different media; development of a social media platform;
- Fundraising for the organisation of the Rare Disease Day 2013 with around 400 participants;
- Further development and maintenance of the website: www.prorare-austria.org;
- Out of around 60 rare disease patient organisation, 20 organisations are members of Pro Rare Austria;
- Member of EURORDIS;

- Active participation at the meetings of the expert committee on rare diseases under the lead of the national coordination centre for rare diseases;
- Establishment of a medical expert committee.

Sources of information on rare diseases and national help lines

Orphanet activities in Austria

As of 2013, the plan is to integrate sustained funding for Orphanet Austria into the rare disease national plan.

Guidelines

The development and implementation of emergency cards for rare disease patients is part of the draft of the rare disease national plan. This will include information on emergency guidelines as provided by Orphanet.

National rare disease events in 2013

A number of events were held to mark the Rare Disease Day 2013, including the march for rare diseases in Vienna on March 2, 2013.

On 27 and 28 September 2013, the 4th Austrian National Conference on Rare Diseases was organised in Innsbruck.

Hosted rare disease events in 2013

The 2nd Conference of 'EB-CLINET - Clinical Network of EB Centres and Experts' was held on 17-18 September 2013 in Salzburg.

Research activities and E-Rare partnership

National research activities

In 2013, the FFG published a specific programme for rare diseases for SME, amounting to €5 million in total.

E-Rare

Austria joined the 5th Joint Transnational Call in 2013; however no Austrian teams participate in the 12 funded projects.

D.2. BELGIUM

National plan/strategy for rare diseases and related actions

At the end 2013, a Plan for rare diseases⁸² was developed based on the analysis of this steering committee and adopted by the Minister of Public Health. Twenty actions are identified in 4 main categories with specific tasks, budget and leading authorities defined for each point. The four main categories included: the improvement of access to diagnostics and information for patients, the optimisation of health care, the improvement of knowledge generation and the governance and sustainability of the plan.

A budget of € 15 million per year is foreseen for the Plan: this budget does not include treatment costs. A unit dedicated to the monitoring and evaluation of the plan will be created to oversee the implementation and define any additional required measures. In addition a working group has been established at the Chronic Disease Observatory to monitor and define unmet needs of patients with rare diseases in Belgium.

Besides the funding for the plan, most of the expenditures for rare diseases are covered by the general health system budget. A Special Solidarity Fund is also in place which can be used for patients whose costs are not covered by the health care system (for example some Orphan medicinal product costs). In addition a small specific budget is allocated specially for rare diseases.

Centres of expertise

In Belgium there are several centres specialised in one rare disease or a group of rare diseases. Some of these centres are recognised by the National Institute for Health and Disability (NIHDI) and work under a convention.

⁸² http://www.laurette-onkelinx.be/articles_docs/Plan_Belge_pour_les_maladies_rares.pdf

These centres include: cystic fibrosis centres, and the centres for metabolic diseases and neuromuscular diseases. A new convention with centres of expertise in haemophilia will start in 2014. New centres will be created on basis of an evaluation of needs in multidisciplinary specific care. A group of experts have developed a tool for prioritisation and the working modalities of the centres of expertise in order to implement this action.

A budget of €2 million is allocated for the development and the strengthening of centres of expertise in the multidisciplinary diagnosis of rare diseases, and expertise laboratories in several specific non –genetic tests used for the diagnosis and the follow-up of rare diseases.

On the other hand, genetic counselling, carried out by a multidisciplinary team, will be financed through a new convention with the 8 Belgian genetics centres. The convention also includes guarantees for the adequate quality control and registration of clinical activities. The Belgian Centres for Human Genetics have a full service offering different types of tests and technologies, and patient and family counseling.

An elaborate mapping of expertise in the Belgian hospitals will be carried out in 2014 by the WIV-ISP. The mapping takes into account the EUCERD recommendations concerning criteria for designation.

Registries

In 2013, an authorisation was granted by the Privacy Commission to start up a first edition of a Central Registry for Rare Diseases. This first edition entails the prospective data-collection on rare disease patients that consult the genetic centres. In the future, a new authorisation request will be filed to allow for data-collection in treatment centres. Work is also underway to include Orpha codes in the health information system in Belgium. The convention has been prolonged for the time period 2014-2016 as one of the actions of the Belgian plan on rare diseases.

Genetic testing

All genetic centres have obtained an accreditation of their diagnostic activities. An accreditation of the laboratories will be obligatory as of January 2014. The reimbursement conditions of genetic tests have been revised. The new nomenclature offers a stratified reimbursement system and includes a comprehensive list of diagnoses and genes for which testing is available in Belgium.

Genetic testing abroad is possible, when referred by the Belgian genetic centres: the genetic centres send the samples to a foreign reference laboratory. The genetic tests carried out abroad will be reimbursed by convention with the 8 Belgian genetic centres. This is one of the actions of the plan. A list of authorised tests and the foreign reference laboratories is available: this initiative is part of a decree for the creation of a convention between the NIHDI and the genetic centres that is in force since 1 January 2013.

National alliances of patient organisations and patient representation

Rare Disease Organisation Belgium (RaDiOrg.be) is a non-profit organisation established in January 2008. RaDiOrg.be is funded by the Federal Government and the Belgian pharmaceutical industry umbrella group Pharma.be and will receive regular structural funding from the former from 2013 onwards.

Sources of information on rare diseases and national help lines

Orphanet activities in Belgium

The Belgian Scientific Institute of Public Health received funding for the period 2012-2013 from the National Institute for Health and Disability Insurance for the translation of the Orphanet portal into the Dutch language. This includes the translation of the structure of the site, the lists of diseases with medical terms and the scientific abstracts. This was one of the measures recommended by the Belgian Fund of Rare Diseases and Orphan Drugs. The Dutch Orphanet team is collaborating with the Belgian collaborating team on this project.

Guidelines

Proposals for the development of good practice guidelines or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

Emergency cards and guidelines

The possibility of introducing and adapting the Orphanet emergency guidelines will be considered in 2014.

Training and education initiatives

Proposals for their development or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

National rare disease events in 2013

To mark of Rare Disease Day 2013 RaDiOrg carried out an awareness campaign using social media⁸³.

Hosted rare disease events in 2013

A number of European events were held in Brussels to mark Rare Disease Day. Eurordis co-hosted with Members of the European Parliament a Policy Discussion Meeting entitled “*Faster Access to Medicines for Rare Disease Patients*”, designed to move forward the process of improving access to treatment in the context of the revision of the EU Transparency Directive. The event was attended by 100 participants, and watched simultaneously by over 200 viewers from 10 countries through a live feed.

Orphan medicinal products⁸⁴

Orphan medicinal product incentives

Since 2006, at the initiative of the NIHDI, the revenues of orphan medicinal products are no longer subject to so called ‘pharmaceutical taxes’ (i.e. taxes, earmarked for social security), on sales of reimbursable drugs. But since 2013, given the expenditures for these products, the government has decided to engage the firms with the creation of a tax, lower than those in charge of firms with non-orphan drugs.

D.3. BULGARIA

National plan/strategy for rare diseases and related actions

On 27 November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009 – 2013).

The Plan officially ended on 31 December 31. Before that, the Ministry of Health had established a working group to prepare a draft for a Second National Plan. The Plan is expected to work closely with the National Rare Disease Registry and the centres of expertise for rare diseases, both of which are supposed to be officialised by the end of 2014. However, no schedule for the adoption and the implementation of the Second Plan was available by the end of 2013.

Centres of expertise

Significant progress was achieved in 2013 regarding the centres of expertise for rare diseases in Bulgaria. The National Assembly voted amendments in the Health Act (Article 144a), requiring the Minister of Health to adopt a regulation, which will establish a National Registry for Rare Diseases, as well as will determine the criteria for designation of centres of expertise for rare diseases. The Ministry of Health established a working group, which prepared a draft regulation, containing criteria for designation of centres of expertise and reference networks for rare diseases, as well as rules and procedures for their implementation, monitoring and evaluation. The draft regulation also envisages the establishment of a permanent National Rare Diseases Council to the Ministry of Health, as well as an official list of rare diseases. The draft was discussed at several meetings, including the National Conference for Rare Diseases in September 2013. The final draft was submitted to the Ministry of Health early in 2014. This legislation is expected to be approved by the Ministry of Health and to come into force by the end of 2014.

Since September 2013, RareDis and ICRDOD were merged into the Institute for Rare Diseases (IRD), together with the newly-established Centre for Health Technology Assessment and Analyses (CAHTA).

Registries

The idea to implement a National Registry for Rare Diseases re-emerged in 2013. This was motivated by the upcoming implementation of the centres of expertise for rare diseases in the country. Initial plans suggest that the Registry will collect data from these centres and prepare annual reports on rare disease epidemiology. Thus, the Registry will contain only data for rare diseases, for which there are officially designated centres of

⁸³ <http://radiorg.be/activiteiten/Zeldzame%20ziektendag/RDD%202013>

⁸⁴ This section has been written with information from the section on Belgium in the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp35-45).

expertise. However, by the end of 2013 it is not yet decided which institution will coordinate and manage the Registry.

In 2013 ICRDOD established two new registries – for primary myelofibrosis and neuroendocrine tumours.

Sources of information on rare diseases and national help lines

Official information centre for rare diseases

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria⁸⁵. The report contains 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive drug list and reimbursement; mechanisms for accelerated access to innovative medicines; conclusions. There are 2 annexes, attached to the review: list of orphan medicinal products in EU and Bulgaria, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorisation holder and date of marketing authorisation for each item (additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds); and a list of references.

Training and education initiatives

Bulgarian rare diseases stakeholders are active in promoting EU rare policy at local and regional level. The country hosted the First Rare Diseases Summer School for Health Authorities and Legislators⁸⁶, an event designed to raise awareness of rare diseases among Eastern European health authorities and legislators. The event was successfully organised again in 2012 and 2013 in Greece and Turkey respectively. This initiative is a joint initiative of BAPES, the National Association of Rare Diseases Patient Organisations “Genetics” (Russia) and the Italian National Centre for Rare Diseases (CNMR). School participants come from a wide range of public fields – legislative bodies and health authorities, medical institutions, academia. The week-long event covers a variety of topics.

National rare disease events in 2013

Rare Disease Day was marked on 28 February 2013 with events organised by the National Alliance of People with Rare Diseases⁸⁷. A series of information, education and charity events took place with a balloon launch in front of the Ministry of Health in Sofia, followed by an official press conference. The Second Balkan Conference of Patients with Rare Diseases, entitled “Communication and Support to Patients, Based on Modern Technologies” was held in April in Sofia. Outside of Sofia, a series of rare diseases events were organised in the towns of Plovdiv, Varna, Burgas, Stara Zagora, Pleven and Sandanski.

The 4th Annual Conference on Rare Diseases and Orphan Drugs was organised on 13-14 September 2013 in Plovdiv⁸⁸. The First National Conference on Rare Diseases for Medical Students was held in parallel, bringing together more than 130 students from medical universities across Bulgaria and neighbouring countries.

Hosted rare disease events in 2013

The Bulgarian Association for Promotion of Education and Science launched and organised in 2005, 2006, 2008 and 2009, the annual “Eastern European Conference on Rare Diseases and Orphan Drugs”. In 2010 for the very first time the event was hosted and co-organised outside Bulgaria, in Saint Petersburg, Russia, in conjunction with the first All-Russian Conference for Rare Diseases and Rarely Used Medical Technologies. It has proved to be an efficient strategy to foster rare diseases progress in Eastern Europe. In 2011, the sixth edition⁸⁹ of this initiative was held and co-organised in Istanbul, Turkey. BAPES acted as a co-organiser of the International Conference on Rare Diseases (ICORD) in 2013, an event that was held on October 31 – November 2 in St. Petersburg, Russia. The Bulgarian National Alliance of People with Rare Diseases initiated and organised a Balkan patient meeting on 24 March 2012 in Sofia and again on 20-21 April 2013. Leading rare diseases experts and patients from Balkan countries took part in this event.

⁸⁵ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

⁸⁶ http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf

⁸⁷ <http://rare-bg.com/>

⁸⁸ www.conf2013.raredis.org

⁸⁹ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

Orphan medicinal products

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria⁹⁰. The report contains information on important orphan medicinal products activities and explained how they are set up in Bulgaria in 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive Drug List (PDL) and reimbursement; mechanisms for accelerated access to innovative medicines; and conclusions.

Orphan medicinal product committee

Orphan medicinal products are subject as are all other medicinal products to the Commissions on the pricing of medicines and on the Positive drug list. In order to optimise these procedures, in 2011 the two commissions were merged into a single one under the Ministry of Health. Subsequently, the Parliament adopted in 2012 new legislation, by which a National Council for Pricing and Reimbursement of Medicinal Products replaced the Commission at the beginning of 2013. The new body has a status of a State agency and is responsible for both pricing and reimbursement of all medicinal products. Medicinal products' safety is monitored by the Bulgarian Drugs Agency.

Other initiatives to improve access to orphan medicinal products

The Centre for Health Technology Assessment and Analyses (CAHTA) officially started activities in September 2013. CAHTA currently operates as an independent unit within the Institute of Rare Diseases in Plovdiv, Bulgaria.

The idea behind the establishment of CAHTA is to complement the current activities of the Institute by covering the increasingly dynamic field of health technology assessment (HTA). Introducing and applying the HTA concept in Bulgaria will allow for more transparency, objectivity and efficiency in the health system. HTA is greatly important in the field of rare diseases and orphan drugs. The extended life expectancy and improved quality of life for patients with rare diseases are the most important outcomes of all rare disease policies. These two directly depend on the timely access to advanced diagnostic and therapeutic health technologies. Proper and reliable assessment of innovative health technologies is not only important for rare diseases – it is crucial for the overall effectiveness of the entire health care system in Bulgaria.

In October 2013 CAHTA co-organised a public lecture and discussion on HTA prospects for Bulgaria at the Medical University of Plovdiv. Professor Ken Stein (University of Exeter Medical School, UK), Dr Edmund Jessop (National Health System England, UK) and Dr. Domenica Taruscio (Istituto Superiore di Sanità, Italy) were guest speakers and moderators. The discussion was followed by a training workshop on HTA on 5 October for all interested stakeholders.

D.4. CROATIA

National plan/strategy for rare diseases and related actions

During 2013 the National Committee for Rare Diseases met on the regular basis which resulted in creating the national plan for rare diseases.

The Croatian national plan for rare diseases has been developed around of the following nine priority areas:

1. Promotion of the knowledge and the availability of information on rare diseases;
2. Support of rare disease registries and securing of their sustainability;
3. Facilitation of referral centres and centres of expertise activities;
4. Improvement of the availability and quality of health services for rare disease patients (prevention, diagnosis, treatment);
5. Improvement of access to treatment with orphan medicinal products;
6. Securing the availability of special social services for rare diseases patients.
7. Empowerment of patient's organisations;
8. Encouraging research activities in the field of rare diseases;

⁹⁰ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

9. International networking in the field of rare diseases.

The draft was presented to the Croatian Society of Patients with Rare Diseases in December 2012 and further amended in 2013 after public consultation. The Croatian national plan is currently awaiting the final acceptance by the MoH. The presentation to the Parliament was scheduled for 2014.

Neonatal screening policy

In 2013 Committee for the Neonatal Screening of the Ministry of Health has been established in order to improve regulation of neonatal screening and foster the screening activities.

Sources of information on rare diseases and national help lines

Orphanet activities in Croatia

Since 1 July 2013 Croatian Alliance for Rare Diseases is collecting data.

Guidelines

Guidelines have been developed for the treatment of adult patients with Gaucher and Fabry disease.

National rare disease events in 2013

The Croatian Alliance for Rare Diseases organised a number of events to mark Rare Disease Day in 2013. Promotion of National plan and Help Line, as well as presentation of activities of patient organisations throughout 7 towns in Croatia was organised.

Hosted rare disease events in 2013

The EUROCAT 12th European Symposium on Congenital Anomalies was held on 14 June 2013 in Zagreb. The Eurordis Membership Meeting was held in Dubrovnik, 30 May – 2 June 2013.

Orphan medicinal products

Orphan medicinal product market availability situation

In 2013 Croatian Institute for Health Insurance released updates of the List of Especially Expensive Drugs which includes drugs for several rare diseases (drugs for multiple sclerosis, some cancers, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, home treatment of hemophyllia, peginterferon, growth hormone, enzyme replacement therapy).

D.5. CYPRUS

National plan/strategy for rare diseases and related actions

The Cyprus National Strategic Plan for Rare Diseases⁹¹ (CNSPRD) was approved by the Council of Ministers of the Republic of Cyprus in November 2012. Following the approval of the CNSPRD, the National Committee for Rare Diseases was appointed by the Council of Ministers with the task of implementing as well as monitoring the progress of the plan. In addition, the National Committee for Rare Diseases is responsible for defining a number of priority actions with objectives and follow-up mechanisms. The Committee met for the first time in January 2013 and is having monthly meetings since then. Work is also being produced through subcommittees and devoted subgroups. During 2013, the actions of the CNSPRD were prioritised and those requiring little or no budget, such as training initiatives and public awareness raising activities were put into action, since due to current national financial circumstances no funding was available to implement the CNSPRD as a whole. In the past year, workshops, lectures, seminars and interviews addressing the general public, university students, health-care professionals and other relevant groups were organised. In addition, during 2013 the CNCRD addressed the three relevant ministries, those of Health, Education and Culture and Labour and Social Insurance in order to establish a dialogue with authorities on important policy matters. Furthermore the CNCRD contacted all University schools that offer education in fields relevant to rare disorders such as Medicine, Nursing, Physiotherapy, Speech therapy, Biology etc requesting the incorporation of rare

⁹¹ [http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/\\$file/Strategic%20Plan%20Rare%20Diseases.pdf](http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/$file/Strategic%20Plan%20Rare%20Diseases.pdf)

disorders into their teaching curriculum. Collaboration with National Medical Associations and scientific societies has also been established. Finally, although rare cancers are included in the CNSPRD, since they are also addressed by the National plan against Cancer and the National Committee for Cancer, collaboration between the two committees has been initiated.

Among steps of action the necessity of introducing a help line has been discussed as well as the introduction of a special medical card and an alert card for patients.

Centres of expertise

The procedure for officially designating Centres of Expertise for rare diseases in Cyprus is currently under discussion.

Registries

The possibility of introducing a common platform for registries of rare disorders is under consideration.

Neonatal screening policy

In June 2013 a National Committee for Neonatal Screening was appointed by the Ministry of Health, with the task of revisiting the current practices, discussing the possible need for expansion of the current policy and providing a plan of action in the field. The committee is multidisciplinary and consists of experts as well as stakeholder representatives. It is expected to complete its work by the end of 2015. This appointment was the reflection of the Ministry of Health to the report and recommendations of an Advisory Committee, works held between 2011 and 2013. This advisory committee addressed the current situation of newborn screening in Cyprus and evaluated the new emerging needs and possible expansion of the offered screening program. The advisory committee prepared a report summarising their findings and recommending the establishment of a National Committee. This report was accepted and endorsed by the Ministry of Health.

National alliances of patient organisations and patient representation

In 2013 two new patient organisations addressing rare diseases have been established, the Inherited Metabolic Disorders organisation 'Aspida Zois' and the Rare Genetic Disorders organisation 'Monadika Hamogela' or 'Unique Smiles'. Both these organisations became members of the Cyprus Alliance for Rare Disorders (CARD).

National rare disease events in 2013

The National Committee for Rare Diseases celebrated Rare Diseases Day 2013 on the 6 March 2013 inviting stakeholders including patients, organisations, physicians, researchers, scientists, authorities, pharmaceutical companies, the public and the media to an open meeting/ discussion. The agenda consisted of short introductory presentations by experts in rare diseases and by patients outlining their experiences in living with a rare disorder in Cyprus. The discussion, which was vivid, addressed the problems and expectations of patients as well as the application of the National plan and the prioritization of actions. The event took place at the Makarios Medical centre.

A Europlan national conference was held on the 14 & 15 November 2013, bringing together stakeholders to discuss the implementation of the National Plan for rare diseases. The workshops of this conference addressed the following fields: Strategy to action plan and indicators, Registries, Social Inclusion and Centres of Expertise and European Reference Networks. The participation was very active and the discussion revealed many aspects of the present situation, including weaknesses, obstacles and strengths as well as actions to be taken.

D.6. CZECH REPUBLIC

National plan/strategy for rare diseases and related actions

In order to fulfill the priority aims of the Czech National Plan for 2013 the Taskforce met four times and among others endorsed presentations of representatives of various professional societies for the establishment of respective centers of expertise in the country (e.g. for neurology, endocrinology, rheumatology, orofacial abnormalities, immune deficiencies, oncology, nephrology, hematology). Based on the endorsements of the

Czech Ministry of Health envisages to publish official tenders for their establishment using EUCERD criteria⁹². The aforementioned EUCERD guidelines are intended to serve as basis for the crossborder health care in rare diseases related to the implementation of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare⁹³.

Centres of expertise

Based on the work of the Taskforce and including the entry into force of Law 372/2011Sb which in its article 112 provided legal basis for establishment of expert centres (not only for rare diseases), a group of rare disease centres was officially established on 28 May 2012 and published in Bulletin n. 4 / 2012 of the Czech Ministry of Health⁹⁴ – section 4 “Basic network of rare disease centres”. Following the presentation of *de facto* activities of various professional groups, active mainly within the major faculty hospitals (e.g. FN Brno⁹⁵, FN Motol⁹⁶, VFN Praha⁹⁷, FN HK⁹⁸, FN Olomouc⁹⁹ and FN Plzeň¹⁰⁰), *de iure* recognition of their “centre status” activities will be carried out by the Ministry of Health during 2014. However, it needs to be noted that establishment of centres from the Ministry of Health does not entitle them to “centre-based health care reimbursement”, which has to be assured independently through subsequent and complicated negotiations with the various health insurance companies. There are no legal provisions which would guarantee that *de iure* rare disease centers of expertise are eligible to become “centres with a specific contract”, an issue particularly important for reimbursement of orphan medicinal products. In 2013 new rare disease centres were not established.

Registries

The Interministerial and interdisciplinary commission for rare diseases is in the process of establishing the National registry of rare diseases, which will serve as a “confederated database” of all other disseminated registries in centres to be established. As a pilot projects serves the dedicated registry initiative of the Institute of Biostatistics and Analysis¹⁰¹ at the Masaryk University in Brno¹⁰².

In 2013 the Czech Institute of medical informatics and statistics¹⁰³ started a compilation of rare disease registries in the country and established collaboration with the EPIRARE¹⁰⁴ and RD-Connect¹⁰⁵ projects in terms of mapping and standardisation of registries.

National alliances of patient organisations and patient representation

The Czech Association for Rare Diseases¹⁰⁶ (ČAVO) counted 30 members - patient organisations representing various rare diseases and 10 individual members who represent Ultra rare diagnoses. ČAVO organised meetings with members every month, published a newsletter, run awareness campaign for both public and health professionals, educated the member platform in areas of interest, such as centralised care, social and legal issues in relation to rare diseases. ČAVO held two major seminars in 2013 for its members and co-organised one Czech Parliament hearing on rare diseases in May 2013.

Sources of information on rare diseases and national help lines

Help line

A help line for rare diseases was not active in 2013, but the National Coordination Centre for Rare Diseases and ČAVO responded to lay and professional public enquiries by email. A dedicated help email is planned for operation from May 2014.

⁹² http://www.eucerd.eu/?post_type=document&p=1224

⁹³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF>

⁹⁴ http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c4/2012_6288_2510_11.html

⁹⁵ www.fnbrno.cz

⁹⁶ www.fnmotol.cz

⁹⁷ www.vfn.cz

⁹⁸ www.fnhk.cz

⁹⁹ www.fnol.cz

¹⁰⁰ www.fnplzen.cz

¹⁰¹ <http://www.iba.muni.cz/index-en.php>

¹⁰² www.registry.cz

¹⁰³ www.uzis.cz

¹⁰⁴ <http://www.epirare.eu/>

¹⁰⁵ www.rd-connect.eu

¹⁰⁶ www.vzacna-onemocneni.cz

Other sources of information

The National Alliance for Rare Diseases¹⁰⁷ has started to prepare an integrated server which will unify all disseminated resources under one web portal, including current and expanded neonatal screening¹⁰⁸.

Training and education initiatives

Rare disease information was added into the medical genetics training curriculum at the Masaryk University Brno¹⁰⁹ (4th year) and Charles University Prague – 2 Faculty of Medicine (5th year¹¹⁰).

National rare disease events in 2013

A number of events were organised by rare disease patient organisations in the Czech Republic to mark Rare Disease Day 2013, mainly in collaboration with ČAVO and Debra¹¹¹.

Hosted rare disease events in 2013

EuroGentest organised its 3rd International Symposium “Moving Next Generation Sequencing into Diagnostics” in (7 March 2013)¹¹². IRDiRC organised together with the National Centre for Rare Diseases an international workshop “Rare Genetic Diseases: Diagnosis and Discovery Workshop Partnership Opportunities with Central/Eastern Europe and the Middle East” on 3 December 2013¹¹³, following the meeting of the IRDiRC Diagnostics Committee.

D.7. DENMARK

National plan/strategy for rare diseases and related actions

Access to health care at hospitals and GPs is free of charge for all citizens independently of diagnoses and prevalence. Patients also have a right to choose between relevant hospitals. Access to social services and support for patients is also free of charge and given depending on need not diagnosis.

There is currently no specific national/strategy plan for rare diseases in Denmark involving all sectors, but regarding the hospital sector the Danish Health and Medicines Authority as the statutory competent authority has approved centres of expertise/referral centres for rare diseases in 2010 as part of a comprehensive planning of highly specialized hospital services in Denmark accordingly to the health care act.

Since 1993 The National Board of Health has published a list of centres of expertise designated by the National Board of Health. This list of centres has been revised regularly through the years and is now developed to the above mentioned approval system.

The working group with the task to elaborate a national plan for RD has a broad representation of stakeholders and was founded at the end of 2011 and met at the start of February 2012 for the first time. The recommendations in the previous report on rare diseases from 2001 are being assessed to see what is still needed, what has changed and what new recommendations can be added considering the European perspective and the recommendations for a national strategy. The subject of centres of expertise is a key area of consideration but many other subjects are dealt with. The working groups' proposal for a national strategy/ is scheduled to be submitted to the Ministry of Health early 2014. There is no a specific budget for the strategy.

In October 2013, with a new disability policy action plan, entitled "A Society for All" was launched which will hopefully improve aspects of care for all disabled people and patients, including rare disease patients.

Centres of expertise

The National Board of Health has in the National Plan for highly specialised hospital services issued about 1100 approvals of medical highly specialised functions and estimates that about 100 -120 of these are related to

¹⁰⁷ www.vzacna-onemocneni.cz

¹⁰⁸ <http://novorozenecky-screening.cz>

¹⁰⁹ www.muni.cz

¹¹⁰ www.lf2.cuni.cz

¹¹¹ <http://www.debra-cz.org/>

¹¹² [http://www.eurogentest.org/index.php?id=213&tx_ttnews\[tt_news\]=38&cHash=26c3f0e62805fc74baf31dda47d5a069](http://www.eurogentest.org/index.php?id=213&tx_ttnews[tt_news]=38&cHash=26c3f0e62805fc74baf31dda47d5a069)

¹¹³ http://www.irdirc.org/wp-content/uploads/2014/02/Rare-Genetic-Diseases-Workshop_final-version_public.pdf

various diseases or groups of diseases which can be classified as rare. In General the approvals will last for a duration of 3 years. A revision process for these services will start in March 2014.

Registries

In 2013 an article with an overview of Danish registries for studies of medical genetic diseases was published¹¹⁴.

National alliances of patient organisations and patient representation

Rare Diseases Denmark (RDD), founded in 1985, is the national alliance of 48 rare disease patient organisations/societies covering 11,500 members.

Over 2009 -2012 RDD developed a special training programme for families with children affected by rare diseases under the age of 18 called “Rare Family Days”. Some preliminary results were presented by RDD at the ECRD conference in Brussels and the final results were published in 2013¹¹⁵, along with a new concept for “Rare Family Days”.

Also in 2013, RDD contributed to the work of National Board of Health’s working group to elaborate a national strategy for Rare Diseases.

Hosted rare disease events in 2013

In October 2013, Rare Diseases Denmark hosted a EUCERD Joint Action Workshop on training of social service providers, - organised through the EUCERD Joint Action N°2011 22 01.

Specialised social services

The National Board of Social Services is an independent subdivision of The Ministry of Social Affairs, Children and Integration. In 2007 Denmark went through a structural reform, which reduced the number of municipalities from 275 to 98 and reduced the 14 counties to 5 regions. As a part of the reform the municipalities are to take care of all social services – also the specialised ones, previously a organised at county level. An evaluation of the reform conducted in 2012-13 has shown that the reform seems to have had serious consequences on the specialised functions. Therefore it was decided by the parliament that the National Board on Social Services from 2014 will have a new monitoring role, keeping an eye on the need for and development in specialised social and educational services – with a special focus on citizens with rare diseases/disabilities.

D.8. ESTONIA

National plan/strategy for rare diseases and related actions

The plan for rare diseases was finalised in 2013 and urgent activities have been selected and added to the activity plan of the Estonian National Health Plan 2009-2020.

Centres of expertise

Tartu University Hospital fulfils the criteria approved by EUCERD. Consequently there are no plans to elaborate special designation procedure for centres expertise in Estonia.

National rare disease events in 2013

Due to Estonia’s small size, there are no special annual rare disease events, nonetheless rare diseases are given a spotlight during the annual meetings of the Estonian Society of Human Genetics and Estonian Society of Laboratory Medicine.

¹¹⁴ Mary Nguyen Nielsen et al. Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. Clinical epidemiology 2013, 3:5 249-262

¹¹⁵ <http://www.sjaeldnediagnoser.dk/documents/9FEBD7DD-09F7-48AF-93AC-D41985D643EC.pdf>

D.9. FINLAND

National plan/strategy for rare diseases and related actions

There is currently no officially accepted national plan/strategy for rare diseases, but a draft plan prepared by the RD Steering Committee has been handed to the Ministry of Social Affairs and Health. The process towards national plan started already 2011 when funding specifically focused on national plan related activities was applied from the Ministry of Social Affairs and Health (this was accepted in 2012). During 2011 a nationwide survey was performed to identify centres who consider themselves as experts related to a rare disease or disease group. The Ministry of Social Affairs and Health decided to invite stakeholders in the field to become members of a steering committee, including hospital districts, governmental institutes like the National Institute for Health and Welfare, Väestöliitto, the Orphanet National Advisory Board, the umbrella organisation for rare diseases HARSO, Helsinki University Hospital, and the Harvinaiset Network for Rare Diseases to name representatives for the steering committee to elaborating the national plan¹¹⁶. Discussions focused on establishing centres of expertise, with a step which will include patients before they reach the centres (i.e. early health care pathways to diagnostic processes). This multi-disciplinary steering group finalised its report which introduces a suggestion for the Plan by the end on 2013 (some final reviewing still took place in early 2014) and handed the Plan to the Ministry of Social Affairs and Health in March 2014. However, a healthcare reform is underway which may slow down the work on the plan

The draft of the Plan focuses on the following themes:

1. Rare diseases research
2. Diagnostics and its challenges
3. The development of care
4. Centres of expertise However, a healthcare reform is underway which may slow down the work on the plan
5. The development of social services
6. The empowerment of rare disease patients
7. The implementation, monitoring and financing of the national plan as well as international networking.

Planning is also underway for a national plan for cancer treatment and research with the hope that the process for the rare disease and cancer plans to feed into one another.

National rare disease events in 2013

International Rare Disease Day 2013 was coordinated by The Finnish Network for Rare Diseases, Harvinaiset-verkosto. A « rare market » was organised at the Helsinki Vocational College which gave a place for patient organisations and stakeholders to meet.

The fifth National Rare Diseases Day took place in Helsinki on 25 October 2013. The annual event is organised by Swedish Orphan Biovitrum and provides a forum for the discussion of questions concerning research and management of rare diseases. Amongst the 180 participants were healthcare and social care professionals and representatives of patient organisations.

Hosted rare disease events in 2013

On 21 September 2013, a Europlan national conference was organised in Helsinki by HARSO.

D.10. FRANCE

National plan/strategy for rare diseases and related actions

Second French National Plan for Rare Diseases 2011-2014

The Steering Committee of the plan held two meetings in 2013 on 19 March and 19 November. These meetings concluded that significant progress has been made to date which is in line with the objectives of the Second French National Plan.

¹¹⁶ <http://www.stm.fi/ylakulma/artikkeli/-/view/1814973>

In the area of research, a significant development has been the setting up of a funding process to support Preclinical and Early Clinical Research. This is especially important as France provides sources of funding for basic research (from the “*Agence nationale de la recherche*” – ANR – “National Research Agency”, financed by the Ministry for Research) and for academic clinical research (from the “*Programme hospitalier de recherche Clinique*” – PHRC – “Hospital Clinical Research Programme” - financed by the Ministry of Health), but not for research projects that fall somewhere in between basic and clinical research. An annual call for proposals for translational research in health was announced and launched in 2013.

A total of 34 university hospitals received funds (€9.6 million over 2 years) to obtain necessary equipment to provide new generation sequencing services to speed up standard diagnosis. An in-depth reflexion has been in progress in 2013 to design one national NGS platform for complex diagnosis and research.

The initiative to establish a French national rare diseases databank (“*Banque nationale de données maladies rares*” - BNDMR¹¹⁷) in order to have a central data repository on rare disease patients from various existing sources, for health care planning and clinical research, began in 2011. The minimum dataset was approved during the Steering Committee meeting on 19 March 2013. A national interoperability framework was also defined in 2013. A specific steering committee was created in November 2013 to follow the implementation of the BNDMR.

In the area of health care delivery, improving the way Reference Centres are evaluated is one of the main objectives of the second plan, to ease the reporting carried out by the centres and to create the tools for an accurate assessment on which to base decision on the renewal of the designation and on the allocation of funds. An annual reporting system and a new external evaluation process were defined after 2 years of solid effort by working groups composed of representatives of Reference Centres, patients’ associations, French National Authority for Health (“HAS”), French Agency for the Evaluation of Research and Higher Education (“AERES”) and Ministry of Health. The new process will be ready to be launched in 2014.

Another main objective of the second plan is to reorganise Reference Centres and group them in a functional way that maximises collaboration and allows better and easier orientation of patients. These “national networks for rare diseases” (“*filiales de santé maladies rares*”) will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: Reference and Competence Centres, diagnostic and research laboratories, imaging, health and social care, professionals and patients’ associations etc. Preliminary work and surveys in 2012 identified 23 possible groupings of Reference Centres. The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres. At the end of the call, in November 2013, 32 projects have been received. The “Permanent Working Group”, planned to monitor the activity of Reference Centres and national networks, held a first meeting on 18 December 2013 and began to examine the submitted projects. The national networks will be designated by the Ministry of Health in early 2014.

In conclusion, the second French plan is well on the way and several initiatives delineated in the plan have been implemented. A new leader of the implementation of the plan was named in July 2013. The Steering Committee recognises that the final months of the plan will present challenges as the rare disease community will have to prepare for the future in the context of a constrained budget but also to build on all the improvements resulting from the two national plans.

Second French National Plan for Cancers (including rare cancers) 2009-2013

A second National Plan for Cancers¹¹⁸ was launched on 2 November 2009 for the period 2009-2013. The final report concerning the implementation of the cancer plan, including a section on the actions in the field of rare cancers, was published in 2013¹¹⁹.

As for the preparation of the third French National Plan for Cancers (including rare cancers) 2014-2019: recommendations for a third plan for cancers¹²⁰ in the field were transmitted to the Minister of Health in autumn 2013. A third National Plan for Cancers was then prepared and published on 4 February 2014¹²¹. Organisation of care for adults with a complex cancer, improvement of the organisation of second opinion in pathology for rare cancers and organisation of care for very rare cancers in children are planned.

¹¹⁷ <http://www.bndmr.fr/>

¹¹⁸ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

¹¹⁹ <http://www.plan-cancer.gouv.fr/accueil/actualites/43-actualites/1204-publication-du-rapport-final-au-president-de-la-republique-du-plan-cancer-2009-2013.html>

¹²⁰ <http://www.sante.gouv.fr/IMG/pdf/Recommandations-pour-le-3e-plan-cancer.pdf>

¹²¹ <http://www.e-cancer.fr/publications> (english) <http://www.e-cancer.fr/le-plan-cancer?gclid=CKLYntPlyb4CFbShtAodTDoAcA>

French National Plan for Rare Disabilities 2009-2013

A fourth national resource centre for patients with rare disabilities and severe epilepsy was created in 2013. Inter-regional intermediary teams (*“equipes relais”*) of these national centres were launched in 2013 with the aim of their complete deployment in 2014-2015. Cooperation between national resource centres and inter-regional teams for rare disabilities and Reference Centres for rare diseases is also underway. A leaflet¹²² was published describing the national organisation of care in this area.

The Ministry of Social Affairs and Health has asked for an evaluation of the first plan and will announce a second one in 2014 based on various studies conducted during the first one, such as the expert report conducted by INSERM at the request of the CNSA entitled¹²³ *“Rare handicaps: context, purposes, perspectives”*. It highlights the need to describe rare disabilities with the International Classification of Functioning, Disability and Health (ICF), the utility of creating national and international registries or databases, and suggests strengthening the organisation created by the first plan.

Other French national initiatives related to rare diseases

On 2 May 2013, the third National Plan for Autism for the period 2013-2017 was published by the Ministry of Social Affairs and Health. This plan aimed at improving early diagnosis and early care, structuring healthcare, educational and social pathways for patients, supporting families, improving training for all the professionals in charge of patients, and strengthening research¹²⁴.

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo (*“Rare Diseases Cohorts”*) project for duration of 10 years and for a total of €10 million. The RaDiCo project showed accelerated development in 2013¹²⁵, and prepared the launch its first call for rare diseases cohort proposals at the beginning of January 2014. The RaDiCo projet has developed very close links with the BNDMR.

Centres of expertise

In 2013 major steps were made to coordinate individual Reference Centres and group them in a functional way that maximises collaboration across the country. The *“national networks for rare diseases”* (*“filieres de santé maladies rares”*) will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: not only Reference and Competence Centres, but also diagnostic and research laboratories, imaging, health and social care, professionals and patients’ associations etc. The designated networks will receive funds from the Ministry of Health for their coordination activity. A preliminary survey identified 23 possible groups gathering nearly all the 131 Reference Centres (some centres do not fall in any of these groups). The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres: at the end of the call, in November, 32 projects have been received. The Permanent Working Group began to analyse these projects in December 2013. The result of this call is expected in early 2014¹²⁶.

In July 2013, the Ministry of Health published a directive concerning the process for succession as coordinator of a Reference Centre, and for the creation or abrogation of a Competence Centre linked to a Reference Centre.

Three *“national resource centres”* for rare disabilities have been designated in 2011, and a fourth one in 2013 thanks to the French National Plan for Rare Disabilities 2009-2013¹²⁷.

Registries

A National Rare Disease Registry Committee was created in October 2006 as part of objective 1 - *“Improve knowledge of epidemiology of rare diseases”* - of the first National Plan for Rare Diseases. In 2012, a reflection began on a possible evolution of the Committee’s missions and the needs of the other registries and databases existing in France for support and evaluation and in April 2013 the committee was dissolved at the same time as the national committee created in 1996 for the evaluation of non-rare disease registries. The InVS, Inserm and INCa launched a call for experts in October 2013 in order to create a Registry Evaluation Committee which will consider, amongst others, rare disease registries. This committee will consist exclusively of experts of registries, epidemiology and public health.

¹²² <http://www.cnsa.fr/IMG/pdf/Memos23-WEB.pdf>

¹²³ The expert report has been published in May 2013: <http://www.inserm.fr/actualites/rubriques/actualites-societe/handicaps-rares-contextes-enjeux-et-perspectives-une-expertise-collective-de-l-inserm>

¹²⁴ <http://www.social-sante.gouv.fr/actualite-presse,42/breves,2325/presentation-du-3eme-plan-autisme,15797.html>

¹²⁵ <http://www.radico.fr>

¹²⁶ The list of the first 15 accepted *“national networks for rare diseases”* was published on the website of the Ministry of Health on 28 February 2014. <http://www.sante.gouv.fr/les-filieres-de-sante-maladies-rares.html>

¹²⁷ http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf; http://www.cnsa.fr/article.php3?id_article=726

The Second National Plan for Rare Diseases also has foreseen the creation of a National Rare Disease Database (BNDMR). A minimum data set (MDS) common to all rare disease centres of expertise and to all rare diseases was discussed and validated by the Steering Committee of the plan in March 2013. The MDS will be entered through an application called BaMaRa (“Banque Maladies Rares” – Rare Diseases Databank), either directly by the centres of expertise, or through their own application if appropriate. To enable data flows between French hospitals and the BaMaRa, a national interoperability framework was defined in 2013. It consists in setting the necessary compatibility elements such as patient identification, data elements and nomenclatures, technical data flows and security. It will help gathering data at the Reference and Competence Centre level and linking this information to biobank data and other national databases (medico-economic databases, national health insurance databases etc.). A data warehouse, the National Rare Disease Database (BNDMR), will host several types of de-identified national rare disease data sets in accordance with the Data Protection Act. A steering committee specific of the BNDMR was set up in 2013 including representatives from the concerned ministries and stakeholders, including patients’ associations. In 2013, the BNDMR team also began to develop a specific application named LORD (Linking Open Rare Disease data) to help with rare disease diagnosis coding in hospital health information systems¹²⁸. This application will be used at national level to help coding RD patients either in hospital information systems or registries.

Genetic testing

Guidelines for good practices related to the examination of genetic characteristics in the medical context in order to assure quality of care were finalised in at the end of 2012, and published in the form of an official text on 2 June 2013¹²⁹. These guidelines describe in particular information to be delivered to patients before and after performing genetic tests.

Sources of information on rare diseases and national help lines

Orphanet activities in France

In December 2009, Orphanet signed a partnership with the National Solidarity Fund for Autonomy (CNSA) and leads a project, in the framework of both the National Plan for Rare Disabilities and the National Plan for Rare Diseases, to develop and make available the information concerning the disabilities caused by rare diseases. The CNSA decided to maintain the cooperation for three more years in March 2013.

Guidelines

During the first national plan up to December 2012, the Reference Centres produced, with the sustained help of the HAS, 50 national good practice guidelines (“PNDS”) for diagnosis, treatment and follow-up of patients with rare disease. Only 2 new PNDS were published in 2013.

Training and education initiatives

In 2013, the French Foundation for Rare Diseases organised 3 national workshops designed for rare diseases researchers. A total of 450 participants had the opportunity to meet up with technology platforms and scientific experts in the field of proteomics, animal models and molecular screening, with the objective to boost the development of cutting-edge research projects ahead of the launch of dedicated call for proposals by the FFRD. The FFRD also initiated a reflection on the first national academic training dedicated to rare diseases research. Partner universities have been contacted and details of the objectives, programme and access will be discussed over 2014 for a national implementation as early as 2015.

National rare disease events 2013

To mark the Rare Disease Day 2013 in France, a gathering took place at the Pont des Arts in Paris including the members of the Rare Disease Platform to raise hands in solidarity. Orphanet also marked the day with the launch of their mobile application. From 28 February to 2 March for the third year in a row, an awareness raising campaign was organised on several train lines to raise awareness of this issue amongst the passengers using the service. The Rare Disease Platform also held a press conference on 21 February.

On 12 March, a regional event was organised in Limoges by the Regional Health Agency (“Agence régionale de santé”) to bring together healthcare professionals, regional administrative officers and patients’ associations, for discussions concerning rare diseases and implementation of the plans in Limousin Region, with presentations from actors in the field and regional decision makers.

¹²⁸ This application was launched in early 2014: <http://enlord.bndmr.fr>

¹²⁹ http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id

On 23 September, Orphanet and the French Rare Disease Alliance organised in Paris their annual forum for patient organisations on the theme of information and communication technologies. This forum has become, over the years, a major event for many patients' organisations, and this year's event was attended by over 100 attendees. The theme for 2013 was "ICT for the collection and sharing of information on rare diseases". The first part was dedicated to the latest news of the French rare diseases community, and then the role of patients and patient organisations in registries and cohorts was discussed. The second part focused on how patients can play a role in data collection by highlighting the benefits and the risks they are exposed to.

On 16 September, a regional event was organised in Marseille by the Rare Diseases Alliance, bringing together more than 150 participants from patients' organisations and from the clinics, research and medico and social care areas with the participation of French Ministry of Health representative.

On 17-18 October, the French Foundation for Rare Diseases supported the organisation of Orphan Drug and Rare Disease Seminar in Marseille organised by Eudipharm, F-CRIN and OrphanDev with the aim to raise awareness among clinical research stakeholders on drug development specificities in the rare diseases field.

On 21 November, a Rare Diseases Conference, organized by the Regional Health Agency, in partnership with the Rare Diseases Alliance and the French Foundation for Rare Diseases, was organised in Rennes in order to inform the public about the availability of regional care, medical resources and technical facilities dedicated to rare diseases patients. This meeting also aimed at bridging teams and dedicated platforms at national and regional levels, raising awareness on latest developments of research as well as addressing social and ethical implications associated with rare diseases.

On 28-29 November, the third edition of the "Rare Conferences", Rare2013¹³⁰, was organised by Eurobiomed in Montpellier with over 300 participants attending the presentations and roundtables to hear about advances in the field of rare diseases.

Each year in December, an annual *Téléthon* is organised by the AFM-Téléthon ("*Association française contre les myopathies*" - French Muscular Dystrophy Association) over 30 hours to raise funds. The funds raised go towards rare disease research, information services (including the French Rare Disease Platform), awareness campaigns, patient care and patient organisations. In 2013, the 27th edition of the *Téléthon* took place on 6-7 December, raising over 78 million Euros. On the same weekend, the 14th Rare Disease March took place in Paris, organised by the Rare Disease Alliance, bringing together 2000 participants.

Hosted events in 2013

Amongst the events hosted by France in the field of rare diseases were: the European Society of Human Genetics (Paris, 8-12 June 2013), Orphan Drug & Rare Disease Seminar "Accelerating access to therapeutic innovation" (17-18 October 2013, Marseille), 16th International Conference on Behçet's Disease (18-20 September 2013, Paris), 2nd International Symposium on Hypothalamic Hamartomas (20-21 September 2013, Marseille), 2nd International Expert Meeting on Congenital Melanocytic Nevi and Neurocutaneous Melanocytosis (28-30 September 2013, Marseille), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France), Myasthenia 2013 (1-2 July 2013, Paris), European Human Genetics Conference 2013 (8-11 June 2013, Paris), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France).

The French National Cancer Institute, associated partner of EPAAC (European partnership action against cancer) work package 7 (WP7) organised a workshop on rare cancers in July 2013. The purpose of this workshop was to explore the feasibility and relevance to harmonize clinical practice guidelines at European level in the context of rare cancers (with sarcoma as an example), taking into account the results of the survey which has been conducted in the frame of EPAAC WP7 on existing rare cancer networks and patients groups in Europe. A report of this workshop was presented in Open Forum EPAAC in Slovenia in November 2013¹³¹.

Research activities and E-Rare partnership

National research activities

Flagship of the Second National Plan, the French Foundation for Rare Diseases (FFRD) has been actively promoting rare diseases research since its launch in February 2012. The unique cooperative framework is proving to be an efficient design to implement the main objective to accelerate rare diseases research, and more specifically, to bridge all rare diseases stakeholders in order to:

¹³⁰ <http://www.rare2013.com/>

¹³¹ More than a European sound box: capitalising on the added value of the European perspective in cancer treatment. JM Borrás, J Prades, J-M Bréchet, S Faithfull, A Trama, P G Casali. In: Boosting Innovation and Cooperation in European Cancer Control – Key Findings from the European partnership for Action Against Cancer (EPAAC), ed Jose M Martin-Morena, Tit Albrecht, Sandra Rados Krnel, Ljubljana 2013, pp 117-139.

(1) Understand rare diseases

The French Foundation for Rare Diseases carefully selected 7 technology platforms, both public and private, with whom it initiated partnerships in order to fulfil key needs in the area of rare diseases research: by the end of 2013, the FFRD had launched 4 calls for projects to facilitate researchers' access to NGS technologies and identify the genetics underlying rare diseases not characterized to date, as well as 1 call for projects to develop mouse models and study further functional mechanisms involved in rare diseases. A total of 213 projects were received. A selective scientific process involving 150 experts led to the funding of 95 projects all over the national territory (77 NGS and 18 animal models) for a total of over €1.7 million. In parallel to its own sources of funding and call for proposals, the FFRD has also been involved in providing information to the French rare diseases research community on several other funding opportunities both at the French level (nationally and regionally) and at the EU level (such as IMI, COST, FP7, DG SANCO funding programmes for instance).

(2) Develop new treatments

Following a national workshop organised at the *College de France* in July 2013 to enable scientists to share knowledge and experiences in the field of molecular screening of drug candidates, the FFRD launched its first dedicated call for projects in October 2013. A total of 15 high-flying projects are currently under selection, in collaboration with 5 dedicated technology platforms. In parallel, the FFRD actively engaged in anticipating the R&D needs of innovative diagnostic and therapeutic approaches. This led to the detection of 66 promising candidates in 2013, including new molecules, repurposed drugs and innovative medical devices. Guidance is provided at each step of development together with dedicated partners (IP experts, national and EU regulatory agencies, pharma/biotech, investment funds etc.). As an example, a total of 10 procedures of orphan designation have been initiated in 2013 with the support of OrphanDev, a national network dedicated to methodological support to clinical studies. Similarly, 5 public-private partnerships were proposed in order to accelerate the pre-clinical and clinical development of academic proofs of concept opening the way to new therapeutic strategies. Finally, the FFRD initiated a think tank of pharmaceutical companies to start working on topics such as databases and registries from the perspective of private contributors, as well as orphan drug economics.

(3) Improve patients' care

As rare diseases scientific and clinical research is tightly linked to societal challenges, the FFRD has been actively promoting humanities and social sciences research. In December 2012, a first dedicated call for proposals was launched, in collaboration with the National Solidarity Fund for Autonomy ("*Caisse nationale de solidarité pour l'autonomie*" – CNSA) and the General Directorate for Health ("*Direction Générale de la Santé*" - DGS) to address three different areas: diagnostic pathway; ethical and societal impact of new technologies in the field of genetics; social, educational and professional integration of patients affected by a rare disease. FFRD regional coordinators supported connections between academic researchers, clinicians and patients' organisations. A total of 77 projects involving 188 research teams and 38 patients' organisations all over France were submitted to the assessment of 88 experts from both the rare diseases clinical and social/humanities fields. In 2013, €643 was allocated to 10 successful projects. The high demand encouraged renewing this call for proposals on an annual basis. At the end of 2013, a similar call for proposals was thus implemented and received 80 letters of intents (involving 257 research teams, 61 patients' organisations) that are currently under selection, with results expected for June 2014. Additionally, the FFRD has been initiating and driving boards of experts at the national levels in order to discuss essential updates, especially in the field of patients' protection and information, including a reflection on a consensus document for informed consent for genetic testing, whose results have been invited to be presented at the national "*Assises de Génétique*" congress, bringing together clinicians, geneticists and all involved learned societies for an update on the clinical genetics developments in January 2014.

In parallel, the FFRD has been actively participating in national and international public health and research policies and frameworks. One main objective is to participate in and promote international collaborations. This includes raising awareness for acquainted international research policies and rare diseases researchers' access to the resulting opportunities, such as dedicated funding lines included in the H2020 programme, as well as an active commitment within international consortia such as E-rare and IRDiRC thereafter described. The FFRD also initiated an innovative cooperation programme with The World Academy of Sciences in order to promote rare diseases research collaborations with emerging countries. This led to the launch of a first joint call for proposals, targeting scientists from the wider Mediterranean and Middle-Eastern areas in October 2013. A

total of 90 teams from 17 countries were involved in the submission of 19 international collaborative proposals dedicated to bring together the rare diseases research and clinical communities on key issues. Projects are under international selection, with results expected for the beginning of 2014.

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which was launched at the beginning of 2013 (called “*Programme de recherche translationnelle en santé*” – PRTS, Programme for translational research in Health¹³²). This call for proposals is not specifically for rare diseases. The first objective of this programme is to select and fund research projects at the interface between basic research projects currently funded by ANR and clinical research projects currently funded by PHRC.

In addition, some charities, private foundations or patient organisations provide funding for research, such as the AFM-Téléthon (French Muscular Dystrophy Association). In 2013, the AFM-Téléthon (which has been developing a variety of innovative therapeutic approaches over the past 25 years) and the *Fonds National d’Amorçage* (FNA) (which provides public funds towards innovative biotherapies and rare diseases thanks to the French “*Programme d’Investissements d’Avenir*”) have moved closer to constitute the first seed fund dedicated to innovative biotherapies and rare diseases. This action forms part of an “*Environmental, Social and Governance*” process. With an initial endowment of €50 million, for a final target of €120 million, the fund aims to create a portfolio of 12 to 15 participants in companies at the seed stage. The amount invested will be between €3 and €10 million per company. The AFM-Téléthon has contributed to a budget of €30 million, and CDC Entreprise, via the FNA, has bestowed €20 million. The fund will target innovative SMEs with strong development potential that have been in existence for less than eight years. They must also follow standards that are consistent with the industrial development of therapies such as gene therapy, cell therapy, pharmacological modulation of gene expression, monoclonal antibodies, therapeutic proteins and immunotherapies.

E-Rare

From April 2013, the French Foundation for Rare Diseases is in charge of the E-Rare 2 coordination on behalf of INSERM. France participated in the 5th Joint Transnational Call in 2013, with French teams participating in 9 out of the 12 consortia selected for funding. The E-Rare 2 consortium now brings together 18 ministries and funding national agencies from 15 countries to support projects in translational research on rare diseases across Europe and worldwide. In December 2013, the consortium launched its annual Joint Call 2014 on “innovative therapeutic approaches for rare diseases” with a budget of €13 million.

IRDiRC

In 2013, the AFM-Téléthon (French Muscular Dystrophy Association), the French National Agency for Research (*Agence Nationale de la Recherche – ANR*), and *Lysogene* (all French-based organisations) were committed members of the International Rare Disease Research Consortium (IRDiRC). Since October 2012, the French Foundation for Rare Diseases has been actively involved, together with Orphanet, in the IRDiRC Scientific Secretariat¹³³. At the end of 2013, French representatives were also involved in Scientific Committees: 2 members out of 11 were French in the Interdisciplinary Scientific Committee and 3 out of 17 in the Therapy Scientific Committee which was chaired by the French CEO of EURORDIS. In 2013, French scientists also took part in 10 of the 12 established IRDiRC Working Groups.

Orphan medicinal products^{134,135}

Orphan medicinal product incentives

Initiatives are in place to stimulate the development of orphan medicinal products: research support is provided through national funding programmes: the Hospital Clinical Research Programme (“*PHRC*”). As far as research support is concerned, the French Foundation for Rare Diseases also supported the identification of new molecules with opportunities to become new drugs, through the launch of a first high throughput molecular screening call in 2013 (results to be published mid-2014). It also brought support to research teams in the implementation of all relevant steps to move from a scientific hypothesis to a research protocol (orphan designation – in liaising with OrphanDev, study design, funding etc.).

¹³² www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/

¹³³ In February 2014, the French Foundation for Rare Diseases joined them in IRDiRC as a funder member and a member of the Executive Committee.

¹³⁴ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

¹³⁵ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (pp12-14)

Specialised social services

On 31 May 2013, a Decree was published concerning the skills and qualifications required of those in charge of giving and coordinating therapeutic education of patients.

D.11. GERMANY¹³⁶

National Plan of Action for People with Rare Diseases

At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, the German National Plan of Action for People with Rare Diseases¹³⁷ was adopted in August 2013. A total of 52 policy proposals have been included in this plan covering 7 action fields. This publication of these policy proposals concludes the first phase of the National Plan of Action for People with Rare Diseases. Now begins the implementation and monitoring phase of the suggested proposals.

Centres of expertise

To facilitate the implementation of the three-tiered model of centres for rare diseases two actions were proposed by NAMSE. First existing funding options are to be used to ensure funding for the three-tiered structure of the centres for rare diseases. Once questions of funding and implementation have been resolved, it is recommended that the care providers implement the three-tiered model of NAMSE. Secondly a working group has been established in NAMSE by the steering committee to prepare the designation process for the three-tiered model of centres for rare diseases, taking into account the commonly agreed upon criteria published in the National Plan of Action. By now, a transparent preliminary procedure to designate the centres is under development by NAMSE.

The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner). The group decided in 2013 to continue the state-wide cooperation of these centres; to share the experiences of the centres, with particular emphasis on their coordinating functions in both the framework of the medical faculties and the administration of the university hospitals ; to share efforts to attain sustainability; to help patients with rare and very rare diseases, and their responsible physicians/experts or clinical departments, to find and use the best expertise available; to coordinate an application for financial support for clinical research; to share information on the participation of National or European institutions for research and clinical care in the field of rare diseases.

Registries

NAMSE recommends to set up a web-portal of registries concerning rare diseases in Germany. This facilitates access to existing registries, for example, through a webportal – a “telephone book” of such registries as it were. This webportal could represent in the future the national interface to communicate with the European registry platform of the EU-Commission Joint Research Centre in Ispra. Further NAMSE recommends to develop a prototypical registry for a “Disease-Specific Registries of Rare Diseases”. This prototype – or individual software modules contained therein – should be adaptable for existing registries. A standardization of all existing registries is desirable.

Further NAMSE recommends a uniform coding scheme for all patients with rare diseases employing the Orpha diagnostic coding system in conjunction with ICD-10 GM and in anticipation of the publication of ICD-11. The German Federal Ministry of health supports a project to include Orphacodes into the current coding system of the ICD-10 GM to ensure that rare diseases are coded in health information systems.

Sources of information on rare diseases and national help lines

Orphanet activities in Germany

NAMSE recommends to set up a central and integrated information portal for rare diseases on the Internet with the focus on quality-assured knowledge for patients, their relatives and experts. An interactive map of all care-giving structures (se-atlas) is being developed as one part of the portal. The different care offers should be

¹³⁶ The German Federal Ministry of Health can only verify the information and data which concern federal responsibilities. The information provided here is illustrative and not exhaustive, and that it is validated by the EUCERD/ECEGRD Member State representative to the best of their knowledge.

¹³⁷ <http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf>

presented by the map and additional information on contact details of the professionals and institutions for the respective disease. www.se-atlas.de

Help line

NAMSE maintains that a hotline can become an important, low-threshold part of an internet-based information portal on rare diseases. NAMSE recommends setting up a pilot project to determine which target groups would make best use of such a hotline, what types of questions would most often be posed and what answers can best be delivered to these questions. This information would serve to determine the probable frequency and type of questions and how to plan to best meet these demands. A project (ZIPSE) funded by the Federal Ministry of Health concerning an information portal for rare diseases is going to examine the need for such a service.

Training and education initiatives

Germany is elaborating a national catalogue of learning objectives for medicine for medical students. In this process criteria are being developed to integrate rare diseases in this catalogue to better incorporate them in basic medical training.

National rare disease events in 2013

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

To mark Rare Disease Day 2013 a number of events were held across Germany to raise awareness of rare diseases in Berlin, Bielefeld, Dessau, Essen, Flensburg, Hamburg, Cologne, Münster, Nuremberg and Würzburg. The events included information stands and fairs, press conferences and balloon campaigns. Hospitals, medical professionals, health insurers and celebrities joined the cause to raise public awareness of rare diseases. In addition, the annual Eva Luise Köhler Research Prize for Rare Diseases was awarded in Berlin.

The ACHSE-Central Prize for Patient-Centered Care (ACHSE-Central Versorgungspreis) was awarded in Düsseldorf on 26 June 2013.

The Innovation-Congress “Rare heroes – Orphan Drugs and Rare Diseases in Germany” (Innovationskongress “Seltene Helden – Orphan Drugs und Seltene Erkrankungen in Deutschland) was held on 13 October 2013 by the Institute for Health and Social Research - IGES, Berlin

The Workshop “Registries for patients with undiagnosed Rare Diseases” was held on 21 November 2013 by Reseach for Rare (Research Networks sponsored by BMBF), TMF e.V. and ACHSE e.V.

Hosted rare disease events in 2013

Amongst the events hosted in Germany and announced in *OrphaNews Europe* was the LeukoTreat Final Public Conference (3-6 July 2013, Berlin).

Research activities and E-Rare partnership

National research activities

Additional funding of rare disease research is ongoing in other funding initiatives of the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) such as the National Genome Research Network (NGFN), Innovative Therapies, Regenerative Medicine, Molecular Diagnostics, Clinical Trials and others with about €20 million in 2013. All these activities are funded within the framework programme “Health research”. In co-operation with the Federal Ministry of Health, the *BMBF* assumes responsibility for the programme which is financed with funds from the *BMBF*. The support of RD research continues to be an important topic within this framework programme.

In 2013, the BMBF has commissioned a survey to collect information on funded research projects in Germany. The results are expected for summer 2014 and will be taken into account for the strategic development of future RD research funding.

E-Rare

Germany participated in the 5th Joint Transnational Call in 2013 with German research groups participating in 8 of the 12 projects selected for funding with about € 2.8 million.

D.12. GREECE

National plan/strategy for rare diseases and related actions

In November 2012 a Steering Committee for Rare Diseases was appointed by the General Secretary of the Ministry of Health to review and supplement the plan proposed during the Europlan meeting in 2010 and submit it to the Ministry for discussion, adoption and implementation. This Committee was recently replaced by another one which has not yet started work.

Sources of information on rare diseases and national help lines

Orphanet activities in Greece

A translation of Orphanet abstracts into Greek was initiated in 2013.

In 2013 Orphanet became the official database and contact point for rare diseases, operating as the National Contact Point foreseen in the implementation of the EU Cross-Border Healthcare Directive.

National rare disease events in 2013

The Greek Alliance for Rare Diseases (PESPA) organised a series of events to mark Rare Disease Day 2013 including a series of speeches regarding the subject: “Rare Disorders Without Borders”, at the Eugenides Foundation, from selected scientists and patients, the distribution of printed material in various focal points, the creation and screening of a TV advert on a variety of TV stations, throughout February 2013, culminating on Rare Disease Day (28 February 2013) with the organisation of various events including the events organised by the patient association members of PESPA, an event with PESPA members at the Acropolis Museum, an event with patient organisations at Zapeio, and press releases. KEELPNO organised a one day event entitled: “Rare Diseases: the Greek reality” in order to inform scientists, health professionals and patients on the initiatives regarding rare diseases in the country

D.13. HUNGARY

National plan/strategy for rare diseases and related actions

By the end of 2012 the National Plan for Rare Diseases was submitted to the Ministry of Health. The fourth Hungarian Europlan conference on 25-26 October 2013, organised with the participation of the Ministry of Health, examined the document and the budgetary question: the conference was a lively one thanks to the signing of National Plan for Rare Diseases by the Minister of Human Resources. The National Plan for Rare Diseases has now been approved (at the end of 2013)¹³⁸ and there is an elaborated budgetary plan for the 7 year strategy. The approval of the budget proposal is expected in 2014 in order to finalise the plan. The National Plan for Rare Diseases covers widely the needs of RD patients, extending all important areas and in harmony with the EU recommendations. All stakeholder groups supported the implementation of National Plan for Rare Diseases, including the allocation of a dedicated budget. The implementation of National Plan for Rare Diseases is jeopardized by some uncertainty caused by the prospective MP election, therefore the enhancement of national and international advocacy work is continuously necessary. Beside the National Plan for Rare Diseases the Ministry plans rare disease specific communications in project “Development of public health communication” supported by Cohesion Fund.

¹³⁸ http://ec.europa.eu/health/rare_diseases/docs/national_hungary_en.pdf

In 2012 an expert group was also established at the Ministry of Health to identify the technical specification for a pilot study concerning the introduction of Orphacodes into hospital and healthcare centre records and the study started in 2013.

The formation of a RD help line system, together with the development of rare disease emergency cards was also discussed in the 4th Europlan conference. However, no steps have been made yet.

Centres of expertise

NRDC initiated a collaboration with the National Health Insurance Fund for the listing and transparent accreditation of centres of expertise, hospitals, and laboratories working in the field of rare diseases taking into account existing resources and their concentration, as well as eliminating parallelism and formalising existing informal relations and determining patients' pathways. The research project final report is expected to be published in 2014.

The legal base for establishing rare diseases expert centres had been set up at the end of 2013 by the Ministry of Health. The details of the designation process are to be elaborated.

Registries

The National Register of Congenital Anomalies (VRONY) operates countrywide according to the EUROCAT protocol. The former case definition of VRONY (congenital anomalies diagnosed from conception to the end of the first year of the newborn) has been extended by eliminating the age limit. Consequently, all the diagnosed congenital anomalies are to be reported from 2013 in an obligatory manner. The NRDC has initiated the establishment of an overall register for rare diseases.

National alliances of patient organisations and patient representation

During 2013 HUFERDIS played an important role in of the establishment of Hungarian National Patient Forum, resulting the election of its president as the Coordinator of the Forum. The federation was also a funder member of the new Hungarian Alliance of Patient Organisations (HAPO).

Sources of information on rare diseases and national help lines

Helpline

HUFERDIS started a process to establish the necessary help line system, by applying for a Norwegian grant.

National rare disease events in 2013

HUFERDIS, the Hungarian rare disease alliance, organised a number of events to mark Rare Disease Day in Hungary in both Budapest and Pécs.

In the central event, there were parallel professional meetings in Budapest. A professional conference brought together patient associations, healthcare professionals, pharmacists, technical diagnostic support specialists and also decision makers to share their opinions and ideas on how to act in the field. There was a roundtable discussion about the National Plan for Rare Diseases, updating the authorisation procedures concerning rare diseases. An overview of diagnostic opportunities and new horizons was given, summarising the experiences and finished projects from last year's efforts. There were several useful programmes for families as well, including patient organisation presentation booths, poster sessions, a press conference, play ground, crafts and entertainment. HUFERDIS also organised a Rare Beauties exhibition to mark the Day in an artistic fashion. A Solidarity Walk of 1,7 km through the City Park was also organised bringing together patients and those supporting them.

As a joint effort of the Department of Medical Genetics of the University of Pécs, the Éltes Mátyás School for Children with Special Needs, and the Pécs Gallery at the Zsolnay Cultural Center, an information day for all rare disease patients in the region was held on 23 February 2013. The Zsolnay Cultural Centre, located on the site of the famous Zsolnay porcelain factory in Pécs, proved to be an attractive location for the patients, families, caregivers, and local people interested in rare diseases. The backbone of the program consisted of musical performances by the students of the Éltes Mátyás School, many of whom are affected by rare diseases themselves, and information stands of various Hungarian rare disease patient organisations and caregivers from the region. Speeches given by the Dean of the Medical Faculty, the Director of the Clinical Centre, and the Vice Rector of the University, stressed the role of the University and its academic resources in the region's rare disease care and research.

As previously mentioned, the fourth Hungarian Conference on Rare Diseases was organised by HUFERDIS on 25 October 2013 as part of the Europlan initiative, when the Hungarian National Plan for Rare Diseases was publicly presented for the first time. It is a strategy of health policy from 2014-2020 for RD.

Research activities and E-Rare partnership

E-Rare

Hungary participated in the 5th Joint Transnational Call in 2013 although no Hungarian teams participate in the selected projects.

D.14. IRELAND

National plan/strategy for rare diseases and related actions

The Health Service Executive National Advocacy Unit is supporting the Department of Health in its initiative to develop a national rare disease plan. The patient-centred policy framework will encompass actions targeting the prevention, detection and treatment of rare diseases based on the principles of quality care and equity. The policy will operate over a five-year period and define priority actions, subject to resource availability, in the areas of centres of expertise, orphan drugs and technologies, research and information and patient empowerment and support.

The Institute of Public Health, which is providing support for the development of the Plan, is preparing a report on both aspects of the consultation process (completed in 2012) which it intends to publish alongside the Plan itself. The Plan was finalised in 2013 and should be published in 2014 once a budget has been determined for the foreseen actions.

A Clinical Lead in Rare Diseases in the Health Service Executive was recruited in 2013 to guide the implementation of the plan.

Centres of expertise

A policy concerning centres of expertise is under development as part of the national plan for rare diseases.

Registries

Part of a national strategy on Patient Registries in Ireland is the mainstreaming of the role and work of registries into existing and forthcoming policy. The immediate priority is the inclusion of a stronger focus on Patient Registries in: the programme of work of the Quality and Clinical Care Directorate of the HSE, including the development of clinical standards in specific areas of policy and the appointment of clinical leads in particular areas of policy; the work of the Health Information and Quality Authority; and the Health Information Bill. The Health Information Bill was published in 2013 and addresses ethical and legal issues concerning data collection and sharing patient data.

Neonatal screening policy

All cards from 1984 onwards have been archived, but the Office of the Data Protection Commissioner, following a complaint in 2009, indicated that newborn screening cards currently stored without explicit consent should be disposed. The Minister for Health requested the HSE to conduct a review of the decision to destroy these cards following receipt of representations from a number of people and organisations, who pointed out their potential value for research. The review examined both the legal and ethical basis for retention of newborn screening cards and the potential use of the existing cards for research purposes. The report and recommendations of the review group were submitted in January 2012. The review re-affirmed the original decision reached in 2010, i.e. that in order to meet both ethical and legal obligations, newborn screening cards older than ten years should be destroyed. Following careful consideration this recommendation was accepted. The Review Group also explored how the cards could be made available to the research community in a way which is compatible with ethical and legal obligations. In the interests of facilitating research, the HSE launched a public information campaign on 8 January 2013. This campaign offering members of the public the opportunity to have their screening card returned to them, prior to any destruction of the cards taking place, ended on 31 March 2013. The HSE has received approximately 40,000 requests from people seeking to have cards returned to them.

The Minister has sought advice from the Attorney General on how the remaining New Born Screening Cards can be retained in compliance with Irish and EU data protection legislation. The Minister has also

requested that no destruction of the cards begins before an expert group has had an opportunity to consider the matter further.

Guidelines

Clinical guidelines exist for certain rare diseases. The need for an overall Clinical Programme for Rare Diseases has been accepted by the Minister for Health and the appointment of a National Clinical Lead in Rare Diseases in the Health Service Executive took place in late 2013. It is anticipated that one of the roles of the person appointed to this position will be to instigate the development of clinical guidelines.

National rare disease events in 2013

To mark Rare Disease Day 2013 an all Ireland meeting of patients' organisations, science and industry was organised and the Irish Presidency of the Council of the European Union was held in the City Hall in Dublin¹³⁹. The conference was organised by The Rare Disease Taskforce in Ireland which brings together the Genetic and Rare Disorders Organisation (GRDO), Irish Platform for Patient's, Science and Industry (IPPOSI) and the Medical Research Charities Group (MRCG) along with the Northern Ireland Rare Disease Partnership (NIRDP) and Rare Disease UK.

Hosted rare disease events in 2013

The following events were hosted in Ireland: International Rare Diseases Research Consortium Conference 2013 (16-17 April 2013, Dublin), 10th HHT Scientific Conference (12-15 June 2013, Cork), 9th European Cytogenetics Conference (29 June - 2 July 2013, Dublin).

D.15. ITALY

National plan/strategy for rare diseases and related actions

In 2011, a working group was established at the Ministry of Health in Rome to thoroughly analyse the issues related to the National Plan for Rare Diseases and to draft the preliminary document. On 23 February 2012, a conference was organised at the Chamber of Deputies, and a white paper presented, with the aim of encouraging the government to put in place the rare diseases plan. Between March and April 2012 both Orphanet and UNIAMO organised public consultation on rare diseases with the aim of providing input from stakeholders into the process. The working group of the Ministry of Health preparing the draft of the national plan concluded in June 2012, and the document was sent by the Ministry of Health to AIFA for comments, and subsequently again to the Ministry of Health for final assessment. The document was presented in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step was for the document to be implemented by the stakeholders, from January to February 2013. Their comments were evaluated and included in the document in March 2013 by the Ministry of Health and sent for approval by the permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano.

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

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

Rare Diseases Interregional Board

In 2013, the Health Commission officially adopted two other documents elaborated by the RD Interregional Board: one dealing with the identification of common regional modalities and pathways for the delivery of home cared therapies to RD patients; another one, addressed in particular to AIFA, containing the Regions' proposals regarding the main open issues in the field of the drug provision to RD patients. The contents of both

¹³⁹ <http://vimeo.com/channels/rdwb13>

these documents have been shared with the Interregional Pharmaceutical Board, in which all Regional Pharmaceutical Services are represented. Furthermore, the collaboration with the Pharmaceutical Interregional Board has led to the production of a list of off-label drugs and drugs marketed abroad for rare diseases, partially refundable by AIFA to Regions, which normally cover with their budget these costs.

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

Registries

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

Neonatal screening policy

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

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

Genetic testing

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

The CNMR-ISS is in charge of carrying out the National External Quality Control Scheme for genetic tests. This scheme includes molecular and cytogenetic tests and has been addressed to public laboratories which provide genetic tests. To date eight rounds have been completed and overall 112 laboratories have been monitored in the context of the National External Quality Control Scheme

National alliances of patient organisations and patient representation

In Italy, UNIAMO FIMR is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 100 patient organisations representing more than 600 rare diseases. In 2013, within the "*Conoscere per assistere*" project addressed to general practitioners (GPs) and paediatricians (PLS), supported by Farindustria, UNIAMO FIMR, in collaboration with the federation of paediatricians and general practitioners (FIMP, FIMMG), and scientific societies of physicians (SIP, SIMG, SIMGEPED, SIGU) organized 3 training courses in Florence (April), Potenza (May), and Turin (October). The major topics of these courses included: how to suspect a rare disease, how to manage the transition of rare disease patients from paediatric into adult age.

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

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

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

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

Sources of information on rare diseases and national help lines

Orphanet activity in Italy

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

Guidelines

In 2012, CNMR, 13 institutional partners and one SME have been awarded with a grant by the European Commission, under the Seventh Framework Programme (FP7/2007-2013) for a four-year research project entitled RARE-BestPractices (www.rare-bestpractices.eu), commencing in January 2013. RARE-BestPractices is a platform for sharing best practices for the management of rare diseases. This project brings together a team of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, rare disease epidemiology and public health. The overall aim of the project is to improve the care of patients by disseminating globally best practices for the management of persons with rare diseases. The CNMR acts as coordinator of 14 partners across Europe, all with strong commitment in research on rare diseases, public health and evidence based medicine. The project’s aims to provide reliable informative resources for the rare disease community by creating a collection of methodologically trustworthy and up-to-date guidelines for the management of rare disease; to develop a standard methodology suitable for the development of RD guidelines; to set up training activities and training tools targeted at key stakeholders for the production of high quality rare disease guidelines. Other key elements of the platform are the identification of mechanisms to address the limitations of the evidence, set priorities for rare disease research and propose improvements in pre-approval and post-marketing studies.

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

Training and education initiatives

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

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

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

for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

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

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

National rare disease events in 2013

Since February 2008, UNIAMO FIMR coordinates the Rare Disease Day events organised by its members throughout the national territory. It provides them with information leaflets, posters, gadgets, T-shirts and banners, created in collaboration with Farindustria, the Serono Foundation and Novartis. Awareness was achieved through over one hundred local events, in squares, sports halls and schools and through many articles and interviews on rare diseases in newspapers and on TV.

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

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

Hosted rare disease events in 2013

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

Research activities and E-Rare partnership

National research activities

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

E-Rare

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

Orphan medicinal products

Orphan medicinal product reimbursement policy

The RD Interregional Board has issued a document, approved by the National Health Commission, defining a proposal for the transfer of data regarding orphan drugs prescription from regional registries directly to AIFA, as many information systems set up at regional level collect this information routinely from clinicians working in Centres of expertise.

Other initiatives to improve access to orphan medicinal products

In 2013, the RD Interregional Board produced a document, approved by the National Health Commission, defining common modalities and pathways to access home cared infusion therapies for RD patients.

D.16. LATVIA

National plan/strategy for rare diseases and related actions

Work has recently been finished on a national plan by the working group, which included health care specialists and representatives from the Ministry of Health. In December 2011, the plan was written and submitted to the Ministry of Health for evaluation. The costs related to rare diseases are currently included in the national health care budget. A public consultation of the plan was launched in 2012 and the results were analysed by the Ministry of Health. A number of meetings with different stakeholders were held, and as a result, the plan was further elaborated. The plan was adopted in 2013, no additional funding has been secured, therefore major activities are related to update of regulations concerning rare diseases. The activities are now being implemented including the approval of an act concerning registries and plans to include Orphacodes and ICD codes in the congenital anomalies and cancer registries.

The Cardiovascular Health Improvement Action Plan (2013-2015) was adopted in 2013 and includes activities in field of health promotion, improving cardiovascular diseases treatment and early diagnostic on congenital malformation of the heart.

Centres of expertise

There are currently no official designated centres of expertise for rare diseases in Latvia but a meeting was held in 2013 to discuss possible criteria for national centres of expertise. A legal framework for centres of expertise, including those for rare diseases, is expected in the future.

The Ministry of Health, Orphanet team and experts from 3 University hospitals have been started work on developing national criteria for centres of expertise to be registered in Orphanet database and met in February 2013 to discuss this issue.

Guidelines

In Latvia clinical guidelines for RD at national level have not been approved. The Centre of Endocrinology of Pauls Stradins University hospital in collaboration with Riga East University hospital endocrinologists and Latvian State University Children's Hospital endocrinologists issued in 2013 "Diagnostic algorithms of rare endocrine diseases". These recommendations contain information of patients with a suspected rare endocrine disease in an organised and short form. The recommendations are aimed to help general practitioners and endocrinologists to think about rare diseases when presented with certain types of patients.

Training and education initiatives

Every year the "Baltic metabolic specialist meeting" is held; the 2013 was held in Riga. The meetings bring together most geneticists and laboratory specialists from Baltic countries. Pauls Stradins University hospital organises post-diploma educational courses for different specialists in most areas of medicine, endocrinology among them. The programme usually covers not only the most common clinical conditions but rare diseases also.

In 2013, the Latvian Haemophilia Society intensified cooperation with Lithuanian Haemophilia Society in order to provide disease specific training for physiotherapists who work with people with bleeding disorders in Latvian State University Children's Hospital and the Riga East University Hospital. The adult haemophilia

treatment centre in The Riga East University Hospital also runs various training sessions for nurses and other medical staff to raise awareness and knowledge of bleeding disorders and related health issues.

National rare disease events in 2013

The Rare Disease Association Caladrius and the Centre for Disease Prevention and Control of Latvia marked the day by an event entitled “Rare and Friendly”. In support of rare disease patients in Latvia. Children, musicians Jenny May and Intars Busulis and hockey club Dinamo Riga participated in a photo shoot with patients. These sessions were not only to provide a pleasant surprise for patients with rare diseases, but also to show that people with rare illnesses are as important as the other members of the community, but they need public support to obtain the necessary health care. The event was followed by a press conference for public and media representatives about genetic and rare diseases

In July 2013, Latvia Hemophilia Society, one of the oldest patient organisations in Latvia, celebrated its 20th anniversary.

Hosted rare disease events in 2013

No hosted events were reported.

Specialised social services

As of 1 January 2013 a new service for persons with disabilities (including persons with disabilities of rare diseases) has been launched, a municipality based service of an assistant for performing activities outside home (to get to a place where person work, learn, get to the rehabilitation institution etc.). An assistant service is eligible to: persons with Group I or Group II disability¹⁴⁰, on the basis of conclusion by the State Medical Commission for the Assessment of Health Condition and Working Ability on the necessity for a service of an assistant; persons with disability aged 5 to 18 years¹⁴¹, on the basis of conclusion by the State Medical Commission for the Assessment of Health Condition and Working Ability on the necessity for special care due to severe functional impairments. The service of an assistant amounts to 40 hours a week within the territory of Latvia (except for persons with Group I visual disability who receive a benefit for using a service of an assistant 10 hours a week and who receive a service up to 30 hours a week if a service of assistant exceeds 10 hours a week that is specified by the municipality social service office).

In 2013 PHA Latvia financially supported the first pulmonary endarterectomy for CTEPH patient, organised the Summer Health camp for 40 rare disease patients and their relatives (caregivers), including children with rare diseases and their parents, managed the Charity Sport games to seek fundraising for PAH patients, and proceeded the oxygen home care therapy supporting for PAH patients.

D.17. LITHUANIA

National plan/strategy for rare diseases and related actions

On 18 October 2012, the national plan for rare diseases was approved by Order No V-938 of the Minister of Health, and a national rare diseases coordination committee was formed, including delegated experts from university hospitals, universities, non-governmental organisations, state institutions representatives to oversee the plan. There was a Europlan conference¹⁴² on 14 November 2013 under the auspices of the Lithuanian presidency to discuss the implementation of the plan.

In 2013 10,4 million litas (about 3 million euros) were allocated to reimbursing rare medicinal products and devices.

¹⁴⁰ For the persons from 18 years of age depending upon the level of limitation of physical or mental abilities shall be determined to have the following:

- a) Group I disability – very severe disability,
- b) Group II disability – severe disability,
- c) Group III disability – moderately expressed disability.

¹⁴¹ For a person up to the age of 18 disability is determined without being divided into groups.

¹⁴² <http://www.eurordis.org/sites/default/files/flags/finalreport-lithuania.pdf>

Registries

Establishment of various diseases registries is quite a long and costly process, this is why Lithuania is looking to innovate by establishing electronic, platform-based registries during the period of implementation of E-Health project 2013-2015. Registries of separate diseases (rare included) will function as subsystem of National E-Health information system and will be integrated into common data network.

Neonatal screening policy

The mandatory screening of newborns' hearing was approved by the Order of the Minister of Health (No V-612, 2013-06-11) in 2013.

Training and education initiatives

A training program for the improvement in rare diseases diagnostics for doctors has been initiated and a training cycle called "Rare diseases" has been introduced for medical students.

National rare disease events in 2013

The "National Activities Related to Rare Diseases" conference was held in Vilnius on 14 November 2013, under the auspices of the EU Lithuanian presidency. The conference brought together representatives of patient organisations, academics, healthcare professionals, public authorities and others. The participants gathered to exchange experience on management of rare diseases, implementation of national plans and strategies with regard to rare diseases, progress of the establishment of rare diseases centres, readiness to participate in the activities of European reference networks, research in the area of rare diseases, and examination of difficult clinical cases of rare diseases.

Many of articles dedicated to the Rare Disease Day 2013 were publicised using the mass media. Also, an official opening of the Centre of Rare Gastrointestinal and Liver Diseases at the Hospital of Lithuanian University of Health Sciences Kaunas Clinics was announced on the same day.

Various topics on rare diseases were delivered during the following meetings: Annual conference Pulmonology, Allergology and Clinical Immunology 3 May 2013 in Kaunas, the Conference on Diagnosis and treatment of gastrointestinal neuroendocrine tumours 17 May 2013, Kaunas, the 12th conference of Baltic child neurology association 30 May – 1 June 2013, Kaunas, and the Seminar on cystic fibrosis 8 November, Seimas of the Republic of Lithuania, Vilnius.

Also the conference dedicated for the Rare Disease Day was held in Vilnius University Children's Hospital. Social media has also been highly involved in Rare Disease Day campaign. This year periodicals and online portals have shared stories about rare disease patients, the importance of diagnostics and problems that they face every day.

Hosted rare disease events in 2013

On 14 November 2013 the conference "National Activities Related to Rare Diseases" was held in Vilnius, under the auspices of Lithuanian presidency. The Conference was organised in collaboration with Vilnius University, Lithuanian University of Health Sciences, European Commission, EURORDIS and the expert speakers from Italy, Bulgaria, Germany, Spain and Baltic countries were welcomed.

D.18. LUXEMBOURG

National plan/strategy for rare diseases and related actions

Concertation for the elaboration of a national strategy was reinforced at national level in 2013 based on a broad interdisciplinary Europlan conference. A number of meetings were held before the November 2013 Europlan conference¹⁴³ to raise awareness amongst key stakeholders from different domains (political, medical, patient associations, education, social services, reimbursement etc.) regarding specific problems

¹⁴³ <http://www.eurordis.org/sites/default/files/flags/finalreport-luxembourg.pdf>

linked to rare diseases. A great majority of the addressed stakeholders participated very actively in the Europlan conference which aimed to contribute to the identification of concrete proposals for the elaboration of a national strategy. This endeavour will be carried on in 2014/2015.

Registries

A special effort has been made since 2013 to include Orphacodes when possible to the causes of death registration.

National rare disease events in 2013

During 2013 several awareness-raising activities were organised by ALAN absl partly together with other partners. To mark Rare Disease Day 2013, a day of festivities was organised to raise public awareness and funding. An art exhibition dealing with different aspects of rare diseases ran from December 2013 to February 2014

A major event was the organisation of a Europlan national conference¹⁴⁴ on 19-20 November 2013 with the participation of members from the European Commission, Eurordis and EUCERD, gathering a huge number of national key stakeholders from the medical, the political and the social security fields. Many patient associations participated, as well as research centres and social services. The aim of the conference was to contribute to: increasing the awareness of the specific problems linked to rare diseases, identifying key persons for the contribution in the existing taskforce, identifying the main problems existing in the area of rare diseases, defining priorities for action, and beginning the formulation of the national rare disease strategy.

Hosted rare disease events in 2013

The meetings of the EUCERD were hosted by the European Commission in Luxembourg in 2013.

D.19. MALTA

National plan/strategy for rare diseases and related actions

An advanced first draft of the National Plan on Rare Diseases was completed in 2012. An internal consultation exercise was also completed. A public consultation will be held in 2014. There will probably be a policy commitment to rare diseases in the near future but there may not be a budget specifically for these actions.

Registries

During 2013 Malta started looking actively at the feasibility of introducing a suitable coding system, specifically Orphacodes. This will be further followed up in 2014.

National alliances of patient organisations and patient representation

Until Rare Disease Day 2013, Malta did not have an official national alliance of rare diseases patient organisations. However, this role is increasingly being assumed by the Malta Blood Donors Association, in founding and registering a National Alliance for Rare Diseases, which will be better known as The Malta Alliance for Rare Disorders (MARD).

MARD aims to intensify the awareness amongst the general public and decision-makers about rare diseases and their impact on patients' lives. Its objectives are designed primarily for patients, patients' organisations and their representatives, bringing together other stakeholders such as politicians, public authorities, policy-makers, industry representatives, researchers, health professionals and individuals who have a genuine interest in rare diseases. MARD will be representing EURORDIS in Malta.

National rare disease events in 2013

To mark Rare Disease Day 2013, the Malta Blood Donors Association organised a number of events, including media events and meetings with political decision-makers.

¹⁴⁴ <http://www.eurordis.org/sites/default/files/flags/finalreport-luxembourg.pdf>

D.20. THE NETHERLANDS

National plan/strategy for rare diseases and related actions

The National Plan for Rare Diseases was adopted in October 2013¹⁴⁵ and presented on 10 October 2013 by a delegation of The Netherlands Organization for Health Research and Development (ZonMw) to Minister Schippers of Health, Welfare and Sport (VWS). On 14 November the Minister sent the plan along with her reaction to Parliament. The Dutch National Plan identifies bottlenecks and recommendations, and it encourages field parties to feel responsible. The key bottlenecks for the plan include lack of knowledge about rare diseases, insufficient medical research on causes and course of rare diseases as well as inability of patient organisations to work well together. The plan recommends emphasising knowledge about rare disease through training and establishment of expert centers, make the information widely accessible to diverse audiences; make financial resources available for research and development of treatment as well as maintaining consistent policy for claims and reimbursement of orphan drugs. Finally the plan aims to appoint a director or coordinator to promote all recommendations, and avoid fragmentation and unnecessary duplication within the rare disease field.

Sources of information on rare diseases and national help lines

Other sources of information on rare diseases

website www.erfelijkheid.nl contains a database of approximately 500 rare diseases with information for both lay-persons and professionals. In 2013, 50 new rare diseases (all chromosome disorders) were added to the database. In addition, public information is available on genetic, biomedical and pregnancy related issues¹⁴⁶. Since 2010 videos were added to the website. In 2012 ten new videos were produced and added. Using videos, disease characteristics can be visualised in order to improve the dissemination of information for both patients and medical professionals.

While www.erfelijkheid.nl is successfully reaching an audience of patient, their family and the general public, Erfocentrum also participates in the website www.huisartsengenetica.nl, which focuses on general practitioners. Erfocentrum also provides news on genomics and rare diseases via email to more than 100 patient organizations and via Twitter to over 400 medical professionals and organisations.

National rare disease events in 2013

On 2 March¹⁴⁷, events for Rare Disease Day were organised by ZonMw, Genzyme and VSOP. A gathering of over 300 adults and children was organised in Utrecht to serve as inspiration to promote research and better care for rare diseases. The children enjoyed creative and cultural programs, while adults participated in an informative meeting. In addition, the annual Angel Awards were also handed out.

A Europlan National Conference was held on 14 & 15 November 2013 in The Hague, co-organised by VSOP and Eurordis with the aim of exploring the provisions and implementation of the newly published Plan for Rare Diseases.

Hosted rare disease events in 2013

Amongst the rare disease events announced in OrphaNews Europe were: 3rd European Rett Syndrome Conference Maastricht, "Research Update & Preventive Management" (17-19 October 2013, Maastricht), 6th International Conference on Children's Bone Health (22-25 June 2013, Rotterdam).

Research activities and E-Rare partnership

E-Rare

In 2013, ZonMw did not participate in the 5th Joint Transnational Call.

¹⁴⁵ http://www.euoplanproject.eu/newsite_986989/Resources/docs/NATIONALPLANS_NETHERLANDS_nl.pdf

¹⁴⁶ These sites provide further web based information: www.biomedisch.nl; www.zwangernu.nl; www.zwangerwijzer.nl; www.slikeerstfoliumzuur.nl; www.prenatalescreening.nl

¹⁴⁷ www.zeldzameziektendag.nl

D.21. POLAND

Definition of a rare disease

During the several public debates on rare diseases, consideration of the adoption of an additional sub-definition of ultra-rare disease has been suggested as the necessary to be incorporated within the Polish health care system. The preliminary assumption is that the ultra-rare disease definition would be based on a prevalence of no more than 1 in 50 000 individuals

National plan/strategy for rare diseases and related actions

By the end of 2012 a strategic document “National Plan for Rare Disease – the roadmap” was prepared and handed to the Minister of Health. A broad consultation process started, and it was scheduled for completion by June 2013 in order to meet the recommendations of the EU Council by the end of 2013.

In summary, in 2013, a total of 42 meetings, consultations, workshops and conferences were held, with active participation of group of ca 400 experts (clinicians, scientists, patients groups, providers, payers, industry, Members of Parliament, Government Officials, health politicians) to work on the document entitled “The National Plan for Rare Diseases – the roadmap”. The final version (no 12.2) was submitted to the Ministry of Health in December 2012, as scheduled. However, the Plan was not adopted in 2013 as it was decided to further develop the defined areas into concrete actions. The revised plan will be submitted for approval in 2014. Work on an organisational, budgetary and legal framework is scheduled, based on the strategic paper “The National Plan for Rare Diseases – the roadmap” which has been accepted by the Ministry of Health and the Government.

Neonatal screening policy

As of 2013 the newborn screening programme includes an additional 20 metabolic disorders which can be diagnosed using tandem mass spectrometry. This program is country-wide, regulated and financed by Ministry of Health and coordinated by the Institute of Mother and Child in Warsaw.

Training and education initiatives

Since 2013 a new medical specialty, paediatric metabolic medicine, has been established, what should improve access for the patients with inborn errors of metabolism to well-educated physicians and facilitate setting of reference centres.

National rare disease events in 2013

The International Rare Disease Day (28 February 2013) was organised by National Forum for the Therapy of Rare Diseases – ORPHAN in the Palace of Culture and Science, which is the most recognisable building in Warsaw. Upon this occasion, topics of the draft paper “National Plan for Rare Disease – the roadmap” have been discussed among patients’ families, professionals and parliament representatives and also in several radio, TV and web interviews. The audio-video installation was provided as a platform for patients to share their thoughts and experiences of living with rare diseases. It was a start of a long-term project of “Rare Diseases are Common” campaign. After opening this exhibition appeared in many other places, travelling across Poland. The volunteers “GENE-ius Agents” educated people about rare diseases on Warsaw streets and in public buses.

An awareness raising campaign entitled “Rare diseases are frequent” kicked off at the Polish Europlan Conference on 27-28 September 2013¹⁴⁸. The European Commission and EURORDIS entrusted to the National Forum for the Therapy of Rare Diseases – ORPHAN to assess the Polish policy towards the issue of rare diseases. On 28 September 2013, during the second day of the Conference a debate and workshop concerning the next steps in relation to the plan was held. The debate tackled philosophical, scientific, and medical issues. Recognised experts in medicine, bioethics and pharmacotherapy along with representatives of the Polish Parliament (Sejm) and national patient organisations attended. Issues regarding evaluation of effectiveness of technology and orphan drugs (HTA) and regulatory restrictions on access to the therapy and issues regarding the prospects for the implementation of the National Plan for Rare Diseases were discussed in details. The purpose of the debate was to reach an unanimous approach and develop recommendations (included in the report) for healthcare policy makers, to let them include the recommendations developed by prominent

¹⁴⁸ <http://www.eurordis.org/sites/default/files/flags/finalreport-poland.pdf>

participants of the health care system focused on rare diseases in their efforts to improve the scope and therapy standards. The recommendations aim to support the Minister of Health in the correct implementation of the state policy regarding rare diseases.

Also a number of meetings for medical students entitled ‘Conversations on rare diseases’ were also organised across Poland in 2013.

Hosted rare disease events in 2013

Amongst the hosted events organised in 2013 was the 9th European inborn errors of metabolism course in Warsaw, Poland (in collaboration with the Children’s Memorial Health Institute) (Warsaw, 25-29 September 2012), Rare diseases and risk of social exclusion (7 October 2013, Warsaw), and the Fourth International Meeting on Primary Central Hypoventilation Syndromes (Warsaw, 13-14 April 2012).

Research activities and E-Rare partnership

E-Rare

Poland participated in the 2013 5th Joint Transnational Call but Polish teams did not participate in the selected projects.

D.22. PORTUGAL

National plan/strategy for rare diseases and related actions

The National Programme for Rare Diseases, published by the Directorate-General of Health in 2008, has developed its activity focusing only on the services depending on the Ministry of Health, thus meaning, today, it must be replaced by a broader national strategy with integrated actions, both at inter-sectoral and inter-institutional level. A new Integrated Strategy for Rare Diseases 2014-2020 is currently being finalised, which replaces the previous Programme and aims to ensure that people with rare diseases have better quality of care, based on the evidence that science has been producing, as well as greater celerity and variety of social responses adapted to each case. This new strategy further aims to guarantee that, in an inter-ministerial, inter-sectoral, inter-institutional and integrated way, priorities in the global approach to rare diseases be refocused, bringing together the contributions of competences and resources of all relevant sectors, in order to cause, in a progressive way, a real change in the complex conditions of the people who suffer from these diseases.

Centres of expertise

Legislation is presently being finalised, in order to identify and officially recognise reference centres that might integrate future European Reference Networks.

Genetic testing

In 2013, the number of clinical cases sent abroad for referral amounted to 159, especially for molecular study and laboratorial genetic testing.

Sources of information on rare diseases and national help lines

Orphanet activity in Portugal

The national team of Orphanet has kept available and updated in Portuguese all menus from the international site¹⁴⁹, all the diseases names, the emergency guides and summaries of diseases (validated by experts in each area).

By the end of 2013, 1065 abstracts of rare disease and 18 emergency guidelines have been translated and validated into Portuguese and entered in the international database; about 200 new abstracts were also translated, and are now waiting to be validated.

During 2013, Orphanet-Portugal continued to collect and validate and significantly increased the information available in the country on national resources and activities related to rare disease and orphan drugs. These included 145 specialised centres, 111 laboratories (33 diagnostic laboratories and 78 research laboratories), 1041 diagnostic tests, 153 research projects, 23 clinical trials, 70 patient organisations and 19

¹⁴⁹ <http://www.orpha.net/consor/cgi-bin/index.php?lng=PT>

registries and biobanks, by December 2013; the list of the orphan drugs available in the country (currently 49, in a total of 88 different presentation and/or dosages) is regularly uptake from each one.

The Orphanet-Portugal team also contributed to the development (in English) and subsequent translation and validation into Portuguese of a leaflet on "Genetic Testing Related Health", produced by the Council of Europe and prepared by EuroGentest (a network of excellence funded by the European Commission) and the PPPC (Public and Professional Policy Committee) of the ESHG (European Society of Human Genetics).

This brochure (in Portuguese) was released during the Rare Disease Day 2013 and is available from the Orphanet national webpage⁵.

In addition, as in previous years, the national team has been committed to the diffusion of the Orphanet portal and services to professionals involved in rare diseases, as well as to patients, families and the general public. This is achieved both through the organisation of specific events, and the participation in several scientific meetings and courses with oral or poster communications and lectures.

In 2013, 6 presentations about Orphanet were made at such meetings, one organised (together with Aliança) by Orphanet Portugal (the Rare Disease Day 2013), and one interview about "Orphanet in Portugal" and published in the magazine "Pontos de Vista", distributed by a daily Journal

Training and education

The Portuguese Society of Human Genetics also approved in 2013 a commission for clinical genetics laboratory, to harmonise education criteria and program for laboratory geneticists; this program has already been accepted by the EBHG.

Two Genetics in Family Medicine courses were organised in 2013, at the Institute of Molecular and Cell Biology (IMCB), in Porto, part of a series of spring and autumn courses, directed mainly to general practitioners, but also other physicians and health professionals. IBMC also has a long-standing programme to receive high school students and teachers for presentations and guided visits to genetic services and research laboratories, all throughout the year.

Raríssimas submitted a project to EEA Grants funding for NGO's (Programa Cidadania Ativa/Fundação Calouste Gulbenkian) in 2013 and has had the approval for its Marcos's Centre – Information and training, to run from 2014 until 2015. Several programmes are being defined to address different training needs, including patients, families, health and education professionals, students and volunteers.

National rare disease events in 2013

A conference was held to mark Rare Diseases Day on the theme of "Rare disorders without borders: National and European Realities" on 23 February 2013 in Porto, organised by Aliança Portuguesa de Associações das Doenças Raras (APADR) and Orphanet Portugal. A large number of stakeholders participated and the day ended with discussions on the status of the National Plan and centres of expertise. The Day was well covered in the national press and media.

Hosted rare disease events in 2013

Amongst the rare disease events hosted in Portugal and announced by OrphaNews Europe was the First International Primary Immunodeficiencies Congress (IPIC) (7-8 November 2013, Estoril).

Research activities and E-Rare partnership

National research activities

FCT is recommending, after proposal of Orphanet Portugal, that "rare disease" and the respective Orpha code(s) are included as keywords in the application forms for projects, if applicable.

E-Rare

In 2013 Portugal joined the 5th Joint Transnational Call but no Portuguese teams participated in the selected projects.

Orphan medicinal products

Orphan medicinal product reimbursement policy

There are no specific provisions in place for the reimbursement of orphan medicinal products. All Portuguese citizens are covered by the National Health Service. The investment of the NHS in orphan medicinal products between January and December 2013 was around €75 million, which represents 7.7 % of the total consumption

of medicines in hospitals. It should be noted that there was an increase of 19.4 % in this group of medicinal products, as compared to the same period of 2012.¹⁵⁰

Specialised social services

Raríssimas has now opened Casa dos Marcos, the first Resource Centre for Rare Diseases in Portugal, gathering social and healthcare services and planning to respond in the educational area as well. Casa dos Marcos has both residential services and ambulatory care and is establishing several partnerships, nationally and internationally, developing innovative projects in various domains. In fact, it has a unique model of assistance with a mix offer that includes services under contract with the State (a long-term care unit, a residential unit, an occupational activity centre and an autonomous residential unit) and private services (respite centre; rehabilitation centre; medical and non-medical consultations). It also includes an information and training centre and a research centre on rare diseases. Holiday camps for patients are also run. Casa dos Marcos costs about €10 million (global investment) and Raríssimas raised about €8 million from private companies.

D.23. ROMANIA

National plan/strategy for rare diseases and related actions

By the end of 2012 the inclusion of the National Plan for Rare Diseases in the National Public Health Strategy was the next step concerning the implementation and monitoring of the plan by the end of 2013. At the end of 2013, the National Council for RD (NCRD) was created by the Ministry of Health (MoH) through a Ministerial Order (1215/2013).

In 2013 RONARD continued its active work in the development of the NPRD. The main activities of the RONARD in 2013 were the following:

- RONARD organised the Rare Diseases Day (RDD) Campaign and during the National Conference for Rare Diseases on 2nd of March 2013, at the end of the RDD campaign it was signed a new partnership agreement¹⁵¹ with Ministry of Health Romania to create the institutional framework for the implementation of the National Plan for Rare Diseases (National Council for Rare Diseases). It is an interdisciplinary scientific body without a legal personality, working as an advisor of the Ministry of Health, providing specialised expertise both from its own team, as well as from specialised teams in different areas, developing criteria for designating centres of expertise in the management of rare diseases, defining evaluation process and identify the Centre of Expertise in Romania, communicating with RONARD and other institutional partners and define priority actions to ensure continuity of care for patients with rare diseases: information, diagnosis, treatment or specific therapies, counselling and patient and family education, training and integration specialists in the community;
- The second Europlan National Conference was organised under the auspices of Ministry of Health Romania at Hotel Parliament in Bucharest, on 24-25 May 2013. The Conference aimed at facilitating dialogue, participation and involvement of all stakeholders in the field of rare diseases in Romania (patients, professionals, authorities, politicians, industry, media, etc.) in order to address solutions that need to be taken to update the proposals of the National Plan for Rare Diseases (NPRD).
- A Resolution of the Europlan Conference has been agreed by all the stakeholders involved in rare diseases field in Romania around the main objectives and future activities for rare diseases in 2013 and the following NPRD for the period: 2014-2020.

Due to the complexity of political and socio-economic situation at the national level, no budget has been allocated for the NPRD in 2013 but it is expected financial support through budgetary integration on MoH.

Rare cancers are mentioned in the NPRD in Romania and future actions will be included for the period 2014-2020.

¹⁵⁰ http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ANALISE_MENSAL_MERCADO/ANALISE_MERCADO_MEDICAMENTOS_CHNM/2013/Rel_Medicamentos%20MeioHospitalar_dez13.pdf

¹⁵¹ http://www.ms.gov.ro/documente/ordin%20boli%20rare_823_1638.pdf

Centres of expertise

The NCRD (National Council of Rare Diseases) started to develop a policy concerning Centres of Expertise for RD. A procedure for the designation and evaluation of centres of expertise is under development using the EUCERD Recommendations on Quality Criteria for Centres of Expertise adapted to the situation in Romania. NCRD will select the criteria, define the policy in the country and organise the national competition for expertise centres. The number of total national/regional centres of expertise is still debateable based on population size and geographic distribution. Following the competition the Centres of Expertise designated will participate in the future European Reference Network.

Registries

Since 2013 NCRD deals with the issue of a national registry for RD but no public financial resources have been allocated so far. At the moment, NCRD selects the common data elements for Rd databases and extends the work by ensuring that the dataset are defined in the same way, using the same standards and same terms. Also, NCRD is considering appropriate EU standardised databases in order to find how to harmonise, share and exchange information. In addition, NCRD establishes baseline measures for data safety and protection. National registries and databases can be use to plan and manage services in the field of RD.

Neonatal screening policy

In 2013, according to the national health policy a mandatory newborn screening program was available for two diseases, phenylketonuria (PKU) and congenital hypothyroidism (CHT), with the goal of screening all infants born in the country. The screening is performed in 4 public medical centres throughout the country (Bucharest, Iasi, Cluj-Napoca and Timisoara). The current health policy improved the management of screening for PKU and CHT at local level, reaching 80% coverage for newborns.

In the last two years, efforts were made via the Health Programme at local level in order to generalise and improve the organisation of neonatal screening for these two disorders, as well as to introduce screening for other (rare) diseases for which some form of treatment is available. Newborn screening tests for other diseases are provided by private clinics / laboratories at full cost or can be carried out in the framework of research programmes (e.g., hearing loss).

However, despite the screening programme, some tests are not available nationwide due to logistic and resource problems and no additional RD have been added to the panel of diseases tested in 2013.

Also, in 2013, Romania continued to join in efforts aimed for the preparation of European guidelines on diagnostic tests or population screening (EUNENBS: European Network of Experts on Newborn Screening) respecting national decisions and competences.

National alliances of patient organisations and patient representation

At the end of 2013, the National Council for RD (NCRD) was created by the Ministry of Health (MoH) through a Ministerial Order (1215/2013) and 3 representatives of the RONARD are full members in the executive committee of the council. The council, as an advisory group for MoH in the field of RD is playing an important support role in the consultation and implementation of the NPRD.

Sources of information on rare diseases and national help lines

Official information centre for rare diseases

In October 2013, RONARD has also launched an online platform for the development of organisational capacity of patients' organisations in Romania: www.aspac.ro.

Help line

At the end of 2013, The Romanian Prader Willi Association has initiated a restructuration of the NoRo HelpLine in order to develop the network of professionals that support the activity at national level.

Guidelines

Before 2013, clinical practice guidelines have been produced for every medical specialty including RD but several of them are at national level (e.g., diagnosis and follow-up in Oncology, Pulmonary Hypertension or Hereditary Angioedema).

In Romania the following translated or elaborated RD guidelines were launched in 2013:

- The Romanian Prader Willi Association translated and printed "A medical alert for Prader Willi Syndrome";

- In cooperation with Romanian Society for Human Genetics and many other professionals a book entitled "Medical Alert in Rare Genetic Diseases, an emergency guideline for 18 rare diseases clusters" was re-published. The book's first edition (including 98 different RD) was elaborated during the implementation of NoRo project.

Training and education initiatives

In November 2013 the 2nd rare diseases training course for medical journalists in Romania and also a course for parents and personal assistants was debuted in December 2013.

Other training courses have been provided through our workshops organised in different conferences during 2013.

National rare disease events in 2013

The Romanian National Alliance for Rare Diseases has marked Rare Disease Day with many events since 2008, with the support of Eurordis and the Romanian Society for Human Genetics. The alliance coordinates efforts and collects the information about the campaign events organised by the member organisations. To mark Rare Disease Day a march for rare diseases took place on 28 February 2013 in Zalau and a workshop on European Reference Networks and Centres of Expertise in Romania for rare diseases, organised by the National Alliance for Rare Diseases Romania, was also organised the week before on 21 February 2013. In addition to these events the first National Conference on Rare Diseases was organised on 2 March 2013 in partnership with the Romanian Society of Medical Genetics and the National Alliance for Rare Diseases with the aim of bringing together different professionals in the field to exchange information on rare diseases.

The Romanian Europlan conference¹⁵² was held on 24-25 May 2013 in Bucharest to facilitate an open dialogue between all stakeholders (patients, professionals, authorities, politicians, industry, media). This event was organised by ANBRaRo under the patronage of the Ministry of Health. The conference rendered support from the Ministry of Health of Romania, who are motivated to carry forth the National Plan for Rare Diseases in the near future. In addition to updating the national plan for Romania, the conference also discussed establishing relevant procedures for assessing the Centres of Expertise as well as finalising the procedure for appointing the National Committee for Rare Diseases and working groups. The process of reimbursement of orphan drugs in Romania was also analysed and alternative strategies to facilitate access to orphan medication were examined. A push towards rare disease research and the identification of possible sources of funding were considered. In conclusion, the outlook for adoption of the long-awaited National Plan for Rare Diseases in Romania looks promising.

In addition a Campaign for rare cancers and CML was organised in September 2013.

Other therapies for rare diseases

The NoRo Centre offers to patients with rare diseases access to therapies such as: medical evaluation, groups of support, psychological counseling, behaviour therapy, speech therapy, physical therapy, massage, sensorial therapy, hydro - kinetic – electric therapy, ergo-therapy, weight management, educational and occupational therapy. The NoRo Centre is accredited for specialised social services by the Ministry of Work and also for medical services from Ministry of Health; it is authorised for training by Ministry of Education and for research capacity by National Agency for Scientific Research. It is a resource centre and could be part of the patients' pathway and network of the future centres of expertise in Romania, ensuring continuity of care while implementing quality standards of services. It is the main goal of ExpertRARE – a project developed by Romanian Prader Willi Association and co-funded by a grant from Switzerland through the Swiss Contribution to the enlarged European Union.

¹⁵² <http://www.eurordis.org/sites/default/files/flags/finalreport-romania.pdf>

D.24. SLOVAK REPUBLIC

Registries

During 2013 the Slovak Society of Medical Genetics together with the NCZI worked on reporting congenital anomalies (including ORPHA, OMIM, codes), so as to use this for future information about rare disease patients.

The use of Orphacodes to code rare diseases is being considered.

National alliances of patient organisations and patient representation

The Slovak RD Alliance leads the activities in the field of rare diseases in Slovakia and thus was the main organiser of the EUROPLAN National Conference on the Rare diseases day in February 2013. The fundamental challenge for the Slovak RD Alliance is to raise public awareness about rare diseases. The representatives of the Slovak RD Alliance are actively involved in the Working group for rare diseases at the Ministry of Health and in 2013 participated in the formation of National Plan for Rare Diseases.

Sources of information on rare diseases and national help lines

Orphanet activities in the Slovak Republic

Since 2006 there is a dedicated Orphanet team in the Slovak Republic, hosted before 2010 by the Institute of Molecular Physiology and Genetics in Bratislava. In 2010, in the context of the Joint Action Orphanet Europe, the Ministry of Health designated the 2nd Department of Paediatrics of the University Children's Hospital Bratislava as the official Orphanet team for Slovak Republic. This team is engaged in collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team launched in 2011 the Orphanet Slovakia national website¹⁵³. Part of the Orphanet Encyclopedia has also been translated to Slovak language and this initial set rare disease descriptions is now available on the Orphanet Slovakia website. In the year 2013 the Slovak Orphanet team was partner of the EUROPLAN National Conference held on the Rare Disease Day (2nd Slovak Rare Disease Conference¹⁵⁴). In April 2014 the Slovak Orphan team organised the 2nd Slovak Rare Disease Conference.

National rare disease events 2013

The main activity of the National Rare Disease Day 2013 in Slovakia was the EUROPLAN National Conference (27-28 February 2013). This second edition was organised by the Slovak RD Alliance in cooperation with the EUCERD representative and under auspices of the Chair of Health Care Committee National Council of the Slovak Republic and member of Parliament of the Slovak Republic - Richard Raši, MD., PhD, MPH., Ministry of Health of the Slovak Republic - Dr. Zuzana Zvolenská and EURORDIS.

The special website dedicated to Rare Disease Day was launched by Slovak RD Alliance (www.zriedkave-choroby.sk) is regularly updated mainly with information and news regarding activities run by Slovak RD Alliance on Rare Disease Day.

On 27 of February there was a press conference, where the representative of Health Care Committee National Council of the Slovak Republic: Richard Raši MD, the representative of EURORDIS Dorica Dan, the representative of professionals Anna Hlavatá MD from University Children's Hospital, the representative of EUCERD Slovakia Frantisek Cisarik MD and the press conference host from Slovak RD Alliance and DebRA SR Beata Ramljaková took part. After the press conference the speakers moved to the Ministry of Health, where together with others involved, the first meeting of the Working Group for Rare Diseases was held. The EUCERD representative from the Czech Republic Milan Macek gave a talk about the experience with the health care for rare disease patients in the Czech Republic. The representatives of the Slovak RD Alliance gave the official translation¹⁵⁵ of the National strategy into English to the representatives of the Ministry of Health. On the next day the Forum of Experts with 164 guests and 16 talks was held. The Conference was divided into three main parts, according the guideline for EUROPLAN conferences. In the first one, the starting points for the creation and formation of the National plan were explained and an update on the legislative status given. Then an update on Orphanet activities was given and professionals were encouraged to register their services. The

¹⁵³ <http://www.orpha.net/national/SK-SK/index/%C3%BAvod/> www.zriedkave-choroby.sk

¹⁵⁴ <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/issue-files/afpuc.2013.60.issue-supplementum8.xml>

¹⁵⁵ http://www.europlanproject.eu/newsite_986989/Resources/docs/NATIONALPLANS_SL_nationalStrategySlovakiaEng.pdf.

availability of orphan medicinal products from the regulatory point of view as well as from the point of view of the health insurance company was discussed. In the next part experience with the newborn screening policy was presented. The issue of registries for rare diseases was also tackled. Finally the Slovak RD Alliance presented its activities and importance of active participation in the creation of the National Plan. Representatives of the patient organisations presented their experience with the specialised social services provided. The national scientific journal *Acta Facultatis Pharmaceuticae Universitatis Comenianae* published the proceedings¹⁵⁶. The conference report is available online¹⁵⁷.

On 24 April 2013, the 2nd Slovak Rare Disease Conference was held in Bratislava. One of the aims was to reflect on the creation of a national network of expert centres for rare diseases. A number of scientific lectures with emphasis on therapeutic approaches were also given.

Izakovic's Memorial is an annual conference organised in Slovak Republic by the Slovak Society of Medical Genetics, related to genetic and rare diseases.

D.25. SLOVENIA

National plan/strategy for rare diseases and related actions

In 2012 a national plan for rare diseases was accepted by the Health Council and the next steps will be to elaborate an action plan and its implementation, as well as to identify funding. The Work Plan for Rare Diseases¹⁵⁸ is designed to serve as a roadmap until 2020 and is qualified as “... an opportunity for better coordination of efforts of all partners involved, establishing health care that will be comprehensive, accessible, timely and patient-focused”.

The Center of Undiagnosed Rare Diseases (CURD) and Center for Mendelian genomics (CMG) have been introduced at the Clinical Institute of Medical Genetics (CIMG), UMCL. CURD serves as a central referral point of patients which need further diagnostic (genetic) evaluation for professionals. The CMG serves as a national and regional center for clinical application of next generation sequencing in clinical practice; medical procedures in this Centre are already covered within the public health system.

CIMG leads the SIGN (Slovenian Italian Genetic Network) crossborder initiative which aims at improvement to the access to diagnosis, therapy and rehabilitation of patients with genetic disorders in the region.

Centres of expertise

The establishment of centres of expertise is foreseen in the national plan for rare diseases.

Registries

A new Healthcare Databases Act, which sanctions the establishment of national registries, is under preparation, and the inclusion of registries in the area of rare diseases is expected. There is a plan to establish a national register for rare diseases.

Sources of information on rare diseases and national help lines

Orphanet activities in Slovenia

Currently the Orphanet national team receives no funds through national plan. There are plans to include national Orphanet in financing.

Official information centre for rare diseases

Establishment of national contact point for patients and professionals to get some extensive information on rare diseases diagnosis and treatment is foreseen in 2014. The Centre for Undiagnosed Rare Diseases is organised as a medical service and financed through genetic program allocated to CIMG.

¹⁵⁶ <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/issue-files/afpuc.2013.60.issue-supplementum8.xml>

¹⁵⁷ <http://www.eurordis.org/sites/default/files/flags/finalreport-slovakia.pdf>

¹⁵⁸ http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf

Help line

There is currently no information help line for rare diseases in Slovenia; it is foreseen though within the national information contact point.

Guidelines

Slovenia has not elaborated emergency guidelines for rare diseases; however they are roughly summarised in the chapter concerning inborn metabolic diseases in a new text book of Paediatrics¹⁵⁹, issued in 2013.

National rare disease events in 2013

The Association of patients with blood diseases organised a meeting on rare disease day in February 2013.

Hosted rare disease events in 2013

The 10th Balkan Congress of Human Genetics and 2nd Alps Adria Meeting on Human Genetics (10-12 October 2013, Bled) was organised.

D.26. SPAIN

National plan/strategies for rare diseases and related actions

The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government expects to raise knowledge and awareness for rare conditions, and establish stronger ties of mutual support. The operation focused on the health, research and social perspective of rare diseases¹⁶⁰.

During 2013 an update of the objectives and recommendations of the strategy on rare diseases of the NHS was carried out by all the stakeholders reaching an agreement. It is currently pending of approving by the Interterritorial Council of the NHS.

One of the activities proposed for the year 2013 was the creation of a map of expert units in rare diseases to facilitate access to the information of the activity carried out in different hospitals in Spain in relation to the RD; to facilitate access to information for citizens, decision-makers and health professionals to establish networks.

The work procedure has been developed in the framework of the strategy on rare diseases of the NHS and was approved by the Interterritorial Council of the SNS on 21 March 2013.

The Interterritorial Council of the NHS approved on 21 March 2013 a common procedure for the good practices (BBPP) identification in the NHS. An ad hoc group was created in the framework of the strategy on rare diseases of the NHS to adapt the common criteria and the assessment tool approved by the CISNS to the field of rare diseases and to evaluate all experience collected. 69 experiences proposals were collected and evaluated for the evaluation group and 8 of them obtained the good practice title and stamp.

A campaign to raise awareness concerning RD was defined by the Ministry of Health and was published on the Internet on 21 October and lasted until 3 November. The Ministry of Health planned a total of 5.092.650 spots that appeared in the main sites of digital newspapers and sites of television.

A specific training course on disabilities in rare diseases for professional evaluators was organised. This course was coordinated by the CREER.

Also among the actions of awareness-raising, to understand the characteristics of these diseases, improve the situation of affected families and promote networks of collaboration and mutual support, the international day of families of 2013 was devoted to relatives of persons with rare diseases.

In October 2013 the Ministry of Health, Social Services and Equality signed a collaboration agreement with the President of RTVE Corporation to broadcast the Telethon of the Spanish year of the rare diseases. This event took place on 2 March 2014 and the income will be allocated to research for rare diseases.

¹⁵⁹ <http://www.dzs.si/artikel/9789610202943+++1/pedijatrija-?folderId=10232173>

¹⁶⁰ <http://www.msc.es/gabinete/notasPrensa.do?id=2611>

Regional initiatives

All regions have been collaborating in the National RD Registry. They contributed to the standardisation of procedures and methods and also in the development of the pilot study. At the end of 2013, they began with the collection of cases from 2010-2012.

Centres of expertise

In Spain, Royal Decree 1302/2006 establishes the procedure and principles for the designation and accreditation of the Reference Centres, Departments and Units (CSUR) of the Spanish NHS. Work continues in other areas of specialisation to define all the diseases and procedures, among them those related to rare diseases, which should be carried out in CSUR. Since 2001, FEDER (The Spanish Federation for Rare Diseases) has been working in the CSUR project with regard to rare diseases, by providing professionals to participate in the groups of experts related to rare diseases.

They are currently in phase of accreditation of the Autonomous Region's proposals related to: Arritmology electrophysiology and paediatrics, Metabolic Congenital Diseases, Genetic neurocutaneous syndromes (Phakomatosis), rare diseases concerned with movement disorders and complex disorders of the autonomic nervous system.

Work is currently being carried out on the definition of the criteria for designation of centres, services and Reference Units of the National Health System for rare cancers and pulmonary hypertension.

Work is continuing on the identification of diseases and procedures for which there is a need a CSUR in the NHS, still expected to finish such identification in 2014.

Reference services are monitored annually. An information system is in place to report on how the activities performed comply with the designation criteria and meet the procedure and result indicators that were included in the designation criteria. The definition of these procedures and result indicators by the corresponding expert groups and units and services designated (agreed by the Interterritorial Council) is very complex, due to the diversity of diseases and procedures, considering that every disease and procedure has its own information system.

Currently, the annual follow-up of 177 CSUR of the NHS is being carried out. These CSUR cover 35 diseases and procedures, and they have been operating during 2009-2013. Each year collected data and indicators are analysed by professionals from CSUR and expert groups in each area of expertise, and if required, appropriate improvements are introduced.

All information concerning the CSUR project is available for health professionals and patients in the Web of the Ministry of Health, Social Services and Equality (MSSSI).

During 2014 the MSSSI will be involved in the implementation of European Reference Networks (ERN) in the context of the Directive of Cross Border Health Care.

Registries

The Spanish Rare Diseases Registries Research Network is a €2.4 million project financed by the Institute of Health Carlos III (ISCIII) for 2011-2014. This project involves all Health Departments of the Autonomous Communities (regions) of Spain, the Institute of Rare Diseases Research (IIER) which acts as a coordinator and leader of the network, the Spanish Ministry of Health, the Spanish Centre of Reference of People and Families affected by RD (CREER¹⁶¹), six Spanish Medical Societies, four research networks, pharmaceutical and biotechnological organisations (ASEBIO¹⁶² and FARMAINDUSTRIA¹⁶³), and the Spanish Federation of RD (FEDER¹⁶⁴) and its foundation (FEDER TELETHON FOUNDATION). The main objective is to develop the National and Regional Registry for rare diseases based on methods for both population-based registries and patient outcomes registries. Industry, patient's organisations, foundations and more than 6 medical societies have signed agreements with the ISCIII to contribute to this national registry and cooperate with the IIER.

Several RD patient registries are being integrated into the central repository of the National RD Registry. At the same time, a preliminary agreement has been reached between SpainRDR and REDECAN, the network of population-based for cancer registries in order to collaborate in the process of rare cancer registration. Currently, SpainRDR is collecting prevalence cases corresponding to the period 2010-2012. A standardized mapping of codifications between ICDs, Orphacodes, SNOMED and OMIM is used. Common Data Elements, Standardised Operating Procedures, ELSI rules and methods for statistical analysis and reporting have been already developed.

¹⁶¹ http://www.creenfermedadesraras.es/creer_06/index.htm

¹⁶² <http://www.asebio.com/es/index.cfm>

¹⁶³ http://www.farmaindustria.es/Farma_Public/index.htm

¹⁶⁴ <http://www.enfermedades-raras.org/>

Neonatal screening policy

National neonatal screening is currently in place for phenylketonuria and hypothyroidism congenital hypothyroidism, phenylketonuria, cystic fibrosis, deficiency of acyl Coenzyme A deshydrogenada medium-chain (MCADD), deficiency of 3-Hydroxy acyl-CoA Dehydrogenase, long-chain (LCHADD), glutaric acidemia type I (GA-I) and sickle cell anaemia.

The incorporation of this population program of neonatal screening in basic common portfolio of NHS services will be accompanied by the development of:

- An information system of neonatal screening at regional and State level allow proper monitoring and evaluation of the population programme.
- A system of quality management that allows addressing homogeneously in all autonomous communities' screening processes, so it is essential to the elaboration of agreed protocols and their implementation in the NHS.

At the beginning of this process, on 18 December 2013 the CISNS adopted the document "Objectives and quality requirements of the Neonatal screening of metabolic diseases of the SNS program": in this document quality objectives are defined for each of the stages of the program and the necessary or recommended requirements for achieving them.

A working group with representatives from the Ministry of Health, and the Regional health services, reviewed scientific evidence and will produce a report and recommendations about population screening programs for the National Health System¹⁶⁵.

Also, the Spanish Network of Agencies for Health Technology Assessment and Benefits of the National Health Service has developed several reports on effectiveness and cost-effectiveness of the neonatal screening program for some rare diseases^{166,167,168,169,170}.

Genetic testing

At the present time, the MSSSI is working together with Regional Governments and Scientific Societies defining the genetic portfolio of services for the NHS and HTA agencies which are involved in the description of the Spanish map of genetic test offered by the NHS.

Sources of information on rare diseases and national help lines

Official information centre for rare diseases

There is no official information centre on rare diseases in Spain but there is a special Unit at the Ministry of Health to answer citizens' questions and to address the 200 rare disease related questions they receive each year. Other services are provided by Orphanet Spain which is supported by the Institute of Health Carlos III.

Guidelines

The Ethics Committee of the Institute of Rare Diseases Research (IIER) has published a series of guideline documents regarding registries, biobanks, and neonatal screening¹⁷¹. Originally published as separate articles in

¹⁶⁵ A document on screening in general (neonatal and cancer screening) was elaborated in 2010 : "Documento marco sobre cribado poblacional" elaborated by the Comisión de Salud Pública del Consejo Interterritorial del SNS (2010) (Committee for Public Health of the Interterritorial Council of the National Health System) (2010)

¹⁶⁶ Paz Valinas L. Cribado neonatal de la fibrosis quística. Eficacia/efectividad y protocolos de implementación. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Agencia de Evaluación de Tecnologías Sanitarias de Galicia; 2013. Informes de evaluación de tecnologías.

¹⁶⁷ Efectividad clínica del cribado neonatal de errores congénitos del metabolismo mediante espectrometría de masas en tandem. Parte I: enfermedad de la orina con olor a jarabe de arce, homocistinuria, acidemia glutarica tipo I, acidemia isovalerica y deficiencia de 3-hidroxi-acil-CoA deshidrogenasa de cadena larga. – Margot Einoder Moreno, Gerardo Atienza Merino. – Santiago de Compostela: Agencia de Evaluación de Tecnologías Sanitarias de Galicia (avalía-t). Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013.

¹⁶⁸ Queiro Verdes T. Cribado neonatal de la anemia falciforme. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Agencia de Evaluación de Tecnologías Sanitarias de Galicia; 2013. Informes de evaluación de tecnologías sanitarias.

¹⁶⁹ Castilla I, Arvelo-Martín A, Valcárcel-Nazco C, Linertová R, Serrano-Aguilar P, Ruiz-Pons M, Posada M, Dulín-Íñiguez E, Espada M, Zubizarreta R. Coste-efectividad del cribado ampliado de errores congénitos del metabolismo mediante espectrometría de masas en tandem. Red Española de Evaluación de Tecnologías y Prestaciones del Sistema Nacional de Salud del Ministerio de Sanidad, Política Social e Igualdad. Servicio de Evaluación del Servicio Canario de la Salud; 2012. Informes de Evaluación de Tecnologías Sanitarias: SESCS Nº 2012/11.

¹⁷⁰ Seoane Mato D, Cantero Muñoz P, Atienza Merino G. Efectividad clínica del cribado neonatal de errores congénitos del metabolismo mediante espectrometría de masas en tandem. Parte II: acidemia metilmalónica, acidemia propionica, tirosinemia tipo I. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Agencia de Evaluación de Tecnologías Sanitarias de Galicia; 2014. Informes de Evaluación de Tecnologías Sanitarias

¹⁷¹ http://www.isciii.es/htdocs/publicaciones/documentos/IIER_Guias_eticas_INGLES.pdf

the Spanish Health Ministry publication *Revista Española de Salud Pública*¹⁷², the Ethics Committee has now grouped the guidelines into one document, entitled *Ethical Guidelines for Biomedical Research*, which it has made available in both Spanish and English languages. The guidelines address issues pertaining to creation, organisation, management, consent, privacy, post-mortem data, and ownership, within the context of existing ethical principles and norms, legal provisions, and international practices.

Training and education initiatives

The Universidad Internacional de Andalucía (UNIA) and the Universidad Pablo de Olavide de Sevilla (UPO) in collaboration with the CIBERER, offers an official Master in 'Rare Disease Diagnosis and Therapy' since 2010. In 2012 and 2013 this course was held again. The IIER has been the as responsible of the training in RD epidemiology in the fourth editions of this Official Master. On the other hand, the IIER has been developing their own training strategy addressed to primary health care workers and physicians in collaboration with the Spanish Society of Primary and Family Medicine. Two different rounds of training courses have been developed during 2013. Finally, the IIER has launched its own on-line training course addressed to those professionals working in the SpainRDR network. It has been followed by more than 60 people and the same online course will be opened to other professionals using the new distant learning ISCIIL platform.

National rare disease events in 2013

FEDER has organised various national conferences on rare diseases and regional conferences. Many other rare disease specific patient associations hold their annual meetings where some time is dedicated to comment on general questions concerning rare diseases. Some Medical and Scientific Societies include round table discussions and conferences related to rare diseases in their annual meetings.

Every year, the Spanish Federation of rare diseases (FEDER) celebrates Rare Disease Day, with hundreds of patient organisations organising a wealth of events.

The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government raised knowledge and awareness for rare conditions, and established stronger ties of mutual support. The operation focused on the health, research and social perspective of rare diseases¹⁷³.

In October 2013 the Ministry of Health, Social Services and Equality organized a scientific meeting "Conocer la rareza, mejorar nuestras vidas. Presente y retos futuros de las enfermedades raras: traslación clínica de la investigación".

Also among the actions of awareness-raising, to understand the characteristics of these diseases, improve the situation of affected families and promote networks of collaboration and mutual support, the international day of families of 2013 was devoted to relatives of persons with rare diseases.

The 5th CIBERER Meeting "Investigar es Avanzar" was held on 27 February 2013 in Madrid to celebrate Rare Disease Day 2013. The main objective of the meeting was to present CIBERER's research activities and scientific advances in rare diseases to the general public. Over 150 people attended the event and counted with the participation of researchers and patient organisation representatives.

The SpainRDR network held its national meeting with the presence of more than 100 participants including the Advisory Board of this network formed by external and well recognized experts in the RD field

CIBERER carried out many activities in the framework of the Spanish Year of Rare Diseases, among which the following could be highlighted as an example, due to their size or international dimension:

- 5th Edition of CIBERER's Meeting "Investigar es Avanzar", 27 February, Madrid.
- DNA-Day CIBERER Workshop, 25-26 April, Instituto de Genética Médica y Molecular (INGEMM). Hospital Universitario La Paz, Madrid
- International Symposium on Mitochondrial diseases, 20-21 May, Fundación Ramón Areces, Madrid.
- International Symposium on Diagnostic Challenges in Intellectual Disabilities by array CGH and Next Generation Sequencing, 3-4 October, Hospital Clínic, Barcelona.

Hosted rare disease events in 2013

Amongst the events announced in *OrphaNews* were: International Congress of Inborn Errors of Metabolism (3-6 September 2013, Barcelona), 1st World Conference on Congenital Disorders of Glycosylation (1-2 September 2013, Barcelona), International Symposium on Urea Cycle Disorders (UCD) (1-2 September 2013, Barcelona),

¹⁷² http://www.msps.es/biblioPublic/publicaciones/recursos_propios/resp/home.htm

¹⁷³ <http://www.msc.es/gabinete/notasPrensa.do?id=2611>

18th Update in the management of gaucher disease and other Lysosomal disorders (13-16 May 2013, Zaragoza).

Research activities and E-Rare partnership

National research activities

On 1 February 2013 the Council of Ministers approved the State Plan for Scientific Research, Technology and Innovation 2013-2016, which represents the instrument intended to develop and finance the activities of the Central Government in R&D to enable the achievement of the objectives and priorities included in the Spanish Strategy for Science, Technology and Innovation 2013-2020.

The State Plan determined as one of its programmatic activities the Strategic Action in Health 2013-2016 (AES), which main aim is to promote the health and welfare of citizens, and is structured as a space for interaction, integrating a synergistic and complementary set of instrumental performances, which results contribute to the consolidation of the NHS as a world leader in terms of its scientific, technological and innovation capabilities. Contributing thus to adapt to Europe, preparing for what would be the 8th Framework Program or Horizon 2020.

In the corresponding calls for granting aid for the Strategic Action in Health, in the frame of the National R&D Plan 2008-2011 and under the Plan for Scientific Research, Technology and Innovation 2013-2016, Rare Diseases have been referred to as one of the priorities in an explicit way.

CIBERER and the National Center for Genome Analysis are collaborating in the massive sequencing and analysis of 279 exomes corresponding to 39 rare diseases and/or groups of pathologies, including mitochondrial, hereditary metabolic, neuromuscular, and sensorineural hearing loss disorders, in a bid to uncover the genetic cause of the conditions. Identification of the genetic basis for these diseases could open new diagnostic pathways. It is anticipated that the study is leading to the identification of the genetic defect in at least 50% of the cases studied.

E-Rare

Spain participated in the 5th Joint Transnational Call in 2013: 3 teams from Spain participated in 5 out of the 12 Consortia funded through the call.

D.27. SWEDEN

National plan for rare diseases and related actions

In 2013, the plan had still not been adopted officially, but meetings of the NSFD were held concerning the plan and steps are being taken to implement some of the proposed measures, including the establishment of a number of centres of expertise.

Centres of expertise

During 2013 NFSD has collected information concerning these centres in Sweden. Criteria for centres of expertise have also been developed. At the university hospitals Centres for Rare Diseases (CSD) are under construction. There are currently two centres founded, at the university hospitals in Gothenburg and in Stockholm. The development and creation of CSDs at the remaining five university hospitals is ongoing. Within each CSD a number of centres of expertise will be established, each with responsibility for a diagnosis, a group of diagnosis or diagnostic group. At the end of 2013, there were 18 centres of expertise established at the two already founded CSDs¹⁷⁴.

Registries

During 2012 and 2013 a group including NFSD and Centre for Rare Diseases Stockholm worked together for the purpose of developing a national register of rare diseases. In 2013 an application of funding of a National

¹⁷⁴<http://www.nfsd.se/hitta-ratt/Samhallsaktorer/Halso--och-sjukvard/Kompetens-inom-området-sallsynta-diagnoser/Centrum-for-sallsynta-diagnoser-med-expertteam/>

Quality Register for Rare Diseases was sent in to SALAR, however funding was not granted. The work with a national register will be continued.

Sources of information on rare diseases and national help lines

Orphanet activities

Orphanet Sweden started a close cooperation during 2012 with the recently installed National Function for Rare Diseases and the Swedish Information Centre for Rare Diseases to optimise the national information resources and became part of the Centre for Rare Diseases Stockholm at the Karolinska Institute in 2013.

Help line

The Swedish Information Centre for Rare Diseases also serves as a public helpline by answering questions, mediating contacts and giving advice on where to find further assistance. Orphanet Sweden also provides information about national and international rare diseases resources.

Other sources of information on rare diseases

In 2013 NFSD launched a new website containing various information and links aimed for persons with rare diseases and professionals.¹⁷⁵

National rare disease events in 2013

Rare Diseases Sweden organised a seminar (“Rare disorders without borders”) to mark Rare Disease Day.

D.28. UNITED KINGDOM

National plan/strategies for rare diseases and related actions

The government issued its UK Strategy for Rare disease in November 2013¹⁷⁶. The strategy, signed by health ministers of all four countries of the United Kingdom, contains 51 commitments to patients with rare disease. These commitments are wide ranging and include diagnosis, information, healthcare, genomics, registries and research. Health systems and other organisations in the four countries will now develop plans to implement the commitments. A Stakeholder Forum has been established to monitor progress in implementing the strategy.

Registries

In England, a government-backed initiative will allow researchers unprecedented access to anonymised patient health records. The Clinical Practice Research Datalink (CPRD) is a new observational data and interventional research service of the National Health Service (NHS), jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is “... designed to maximise the way anonymised NHS clinical data can be linked to enable many types of observational research and deliver research outputs that are beneficial to improving and safeguarding public health”. Data confidentiality is a top priority for the new service and several mechanisms are in place to protect patient privacy. Access to patient data could help rare disease researchers advance knowledge and understanding of rare conditions.

Orphan medicinal products¹⁷⁷

Orphan medicinal product committee

From April 2013 NICE established a new committee to evaluate highly specialised technologies. This committee will take on the role of appraising drugs for ultra-rare conditions. The first product to go through this new procedure is eculizumab for atypical haemolytic uraemic syndrome.

¹⁷⁵ <http://www.nfse.se/>

¹⁷⁶ <https://www.gov.uk/government/publications/rare-diseases-strategy>

¹⁷⁷ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

Orphan medicinal product pricing policy

Control of branded manufacturer prices for all medicines is regulated by the Pharmaceutical Price Regulation Scheme which is essentially a profit cap adjusted to the company's capital in the UK. Value-priced pricing will come into effect from 2014 for newly launched branded medicines¹⁷⁸.

¹⁷⁸ Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Acces Issues, Donald Macarthur (2011) pp.86-7

E. OTHER EUROPEAN COUNTRIES' ACTIVITIES IN 2013

E.1. ICELAND

National plan/strategy for rare diseases and related actions

In 2012, for the first time, Iceland was able to send a representative to a EUCERD meeting, which increased discussion and awareness of rare diseases in Iceland at the level of the Ministry, stakeholders and rehabilitation services. Representatives from these organisations now meet regularly with the purpose to increase awareness of rare diseases within the country. A plan for rare diseases is being defined by a working group with the cooperation of stakeholders. A strategy for disabilities was launched in 2012 and the plan is to revise this document in a few years and include a chapter on rare diseases within it. Currently, there is no specific funding in place for rare diseases.

National rare disease events in 2013

The organisation Unique Children celebrated the Rare Disease Day 2013. This year the organisation donated money to the Children's Hospital in Iceland and to Rjodur which is a centre offering respite care and rehabilitation services for chronically ill and disabled children.

Specialised social services

A new information centre for children with rare disease and their families was opened in Autumn 2012. The centre is called Leiðarljós (Guiding Light) and offers parents of children with rare diseases nursing services, social support as well information regarding available services.

E.2. ISRAEL

National plan/strategy for rare diseases and related actions

The Parliament lobby for rare diseases was founded in 2009 and met again in 2013; several laws have been submitted to the parliament but there is no legislation as of yet.

Centres of expertise

There is a Ministry of Health policy to develop centres of expertise for rare diseases.

Genetic testing

Genetic testing is under the supervision of the Ministry of Health and accreditation is obligatory. There is one private reference laboratory and in many cases the reference laboratories are abroad. There also are Guidelines published by the Medical Genetics Association for prenatal population genetic screening. From the beginning of 2013, the majority of the tests including SMA, Fragile X, Cystic fibrosis are provided for free. While genetic tests should be provided free there are still many challenges; chromosomal microarray are reimbursed for children with mental retardation and malformations and for prenatal testing of fetuses with malformations; mutation analysis and gene sequencing (in part) are reimbursed, although still there are many families who need to pay for genetic tests privately. Genetic testing abroad is possible and testing for any gene is available in private laboratories, but in most cases are not reimbursed and patients pay for these tests privately.

National alliances of patient organisations and patient representation

There are plans to establish an organisation for rare disease patients.

National rare disease events in 2013

A Rare Disease Day event was organised by the Orphanet coordinator at the Meir medical centre with support from the Clalit health insurance fund. A meeting on RASopathies was organised in June 2013.

Hosted rare disease events in 2013

A Cardio-Facio-Cutaneous (CFC) meeting on strategies to study RASopathies and other rare diseases was organised on 24 June 2013 in Haifa.

E-Rare

Israel participated in the 5th Joint Transnational Call in 2013, with teams from Israel participating in 3 out of the 12 projects selected for funding. Israel participated in the 6th joint transnational call in 2014 with teams from Israel participating in 4 projects.

E.3. NORWAY

National plan/strategy for rare diseases and related actions

In March 2012 the Ministry announced that the South-Eastern Norway Regional Health Authority (SE-RHF) should establish a national competence service for rare diagnosis and disabilities to administrate all the national services in this field today, except the services for dual sensory impairment (for which there is established a new national service at Northern Norway Regional Health Authority). The SE-RHF chose to establish a project in 2013, to organise the unit from 1 January 2014. During 2013, some tasks, responsibilities and resources were moved from the Norwegian Directorate of Health to this new central unit. One of these tasks is the national coordination of Orphanet.

Centres of expertise

National competence service

In Norway there are 10 different state-financed centres of expertise for people with rare and less known disorders. They provide services for more than 16 000 persons with more than 350 different rare disorders, which often lead to disability. These centres will be under one administration from 1 January 2014. In order for a service to be established for a rare disease, the condition must meet the criteria of being complex and compound, and there must be a need for multidisciplinary and cross-institutional services. These centres also facilitate the development and dissemination of expertise, and they provide forms of support unmet by standard services. The centres are administered under the South Eastern Norway Regional Health Authority as specialist health care services. The grants to the centres are ear marked to the RHA through the state budget. The centres report to the Regional Health Authority and to the Directorate for Health. See section 4, §4-5 and §4-6 in the above-mentioned regulation for requirements and responsibilities for the national competence services. §4-3 and §4-4 regulate requirements and responsibilities for national and multi-regional treatment services.

In 2013 a project was funded for the organisation of one administrative body for the units dealing with rare diseases, located at Oslo University Hospital. The services will be evaluated through annual and five-year reports.

National alliances of patient organisations and patient representation

There is currently no alliance of rare disease patient organisations in Norway, but the Norwegian Federation of Organisations of Disabled People (FFO) is recognised as the co-ordinating body for organisations of disabled people, including many rare disease patient organisations. The government contributes financially to many patients organisations. There must be at least 250 members in an organisation to qualify for government co-funding. The Directorate of Health initiated a project in 2009 (which has since been finalised) to bring together smaller organisations in order to qualify for financial support, as organisations with less than 250 members may merge with others in order to qualify for government financial support. The Norwegian Directorate for Children, Youth and Family Affairs (BUFdir) is now considering to change the regulations on governmental

support to patient organisations, e.g. to make it possible for people with rare disorders and their family to establish organisations.

National rare disease events in 2013

There are meetings organised at all the resource centres, and annual contact meetings between each centre and their respective regional health authority. Conferences and congresses are organised on special occasions such as Rare Disease Day.

Hosted rare disease events in 2013

A Nordic collaboration meeting for rare diseases was hosted by Norway in September 2013.

E.4. SERBIA

National plan/strategies for rare diseases and related actions

There is currently no national plan for rare diseases in Serbia. A Republic Expert Committee for a Strategy on Rare Diseases has been established and a proposal for a strategy was developed in 2013 envisaging a number of actions over the years leading up to 2020 including: improvement of diagnostics and treatment, improving availability of orphan drugs, registration of rare disease patients, screening for rare diseases, and increasing the participation in patients' associations. The establishment of centres of expertise has been highlighted as a priority topic. The lack of coordination between different parts of public administration is a problem in the field of rare diseases. The Ministry of Health has yet to give their opinion of the proposals. It is hoped that a stakeholder task force will be established to define objectives, activities and next steps for the implementation of key areas of the proposed National Strategy.

Currently there is a policy to provide treatment for limited number of rare diseases and to define centres of expertise for rare diseases.

A Europlan conference, co-organised by the National Organisation for Rare Diseases of Serbia and the Institute for Molecular Genetics and Genetic Engineering of Belgrade University, under the auspices of the Ministry of Health and Eurordis, was held on 6-7 December 2013 in Belgrade bringing together 170 participants from all stakeholder groups. The conference also drew participation from surrounding countries. At the conference the proposal for a national rare disease strategy was presented and priority topics concerning the field of rare diseases were discussed. The conference report is available online for consultation¹⁷⁹.

Centres of expertise

The proposed strategy recommends that centres of expertise should be formed within existing institutions so that existing resources and expertise can be fully utilised. The Republic Expert Committee for Rare Diseases has already determined that 5 centres should be formed.

National alliances of patient organisations and patient representations

The umbrella organisation the National Organisation of Rare Diseases in Serbia (NORBS¹⁸⁰) groups 13 rare disease patient organisations in the country. NORBS organises Rare Disease Day events in Serbia and co-organised the 2013 Europlan conference to discuss a proposal for a national strategy for rare diseases.

National rare disease events in 2013

Rare Disease Day events are organised by NORBS at national level.

A Europlan conference, co-organised by the National Organisation for Rare Diseases of Serbia and the Institute for Molecular Genetics and Genetic Engineering of Belgrade University, under the auspices of the Ministry of Health and Eurordis, was held on 6-7 December 2013 in Belgrade bringing together 170 participants from all stakeholder groups. The conference also drew participation from surrounding countries. At the conference the proposal for a national rare disease strategy was presented and priority topics concerning the field of rare diseases were discussed. The conference report is available online for consultation¹⁸¹.

¹⁷⁹ <http://www.eurordis.org/sites/default/files/flags/finalreport-serbia.pdf>

¹⁸⁰ <http://www.norbs.rs/>

¹⁸¹ <http://www.eurordis.org/sites/default/files/flags/finalreport-serbia.pdf>

E.5. SWITZERLAND

National plan/strategies for rare diseases and related actions

On Rare Disease Day 2013 Pascal Strupler, Director of the Federal Office of Public Health confirmed that the elaboration of a national concept for rare diseases would take place in the second quarter of 2014¹⁸². In 2013 the Federal Office of Public Health recruited a “Rare diseases project manager” to oversee the assessment of the situation of rare diseases in Switzerland and bring stakeholders together. A number of stakeholder meetings were organised in 2013 to advance with the elaboration of the concept. In addition a working group of the Swiss Academy of Science worked on the definition of rare diseases and proposed a set of criteria when establishing reference centres in Switzerland. The concept focuses on issues such as the difficulties to pose an adequate diagnosis in a timely fashion, the provision of high quality medical care, mechanisms that strengthen the resources available to the patients and their relatives as well as to support research projects at national and international level.

Centres of expertise

In 2013, new centres have been named in the field of paediatric oncology (haematopoietic stem cells transplants (autologous and allogeneic), treatment of neuroblastoma, treatment of soft tissue sarcomas and other bone tumours and central nervous system tumours), adult oncology (haematopoietic stem cells transplants) and cochlear implants.

Neonatal screening policy

The request to implement the neonatal screening for cystic fibrosis, initiated by the Swiss Cystic Fibrosis Task Force, was approved from the Federal Office of Public Health for a 2-year-pilot project starting in January 2011, and extended with an open end date from 2013.

National alliances of patient organisations

In the framework of the third International Rare Disease Day in Switzerland in February 2013, a conference jointly organized by ProRaris and the newly founded Radiz (Rare Disease Initiative Zurich) took place at the University of Zurich. The conference topic was “putting together our know-how to increase the quality of care for rare diseases”. Stakeholders of various fields (politics, insurance, administration, medicine etc.) were present and discussed issues related to the formation of a national strategy for rare diseases (see also the announcement of the Director of the Federal Office of Public Health, Mr. Pascal Strupler above). The event received excellent press coverage, including articles in widely read papers in all regions of Switzerland, as well as radio and TV-interviews.

At the end of August 2012 ProRaris submitted a case study on the unequal treatment of the reimbursement of drugs for patients with rare diseases among various insurance companies in different cantons to the director of the Federal Office of Public Health, Mr. Pascal Strupler. In his answer he announced a close monitoring of the interpretation of articles 71 a and b of the ordinance on health insurance (Krankenversicherungsverordnung) on which the decisions of the insurance companies are based until the end of 2013. An evaluation was carried out in 2013¹⁸³.

Sources of information on rare diseases and national help lines

Help line

There is currently no help line available for rare diseases in Switzerland. However, a joint venture between the University Hospital of Lausanne (CHUV) and the University Hospital of Geneva (HUG) with the support of Orphanet Switzerland was initiated in 2012 in order to create a regional portal on rare diseases and to establish a helpline which was launched in 2013 (www.infomaladiesrares.ch). This francophone portal provides access to current information on specialised clinics and allows a greater visibility of local and regional resources, based on existing Orphanet data. This service will be completed by a Helpline in 2014.

Other sources of information on rare diseases

The GDK/CDS supports the establishment of cantonal information and counselling centres for prenatal testing and the HGTA requires non directive genetic counselling before and after genetic testing. However, the

¹⁸² <http://www.orphanet.ch/PDF/ProRaris25022013cloture.pdf>

¹⁸³ Evaluation of the implementation of article 71 a and 71 b KVV, accessible at <http://www.bag.admin.ch/evaluation/01759/02074/13897/index.html?lang=de>

existence of four national languages complicates the organisation of collective national projects. Orphanet Switzerland is currently the only rare disease project supported financially by the GDK/CDS.

The Federal Office of Public health publishes the list of the laboratories with an authorisation to execute genetic tests.¹⁸⁴

In 2013 the “*Romand (French speaking part of Switzerland) portal on rare diseases*” www.info-maladies-rares.ch was launched.

Guidelines

No specific information reported.

Training and education initiatives

On 4 -6 July 2013 Radiz (Rare Diseases Initiative Zürich), a clinical research priority program of the University of Zurich, organised its first yearly summer school on rare diseases at the lake of Zurich. The summer school’s main goal is to motivate bright young clinicians and scientists to work in the field of rare disease and to make them aware of the many opportunities, but also the challenges. The summer school focuses on a wide variety of subjects in the rare disease arena, from disease mechanisms and animal models, to improving diagnoses and novel therapeutics, with lectures and workshops on drug development, model organisms, how to choose clinical endpoints, clinical trials, regulatory aspects, patient registries, patient initiated research, ethical considerations, as well as what rare diseases may tell us about common diseases. The 2013 summer school was attended by 30 young clinicians and researchers. A 2nd Radiz summer school will take place in July 2014.

National rare disease events in 2013

To mark Rare Disease Day 2013, a number of events were organised and initiatives launched. On 22 February the University of Zurich, University Children’s Hospital Zurich and University Hospital Zurich joined forces to launch Radiz with a kick-off meeting followed by a networking dinner with the Gebert-Rüf foundation and a press release entitled “An end to the Odyssey”¹⁸⁵. The following day (23 February 2013) ProRaris, in partnership with Radiz, organised for the 3rd year in a row a conference to discuss the situation for rare disease patients in Switzerland at the University of Zurich which was attended by stakeholders and key political decision makers in Switzerland. The Day was also marked by the launch of the “*Romand (French speaking part of Switzerland) portal on rare diseases*” www.info-maladies-rares.ch.

Hosted rare disease events in 2013

Amongst the rare disease events hosted in Switzerland in 2013 and announced in *OrphaNews* was Autoinflammation 2013 - 7th International Congress of the International Society of Systemic Auto-Inflammatory Diseases (22- 26 May 2013, Lausanne).

Research activities and E-Rare partnership

National research activities

The *Gebert Rüf Foundation*¹⁸⁶, a Swiss grant programme specifically for rare diseases, announced its fifth call for projects in 2013. The independent foundation is committing CHF2 million (€1.66 million) per year to researchers based at Swiss universities, university hospitals, federal institutes of technology and universities of applied sciences. The Rare Diseases – New Approaches grant programme, which launched in 2009, is established as a five-year area of activity. The initiative aims at developing and implementing innovative technologies or approaches in the diagnosis and treatment of rare diseases. In 2013 5 finalists were chosen from the 73 submissions received. The knowledge gained should lead to a better understanding of the genetic, molecular and biochemical processes underlying these diseases and pave the way towards new forms of treatment or diagnostics. A further aim is to improve the transfer of basic research findings into clinical practice. The focus must be on innovation, feasibility and effectiveness, while attaining high scientific and technological standards.

¹⁸⁴ <http://www.bag.admin.ch/themen/medizin/00683/02724/03677/index.html?lang=de>

¹⁸⁵ www.orphanet.ch/PDF/press_release_Radiz.pdf

¹⁸⁶ <http://www.grstiftung.ch/en.html> - http://www.grstiftung.ch/en/portfolio/activity/active_areas/rare-diseases.html

⁶ <http://www.blackswanfoundation.ch/>

E-Rare

Since 2013 Switzerland is a member of the E-Rare project and the BLACKSWAN Foundation is an active collaborator of the network. Switzerland participated in the 5th Joint Transnational call in 2013 with Swiss teams participating in 2 out of the 12 consortia selected for funding.

E.6. TURKEY

National plan/strategies for rare diseases and related actions

A second symposium was held in November 2013 is to discuss the areas to be considered in the scope of a national plan for rare diseases.

National alliances of patient organisations and patient representations

The Turkish Rare Diseases Platform¹⁸⁷ is a new Platform bringing together yet a few rare disease patient organisations in Turkey. Established on 28 February 2013, it aims to motivate rare disease patient communities to come together and share their know-how to bring more service to rare diseases patients, family members and caretakers. It aims to be the platform to voice the issues of rare diseases patient associations and rare diseases patients and caretakers.

National rare disease events in 2013

Some rare diseases have an annual designated day (e.g. phenylketonuria day, 1 June) to raise awareness of these diseases. A second symposium on rare diseases was held in November 2013 is to discuss the areas to be considered in the scope of a national plan for rare diseases.

Research activities and E-Rare partnership

E-Rare

Turkey, represented by TÜBİTAK, has been a member of the E-Rare and E-Rare-2 projects. The Turkish funding commitment was 0,6 M€ for the fifth call Launched in 2013, however Turkish teams were not amongst those participating in the selected projects.

Orphan medicinal products

Orphan medicinal product incentives

The Orphan Drug Study Group (ODSG), formed in 2010 by the Ministry of Health (MOH) have proposed a draft National Draft Guideline for Orphan Medicines, including incentives for the development and registration of orphan drugs, which has been publicly available since 2011. The Ministry of Health updated the draft guideline in 2013 but did not share information on proposed changes. The updated version is waiting for approval by the head of the regulatory agency TITCK. Publication of the final National Guideline is not expected before the end of 2014.

¹⁸⁷ <http://www.enderhastaliklar.org/>

CONTRIBUTORS AND SOURCES¹⁸⁸

A full list of the over one hundred contributors to the State of the Art report and its sources can be found here:

http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivities_ContributionsSources.pdf

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METHODOLOGY AND STRUCTURE

1. SOURCES

The main sources of data for the update of the present report were those collected through the systematic surveillance of international literature and the systematic query of key stakeholders carried out in order to produce the OrphaNews Europe newsletter, various reports published by the European Commission (including past reports of the workshops of the EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan medicinal products. The principal information sources and the collection of data are described in detail here below.

- **European Commission websites and documents**

Information and documentation from the European Commission was used in order to establish this report, principally accessed through the rare disease information web pages of the Directorate General Public Health¹⁸⁹ and Directorate General Research CORDIS website¹⁹⁰ as well as the site of the European Medicines Agency¹⁹¹, in particular the pages of the COMP¹⁹² (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**

Data from the OrphaNews Europe¹⁹³ newsletter for the 2013 period was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France¹⁹⁴ (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

¹⁸⁸ The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive. All websites and documents were last accessed in May 2014.

¹⁸⁹ http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

¹⁹⁰ http://cordis.europa.eu/home_fr.html

¹⁹¹ www.ema.europa.eu

¹⁹² http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30

¹⁹³ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

¹⁹⁴ <http://www.orpha.net/actor/cgi-bin/OAhome.php>

- **EUCERD Publications**

Parts III, IV and V of this report present an update of the information previously published in the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*¹⁹⁵ (July 2010), *2011 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD*¹⁹⁶, *2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD*¹⁹⁷, and the *2013 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD*¹⁹⁸. The methodology for the production of these previous reports is outlined in their respective introductions. In addition, reports from previous workshops of the EUCERD, including the EUCERD Joint Action have been used.

- **Reports of the EUCERD meetings**

The reports of 2013 meetings of the EUCERD were used in order to identify upcoming initiatives and incentives in the field of rare diseases, and to report on the events held to mark Rare Disease Day 2013.

- **Reports on orphan medicinal products**

The information provided for each Member State concerning the state of affairs in the field of orphan medicinal products has been elaborated, when referenced, from the basis of the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*¹⁹⁹ published in 2006 by the European Commission and produced using data collected by the EMA and Orphanet. This information has been updated when information is available and quoted when still applicable. Another valuable source of information on Orphan Drug policy, at EU and Member State levels was the 2009 KCE 112B report published by the KCE-Belgian Federal Centre of Healthcare Expertise (*Federaal Kenniscentrum voor de Gezondheidszorg/Centre federal d'expertise des soins de santé*) entitled "*Orphan Disease and Orphan Drug Policies*" (*Politiques relatives aux maladies orphelines et aux médicaments orphelins*)²⁰⁰. This report notably provided information for the Member State sections on Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The Office of Health Economics Briefing Document "*Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries (No. 52 October 2009)*" also provided information on orphan medicinal product availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V was added during the revision of the 2012 edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*²⁰¹ by Donald Macarthur: this report is referenced in footnotes when used.

- **EURORDIS website and websites of national alliances of patient organisation**

The site of EURORDIS, the European Organisation for Rare Diseases²⁰² was used to provide information on EURORDIS activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national patient alliances were also consulted for information. In addition to this the Rare Disease Day site²⁰³, maintained by EURORDIS, also provided information on events at Member State level²⁰⁴ concerning Rare Disease Day.

- **Orphanet**

¹⁹⁵ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

¹⁹⁶ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf> ;
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf> ; and
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

¹⁹⁷ <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf> ;
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesII.pdf> ; and
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf>

¹⁹⁸ <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf>

¹⁹⁹ http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

²⁰⁰ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*

https://kce.fgov.be/sites/default/files/page_documents/d20091027332.pdf

²⁰¹ <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

²⁰² <http://www.EURORDIS.org/secteur.php3>

²⁰³ <http://www.rarediseaseday.org/>

²⁰⁴ <http://www.rarediseaseday.org/country/finder>

The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials, patient organisations and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links²⁰⁵ to other web-based information services and help-lines which were used to collect information at country-level. The Orphanet Country Coordinators also provided valuable input into the elaboration of information at country level, notably via contributions to OrphaNetWork News. The national Orphanet websites were also consulted to gather national events and initiatives.

A selected bibliography and contributions are provided at the end of each volume of the report.

2. METHODOLOGY

The present report provides an updated compilation of information from the previous reports of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the European Union Committee of Experts on Rare Diseases, 2011 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases, 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases and 2013 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Disease*) which have covered activities up to the end of 2012. The present edition takes into account advances and activities in the field of rare diseases and orphan medicinal products at EU and MS level in 2013.

Once this information from the previous report was updated using the sources cited above, a draft of each country section (Part V) was sent in March 2014 to EC Expert Group on Rare Diseases Member States representatives with a guidance document providing an explanation of the type of information to include if available for each category. The Member State representatives were asked to contact a range of identified key stakeholders in their country for input. The stakeholders identified for each country included: the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, partners of the E-Rare consortium, Member State representatives on the COMP, representatives of national competent authorities, coordinators of national plans for rare diseases and other rare diseases experts identified at national level. The Member State representatives integrated the stakeholder feedback into their report before returning it to the Scientific Secretariat for homogenisation and extraction of developments in 2013 to be included in Part II. Final drafts of Parts II, V, VI concerning their country were sent to the EC Expert Group on Rare Diseases Member State representatives for final validation, to the best of their knowledge, in May 2014.

Part III and IV of the report on activities at European Union level was for input, to the best of their ability, to colleagues at the European Commission and the European Medicines Agency (EMA) respectively: this process was carried out in April 2014 by the Scientific Secretariat of the EUCERD Joint Action. The European Commission and its agencies are not responsible, however, for the completeness and the accuracy of the information presented in this report. The new activities in 2013 were extracted and added to Part II.

Part I was the final volume of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe is the result of an analysis of the information collected for Parts II, III, IV and V. Part I was drafted by the Scientific Secretariat of the EUCERD Joint Action and then sent to all EC Expert Group on Rare Diseases Member State representatives for their input concerning their country's activities before publication in June 2014.

²⁰⁵ <http://www.orpha.net/consor/cgi-bin/Directory>Contact.php?lng=EN>

3. REPORT STRUCTURE

The report is structured into three main parts: Part I consists of an overview of the activities in the field of rare diseases in Europe at EU and MS level; Part II is an extraction of the developments at EU and MS level in 2013 based on Parts III, IV and V; Part III concerns activities of the European Commission; Part IV concerns European Medicines Agency activities and other European activities/events at European level apart from the activities of the European Commission; Part V concerns activities at EU MS level, as well as five other non-EU European countries where information was available; Part V provides the content of Parts II and V in individual country-specific reports.

Each part is followed by a link to a selected bibliography outlining the sources used to produce that part of the report, which includes a list of the European Commission documents referred to in the report and a list of web addresses by country listing national sources of information on rare diseases and links to documents concerning national plans or strategies for rare diseases when in place. Each part is also followed by a link to the list of contributors to the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous edition of the report. A list of frequently used acronyms has also been included in each part to ease reading.

Part I provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts III, IV and V, which serve to provide more detailed background information at EU and MS level. The overview is structured into a number of topics: political framework, expert services in Europe, research and development, orphan medicinal products and therapies for rare diseases, patient organisations and information services.

Part II is a new section of the report, providing information extracted from Parts III, IV and V, relative only to the new activities and initiatives reported for the year 2013.

Part III of the report focuses on activities in the field of rare diseases at EC level is split into four sub-sections:

1. EC activities related to rare diseases in the field of public health;
2. EC activities related to rare diseases in the field of research;
3. EC activities in the field of orphan medicinal products and therapies for rare diseases.

The sub-section concerning the EC activities actions in the area of Public Health is divided into three parts: an overview of DG Health and Consumers' activities in the field of public health, activities in the field of rare diseases funded by DG Health and Consumers, and activities of DG Health and Consumers indirectly related to rare diseases. The sub-section concerning the EC activities in the field related to research in the field of rare diseases presents information concerning DG Research and Innovation's 5th, 6th and 7th framework programmes for research, technological development and demonstration activities and Horizon 2020 related to rare diseases, as well as information concerning the International Rare Disease Research Consortium (IRDiRC).

Part IV of the report contains information on the activities in the field of rare diseases of the EMA and other rare disease activities at the European level, including selected transversal EU activities and conferences at European level:

- European Medicine Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases, EMA Committee for Orphan Medicinal Products' activities, EMA Committee on Human Medicinal Products' activities, European legislation and activities in the field of clinical trials, European legislation and activities in the field of advanced therapies, European legislation and activities in the field of medicinal products for paediatric use, other EMA activities and initiatives relevant to rare diseases and orphan medicinal products, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan medicinal products.
- The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-

Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2013.

Part V concerns the rare disease activities in the field of rare diseases in each of the EU Member States plus Iceland, Norway, and Switzerland in addition to Serbia and Turkey as candidates for EU membership, as well as Israel. These sections are organised in alphabetical order by country.

The information on each country is clearly divided into a number of categories:

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise²⁰⁶
- Registries
- Neonatal screening policy
- Genetic testing²⁰⁷
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Guidelines
- Training and education initiatives
- National rare disease events in 2013²⁰⁸
- Hosted rare disease events in 2013²⁰⁹
- Research activities (National research activities, Participation in European research projects²¹⁰, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability²¹¹, Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products), Other therapies for rare diseases
- Orphan devices
- Specialised social services

The categories for which information is provided depend wholly on the information available following data collection from the described sources and contact with stakeholders. If no detail has been given for a topic, the mention “no specific activity/information reported” has been added.

Part VI concerns the rare disease activities in the field of rare diseases in each of the EU Member States plus Iceland, Norway and Switzerland in addition to Serbia and Turkey as candidates for EU membership, as well as Israel. This section is the same as Parts II and V, except that the information is presented as a separate document for each country to facilitate dissemination at country level.

Each section has two parts: firstly the state of the art up until the end of 2013, and secondly the state of the art of activities in 2013 only so as to easily identify new actions and activities.

²⁰⁶ The term “official centre of expertise” used in this report means officially designated via a (ministerial) procedure.

²⁰⁷ This section contains data extracted in January 2014 from www.orpha.net of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term ‘estimated’ is used as the concept of a single disease is a variable one).

²⁰⁸ As announced in OrphaNews Europe.

²⁰⁹ As announced in OrphaNews Europe.

²¹⁰ Number of projects (Framework Programme 7 funded, including E-Rare) in which research teams from the country are participating as extracted from www.orpha.net in March 2014.

²¹¹ Contacts were asked to provide information on availability of orphan medicinal products (i.e. which drugs are launched on the market/sold at national level). As this information is often hard to identify, some countries instead provided information on which drugs are accessible (i.e. reimbursed, on a positive drug list etc.). It is explicitly explained in each case which of these concepts is being referred to.

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