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Table 1. List of most frequent abbreviations in this report

CoE(s)	Centre(s) of Expertise
EC	European Commission
ERN(s)	European Reference Network(s)
EJP RD	European Joint programme on Rare Diseases
ePAG(s)	European Patient Advocay Group(s)
ExCom	Executive Committee
FAIR	Findable, Accessible, Interoperable and Reusable
GA	General Assembly
GB	Governing Board
GDPR	General Data Protection Regulation
HE	Horizon Europe
IRDiRC	International Rare Disease Research Consortium
JTC(s)	Joint Transnational Call(s)
M	Month
MS	Member States
MS Teams	Microsoft Teams
NGS	Next Generation Sequencing
NMG(s)	National Mirror Group(s)
NP/NS	National Plan/National Strategy
OG	Operating Group
PAO(s)	Patient Advocacy Organisation(s)
PB	Policy Board
VP	Virtual Platform
WP(s)	Work Package(s)

1. Executive Summary

[This includes links to the specific place of the Report where each subject is summarized]

The Strategic Workshop with **national policy makers** held online on 8 July 2021 represented a major activity of the Work Package 2 (WP2) "Integrative research and innovation strategy", within **Task 2.5 "Translation/impact of prioritization on national and EU strategies"** of the European Joint Programme on Rare Diseases.

The meeting concentrated on the ***status quo* of the national, European and international undertakings** consistent and complementary with the relevant actions of the EJP RD. A zoom has been set on the particular **experiences of 4 countries** (Czech Republic, Luxembourg, Portugal and Romania), as examples, with regard to **best practices and challenges** and with a special focus on **National Plans and Strategies (NP/NS) for RD**, as key tools to reach a common RD strategy. Specific attention has been paid to **EU-13 Countries**[1], with respect to their **advancements, obstacles and needs**.

Furthermore, **the way forward** to leverage the potential of all RD stakeholders has been explored, keeping in mind the ambitious goals set by the **International RD Research Consortium (IRDiRC)** and considering the valuable results obtained through the **Rare 2030 Foresight Study**. Moreover, the contribution that could be provided through the constitution and activity of **National Mirror Groups (NMGs)** has been stressed out with some real examples.

Finally, the **possible future scenarios** of the European RD ecosystem have been illustrated through the presentation of the **forthcoming RD Partnership under Horizon Europe (HE).**

The following **key-points** summarise the most important conclusions of the Workshop:

- The importance of collaboration and creation of **synergies** between the national and EU efforts, as well as the sharing of knowledge for the future of RD activities
- The relevance of the **NMGs** to increase the countries' capabilities to integrate themselves in the European RD community.
- The value of the in-kind contributions and of the awareness on the **already existing tools** that can be exploited and improved in the future.
- The necessity to **rethink the model of collaboration** for the coming RD Partnership, from the sustainability to the participation and integration of the different countries and stakeholders.
- The challenge to pursue simultaneously two paths: having **general EU shared rules for the NP/NS for RD** on the one side, and the possibility to adapt and shape these rules to **the context of the different countries**, on the other, for a new generation of efficient RD policies.

[1] EU-13 Countries: Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovenia, Slovakia

As a way to facilitate the implementation of these broad and ambitious goals, several **actions** can be proposed, (also upon the request of some participants to the Workshop, for some of those actions)**:**

- Adopt the recommendation to keep the NP/NS updated in every country.
- Further promote the **establishment of the NMGs** for the set-up of the dialogue with and between the regional and national stakeholders. Their establishment will enable the identification of specific interlocutors that are essential. **National Conferences** (on the example of those set up in the context of the EUROPLAN Project) with multistakeholder groups could be proposed, in order to share and update the experience of the countries that already established a NMG and better understand the difficulties of the countries that to date have not constituted such groups.
- Creation of an **EU web portal to connect stakeholders** involved in the planning/implementation of NP/NS for the sharing of best practices and critical **issues** and to take up the debate on relevant topics of NP/NS that were left behind after the expiry of the Committee of RD Experts, of the European Commission. The platform should also foresee the **collection of the existing NP/NS for RD,** their translation in English, and should be freely available for consultation. Through the web portal, also online or face to face meetings, as well as online training events on RD policy issues could be proposed. To collect the information on **best practices and unmet needs**, a **survey** spread through the web portal could address two relevant aspects that emerged from the meeting: (i) best practices/lessons learned by the countries that adopted a NP/NS for RD and **country specific obstacles** from all countries; (ii) a **focus on the research area** to better understand and analyse the common and country-specific difficulties for the participation in research projects and the collaboration in international Partnerships. Furthermore, a section of the survey could be dedicated to highlighting successful strategies that were adopted by the countries during the **COVID-19 pandemic,** and that could be integrated in the RD strategies (e.g., recourse to telemedicine). The target of the survey should be the Ministries involved in the RD policies and national RD committees.
- Address the **needs of the EU-13 or under-represented countries** by organising workshops, online or face to face, to enhance their capabilities to participate in international projects and to establish partnerships. The workshops could run in English or in local language. Also, the production of guidelines addressing research related topics could be produced and made available. Moreover, and attending a specific request from these countries, tools to raise awareness on the existing national resources should be developed and spread through the local authorities.
- Organise **workshops** (also online) on the **sustainability of research projects**, addressing local resources and national policy makers, as well as EU/international bodies.
- Spread the information on the **availability of 6 months fellowships** offered by the EJP RD to **PhD students** for the mobility between ERNs.
- Produce **documents** to be widely disseminated on the importance of the **investments to share knowledge** and of **FAIR data.**

In the following pages (including Annexes) a detailed summary of each section of the Strategic Workshop is offered for the participants to the Workshop as a reference document, and for interested readers, since this will be a public document.

First Strategic Workshop with National Policy Makers

Title of the workshop: "Alignment of national rare disease strategies with the European Joint Programme on Rare Diseases (EJP RD)"

2. Introduction

The workshop "Alignment of national rare disease strategies with the European Joint Programme on Rare Diseases (EJP RD)" has been organised as online workshop on 8 July 2021, following the Policy Board/Governing Board (PB/GB) meeting of July 7th, 2021. It is a specific action of Task 2.5 "Translation/impact of prioritization on national and EU strategies" of WP2 "Integrative research and innovation strategy" of the EJP RD.

The meeting was addressed mainly to **relevant policy and research stakeholders and all WP Leaders of the EJP RD.** By Grant, it was planned to be held in Month (M) 33. Since the COVID-19 pandemic outbreak entailed the necessity of several mitigation measures, it was decided in the Annual Work Plan of Year 3 to organise the workshop in an online format in M31. The second edition of this strategic meeting is foreseen to be held in M57.

The **main objective of the workshop was reaching coordinated undertakings at national, European and international level aiming at creating a RD research ecosystem**. The need for cooperation and harmonization of the efforts demanded by the necessities of the RD community to face its multiple challenges has been analysed during the meeting, **taking different perspectives into account**. For this purpose, the meeting organisers (Task 2.5 Leaders in close collaboration with Task Partners and the Coordination Team of the EJP RD) selected a range of topics that could trigger the discussion of the audience around key RD-related issues (for the detailed programme of the meeting see Annex 1). Targets of the meeting were relevant policy and research stakeholders, EJP RD's PB Members, Ministries and Academia involved in the EJP RD, European Reference Networks (ERNs) Coordinators, members of EURORDIS, researchers, and persons directly involved in the NP/NS for RD of their country. See Annex 2, which includes the institutions/companies and countries that were present.

In the present document, the most important points extracted from the full presentations and the discussions will be reported and **summarized in the following sections.**

For the consultation of the itemised report of the presentations, see Annex 3.

3. Morning session

The Workshop started with a welcome address from the workshop organisers (Domenica Taruscio and Claudio Carta from Istituto Superiore di Sanità, Rome, Italy and Eva Bermejo and Manuel Posada from Institute of Health Carlos III, Madrid, Spain).

3.1. Setting the scene

3.1.1. **"Building the European ecosystem for rare disease research - how EJP RD leverages the potential of every stakeholder"**

*(**Daria Julkowska**, Institut National de la Santé et de la Recherche Medicale, France)*

The presentation has highlighted the importance of the alignment between the national, European and international RD activities and has illustrated how the participation to common activities can leverage the potential of the different stakeholders involved in the EJP RD and beyond. To this purpose, the multiple facets that underlie the EJP RD have been presented.

The different EJP RD **Pillar-related activities (ongoing, concluded and future)** have been illustrated, stressing the **achievements and results,** and focusing on their capacity to **leverage the potential of the involved stakeholders**.

Overall, from the given overview, it comes out that EJP RD is a network accelerating connection with experts inside and beyond the project, for the benefits of the RD community, aspiring to take full advantage of the capacities of all involved stakeholders and creating a virtuous circle for research on RD.

3.1.2. **"Analysis of national state of play and alignment process with EJP RD"**

*(**Claudio Carta**, Domenica Taruscio, Eva Bermejo, Manuel Posada, Laura Lee Cellai, Marta De Santis)*

The second presentation of the morning session aimed at setting the scene for the comprehension of the alignment status of the national RD strategies with the EJP RD through the presentation of the results of the survey targeting key persons/officers involved in the implementation/development of NP/NS for RD (or in other relevant RD initiatives at national level) in the EJP RD participating countries.

The **transversal survey** represented one of the major activities carried out by Task 2.5 of the EJP RD and intended to **analyse the presence of relevant/complementary RD-related actions** performed at national level, with **a specific focus on EU-13 Countries** regarding their specific needs, obstacles and advancements.

The results presented in the meeting gave a **general overview of the state of the art** in the countries that participated to the survey. The presentation stressed the **main challenging areas** that emerged through the survey, suggesting these as areas that require targeted interventions through national and European/transnational strategies, to promote the desirable alignment with the EJP RD objectives. To this purpose, **broad suggestions for Pillar specific interventions** have been listed.

Regarding the **focus on EU-13 Countries**, critical aspects for the development, improvement and translation of RD research results, as well as for the participation in EU/international projects in the RD field have been assessed through the survey, and figure as areas that claim for specific strategic interventions to overcome gaps and obstacles.

Highlights from the discussion
In the discussion arisen after these two presentations, the connection and alignment between EJP RD and other relevant projects (e.g., 1+Million Genomes) has been cited as an important element to be promoted, to overcome some of the identified obstacles. Moreover, the importance of the **dialogue with the regional and national stakeholders for the orientation of the forthcoming RD projects** has been pointed out, as well as the reaffirmation of the need for a **dedicated attention to the EU-13 Countries** to enable their full participation. WP2 discussed on these points after the Workshop and concluded that this also emphasises the need for the establishment of the **NMGs**.

3.2. From national to European RD strategies: the experience of some specific countries

The morning session went on with the **focus on the experiences of four selected countries** that contributed to the survey. Their selection was made according to different criteria: two of them are EU-13 Countries (Romania and Czech Republic), one is an EU-14 Country[2] (Portugal), and one is a small-population EU-14 Country (Luxembourg).

This part of the session was dedicated to illustrating the **best practices and challenges** of the presenting countries, that could allow to draw a path to enhance the alignment of the regional, national and European RD strategies/plans with the EJP RD activities.

3.2.1. Integrated Strategy for Rare Diseases 2015-2020 - Portugal

*(**Carla Pereira**, Directorate-General of Health, Portugal)*

The presentation illustrated the Portuguese *Integrated Strategy for Rare Diseases 2015-2020* and the results achieved through its implementation, as well as the future actions that will be addressed by the forthcoming NS for RD in Portugal.

The *Integrated Strategy for RD 2015-2020* aimed to address and face the issues of research, training, and knowledge sharing, and dedicated an attention to the drawing of specific strategies to also face the needs of diagnosis, drug therapies, rehabilitation, social inclusion and special education.

The **general achievements and results** obtained through the implementation of the 2015-2020 Strategy include an enhancement in the number of patients identified in the National Health Service as suffering from RD, an increased number of available genetic tests, an augmentation of the information available to citizens, an increment of the possibility to access new and costly treatments, and an increased number of Centres of Excellence for RD.

Throughout the presentation, the importance of the **collaboration with the patients' associations** for the assessment of the patients' needs has been pointed out.

With regard to the **critical issues**, the **research area** has been cited as one of the most critical fields of the RD Strategy of Portugal.

Overall, the continuity of the National Strategy for RD has been reported as a goal that aims at achieving the adequacy of taken in charge of people with RD. An **analysis dated December 2020** detected some of the challenges that still have to be faced by the next NS for RD. Among these, the following emerged as the most

[2] EU-14 Countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden

relevant: (i) the reduced average life expectancy of persons with RD, (ii) the associated comorbidities, (iii) the under-investment in research, (iv) the limitations in access to health services.

Reference was made on the outbreak of the COVID-19 pandemic that brought to a redirection of budget towards infectious diseases and impacted on the access to care of RD patients at national and international level.

Finally, it has been stressed out that the **lessons learned** in the 5 years of the Strategy allowed to determine the **priority actions for the upcoming Portuguese Strategy** to tackle the identified challenges. These actions concern the enhancement of the Inter-ministerial Cooperation, the set-up of a National Registry for RD, the adoption of timely new diagnostics and forms of treatment, the promotion of national research, and the integration of the health care and social responses.

3.2.2. The National Rare Disease Plan in Luxembourg

*(**Francesca Poloni**, Direction de la Santé, Service de Coordination des plans nationaux, Gouvernement Du Grand-Duché, Luxembourg)*

The presentation focused on the structure of the running NP for RD and stressed out the ongoing projects, the main achievements and critical points, and the near future propositions of the NP of the country.

The NP for RD foresees 5 strategic areas, with 26 goals, composed of specific measures and actions. The 5 strategic areas cover the topics of the governance, healthcare, information, RD registry and research, and psychosocial aspects.

The **strategy** of the NP for RD has been illustrated through a model called "**RD house**" ("**Maison Maladies Rares**") with several rooms inside and on top the Governance. Each room addresses a different topic/objective of the NP.

The **ongoing projects** implemented in the framework of this "RD house" include the screening of some diseases (e.g., Severe Child Hearth Disease, SCHD), the reimbursement of healthcare services, the genetic counselling, the mapping of resources and the RD codification.

It has been reported that, in the three years of implementation of the NP for RD, 54% of the goals were achieved or ongoing.

Furthermore, it has been illustrated that for the care of the RD patients, with or without diagnosis, there is currently some ongoing work to develop **2 integrated health pathways: a psycho-social and a medical pathway.**

The main reported **achievements of the NP for RD** have been: the establishment of a RD Infoline (operating via telephone or email), the production of National Guidelines for Orientation in the RD field, the set-up of a National Hub for the access to the ERN, the inventory of RDs in Luxembourg, the delivery of Orphacode Trainings, and the creation of a RD Registry Strategy.

Once again **research on RD** has been pointed out as a **main critical point** and the difficulty in collaborating in international partnerships has been stressed too. In addition, the absence of a critical mass of patients does not allow to develop national clinical trials and knowledge, and there is also a lack of a legal basis for a national RD registry.

As for the **near future prospective for the NP for RD,** a request to extend the NP for a further year is envisaged (motivated by a slow-down of the activities, caused by the COVID-19 pandemic) to allow a needs-assessment for the second NP. Moreover, it is planned to work on the legal basis of the national RD Registry, as above mentioned, on the development of more "rooms" of the "RD house", on the promotion of RD research by collaborating in international partnerships, on the development and expansion of the screening programme and on the definition of a clinical path for RD from diagnosis to treatment to follow-up.

3.2.3. From national to European RD strategies: the experience in Romania

*(**Emilia Severin**, Carol Davila University of Medicine and Pharmacy, Romania)*

The focus of the talk has been set on the development of the NP for RD and on their achievements; the contribution of the Romanian National Alliance for RD (RONARD) has been stressed. Moreover, attention has been given to the impact of the COVID-19 pandemic on triggering the recourse to innovative measures that could be included in the forthcoming NP for RD.

Romania joined the European Union in 2017 and harmonised its legislation with the EU requirements, undertaking new strategic directions for the health system reform, including rare diseases. In this process, the **Romanian National Alliance for RD** (**RONARD,** founded in 2007), had a pivotal role.

In 2008, the first partnership between the Romanian Ministry of Health (MoH) and RONARD took place, followed by a first NP for RD (2010-2014). In 2013, a second partnership was stipulated, and a National Advisory Council for RD was established by the MoH. The second NP for RD (2014-2020) has been included in the National Public Health Strategy, and in 2016 an official political decision of the Romanian MoH supported the designation of **Centres of Expertise (CoE)** on RD, and the country's membership application for the **ERNs'**.

The **priorities** that were identified in the planning process of the NP for RD encompassed, among others, the needs assessment, the active participation of the stakeholders, the access to information on RD, the awareness-raising of the community and policy decision makers, the adoption of innovative treatments, the development of legal and institutional frameworks, the timely diagnosis, the empowerment of the patients' organisations, the development of human resources, and the financial support for national research programs on RD.

With regard to the **achievements of the NP for RD,** the underlined results comprise the legal framework, the collaboration of the Centres of Expertise and ERNs, the

adoption of case management, the strengthening of genetic testing, the endorsed trainings, the creation of an Information Centre, the raising of awareness campaigns, the realisation of a medical school for journalists and the approval of more than 60 Orphan Medical Products.

Two **virtuous national examples in the RD field** have been presented, namely the NoRo experience (a reference centre for RD providing therapeutic and medical services, with the main objective to provide integrated social care services to people affected by RD and their families) and the INNOVCare Project (that addresses the social challenges faced by RD patients as well as the gaps in the coordination between medical, social and support services in EU MS).

Furthermore, the **impact of the COVID-19 pandemic** has been highlighted also for the Romanian RD community. Through the experience gained during the pandemic, both patients and Centres of Expertise draw attention to the need for updating and completing the legal framework in the health, social and education fields. In fact, telemedicine has been included in the law regulating medical care in Romania, and the use of telemedicine has been proposed to be included in the next NP for RD.

The **challenges to be tackled by the next NP for RD** have been summarised in terms of absence of a National Registry for Rare Diseases, a National Coordination Hub, a National RD Network, and of an adequate budget for the complex needs of patients, for drug reimbursement, and for research projects.

Finally, it has been reported that a **new NP for RD for the period of 2021-2027** is in the process of approval.

3.2.4. From national to European RD strategies: the experience in the Czech Republic

*(**Milan Macek**, Charles University 2nd Faculty of Medicine, Czech Republic)*

The activities of the National Coordination Centre (NCC) and its involvement in the NP for RD, as well as in RD research have been illustrated, pointing out also the main achievements and critical issues of the country in the RD field.

The NCC for RD of Prague is a delegated authority from the MoH and is the sponsor of the **10 years' NS for RD**. The MoH works together with other resources and Ministries, such as the Ministry of Youth, Sport and Education, that is involved in the EJP RD.

Regarding the public health policies, the public health insurance is mandatory in the country, and RD care is covered, including the Orphan Medical Products.

The main impetus to adopt a RD Strategy came from the EU Council Recommendation in the field of RD of 2009, and a first NS for the period 2010-2020 was adopted by the country. Within the Strategy, there have been **3 National action plans** with a duration of 3 years each, the last of which has expired at the end of 2020. A 4th National Action Plan is in the process of approval.

Besides this legal framework of the NP for RD, still great **difficulties** are linked to its financial support.
The main cited **achievements** of the country have been, among others: the joining to Orphanet (2016) and translation of the Orpha code in Czech, the collaboration with the National Institute for Health Informatics and Statistics, the participation in 18 international projects, mainly linked with the work of the ERNs, a wide collaboration with the National Alliance (which is part of the European Patient Advocay Groups (ePAGs) and member of EURORDIS), the creation in 2017 of a help-email in paediatric and adult domain, the introduction of the term RD in the healthcare legislature terms of care, and the running of a dedicated website as powerful tool for raising awareness.

On the other side, in terms of **gaps**, also for Czech Republic funding has been referred as a major criticality, and the **research area** has been identified as one of the most critical ones.

The presentation focused moreover on the **main mechanisms of funding** of the country, where 3 major agencies have been reported, the Healthcare Agency, the Technological Agency, and the Grant Agency.

A successful area, financed by the public health insurance, is **new-born screening**, that screens for 18 diseases, and looks forward to including further conditions (although the impact of COVID-19 slowed down this intention).

As for the other countries, COVID-19 pandemic caused important consequences, also for RD research, like the re-shaping of research funding**.**

3.3. Open discussion (morning)

As **research emerged to be the most critical field** in all presenting countries, the discussion concentrated mostly on this topic.

Below the **highlights that emerged during the discussion:**

• The **organisation of small workshops, online or face to face, on the sustainability of research projects** could be desirable for a bottom-up support of research; the workshops should address local resources and national policy makers, and the participation of EU/international bodies should be encouraged, too.
• The awareness of national policy makers should be stimulated on the **potential of national research** and on already existing local resources.
• Research-dedicated funding should be foreseen to **boost research at national level** and be up to date with the momentum of research at international level. An example has been cited from the contingency situation brought by the COVID-19 pandemic, when the Czech Government took advantage of the existence of a functioning infrastructure for gene sequencing that could work at national level, without recurring to international infrastructures. This rose national awareness on the importance of research both on genomics and on rare conditions/complications; this virtuous application encountered nevertheless bureaucratic bottlenecks for the reimbursement.
• With regard to the NP/NS for RD, it has been underlined that not only their existence is of crucial importance, but also their support through national funding. This consideration stressed the **2 needed levels in RD policies: (i) the existence of a NP/NS for RD; and (ii) national support to implement it**.
• The possibility to organise 6–months' **mobility fellowships for PhD students between ERNs** has been recalled, as an opportunity to train new generations of researchers.

4. Afternoon session

The afternoon session approached the overall goals set by the **International Rare Disease Research Consortium (IRDiRC)**, the recommendations developed under the **Rare 2030 Foresight Study** for the future of robust RD policies, the added value provided by the **establishment of NMGs** and an overview of the **forthcoming RD Partnership** under Horizon Europe.

4.1. Capturing the national potential - many ways forward

4.1.1. From national/EU to international level: IRDiRC & Clinical Research Networks

*(**Lucia Monaco**, Italian Telethon Foundation, Chair of the International Rare Disease Research Consortium, Italy)*

Rima Nabbout, Hôpital Necker Enfants Malades, Université Paris Descartes, Institute Imagine, INSERM, France)

The presentation focused on an overview on IRDiRC, the International Rare Disease Research Consortium, and on its multifaceted activities. Moreover, the work of an IRDiRC Taskforce on Clinical Research Networks has been illustrated.

IRDiRC is constituted by international co-operation initiatives to stimulate, better coordinate and maximise the outputs of RD dedicated research efforts around the world, with an axis constituted by its goals. With its activities, IRDiRC allows to **pool a wide set of complementary competencies, global expertise and collective intelligence,** and is widely recognised as a **driver of international initiatives**.

IRDIRC's **vision** is to "*enable all people living with a RD to receive an accurate diagnosis, care and available therapy within one year of coming to medical attention*". Its 3 goals, to be reached by 2027 are: 1. "All patients coming to medical attention with a suspected RD will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosed individuals will enter a globally coordinated diagnostic and research pipeline." 2. "One thousand new therapies for RD will be approved, the majority of which will focus on diseases without approved options"; this aspiration is an extension of the initial goal of 200 new approved therapies, that was achieved in advance. 3." Methodologies will be developed to assess impact of diagnosis and therapies on RD patients".

At **Governance level**, IRDiRC foresees the collaboration of the Constituent and Scientific Committees to identify the gaps that need to be addressed and prioritised by the Consortium Assembly, tackling the three IRDiRC goals. The specific identified topics are placed in an annual roadmap and addressed via dedicated Task Forces/Working Groups. A Scientific Secretariat oversees the managing of the activities and is integrated in the EJP RD Coordination Office. The nomination of calls for Task Forces/Working Groups and Scientific Committees is open to the whole research community and is published regularly on the IRDiRC website (www.irdirc.org).

Up to now, several Task Forces have produced **tools for the Community,** e.g., on data sharing and management, addressing the topics of patient data standardisation and sharing, patient privacy regarding genomic/clinical data or patient consent clauses and management.

Regarding the topic of **research and innovation,** several tools and publications have been set up, such as the Orphan drug development guidebook, and critical issues have been addressed like diagnosing the undiagnosed, drug repurposing for RD, small population clinical trials, or the implementation of patient-centred outcome measures.

The achievements reached to date by current and new IRDiRC Task Forces/Working Groups cover 3 main relevant areas: Research and development for RD, Innovation and clinical research, Access and Impact.

The presentation went on with the illustration of the work of the **Task Force on Clinical Research Networks**, addressing the development of recommendations on guiding principles for an international framework in respect to **best practices, interoperability, tools and common goals**. The contents of this part of the presentation will be the objective of a forthcoming publication and will be therefore not further described in this report.

4.1.2. Recommendations from the Rare 2030 project to shape the future of National Plans and Strategies in Europe

*(**Victoria Hedley,** Newcastle Centre for Rare Disease Research and John Walton Muscular Dystrophy Research Centre Newcastle University Translational and Clinical Research Institute International Centre for Life, UK)*

The information on the *status quo* on NP/NS for RD gathered in 2020/2021 in the framework of the *Rare 2030 Foresight* project and the Recommendations obtained through the work of the project have been the main focus of the presentation. The presentation stressed on the key Recommendations chapter from Rare 2030 concerning "long-term, integrated European NP/NS for RD" (Recommendation 1), by illustrating how the *status quo* supports the need for specific European and national actions as a critical step towards a future society, embracing high patient-needs-led innovation, on the one hand, and equitable social justice for people with RD, on the other.

Rare 2030 Foresight, which officially concluded earlier this year, was a broad and ambitious project, with as background, the call for action of the EU launched in **2009 via the Council Recommendation on an action in the field of rare diseases,** that triggered the development and adoption of NP/NS for RD in many countries. It was coordinated by EURORDIS, in which Orphanet and Newcastle University, among others, played a key role. To date, there was a perceived absence of such momentum, and a feeling amongst the RD community that a **renewed drive around**

NP/NS was needed. It is also supposed that these "soft-law" (but nonetheless very influential) policies of the past could no longer keep pace with the needs of the actual RD community.

The Rare 2030 project was articulated in **four stages**, which together worked towards the goal of establishing a roadmap for a **new generation of RD policies.** The four stages were: 1. Establish knowledge, 2. Identify rank trends, 3. Create future scenarios, and 4. Propose policy recommendations.

For the establishing of knowledge on the policies and recommendations to address the current and future needs of the RD population, the long-established Resource on the State of the Art of RD activities in Europe (http://www.rd-action.eu/wp-content/uploads/2018/09/Final-Overview-Report-State-of-the-Art-2018-version.pdf?fbclid=IwAR3gzXxNDJHA7rqOEJapyCJrXVgNy0JG7EzXPgkhdDcxZRXXyocRc351HAg) was adapted and utilised to gather information from as many EU Member States (MS) as possible, asking for the ***status quo* on NP/NS for RD as of March 1st 2021.** It emerged that among the 24/27 countries that adopted a NP/NS for RD at some stage, many had terminated their NP/NS at the end of 2020, without a renewal. However, from the analysis performed, it appeared that there are more issues to consider than merely whether a NP/NS was adopted/was ongoing. In fact, it appeared that at present the field is lacking from a central drive from the EU to address these issues, and that the momentum generated by the Council Recommendation of 2009 has subsided.
The immediate use of the gathered data was to generate **8 Knowledge Base Summaries,** one for each of the following broad topics under the RD "heading": 1. European and national policies and strategies; 2. Data; 3. Accessibility and availability of Orphan Medicinal Products (OMPs) and medical devices; 4. Basic, clinical, translational and social research; 5. Diagnostics; 6. Integrated, person-centred social and holistic care; 7. Patient partnership; and 8. Access to healthcare.

The middle step of the Rare 2030, that followed the establishing of knowledge, was represented by the **ranking of trends** around changing values and technology, and around influences that will affect RD policies of the coming years. High patient-needs-led innovation and strong collective accountability emerged as the most inspiring and preferred directions for the future of European RD policies.

The final stage of the project consisted in the production of a **set of Recommendations.** Each chapter of recommendations addresses one of the topical areas of the project and represents the major output of Rare 2030 as a foresight study. The 8 Recommendations chapters concentrate on the following: 1. European Framework and National Plans; 2. Diagnosis; 3. Healthcare; 4. Integrated and Person-Centred Care; 5. Patient Partnership; 6. Research; 7. Data; and 8. Treatment.
The main conclusion is that the Rare 2030 Foresight study recommends a **new policy framework for RD in Europe** (Recommendation 1) that should **renew the momentum on NP/NS** for RD. This in fact constitutes the core that supports the other 7 chapters of Recommendations generated by the Rare 2030 Project.
This conclusion is of particular interest for the focus of the Strategy meeting, as it concerns long-term, integrated European NP/NS as key policy priority**.**
Since the formal wrap-up of the foresight study Rare2030, **EURORDIS has created a campaign, 'Rare 2030 Action' calling upon the EC and EU MS to introduce a**

European action plan on RD. This action plan is meant to align MS towards common measurable goals to ultimately improve survival, quality of life and social inclusion. Moreover, this effort should support the fulfilment of the United Nations' Sustainable Development Goals.

The presentation stimulated the following comments:

Highlights from the discussion
• The usefulness of having a **continuation budget for assessing the effectiveness of the NP/NS** when transitioning to a new NP/NS. • The importance of considering the **local/national specificities**: e.g., of small-population countries, or of countries that have the same linguistic background or that already constituted spontaneously collaboration on registries (northern EU countries). The local/national specificities should also be considered, knowing that there can be no perfect model for RD NP/NS that will suit for all EU countries. • The question whether a pan European structure or drive to guide all countries and boost their social responsibility is the most suitable solution, taking into account that the local circumstances largely influence the actions, or whether it could be more advisable to have a provision of resources and a common source to which turning in case of need. To this query, it has been answered that both approaches are needed: a **cross-country collaboration to promote and share good practices with an insight to the overlooked needs of some countries**, taking local necessities into account and sustaining a citizen-to citizen collaboration.

4.1.3. Development of the Dutch EJP RD National Mirror Group

*(**Sonja van Weely**, The Netherlands Organisation for Health Research and Development - ZonMw, the Netherlands)*

This contribution presented the experience of the Dutch National Mirror Group as a multistakeholder body that collaborates to the objectives of the EJP RD and represents a two-way path between the national and EJP RD needs and actions.

The Dutch experience on the establishment of a NMG allowed to illustrate an example of the core activities of a NMG, in relation also to the Terms of Reference for the setup of National Mirror Groups, that were defined in the context of the WP 2 "Integrative Research and Innovation Strategy" of the EJP RD.

It has been recalled that the **role of the NMG is to ensure national coordination of and with all RD stakeholders,** to facilitate the alignment between national and EJP RD activities, to contribute to the objectives of the EJP RD and benefit from it.

The RD **stakeholders** that should constitute a NMG are**:** an EJP RD Governing Board representative, EJP RD Policy Board representative(s), (e.g., Ministry of Health, Research or other Ministries), relevant national partners of the EJP RD, relevant national authorities (e.g., representatives of the Ministry of Health, Research, etc., that could be the same members of the above cited Policy Board), representatives of the NP/NS for RD, even in the absence of an approved NP/NS, ERN members,

research institutions involved in RD research (participating to the EJP RD or not), representatives of patient organisations, and representatives of the Orphanet local team.

To achieve its goals, the NMG has to fulfil the **tasks** of coordinating the participation of national stakeholders in the EJP RD activities, defining the national positions and priorities to be translated in the EJP RD Annual Work Plans, and also of ensuring the alignment between EJP RD and national strategies by promoting EJP RD actions and outcomes at national level.

The Netherlands has had several multidisciplinary committees since 2001, with ZonMw (the Dutch funding agency for Research) acting as secretariat, even before the onset of the EJP RD. From 2001-2013, there has been a Dutch Steering Committee on Orphan Drugs who worked on the preparation of the NP for RD (in 2012-2013) with the collaboration of many working groups. On 2015-2017 a Consultation group for the NP for RD was set up, installed by the MoH and with the collaboration also of the Dutch Patient Alliance. The consultation group gave recommendations to the MoH and other stakeholders on the steps to be pursued for policy and actions on rare diseases. A Dutch NMG (working group) was established in May 2019 as "spontaneous initiative" no longer installed by the MoH, but created under the incentive of the EJP RD. The Dutch representative of the EJP RD GB is chair of the Dutch NMG.

The **activities performed by the Dutch NMG** since 2019 encompass: regular meetings, participation to the GB of the EJP RD, discussion of the Annual Work Plan after the PB Meeting, discussion on the use cases for input of national Policy letter and for Dutch/European activities, input to the surveys on NP/NS for RD carried out in WP2 of the EJP RD, contribution to the survey from the patient alliance on the national RD strategy, RD community representation in the Health Research Infrastructure of the Netherlands.

The activities of the Dutch NMG planned for the **near future** regard the elaboration of the Communication plan for the dissemination of the EJP RD activities in the Netherlands, the development of inputs for the Strategic Research and Innovation Agenda for the European Partnership on RD, the support to the alignment of the Health Research Infrastructure with the EJP RD Virtual Platform.

4.1.4. The added value of RD Partnerships

*(**Daria Julkowska**, Institute National de la Santé et de la Recherche Medicale (INSERM), France)*

The presentation focused on the preparation of the RD European Partnership under Horizon Europe and on its overall context regarding opportunities and challenges for RD, tacking stock also of the results obtained through the Rare 2030 Foresight study.

The European Partnerships under Horizon Europe have been introduced as a different scheme, when compared to the EJP RD, and as a new generation of **objective-driven Partnerships**, supporting the agenda of the EU policy objectives.

There are 49 candidate European Partnership**s** for Horizon Europe resulting from the strategic Planning, whose priorities were discussed together with the MS. The European Partnerships are expected to leverage not only on the national potential, but also to collaborate between Partnerships**, establishing synergies**.

It has been stated that the RD Partnership is expected to have a **different funding framework** that might stimulate additional/new bridges between RD activities, leveraging the regional, national, European or international potential. This could encourage the optimisation in the use of the given budget and the balance of the planned activities. Furthermore, there will be a longer-term strategy for HE with an up to 7-year timeframe.

Moreover, it has been reported that the discussion around the RD Partnership started in 2021 and that the launch of the Partnership is expected for 2024. A co-creation and consultation process via structured workshops is planned in 2021 to **build on the lessons learned through the EJP RD, the Rare 2030 Foresight and the experience of the ERNs**.

The **objectives of the RD Partnership** that were proposed in 2019 in preparation of the Candidate Partnerships for HE have been: to contribute towards the objectives of IRDiRC**;** to further develop the ecosystem for discovery research and development of new diagnostic tools and therapies for RD; to collect and share all relevant RD data at EU and international level efficiently utilising data collected by the ERNs**,** to boost the research collaboration in the EU, the Associated countries and in Third Countries; to provide evidence for a fit-for-purpose regulatory framework**;** to reinforce the EU as an effective "hub" for RD research and innovation in the international context of RD.

Furthermore, it has been stressed that the planned broad objectives for the HE RD Partnership are complementary and **in line with the outputs of the Rare 2030** Foresight study.

Considering the current achievements in the RD field and the future opportunities, various **scenarios for the HE RD Partnership** have been presented on the topics of Research Support and collaboration (funding), Exploitation of research and health data, Participation of patients, Expansion of research capacity, Translation and EU competitiveness, Regulatory, Stable collaboration between the RD community and the regulators/policy framework**,** and of National participation. This last point reflects the most the objectives of this Strategic Meeting, as it regards the potential to **build solid bridges** between the already reached achievements and to leverage the capacities to **boost national contributions**.

The possible collaboration of **industry** has been referred as a valuable element of the future Partnership.

4.2. Open discussion (afternoon)

The discussion revolved mainly on the topic of the future RD Partnership.

Below the **highlights that emerged during the discussion**

Highlights from the discussion
• The reduction of the reimbursement rate of the RD Partnership, in comparison to the EJP RD, reinforces the importance of the activities carried out at national level, as the **synergies between the national efforts** will convey, among others, via these activities. • The alignment and complementarity of the national actions is therefore to be enhanced for their European added value.
• The **strong alliance with the patients** is a key point for robust synergies in the strategies at national/EU level.
• Under HE, national inputs from EU/structural funds can count as national inputs to the Partnership; this is advisable and could count as **synergy across EU funding programmes and policies** (which is new in respect to Horizon 2020) and might moreover be of particular interest for EU-13 Countries, who could declare actions implemented at national level as part of the Partnership.
• In the RD Partnership there is the need to revise the way national contribution and participation are considered. To start this process the **dialogue on the needs, on the one hand, and the opportunities on the other, has to be opened**. In this perspective not only being inside the Partnership is valuable, but also to participate in joint research projects or initiatives that can be supported by the Partnership. Moreover, the question has arisen on which should be the most suitable objectives of the Partnership, if the creation of an infrastructure to support the community (and the gathering of the community), or instead a new model to ensure e.g., the integration of national communities that are to date overlooked.
• A concern has raised, whether the decrease in the reimbursement rate of the RD Partnership and the concurrent **recourse to in-kind contribution** will have the effect of making countries like the EU-13 less attractive as partners in the Partnership.
• As **funding of research emerged to be a transversal issue for all countries**, it has been suggested to renew the way to consider the funding process, e.g., by developing approaches that can have a value for investors, private collaborators and industries. It has been hypothesised that this is where the **public-private partnership** could be significant, and that it could be important to reason on endpoints, impacts and on the "market-value" of what will be developed in the Partnership. The private sector could e.g., be of support in envisioning the "market-shape" of the developed outcomes. • The current difficulty of making *open science* with a market approach, or with public/private partnerships has been connected to the lack of a specific mechanism to do that. As *open science* has a cost, a **sustainability model** that allows for making the financial value of this *open science* is desirable.
• The present opportunities of the EJP RD, like the **Networking Scheme and the**

fellowships for trainings, should be exploited to the maximum to start building networks and share knowledge, in order to create a background that can be continued in the future.
• The concern on the loop between the sustainability and the **integration into the Partnerships** has been expressed, stressing that the countries that face more sustainability issues are the same countries who struggle to be included in the Partnerships, and that the sustainability only comes with the integration. • To this purpose the need to strengthen the capabilities of the countries to have economical and human resources to realise the programmes and action has been pointed out. • The constitution of **NMGs** has been brought forward as a starting point to move in the direction of the strengthening of these capabilities.

5. Annex 1 - Programme of the meeting

Meeting Agenda
Strategy Meeting 8 July 2021, online
Integrative research and innovation strategy: "Alignment of national rare diseases strategies with the European Joint Programme on Rare Diseases"

Programme
Morning session
09:30 Welcome address
Domenica Taruscio, Claudio Carta, Eva Bermejo, Manuel Posada

09:45 – 10:45 Session 1 - Setting the scene
09:45 Building the European ecosystem for rare diseases research – how EJP RD leverages the potential of every stakeholder
Daria Julkowska

10:15 Analysis of national state of play and alignment process with EJP RD
Domenica Taruscio, Eva Bermejo, Manuel Posada, Claudio Carta, Laura Lee Cellai, Marta De Santis

10:45-13:00 Session 2 - From national to European RD strategies: the experience in the following Countries
10:45 Portugal
Carla Pereira

11:05 Luxembourg
Francesca Poloni

11:20 Comfort break

11:40 Romania
Emilia Severin

12:00 Czech Republic
Milan Macek

12:20 Open Discussion
13:00 Lunch

Afternoon session
14:00– 16:45 Session 3 – Capturing the national potential - many ways forward
14:00 From national/EU to international level: IRDiRC and Clinical Research Networks
Rima Nabbout, Lucia Monaco

14:30 Recommendations from the Rare 2030 project to shape the future of National Plans and Strategies in Europe

Victoria Hedley

15:00
Development of the Dutch EJP RD National Mirror Group
Sonja van Weely

15:30 The added value of RD Partnerships
Daria Julkowska

16:00 Open Discussion

16:45 Remarks and Conclusions
Domenica Taruscio, Claudio Carta, Eva Bermejo, Manuel Posada, Daria Julkowska

17:00 End of the meeting

Speakers (alphabetic order)

Eva Bermejo, Institute of Health Carlos III, Spain
Claudio Carta, National Centre For Rare Diseases, Istituto Superiore di Sanità, Italy
Laura Lee Cellai, National Centre For Rare Diseases, Istituto Superiore di Sanità, Italy
Marta De Santis, National Centre For Rare Diseases, Istituto Superiore di Sanità, Italy
Victoria Hedley, John Walton Muscular Dystrophy Research Centre Newcastle University Translational and Clinical Research Institute International Centre for Life, UK
Daria Julkowska, Institute National de la Santé et de la Recherche Medicale, France
Milan Macek, Charles University-2nd Faculty of Medicine, Czech Republic
Lucia Monaco, Italian Telethon Foundation, Chair of the International Rare Diseases Research Consortium (IRDiRC), Italy
Rima Nabbout, Hôpital Necker Enfants malades, Université Paris Descartes, Institut Imagine, INSERM, France
Carla Pereira, Directorate-General of Health, Portugal
Francesca Poloni, Ministère de la Santé, Direction de la Santé, Service de coordination des plans nationaux, Le Gouvernement Du Grand-Duché de Luxembourg
Manuel Posada, Institute of Health Carlos III, Spain
Emilia Severin, Carol Davila University of Medicine and Pharmacy, Romania
Domenica Taruscio, National Centre For Rare Diseases, Istituto Superiore di Sanità, Italy
Sonja van Weely, The Netherlands Organisation for Health Research and Development - ZonMw, The Netherlands

6. Annex 2 -Present Institutions/Companies and Countries

Institution/Company	Country
ANR-Agence National de la Recherche	France
APHP-Assistance Publique Hôpitaux de Paris	France
Başkent University, Faculty of Medicine, Department of Public Health	Turkey
Carol Davila University of Medicine and Pharmacy – Bucharest	Romania
Charles University	Czech Republic
Cochrane	Italy
Chief Scientist Office- Ministry of Health CSO-MOH	Israel
Directorate-General of Health	Portugal
EuropaBio	Belgium
EURORDIS	France
Fonds National de la Recherche-FNR	Luxembourg
Fondazione per la Ricerca Farmacologica Gianni Benzi onlus	Italy
Foundation for Rare Diseases	France
French Foundation for Rare Diseases	France
Fundação para a Ciência e a Tecnologia, Lisbon -FCT	Portugal
Health Research Charities Ireland	Ireland
Health Service Executive	Ireland
HUS - ERN-EYE	France
Institut National de la Santé et de la Recherche Medicale-INSERM	France
Centre of Research in Myology at INSERM	France
INSERM Transfert	France
Institute of Rare Diseases Research, at Institute of Health Carlos III-ISCIII	Spain

Institute of Molecular Genetics and Genetic Engineering, University of Belgrade	Serbia
Fondazione Telethon /International Rare Diseases Research Consortium -IRDiRC	Italy
Istituto di Ricovero e Cura a Carattere Scientifico Azienda Ospedaliera- IRCCS AOSP Bologna	Italy
IRCCS Istituto delle Scienze Neurologiche di Bologna	Italy
IRCCS Istituto Giannina Gaslini	Italy
IRCCS policlinico-ospedaliero Sant'Orsola-Malpighi	Italy
Istituto Romagnolo per lo studio dei Tumori- IRST IRCCS	Iyaly
Istituto Superiore di Sanità-ISS	Italy
Istituto Nazionale Tumori Regina Elena	Italy
Leiden University Medical Centre -LUMC	The Netherlands
Maastricht University	The Netherlands
Medical University of Vienna	Austria
Medical University of Warsaw	Poland
Ministry of Education, Youth and Sports-MEYS	Czech Republic
Ministry of Health	Italy
Mater Misericordiae University Hospital, University College Dublin-MMUH, UCD	Ireland
National Center for Research nd Development/ Business & Science Poland-NCBR/BSP	Belgium
Newcastle University	UK
Oasi Research Institute - IRCCS, Troina	Italy
Orphanet Switzerland	Switzerland
Regina Elena National Cancer Institute	Italy
Regione Umbria	Italy
SAN CAMILLO IRCCS	Italy
The Children's Memorial Health Institute	Poland

The Scientific and Technological Research Council of Turkey -TUBITAK	Turkey
Università degli Studi di Modena e Reggio Emilia, Istituto delle Scienze Neurologiche di Bologna- IRCCS	Italy
University Hospital Aachen	Germany
University of Leicester	UK
University of Siena	Italy
University of Siena / Azienda Ospedaliero-Universitaria Senese	Italy
Vereniging Samenwerkende Ouder en Patiëntenorganisaties-The Netherlands (National Patient Alliance for Rare and Genetic Diseases)-VSOP	The Netherlands
Warsaw Medical University	Poland
The Netherlands Organisation for Health Research and Development – ZonMw	The Netherlands

7. Annex 3 - Itemised Report of the presentations

While a more succinct summary of the most important issues approached in the presentations and discussions has been included in the previous pages, an itemized report of the presentations is provided below in this Annex 3.

"Building the European ecosystem for rare disease research - how EJP RD leverages the potential of every stakeholder"
*(**Daria Julkowska**, Institut National de la Santé et de la Recherche Medicale, France)*

The presentation has highlighted the importance of the **alignment between the national, European and international RD activities** and has illustrated how the participation to common activities can leverage the potential of the different stakeholders involved in the EJP RD and beyond. To this purpose, the **multiple facets** that underlie the EJP RD have been presented.

More in **detail**:

- The landscape of the RD research activities in Europe, that gathers the inputs from: the healthcare area (including the ERNs); the patients' needs (mainly EURORDIS), the different funding schemes (e.g., European Research Area Net-ERA-Net); the different types of infrastructures, both RD and non-RD specific; the strategy level, comprising IRDiRC, the European Commission (EC), the MS.
- The main objective, to put all these actors together in a joint effort for the creation of a research and innovation pipeline "from bench to bedside", ensuring a rapid translation of research results into clinical applications and uptake in healthcare, for the benefits of the RD patients.
- The way to reach this wide and challenging objective by building a harmonized and centralized RD research ecosystem integrating existing infrastructures, funding programmes, trainings, tools etc., expanding the existing resources and developing new ones.
- The numbers: e.g., 101 Million € total budget of which 55 Million € from the EC contribution; a reimbursement rate of 70%; 91 beneficiaries including 35 countries (26 from EU Member states, 7 from Associated Countries, and including also Canada and UK); the beneficiaries are represented by hospitals, research institutes, research funding bodies/ministries, universities/hospital universities, EU infrastructures, charities/foundations, EURORDIS, in total gathering 85% of the European Research Community.
- The structure, namely the coordination of all the activities under one single umbrella, with transversal activities (strategy, sustainability, ethics, communication) and 4 non-transversal Pillars, covering the areas of funding (Pillar 1), acceleration of research through the access to data, tools and services and creation of a Virtual Platform (VP) (Pillar 2), capacity building and empowerment (Pillar 3), acceleration of research translation in clinical studies (Pillar 4).
- The Governance, with the General Assembly (GA), that is the ultimate decision-making body, and the GB at the strategy level (in connection with the PB and the NMGs, to ensure the alignment of the strategies); the

Coordination Office (in connection with the EC) at the coordination level; the Executive Committee (ExCom) and Operating Group (OG) at operational level (in connection with the activities of the Pillars and transversal WPs).

- The ambition to become a single-entry point with different types of solutions for all involved actors, namely researchers and clinicians, patients, policy makers and funders, international partners. For all those stakeholders EJP RD dedicates efforts for the development of specific tools.

Then, the different EJP RD Pillar-related activities have been illustrated, stressing the achievements and results.

Pillar 1: Funding

The **funding of collaborative research** that passes through different types of funding activities, with the most relevant being the launching of Joint Transnational Calls (JTCs).

- The JTC 2019 regarded "*Research Projects to accelerate diagnosis and/or explore disease progression and mechanisms of RD*". This JTC has involved 31 funders from 23 countries; 220 projects have been submitted, of these 52 were selected for full proposal phase and 22 full proposals have been funded.
- In 2020, the JTC focused on "*Pre-clinical research to develop effective therapies for RD*", and saw 173 submitted projects, of whom 30 preproposals have been selected for full proposal phase and 18 funded. In these JTCs, 14 new research partners have been included in the full proposal phase, demonstrating a successful widening process.

Highlights
The main effort of the JTCs is to create a joint programme to finance research on RD by bringing different funding bodies from different countries together, agreeing on a common programme and evaluation, and allowing the financing or co-financing of multinational research projects. This is **of particular relevance especially for the countries that are not provided with specific RD funding programmes at national level** and for the well-recognized necessity of collaboration in the RD field. With regard to the unrepresented countries, it has been emphasised that there is a possibility of joining the full proposals, allowing the research consortia to include new teams, sharing in this way expertise and knowledge.

Furthermore, it has been pointed out that the **involvement of patients in research** is fostered at all stages (from the topic definition to the evaluation) with an involvement of the Patients Organisations (PAOs) in the funded projects of the JTCs. The patient-driven orientation has characterised the EJP RD from the beginning, benefiting from the collaboration of EURORDIS and of the patient representatives. The involvement of the patients in research increased from 36% (in 2019) to 78% (in 2020).

Highlights
The EJP RD foresees also **support beyond funding**, with the aim to not only finance research, but also to promote the **networking to share knowledge** and connect

different stakeholders.

The support beyond funding includes:

- The Networking Support Scheme: that is continuously open, supports the sharing of knowledge and networking among stakeholders; 18 networking events have been selected for funding.
- The RD Research Challenges Scheme: to accelerate and provide a proof of concept for the public/private collaboration, and for which 3 of the received applications have been recommended for funding.
- The ERN Support Scheme: foreseeing workshops to enhance and empower mainly the ERNs expertise, providing fellowships to train the new generations of researchers and clinicians and allow the mobility between and inside the ERNs; it also provides funding for PAOs to participate in research projects and create a dedicated guide on patients partnerships in research projects; in the ERN Support Scheme, 15 workshops have been recommended for funding and 33 fellowships have been attributed.

Pillar 2-Virtual Platform (VP) of data, tools and resources

Highlights

The **creation of the VP of data, tools and resources** is a further activity to leverage the potential of the different stakeholders, that aims not only at creating new tools but also at enhancing and exploiting the existing resources.

The **VP intends to connect all resources together** (RD and non-RD specific, e.g., samples, biobanks, registries, infrastructures and tools catalogues, platforms for the analysis for omics-data, curated RD-centred information and data), in a federated model, that is also standardised, GDPR-compliant, sustainable, quality assessed and FAIR* based (*Findable, Accessible, Interoperable, Reusable). The ERNs and the research and clinical community on one side, and the computational research data scientists on the other, figure among the most important stakeholders of the VP, with a process that implies the mutual influence between ERNs/RD researchers and the VP developers.

The issues to be tackled through the creation of the VP regard:

- Counting patients with specific conditions
- Exploring and using RD catalogues to answer questions
- Make consent machine readable for automatic access
- Use of multi-omics data for diagnosis and identification of drug targets.

These issues require for their solutions the following elements:

- The enhancement of existing resources, making resources more RD friendly and proving inter-connectivity
- The need for (meta) data models to link and exchange data across multiple Information Technology (IT) systems
- The development of tools for the discovery of existing resources and available data

- The development of tools and the application of standards to allow access for data reuse
- The creation of an RD portal for exploitable pathways, enabling multi-omics analysis.

Highlights
In this context, it has been furthermore stressed out that through the results on this area, references to standards of EJP RD are appearing in the RD calls of the EC or IMI (Innovative Medicines Initiative). Moreover, this is **triggering international collaborations** e.g., with the Critical Path Institute (C-PATH), that in the United States is working on a similar model for the benefit of the RD community. In addition, the work on the VP of the EJP RD is promoting national alignments, e.g., in France, where this work is connected with the 3rd NP for RD.

Pillar 3: Training and education

Highlights
The training and education activities of the EJP RD leverage the national capacities through their **diversity and transversality**, the large target span that is addressed and the regular revision of the proposed trainings.

The training courses promoted by the EJP RD are:

- An online MOOC (Massive Open Online Course) academic course titled "*Diagnosing RD: from the clinic to research and back*", foreseeing 5 weeks/3 weekly hours programme
- Several residential courses organised in 7 different countries. The residential courses saw the attendance, to date, of 220 participants and the assignment of 18 fellowships. The proposed trainings have been: "*Quality assurance on variant interpretation in Next Generation Sequencing (NGS) diagnostics era*", "*Training on strategies to foster solutions of undiagnosed RD cases*", "*Organising and maximising biological samples data in biobanks*", "*International Summer School on RD registries and FAIRification of data*", "*Orphanet Ontology training*", "*EURORDIS Express Expert Patients and Researchers Summer School*", "*EURORDIS Winter School*", "*EURORDIS Leadership School*"

550 trainees have been trained so far, increasing in this way the knowledge of the multistakeholder RD research community. A special mention has been made for the 7 ERN workshops that have been financed and for the 33 fellowships assigned to the ERNs.

Highlights
The courses are provided and enhanced on a yearly basis and **bring together**

different types of expertise from different stakeholders, integrating already existing courses into the EJP RD and developing new trainings for new identified RD needs. An attention in the training efforts is **dedicated specifically to EU-13 Countries,** ensuring not only the location of the courses in those countries to facilitate a greater accessibility for the local community but also the adaptation of the courses to their specific needs.

Pillar 4: Accelerated translation of research results and clinical trials

Highlights
The EJP RD is also **moving forward to removing barriers** to the improvement of outcomes in translational and clinical research and is promoting innovative methodologies for RD clinical studies. In these areas EJP RD is indeed providing support, mentoring and expertise through specific actions.

The actions launched by the Pillar 4 activities encompass:

- The acceleration of translation of research results, through which the accompaniment in research projects is enacted by expert mentoring from the conception of the projects and throughout their lifespan, facilitating the process of advancement and providing free tools and follow-up
- The clinical studies support office, implemented through specialised infrastructures e.g., ECRIN-European Clinical Research Infrastructure Network, clinical trials execution planning, or facilitating the access to national support and to additional expertise.

The acceleration of translation of results and clinical trials includes also **regulatory issues**, that are faced via:

- The direct collaboration with regulators such as the European Medicines Agency (EMA) and the EU Innovation Network
- The launch of demonstration projects validating novel methodologies in small populations clinical trials
- The international innovation and collaboration with C-PATH to support regulatory research for RD patients.

Highlights
Overall, from the presented overview, it can be affirmed that EJP RD is a network accelerating connection with experts inside and beyond the project, for the benefits of the RD community. In fact, the EJP RD aspires to **taking full advantage of the capacities of all involved stakeholders,** creating a virtuous circle for research on RD.

"Analysis of national state of play and alignment process with EJP RD"
*(**Claudio Carta**, Domenica Taruscio, Eva Bermejo, Manuel Posada, Laura Lee Cellai, Marta De Santis)*

The second presentation of the morning session, aiming at setting the scene for the **comprehension of the alignment status of the national RD strategies with the EJP RD,** focused on the results obtained through a **survey** targeting key persons/officers involved in the implementation/development of NP/NS for RD (or in other relevant RD initiatives) in the EJP RD participating countries.

The survey represented one of the major activities carried out by Task 2.5 "Translation/impact of prioritization on national and EU strategies" of WP2 "Integrative Research and Innovation Strategy", of the EJP RD and intended to analyse the presence of relevant/complementary RD-related actions performed at national level, with **a specific focus on EU-13 Countries** with respect to their specific needs, obstacles and advancements.

The results presented in the meeting gave a **general overview of the state of the art** in the countries that participated to the survey. The presentation stressed moreover the **main challenging areas** that emerged through the survey, suggesting these as areas that require for **targeted interventions through national and European/transnational strategies** to promote the desirable alignment with the EJP RD objectives.

The online survey collected information in Autumn 2020 and in Spring 2021 on the existence of NP/NS for RD and/or of other relevant RD initiatives in the EJP RD countries, as well as information on the alignment status of these RD undertakings with the activities promoted by the 4 non transversal EJP RD Pillars. The EU-13 Countries were asked, in addition, to provide information on their main perceived obstacles and barriers for the development, improvement and translation of RD research results, as well as on the main barriers perceived for the participation in EU/international projects in the RD field.

Presented summary of results:

<u>General information</u>

- By June 2021, 26 countries participated to the survey. 19 of these were EU countries: Belgium, Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Portugal, Romania, Slovakia, Spain, Sweden, The Netherlands; 7 were Other/Associated countries: Armenia, Canada, Georgia, Israel, Serbia, Turkey, UK
- 20 of the 26 countries declared to have adopted a NP/NS for RD at some stage, that at the date of the data collection was either active or expired (Belgium, Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Portugal, Romania, Serbia, Spain, Slovakia, The Netherlands, UK). In 5 countries the NP/NS for RD was under development (Armenia, Canada, Georgia, Israel, Turkey) and in 1 country there was no NP/NS for RD, active, expired or under development (Sweden).

National alignment status with the activities of the 4 non transversal Pillars

According to the main challenges faced by the countries in respect to the national alignment with the EJP RD activities, **broad suggestions for Pillar specific interventions** were prompted during the discussion and have been listed here:

Highlights
Pillar 1 • National and international calls for research projects should be promoted • More investments to share knowledge on RD are needed.
Pillar 2 • The adoption of FAIR data should be encouraged • Multidisciplinary holistic approaches for RD should receive more support.
Pillar 3 • Training activities on specific topics (e.g., FAIR data, data quality trainings) should be increased.
Pillar 4 • The rapid translation of research results in clinical studies and healthcare has to be fostered • More innovative methodologies tailored for clinical trials should be promoted.

Regarding the **focus on EU-13 Countries**, the following critical aspects for the development, improvement and translation of RD research results, as well as for the participation in EU/international projects in the RD field have been illustrated. These figure as areas that claim for specific strategic interventions to overcome gaps and obstacles.

Highlights
Critical points that need to be addressed in EU-13 Countries • Funding • Difficult linking to potential partners • Access to national resources for funding of research and development of RD projects • Bureaucratic application on reporting procedures • Lack of information on funding opportunities.

The EU-13 Countries on which this analysis is based on are: Bulgaria, Croatia, Czech Republic, Estonia, Latvia, Lithuania, Romania, Slovakia.

For the extensive analysis and discussion of the survey results, reference was made to the public deliverable 2.23 "Third Analysis of national state of play and alignment process with EJP RD".

Integrated Strategy for Rare Diseases 2015-2020 – Portugal
*(**Carla Pereira**, Directorate-General of Health, Portugal)*

The presentation illustrated the Integrated Strategy for Rare Diseases 2015-2020 and the achieved results reached through the implementation of the Strategy, as well as the future actions that will be addressed by the forthcoming NS for RD in Portugal.

The **main objectives** of the Strategy 2015-2020 were:

- To make sure that all those with RD have better access to quality of health and social care and treatment, based on the scientific evidence and the availability of faster and diverse social responses adopted to each case
- To ensure an inter-ministerial, intersectoral, inter-institutional and integrated revision of the priorities set for the global approach to the RD, thus gathering all the contributions from the different expertise and the resources from all the relevant sectors, to progressively cause a real change in the complex conditions affecting those with RD.

The **identified challenges** to be tackled by the Strategy 2015-2020 encompassed:

- The unknown real number of RD in Portugal
- The rarity of some diseases
- The inadequate classification of the RD
- The reduced number of clinical and epidemiological studies
- The time required to obtain a correct diagnosis
- The insufficient number of dedicated and specialised centres.

The Integrated Strategy for RD 2015-2020 aimed to address and face the **issues of research, training, and knowledge sharing**, and dedicated an attention to the drawing of specific strategies to also face the **needs of diagnosis, drug therapies, rehabilitation, social inclusion and special education**.

An **inter-ministerial Commission** chaired by the Directorate-General for Health accompanied the 2015-2020 strategy; the Commission was composed by:

- The Directorate-General of Health (DGS)
- The National Institute of Health Doctor Ricardo Jorge (INSA)
- The Central Administration of the Health Systems (ACSS)
- The National Authority of Medicines and Health Products (INFRAMED)
- The Institute for Social Security
- The National Institute for Rehabilitation
- The Agency of Science, Research and Technology
- The Directorate-General for Education (The Specials Needs Education Area).

For the next Strategy, it is foreseen to further include the Ministry of Labour in the Commission.

The **Partners** involved in the definition of the annual Action Plans of the 2015-2020 Strategy have been:

- Professional Associations
- RD Patients' Associations
- The national Association of the Portuguese Municipalities

- The National Association of Local Councils
- The Partners from the Social Sector.

6 priorities were set for the 2015-2020 Strategy:

- Coordination of care
- Access to early diagnosis
- Access to treatment
- Clinical and epidemiological information
- Research
- Social inclusion and citizenship.

For all these priorities, there have been several **implemented actions**, listed below:

1. Coordination of care
    - Establishment of a Coordination Committee for RD Treatment (for Lysosomal Overload and Cystic Fibrosis and- Haemophilia)
    - Elaboration of clinical standards on the diagnostic approach and criteria for the referral of people with RD to the appropriate Reference Centres, along also with the creation of guidelines
    - Creation of virtual guiding books for people living with RD
    - Dissemination of a survey on social responses in order to integrate and support people with RD.
2. Access to diagnosis
    - Application of NGS using gene panels for molecular diagnosis of inherited metabolic disorders
    - Setting of standards regarding the diagnosis and follow-up of the person with Tuberous Sclerosis both in paediatric and adult ages
    - Inclusion of cystic fibrosis into the National Early Diagnosis Programme
    - Performing of the Neonatal Screening which allowed to screen and treat more than 2200 sick children in specialised treatment centres within the first few weeks of life.
3. Access to treatment
    - Implementation of outpatient treatment programmes for people living with Pulmonary Arterial Hypertension, Lysosomal overload diseases and, Paramyloidosis
    - Establishment of 29 RD specific Centres of Expertise
    - Dissemination of the European Treatment Centres in the Orphanet Portal
    - Approval of more than 20 new orphan drugs
    - Support to the integration of Reference Centres for RD in the ERNs.

4. Clinical and epidemiological information
    - Evaluation of the variables to consider in a national RD registry, with reference to a common dataset for the European Rare Disease Registry
    - Creation of a RD Card, registered in 14 Health Unities
    - Presence of a national Orphanet team in the Directorate-General of Health to collaborate with the national Orphanet website team, mainly to translating more than 2000 RD diagnoses with the support of the Orpha terminology

- Spreading of the information on the more than 200 genetic available tests in Portugal.

5. Research
   - Work of the FTCFundacao para a Ciencia e à Tecnologia
   - "RD Symposium 2017. From research, a world of possibilities"
   - Variable number of funded projects, from a minimum of 2 funded projects in 2016 to a maximum of 27 in 2017.

Highlights
The **research area** has been cited as one of the most critical areas of the RD Strategy of Portugal.

6. Social inclusion and citizenship
   - Implementation of the project "*Incluir*" (Inclusion)
   - Organisation of numerous *training the trainers' sessions* to capacitate the professionals, starting with the education and social sectors in identifying, treating and rehabilitating people with RD, thus allowing an inclusive school
   - Organisation of training sessions for the patients' organisations by the INFARMED and the National School of Public Health at Nova University in Lisbon
   - Improvement of the information on new available therapies
   - Support Model for Independent Living (MAVI in Portugal), that provides personal assistance for people with disabilities and pilot projects for the 2017-2020 period (with the Portugal 2020 co-financing) in the Area of Social Inclusion and Employment.

Highlights
The **general achievements and results** obtained through the implementation of the 2015-2020 Strategy, include • More patients with RD identified in the National Health Service • Increased number of available genetic tests • Increased available information for the citizens • Increased access to new and expensive treatments • Increased number of Centres of Excellence for RD.

Throughout the presentation, the importance of the **collaboration with the patients' associations** for the assessment of the patients' needs has been pointed out.

Overall, the **continuity of the National Strategy for RD is a goal** that aims at achieving the adequacy of taking in charge of people with RD, encompassing the areas of education, employment and social needs, too. The following **areas** have been highlighted as key elements to achieve this broader goal:

- personalized treatment
- teamwork
- innovation

- security
- quality
- humanization
- capacitation through literacy
- scientific evidence
- clinical pathway
- individual treatment plan.

An analysis dated from December 2020 detected some of the **challenges that still have to be faced by the next NS for RD**. Among these, the following emerged as the most relevant:

- Reduced average life expectancy of persons with RD
- Associated comorbidities
- Under-investment in research
- Limitations in access to health services
- Increased investments in infectious disease research at the cost of investment in the RD area
- The general fear to access the health services during the COVID-19 pandemic
- Difficulty for patients to circulate and access the needed care at national and international level.

Highlights
The lessons learned in the 5 years of the Strategy allowed to determine the **priority actions** for the **upcoming Portuguese Strategy** to tackle the identified challenges: • Enhance the Interministerial Cooperation • Set up of a National registry for RD • Adopt timely new diagnostic and forms of treatment • Promote national research • Integrate the health care and social responses.

The National Rare Disease Plan in Luxembourg
*(**Francesca Poloni**, Direction de la Santé, Service de Coordination des plans nationaux, Gouvernement Du Grand-Duché, Luxembourg)*

The presentation focused on the running NP for RD and stressed out the ongoing projects, the main achievements and the near future plans of the NP of the country.

First, some contextual aspects of the country have been illustrated: the borders with Belgium, Germany and France, the presence of three official languages (French, German and Luxembourgish), the fact of being one of the smallest sovereign states of Europe as well as one of the least-populous European countries, showing nevertheless one of the highest population growth rates.

Then, the **NP for RD** has been presented. The NP, approved by the Government Council on 2 March 2018, has a **pluriannual budget** (2018-2022), follows the EU Council recommendations of 2009, and is provided by a **National Steering Committee** approved and mandated by the Government; the NP for RD foresees **5 strategic areas**, with **26 goals** composed of **specific measures and actions**.

The **5 strategic areas** cover:

1. Governance
2. Healthcare
3. Information
4. RD Registry and Research
5. Psychosocial aspects.

At **Governance level,** it has been stressed out that the NP for RD has a **Steering Committee**, in charge of the **coordination activity,** and is composed by:

- the Ministry/Directorate of Health (that has the leadership on the NP)
- the Ministry of Social Security
- the Ministry of Family
- the National Laboratory of Health (LNS)
- the Luxembourg Institute of Health (LIH)
- the National Alliance (ALAN)
- Patients associations
- Medical doctors (hospitals)
- Psychosocial representatives.

The activities of all these actors involved in the NP for RD are organised in different **Working Groups with different tasks:**

- Care and treatment
- Coding, registries and RD research
- Social and psychological services
- Creation of a RD information platform.

To implement the NP for RD, the Working Groups produce **projects/position papers** that are presented for approval, first to the Steering Committee, then to the Directorate/ Ministry of Health, and for negotiation with other Ministries, if applicable.

Highlights
Once again, **research on RD** has been pointed out as a main critical point; the difficulty in **collaborating in international partnerships** has been stressed, too.

The **strategy** of the NP for RD has been illustrated through a model called "**RD house**" ("**Maison Maladies Rares**") with several rooms inside and on top the Governance. Each room addresses a different topic/objective of the NP.

The **ongoing projects** implemented in the framework of this "RD house" include:

- The screening of some diseases (e.g., Severe Child Hearth Disease SCHD)
- The reimbursement of healthcare services
- The genetic counselling
- The mapping of resources
- The RD codification.

Among the **involved actors,** there are:

- the Centre Hospitalier Luxembourg (CHL), that since 2020 has a state-hospital agreement with 23 ERNs of Luxembourg, in close collaboration with ALAN
- the LNS
- the MoH.

It has been reported that, **in the three years of implementation of the NP for RD, 54% of the goals were achieved or ongoing**. Furthermore, the collaboration with cross-border countries, the proximity between the Government and the Institutions to face the RD challenges and the **strong commitment of the key institutions** involved in the NP for RD have been pointed out as key to a successful implementation of the NP.

Highlights
The **main achievements** of the NP for RD have been: • the establishment of a RD Infoline (operating via telephone or email) • the production of National Guidelines for Orientation in the RD field • the set-up of a National Hub for the access to the ERN • the inventory of RDs in Luxembourg • the delivery of Orphacode Trainings via the collaboration with Orphanet • the creation of a RD Registry Strategy.

For the **RD patients' care, with or without a diagnosis,** there is currently some ongoing work to develop **2 integrated health pathways, a psycho-social and a medical pathway**, mutually communicating. ALAN and the CHL provide, respectively, the integrated RD psycho-social Consultation and the RD medical Coordination Hub Services, and work both within an RD orientation and coordination cell in the virtual RD House. The psycho-social aspects take care of span from social inclusion to

mental health, family life, patient associations, school, work and social rights. The RD medical Coordination Hub, on the other side of the integrated pathway, collects the contribution from the National Centre of Genetics, from different Hospital Centres of Luxembourg and from other healthcare facilities, in close collaboration with the ERNs.

Highlights
The **absence of a critical mass of patients** does not allow to develop national clinical trials and knowledge, and there is also a **lack of a legal basis for a national RD registry**. In addition, the outbreak of the COVID-19 pandemic entailed a limited availability of resources since March 2020. The **near future plans for the NP for RD** envisage: • the request to extend the NP for a further year (as the outbreak of COVID-19 entailed a slow-down of the RD activities) to allow a needs-assessment for the second NP • the work on the legal basis of the national RD Registry • the development of other "rooms" of the "RD house" • the promotion of RD research by collaborating in international partnerships • the development and expansion of the screening programme (that by the end of 2021 will include 7 diseases) • the definition of a clinical path for RD from diagnosis to treatment to follow-up.

From national to European RD strategies: the experience in Romania
*(**Emilia Severin**, Carol Davila University of Medicine and Pharmacy, Romania*

The focus of the talk has been set on the development of the NP for RD, on its achievements, and the contribution of the Romanian National Alliance for RD (RONARD) has been stressed. Moreover, attention has been given to the impact of the COVID-19 pandemic on triggering the recourse to innovative measure to face some needs.

Romania has been presented as a country in which 54.6% is constituted by urban and 45.4% by rural population. In 2007, it joined the European Union and is one of the EU-13 Countries. The country harmonised its legislation with the EU requirements and undertook new strategic directions for the health system reform, including rare diseases. The EU policy in the RD field impacted significantly on the Romanian health care policy landscape. In fact, the Romanian health RD care policy acted in response to the presence of strong patients' groups, represented by the **Romanian National Alliance for RD (RONARD, founded in 2007)**, to the increased public awareness on RD (thanks to the Rare Disease Day and to information campaigns), and to relevant EU texts and documents (European Commission's Communication on Rare Diseases, 11 November 2008, and the EU Council Recommendation on an action in the field of rare diseases, June 2009).

In 2008 the first partnership between the Romanian Ministry of Health and RONARD took place, followed by a first NP for RD (2010-2014) that, however, had no administrative and financial support (only some RD received such support). In 2013 a second partnership between the Romanian MoH and RONARD was stipulated and. in the same year, a **National Advisory Council for RD** was established by the Romanian MoH (including also the Ministry of Family, Labour and Social aspects), having an advisory role but with no legal personality. The second NP for RD (2014-2020) has been included in the National Public Health Strategy and, in 2016, an official political decision of the Romanian MoH supported the designation of Centres of Expertise (CoE) on RD (using the EUCERD Recommendations on Quality Criteria for CoE adapted to the national situation), and the application for the ERNs membership of the country.

In the planning process of the NP for RD the contribution of the EUROPLAN (European Project for Rare Diseases National Plans Development) has been cited. The priorities that were identified in this **planning process** encompass, among others:

- the needs assessment
- the active participation of the stakeholders
- the adoption of measures to improve access to information on RD
- the awareness-raising of the community and policy decisions makers on RD
- the adoption of innovative treatments
- the development of legal and institutional frameworks
- the timely diagnosis, the improvement of the quality of life
- the empowerment of the patients' organisations
- the development of human resources
- financial support for the development of national research programs on RDs.

Going to the RD country profile as of 2021, the following overview has been given: an estimated RD population of 1,000,000 persons, the presence of 27 CoE and membership in 10 ERNs, the existence of national programs for RD (a dietary treatment of the MoH and a curative treatment of the National Health Insurance), and the contribution of the RONARD (with 48 associations).

Highlights
With regard to the **achievements of the NP for RD,** various results have been underlined: • The attainment of a legal framework • The presence of Centres of Expertise • The presence and collaboration of ERNs • The adoption of case management • The strengthening of genetic testing (National genetic Network and Genetic Centres) • Training and education of medical doctors, parents, personal assistants of persons with RD • Creation of an Information Centre for RD as part of the NoRo Centre Service • Raising awareness campaigns for promoting understanding and action among the general population; realisation of a medical school for journalists for more informed professionals in this area • The approval of more than 60 Orphan Medical Products.

A virtuous example at national level has been brought through the **NoRo experience**. NoRo is a pilot project opened in Zalau in 2011 that provides health, social inclusion, community services an exchange of best practices and is currently managed by the Romanian Prader Willi Association (RPWA). It is a day care centre that can host 35 children and offers an interdisciplinary team, the production of an individual plan for rehabilitation, a patient electronic registry, the orientation to other services and the collaboration with families and schools for the continuity of care. It operates in coordination with the Department of Social Services and the Local County Council. NoRo has been recognized as an **innovative care pathway that brings together national resource centres for RD in partnership with public bodies**. It is provided with a NoRo Helpline (www.edubolirare.ro) as well as a NoRo Radio that helps disseminating information on RD and promotes social integration of persons with RD.

Another example is the **INNOVCare Project**, with the Partnership of the MoH and both RONARD and the Romanian Prader Willi Association, that promotes an innovative patient-centred approach for social care provision to complex conditions. The project already provided training of 1875 community nurses, for their better involvement in the case management of patients with RD. The training aims at developing a collaborative process of assessment, planning, facilitation, care coordination, evaluation and advocacy to meet the individual and family needs. It also aims at reducing the healthcare costs and the length of stay of inpatients. It is expected that the MoH will strengthen the training program and will help and support the development of a Community Nurse Network.

Furthermore, the **impact of the COVID-19 pandemic** has been brought to attention also for the Romanian RD community. The global pandemic has negatively affected person living with RD and their quality of life causing disruption in all aspects of daily life. To that purpose RONARD organised virtual meetings addressed to persons with RD, their families and for involved professionals. Always in the framework of the measures adopted to face the impact of the pandemic on the RD community, the participation to the series of webinars organised by the National Centre for Rare Diseases of the Istituto Superiore di Sanità, Rome, Italy, has been reported. The webinars allowed to focalise on RD specific tasks in the context of the pandemic and to exchange information, communication and interaction.

Highlights
Through the experience gained during the pandemic, both patients and Centres of Expertise draw attention to the need for updating and completing the legal framework in the health, social and education fields. In fact, **the healthcare authorities had to face regulation issues for the implementation of telemedicine, that has been included in the law regulating medical care in Romania**. The implementation of telemedicine solutions has been supported also by RONARD, that proposed the use of **telemedicine as an objective to be included in the next NP for RD**.
The issues that still represent **challenges to be tackled by the next NP for RD** have been summarised as: • The absence of a National Registry for Rare Diseases • The absence of a National Coordination Hub • The absence of a National RD Network • The absence of an adequate budget for the complex needs of patients and for the drug reimbursement • The **absence of research projects due to lack of budget.**

Finally, it has been reported that a new NP for RD for the period of 2021-2027 is in the process of approval.

From national to European RD strategies: the experience in the Czech Republic
*(**Milan Macek,** Charles University 2nd Faculty of Medicine, Czech Republic)*

The activities of the **National Coordination Centre (NCC)** and its involvement in the NP for RD, as well as in RD research have been illustrated, pointing out the main achievements and critical aspects at national level.

The presentation started with the introduction to NCC for RD of Prague, that is a delegated authority from the MoH and is the sponsor of the 10 years NS for RD. The MoH works together with other resources and Ministries, such as the Ministry of Youth, Sport and Education, that is involved in the EJP RD. Right away, it has been pointed out that despite having this official function, the NCC receives **little funding from the Government**, and that a significant amount of work is carried out on self-helping basis.

Country profile and RD policy framework: Czech Republic counts 10 million inhabitants and is bordered by Germany, Austria, Slovakia and Poland. The economic situation is greatly improved since 2004, when the country entered the EU.

Regarding the public health policies, the **public health insurance is mandatory and RD care is covered, including the Orphan Medical Products**.

The main impetus to adopt a RD Strategy came from the EU Council Recommendation in the field of RD of 2009, as a result of which a NS for the period 2010-2020 was adopted by the country. Within the Strategy, there have been 3 National action plans with a duration of 3 years, the last of which has expired at the end of 2020. The 3rd Czech National Action Plan covered the 6 major topics of the EU Council Recommendation, and both Orphanet and EJP RD were embedded in this Action Plan (https://www.vzacna-onemocneni.cz/vzacna-onemocneni/politika-cr-a-vzacna-onemocneni/narodni-akcni-plan-pro-vzacna-onemocneni.html). The 4th National Action Plan will consist in a Government Resolution, which entails a legal binding.

Highlights
Besides this legal framework of the NP for RD, **still great difficulties are linked to its financial support.**

The presentation focused then mainly on the country **achievements in the RD field and on the strengths/critical issues of the RD research area at national level**.

The main cited **achievements** have been:

- The joining to Orphanet (2016) and translation of the RD code in Czech
- The collaboration with the National Institute for Health Informatics and Statistics, that is part of the RD code project as well; the Institute hosted several workshops and engaged in the work of the translation of the entire Orpha-nomenclature in Czech (which is a legal prerequisite for the adoption of the Orpha Coding by the healthcare system)
- The participation in 18 international projects, mainly linked with the work of the ERNs. The ERNs collaborated for the implementation of an undiagnosed RD programme in Czech Republic on Human Phenotype Ontology (HPO) and exome sequencing

- A wide collaboration with the National Alliance, that is very active in the media for raising awareness and leading large campaigns. The National Alliance is part of the European Patient Advocay Groups (ePAGs) and member of EURORDIS
- The inkind contribution services offered by the major polling companies
- The creation in 2017 of a help-email in paediatric and adult domain, led by The National Alliance and with the commitment of NCC; one of the provided services is the support to the differential diagnosis, connecting medical doctors with ERNs
- The introduction of the term RD in the healthcare legislature terms of care, thanks to the National Alliance, with the result that the 6 health insurance companies that administer the public health recognize since 2017also RD
- The running of a dedicated website by the National Alliance on patient real life stories as powerful tool for raising awareness.

Highlights
In terms of **gaps**, also for Czech Republic **funding** turned out to be a major criticality as **there is not an effective RD dedicated budget line in the country.**

The presentation focused moreover on the main **mechanisms of funding** of the country, and **3 major agencies** have been reported:

- The Healthcare Agency, that is under the MoH
- The Technological Agency is involved in public/private Partnerships
- The Grant Agency.

With regard to the Healthcare Agency, it has been pointed out, as critical point, that the applications have to comply into specific panels e.g., cardiac or endocrine diseases; the result is the presence of **scattered projects on RD and the lack of dedicated RD efforts**. This scattering happens despite the fact that the NS for RD stipulates that this specific agency should have a dedicated budget for RD.

The Technological Agency is **involved in public/private Partnerships**, that successfully started with NCC the National Genome Project, the first Population Genomics project, trying to map the local genome on a representative cohort of random individuals. The relevance of this work relies greatly on the fact that in international databases central European populations are grossly underrepresented, and there is the need to filter the common variants in order to "decrease the noise" in genome testing.

Thirdly, the Grant Agency, that is the National Science Foundation, dedicating **great amount of funding to preclinical research.**

A successful area, financed by the public health insurance, is the new-born screening, that screens for 18 diseases, and looks forward to including further diseases (although the impact of COVID-19 slowed down this intention).

The major financial support has been received between 2017-19, in the context of a grant project with the University of Bergen, by means of which the professionalisation of the National Alliance and of the NCC has been improved.

A project on **Roma-gypsies and their specific RD issues** (Roma population is 3-4% of Czech population) has been presented as a **possible near-future project**.

Highlights
In general, a high quality of healthcare has been stressed out for the country thanks to the **high involvement of the ERNs**, with a special mention to paediatric care as hallmark. Aside these achievements, **the research area represents still a challenge.**

Czech Republic participated in 2019 in 6 EJP RD projects, but in 2020 the Ministry of Education, Youth and Sports withdraw from participating to the EJP RD for the **redirection of funding to research towards COVID-19**, and in 2021 there have been no Czech applications, despite the ERNs potentiality in Czech Republic to participate in EJP RD calls.

Finally, it has been reported that for 2022 it is foreseen that the country will collaborate in most EURORDIS initiatives.

From national/EU to international level: IRDiRC & Clinical Research Networks
*(**Lucia Monaco**, Italian Telethon Foundation, Chair of the International Rare Disease Research Consortium, Italy*

***Rima Nabbout**, Hôpital Necker Enfants Malades, Université Paris Descartes, Institute Imagine, INSERM, France)*

The presentation focused on an overview on **IRDiRC, the International Rare Disease Research Consortium,** and on its multifaceted activities**.**

IRDiRC is constituted by international co-operation initiatives to **stimulate, better coordinate and maximise the outputs of RD dedicated research efforts around the world**. IRDiRC was launched in 2011 and includes a wide range of actors, such as 33 research funders, 13 companies, 16 patient advocate groups and 3 scientific committees (for diagnosis, therapies and an interdisciplinary committee). With its activities, IRDiRC allows to pool a wide set of complementary competencies, global expertise and collective intelligence**,** and is widely recognised as a driver of international initiatives. It counts 62 Member organisations from 22 countries and aims at widening its presence to further regions.

Highlights
The IRDiRC **vision** is to **"enable all people living with a RD to receive an accurate diagnosis, care and available therapy within one year of coming to medical attention"**. Its **3 goals, to be reached by 2027,** are: • All patients coming to medical attention with a suspected RD will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosed individuals will enter a globally coordinated diagnostic and research pipeline • One thousand new therapies for RD will be approved, the majority of which will focus on diseases without approved options; this aspiration is an extension of the initial goal of 200 new approved therapies, that was achieved in advance • Methodologies will be developed to assess impact of diagnosis and therapies on RD patients.

At **Governance level**, IRDiRC foresees the collaboration of the Constituent and Scientific Committees (that work under a Consortium Assembly and an Operating Committee) to identify the gaps that need to be addressed and prioritised by the Consortium Assembly, tackling the three IRDiRC goals. The specific identified topics are placed in an annual roadmap and addressed via dedicated Task Forces/Working Groups. A Scientific Secretariat oversees the managing of the activities and is **integrated in the EJP RD Coordination Office**. The **nomination of calls** for Task Forces/Working Groups and Scientific Committees is open to the whole research community and is published regularly on the IRDiRC website (www.irdirc.org).

For the composition of the **Task Forces/Working Groups** the criteria of geographical balance and composite expertise are taken into account.

Up to now, several Task Forces have produced **tools for the Community** e.g., on data sharing and management, addressing the topics of patient data standardisation and sharing, patient privacy regarding genomic/clinical data or patient consent clauses and management.

Highlights

Regarding the topic of **research and innovation,** several tools and publications have been set up, such as the Orphan drug development guidebook, and critical issues have been addressed like diagnosing the undiagnosed, drug repurposing for RD, small population clinical trials, implementation of patient-centred outcome measures.

The **achievements** reached to date by current and new IRDiRC Task Forces/Working Groups (named in quotation marks below and briefly described) cover **3 main relevant areas:**

- Research and development for RD: "Pluto Project" on disregarded diseases that do not have dedicated studies and treatments due to the very rarity of the conditions; "New Technologies" for new diagnostic tools, to complement the existing diagnostic tools; "Chrysalis Project" facilitating the translation of basic research into concrete outputs by making RD research more attractive to industry
- Innovation and clinical research: "Clinical Research Networks (CRN) for RD", leveraging the existing clinical ecosystem and widening the view beyond the borders of Europe; "Shared Molecular Etiologies" increasing patient access to clinical trials; "Sustainable Economic Models & Drug Repurposing Guidebook", for drug repurposing
- Access and impact: "Indigenous Population", to go beyond the barriers of diagnosis; "RD Treatment Access", to pass the berries of therapies; "Methodologies for impact assessment", to assess the impact of diagnosis and therapies on people's lives.

The presentation went on with the illustration of the work of the **Task Force on "Clinical Research Networks (CRN) for RD"**. The work focuses on the analysis of what is existing in national/transnational Clinical Research Networks to better understand their needs and obstacles for the achievement of relevant RD collaboration and dissemination goals. The aim is the **development of recommendations on guiding principles for an international framework** in respect to best practices, interoperability, tools and common goals.

The contents of this part of the presentation will be the objective of a forthcoming publication and will be therefore not further described in this report.

Recommendations from the Rare 2030 project to shape the future of National Plans and Strategies in Europe

*(**Victoria Hedley**, Newcastle Centre for Rare Disease Research and John Walton Muscular Dystrophy Research Centre Newcastle University Translational and Clinical Research Institute International Centre for Life, UK)*

The information on the *status quo* on NP/NS for RD gathered in 2020/2021 in the framework of the Rare 2030 Foresight project and the Recommendations obtained through the work of the project have been the main focus of the presentation. In particular, the presentation focused on the key Recommendation chapter from Rare 2030 concerning "long-term, integrated European NP/NS for RD" (Recommendation 1), by illustrating how the *status quo* supports the need for specific European and national actions in this space as a critical step towards a preferred future society embracing high patient-needs-led innovation, on the one hand, and equitable social justice for people with RD, on the other.

Rare 2030 Foresight, which officially concluded earlier in year 2021, was a **broad and ambitious project**, coordinated by EURORDIS in which Orphanet, and Newcastle University played a key role, among others. The project was very much **i**n line with previous initiatives, such as the EUCERD Joint Action and RD ACTION, and ensured the involvement of the ERNs (with MetabERN and ERN BOND as direct partners and all ERNs acting as a key part of a multistakeholder panel of 200+ experts (https://www.rare2030.eu/panel-of-experts/). As background, the call for action of the EU (launched in 2009 via the Council Recommendation on an action in the field of rare diseases) chick-started many subsequent actions regarding national policies for RD: at the time of the Council Recommendation was launched, only 5 EU MS had adopted a NP/NS (France, Bulgaria, Spain, Greece and Portugal). However, there is a perceived absence of such momentum, at present, and a feeling amongst the RD community that a renewed drive around NP/NS is very much needed. It is also likely that those "soft-law", but nonetheless very influential policies of the past no longer keep pace with the needs of the actual RD community well over a decade later.

The **Rare 2030** project can be articulated in four stages, which together work towards the goal of establishing a roadmap towards a **new generation of RD policies.**

The four stages are:

1. Establish knowledge
2. Identify rank trends
3. Create future scenarios
4. Propose policy recommendations.

Stage 1: Establishing knowledge

Before creating new policies or recommendations to address the current and future needs of the RD population, it is necessary to understand what the *status quo* is. For these activities, the long-established *Resource on the State of the Art of RD activities in Europe* was adapted and utilised to gather information from as many EU MS as possible. **Data Contributing Committees** in each country were constituted/refreshed, including representatives from national authorities, Orphanet national representatives, and patients' representatives from the national alliances, and where possible, Board of MS of ERNs representatives). By means of the Data Contributing

Committees, the Rare 2030 collected information via **dedicated surveys** in October 2020 (reviewed in February and March 2021), asking for the ***status quo* on NP/NS for RD as of March 1st 2021** (https://link.springer.com/article/10.1007/s12687-021-00525-4). These Committees updated their "State of the Art Resource" surveys, which were designed to collect the data which countries agreed to provide regularly, when they unanimously adopted the **EUCERD Recommendations on Core Indicators** for NP/NS for RD in 2013. The information collected was used under the project lifespan to:

- Allow for cross-EU comparison
- Assess the fulfilment of the EUCERD Recommendations on Core Indicators for RD NP/NS in the countries
- Enable national reports for the involved countries.

The immediate use of that data, under Rare 2030, was to generate 8 *Knowledge Base Summaries*, one for each broad topic under the RD "heading" **(https://www.rare2030.eu/knowledgebase/).**

The summaries cover the topics of:

- European and national policies and strategies
- Data
- Accessibility and availability of OMPs and medical devices
- Basic, clinical, translational and social research
- Diagnostics
- Integrated, person-centred social and holistic care
- Patient partnerships
- Access to Healthcare

(For the **Post-Rare 2030** future, the plan is to **open the data collection beyond the EU MS** and to collaborate with EURORDIS and Orphanet with a dedicated funding to evolve and sustain the State of the Art Resource).

The national pictures are pooled to include maps and tables and summaries for many key topics, which feature prominently in these 2019 'Knowledge Base Summaries'. Although these documents address the *status quo* for topics such as new-born screening and helplines, which should be addressed *within* NP/NS, major emphasis was placed on that high-level *status quo* of NP/NS themselves. Complete/mostly complete responses were obtained in late 2020 and Spring 2021 from all MS except 3 (Estonia, Greece and Poland). The key point to emphasise is that although (by 31 March 2021) **24 out of 27 EU MS had adopted a NP/NS for RD at some stage**, this does not mean that all those countries have active, dynamic NP/NS today.

Highlights
As of the 24/27 countries that adopted a NP/NS for RD at some stage, it has been stressed out that **the adoption itself does not automatically entail that the NP/NS is**

active.

There is significant variety in how NP/NS were established: some countries decided from the beginning, others at a later stage, to adopt open-ended NP/NS, while **the majority of the countries opted for time-bound NP/NS** --logically therefore, unless renewed, a certain number of NP/NS would expire, and indeed the data collection under Rare 2030 has shown this to be the case.
It is essential to underline that **the expiry/absence of a NP/NS does not mean the inactivity of the country in the RD field;** nevertheless, it has been stated that the lapse of these documents is a cause for concern, as a robust, in-date, well-implemented NP/NS should be the 'glue' holding all national activities together. Therefore, it seems that the **momentum that was generated in 2009 has declined somewhat.**

The *state of the art* surveys (although as ever, the data accuracy depends upon those providing that information, and could always be subject to slight changes) show that, as of March 1st 2021, 6 countries have ongoing, open-ended NP/NS for RD (Austria, Belgium, Cyprus, Lithuania, Germany and –apparently- Denmark, though the data may require an update here). 4 of the time-bound NP/NS are still active i.e., in date (Finland, France, Luxembourg, Romania).14 of the NP/NS that adopted fixed-term lifespans (i.e., have certain dates, e.g., 2014-2018) were apparently expired (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Ireland, Italy, Latvia, Portugal, Slovak Republic, Slovenia, Spain, The Netherlands). Indeed, many of these terminated at the end of 2020, which was a natural endpoint for some. And then there still are the 3 MS that had not yet adopted a NP/NS by this point (Malta, Poland, Sweden).

Highlights

The proportion of countries with technically expired NP/NS (some of which have been that way for many years) is a concern. In some cases, it is clear that things are happening, and groups are meeting to renew those NP/NS, and indeed COVID-19 has slowed this down.
However, from the analysis performed, there are **more issues to consider than merely whether a NP/NS was adopted/exists:** for many countries, the attention under the early year remained on the *adoption* of a NP/NS for RD, sometimes with less emphasis on the extent to which actions in that NP/NS were really specific, actionable, and indeed, how far they were actually implemented. There has been no follow-up initiative looking at the impact and levels of implementation of the NP/NS. **Other many important issues connected with the NP/NS for RD remain somewhat overlooked;** for example, the 2009 Council Recommendation affirmed that the NP/NS for RD should anchor all actions within the health *and* social system, but for some NP/NS this request has not really been addressed and there remains a lack of integration. Moreover, it is often not clear enough who is charge of overseeing the NP/NS of many countries and how the NP/NS were indeed put into effect on the ground. There are important unanswered questions on this vital topic (which have lacked a suitable forum for debate, perhaps, since the expiry of the Expert Groups for RD and the absence of suitable projects to unite these stakeholders), e.g.: whether it is preferable to have a Plan *or* a Strategy, a time-bound or an open-ended document, what should be the ideal lifetime of these documents, whether it is 'safe' for RD to have NP/NS subsumed or embedded in broader national health policies e.g., genomics strategies, and what should

happen in the time span between the expiry and the approval of a further NP/NS for RD.
It appears that, at present, the field is **lacking that central drive from the EU to address these kinds of issues,** and the momentum generated by the Council Recommendation of 2009 has subsided, with the result of **a certain standstill regarding the NP/NS for RD in some countries.**

Stages 2 and 3: Identify rank and trends and create future scenarios

To summarise the middle steps of the Rare 2030 project, in addition to the collection of the *status quo* and the production of the 8 knowledge-based summaries, stages 2 and 3 concerned the **ranking of trends around changing values and technology and influences that will affect RD policies in the coming years** (https://www.rare2030.eu/trends). In combining different progressions of the trends, four possible scenarios for 2030 have been established. On the two axes of individual responsibility vs. collective accountability (axis 1) and patient-needs-led innovation vs. market-led innovation (axis 2), the quadrant characterised by high patient-needs-led innovation and strong collective accountability emerged as the most inspiring and preferred for the future of European RD policies (https://www.rare2030.eu/scenarios/).

Highlights

Thus, it emerged that the **scenario "Investment for social justice"** is the most preferred for the future of RD policies.

Stage 4: proposition of policy recommendations

The final stage of the project was to work with the Panel of Experts and indeed hundreds of additional stakeholders at key events, to produce a set of **Recommendations. Each chapter of recommendations addresses one of the topical areas of the project, and represents the major output of Rare 2030 as a foresight study** (http://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf).
The 8 Recommendations chapters concentrate on the following:

1. European Framework and National Plans
2. Diagnosis
3. Healthcare
4. Integrated and Person-Centred Care
5. Patient Partnership
6. Research
7. Data
8. Treatment

To finish the presentation, it is interesting to consider how the *status quo* for NP/NS outlined above has led to the eventual recommendations most concerned with national and European policies and the 'big picture'. After two years of intensive consultation, the **main conclusion** is that the Rare 2030 Foresight study recommends a new policy framework for RD in Europe (Recommendation 1) that should renew the momentum on NP/NS for RD. This in fact constitutes the core that supports the other 7 chapters of Recommendations generated by the Rare 2030 Project.

Highlights

This conclusion is of particular interest for the focus of the Strategy meeting, as it

concerns **long-term, integrated European NP/NS.**
A little more specifically, this **1st Recommendation** includes the following points (amongst others):

- European and national plans and strategies should be sustained on a long-term basis, with adequate funding, and should be monitored by the appropriate authorities and key opinion leaders in this field
- a renewed focus should be placed on the state of the art of current NP/NS and the adoption of renewed NP/NS
- A suitable forum should be created or designed to advance multistakeholder policy-oriented debate on RD, enabling the identification of good practices and support for implementation to suit national realities.

With respect to the last point, it has been stressed that **key national figures involved in the ERNs** should be part of a multistakeholder forum to allow the insights and experiences from ERNs, broadly and/or in specific areas, to enrich the contents of future NP/NS.

Moreover, it has been underlined that these 3 headline recommendations highlighted above make reference to a **general European framework** and are **complemented with a number of more specific European and national recommendations**. In this way, the project recommendations provide headline messages that can be conveyed in seconds: slightly more specific recommendations; and more action-focused suggestions aimed to European and national actors respectively. In addition, it has been reported that the elaboration, implementation, evaluation and renewal of robust and effective NP/NS for RD must once again be embraced as key policy priority.

Highlights

To move forward in this direction, and to address some of the issues raised in this presentation, the **following recommendations were selected from Chapter 1** and were highlighted:

- The EU shall consider an updated request to MS in connection with NP/NS for RD, structured within the frameworks of the health and social systems
- The EU multistakeholder tasked with overseeing policy challenges and opportunities for the full breadth of RD care/ rare cancer issues should endure a key focus on revitalising the NP/NS agenda
- Support should be provided from the European level in terms of updated Key Performance Indicators for NP/NS and of identification and dissemination of good practices and solutions to shared challenges
- NP/NS should be robustly evaluated and -in the case of time-bound policies- renewed or replaced by national authorities in a timely and transparent manner. National authorities should ensure intersectoral collaboration in the elaboration, evaluation and implementation of national frameworks for RD/rare cancers, encompassing also social and holistic actions alongside the medical and research angles
- National authorities should dedicate designated funding to implement the NP/NS and their constituent activities (which should include Specific, Measurable, Achievable, Relevant, Timely- SMART objectives, wherever possible)
- The integration of rare cancers (both adults and paediatric cancers) in national cancer control plans should be fostered, with relevant synergies

with national RD plans
- National authorities should avoid subsuming RD into broader health strategies, which reduces addressing their specificities and their strategic prioritisation and, however, where relevant strategies exist (for instance genomics or cancer) appropriate links to the RD field should be ensured
- National authorities should consider the applicability of RD into the United Nations' Sustainable Development Goals and the World Health Organisations' Universal Health Coverage debates and incorporate this into their specific agendas
- Countries should create Mirror Groups on RD research, to interact with the EJP RD Policy Board on research matters and integrate this to their NP/NS for RD/ rare cancers
- By 2025 all countries should have a "live" NP/NS for RD, with a dedicated multistakeholder oversight body, and an annual budget separate from the wider health and social system.

Since the formal wrap-up of the foresight study Rare2030 (to find the main outputs of the project see https://www.rare2030.eu/our-work/#projupdates), a subsequent "call for action" is needed to actually implement these recommendations on the ground. To this end, **EURORDIS has created a campaign, 'Rare 2030 Action'** (https://www.eurordis.org/news/share-your-reason-european-action-rare-diseases **calling upon the EC and EU MS to introduce a European action plan on RD** (https://eurordis.org/content/eurordis-rare-diseases-europe-calls-european-union-action-plan-rare-diseases-meet-unmet-needs-2030)**.** This action plan is meant to align MS towards common measurable goals to ultimately improve survival, quality of life and social inclusion. Moreover, this effort should support the **fulfilment of the United Nations' Sustainable Development Goals**, and, if implemented across sectors and countries, it will work towards the **measurable goals** to: (i) diagnose every person within 6 months instead of the current 5 years average; (ii) reduce premature deaths due to RD; (iii) reduce the economic, social and psychological burden of RD by 1/3; (iv) bring 1000 new medicinal products, including gene and cell therapies, based on European-led research.

Development of the Dutch EJP RD National Mirror Group
*(**Sonja van Weely**, The Netherlands Organisation for Health Research and Development - ZonMw, the Netherlands)*

This contribution presented the experience of the Dutch National Mirror Group as a multistakeholder body that collaborates to the objectives of the EJP RD and represents a two-way path between the national and EJP RD needs and actions.

In the context of **WP 2 "Integrative Research and Innovation Strategy"** of the **EJP RD**, it has been achieved to define **Terms of Reference for the setup of National Mirror Groups** (NMGs). These terms have been shared by the Coordination with the EJP RD Partners and the PB members to make their setup easier.

As the establishment of NMGs turned out to be a complex activity, the Terms of Reference and the core of what should be the activities of the NMGs have been addressed more closely by reference of the **Dutch experience.**

For the definition of the **objective of the NMGs** the following statement has been given:

Highlights
The **role of the NMG is to ensure national coordination of and with all RD stakeholders** to facilitate the alignment between national and EJP RD activities, to contribute to the objectives of the EJP RD and benefit from it.

In this perspective, it has been underlined that the generation of a flow that goes from the national needs to feed the EJP RD activities and from the EJP RD initiatives to meet the local requirements is highly valuable.

Keeping always in mind the specific local conditions of a country (culture, language, population size and composition), and that therefore the creation and **composition of a NMG is at the discretion of each participating country**, it is recommended to involve the following stakeholders in the constitution of the NMGs.

- EJP RD Governing Board representative
- EJP RD Policy Board representative(s), e.g., Ministry of Health, Research or other Ministries
- Relevant national partners of the EJP RD
- Relevant national authorities (e.g., representatives of the Ministry of Health, Research etc., that could be the same members of the above cited Policy Board)
- Representatives of the NP/NS for RD, even in the absence of an approved NP/NS
- ERN members
- Research institutions involved in RD research (participating to the EJP RD or not)
- Representatives of patient organisations
- Representatives of the Orphanet local team.

Highlights
The **role** of the NMGs is mainly to ensure both that **national activities, strategies and needs are taken into account when taking decisions at the EJP RD level** and that the outcomes of the EJP RD are translated into **actions at national level**. Usually, the EJP RD GB representatives of a country will report the NMGs' views and positions during the GB meetings. The **functions** of the NMGs span to: • the coordination of the participation of national actors in the field or RD into the EJP RD activities • the definition of the national positions and priorities to be reported to the EJP RD and for the Annual Work Plans • ensuring the alignment between EJP RD and national strategies by promoting EJP RD actions and outcomes at national level.

It is recommended that the NMGs plan at least one face-to-face meeting once a year, ideally in June to allow the discussion on the proposed Annual Work Plan and before the PB yearly meeting. If considered relevant for the discussion and work on specific subjects, **dedicated working groups can be established within the NMG.**

The NMGs can moreover ask the EJP RD Coordination for support for the preparation/delivery of relevant documents and presentations.

Then the **Dutch experience of NMG** has been presented.

The Netherlands had several multidisciplinary committees with ZonMw (the Dutch funding agency for Research) acting as secretariat, even before the onset of the EJP RD.

In 2001-2013 there was a Dutch Steering Committee on Orphan Drugs who worked on the preparation of the NP for RD in 2012-2013 with the collaboration of many working groups.

On 2015-2017, a Consultation group for the NP for RD, installed by the MoH and with the collaboration also of the Dutch Patient Alliance, was set up and gave recommendations for MoH and other stakeholders on next steps for policy and actions on rare diseases. After 2017, there has been a lack of such multidisciplinary working groups, until a Dutch NMG (working group) has been established in May 2019 under the EJP RD. The Dutch NMG started with a small number of persons, that grow to 23 members in 2020, as "spontaneous initiative" no longer installed by the MoH, but created under the incentive of the EJP RD. The Dutch representative of the EJP RD GB is chair of the Dutch NMG.

The EJP RD involved partners that are member of the Dutch NMG. These are (by Pillar):

- Pillar 1: ZonMw
- Pillar 2: LUMC, Radboud UMC, UMCG, UM, Amsterdam UMC (University Medical Centers)
- Pillar 4: EATRIS (located in the Netherlands)

- Dutch ERN Coordinators (ERN Rita-UMC Utrecht; ERN Genturis, ERN e UROGEN-RadboudUMC; ERNICA, ERN CRANIO-ErasmusMC; ERN GUARD-HEARTH-Amsterdam UMC; ERN-Endo-LUMC)
- Several infrastructures (ELIXIR community/RDs GO FAIR-LUMC; ELIXIR interoperability platform-UM; BBMRI-NL/ELIXIR deputy head-of-node-UMCG; GO FAIR-Amsterdam UMC).

Additional members in the Dutch NMG are:

- Orphanet NL Coordinator/coordinator of Dutch Centres of Expertise
- The Dutch Federation of University Medical Centres (NFU)
- The umbrella of the patient organisation for genetic and rare diseases (VSOP, Vereniging Samenwerkende Ouder- en Patiëntenorganisaties)
- The ePAG VASCERN representative
- The National Health Care Institute
- The MoH
- Representatives of ELIXIR, BBMRI, GO FAIR, ERICA project etc., and therefore linked with other initiatives e.g., on data infrastructures.

Making reference to the **RD research in the Netherlands,** it has been furthermore pointed out that:

- Most of RD research takes place at 7 universities/university medical centres of the country
- Most of the more of 350 centres of excellence for RD are located in the 7 university medical centres
- All university medical centres are involved in developing a federated Dutch national research infrastructure (Health-Research Infrastructure –Health-RI).

The **activities performed by the Dutch NMG** since 2019 encompass:

- 5 meetings of the entire group and 2 with a small subgroup (face-to-face or online)
- Participation to the GB of the EJP RD
- The discussion of the Annual Work Plan after the PB Meeting
- The discussion on the use cases for input of national Policy letter and for Dutch/European activities
- The input to the surveys on NP/NS for RD carried out in WP2 of the EJP RD
- The contribution to the survey from the patient alliance on the national RD strategy
- The RD community representation in the Health-RI.

Highlights
The activities of the Dutch NMG planned for the **near future** regard: • The elaboration of the Communication plan for the dissemination of the EJP RD activities in the Netherlands • The development of inputs for the Strategic Research and Innovation Agenda for the European Partnership on RD • The support to the alignment of the Health Research Infrastructure with the

EJP RD Virtual Platform.

Finally, a list of **"lessons learned" in the experience** of the speaker was shared:

- Some organisation/person is needed to start and take the lead in the creation of an NMG
- It takes time to build a multidisciplinary group
- There should ideally be dedicated human resources
- Stakeholders are committed due to the unmet needs of RD, even in the absence of participation of the MoH
- The collaboration of different stakeholders brings mutual enrichment on activities and ways of thinking
- Within a multistakeholder group like the NMG, it is easier to network and to share new national/European developments that happen in the RD field.

The added value of RD Partnerships
*(**Daria Julkowska**, Institute National de la Santé et de la Recherche Medicale, France)*

The presentation focused on the preparation of the RD European Partnership under Horizon Europe and on its overall context regarding opportunities and challenges for RD, tacking stock also of the results obtained through the Rare 2030 Foresight study.

The European Partnership under Horizon Europe has been introduced as a different scheme, when compared to the EJP RD. It can be considered as a new generation of **objective-driven Partnership**, supporting the agenda of the EU policy objectives.

The **key features** are:

- The strategic orientation and the link with the EU priorities
- A common set of criteria for the life cycle (Horizon Europe regulation Article 8 Annex III)
- A systematic approach
- Simple architecture and toolbox.

There are **3 types of Partnerships for Horizon Europe:**

1. Co-programmed: based on contractual arrangement/memorandum of Understanding (MoU), implemented independently by the partners and by Horizon Europe
2. Co-funded: based on a joint programme agreed by Partners (Grant Agreement) where Member States and Associated Countries design a common programme to be implemented under their responsibility
3. Institutionalised: Partnerships based on Articles 185/187 of the Treaty of the Functioning of the European Union (TFEU)-Regulation supported by Horizon Europe and implemented by a dedicated structure.

The RD Partnership will belong to the above described second type (Co-funded), similarly to the EJP RD. In fact, the EJP RD is a European Joint Programme co-fund instrument, (implemented under Horizon 2020), that will serve as background for the RD Partnership, but with more ambitious strategic orientation and a set of common criteria, approach and architecture, in collaboration with the EC.

There are 49 candidate European Partnerships for Horizon Europe resulting from the strategic Planning, whose priorities were discussed together with the MS. Under Pillar 2 of Horizon Europe "Global Challenges and European industrial competitiveness", Cluster 1 "Health" there is the RD Partnership.

Highlights
It is expected that the **European Partnerships** are going to **leverage not only on the national potential** and be conducive for the European added value, but also that they will collaborate between them **establishing synergies**.

For example, this could be the case of the establishment of synergies between the RD Partnerships with the Partnerships on "Innovative Health" (Cluster 1-Health) and

"Key Digital Technologies" (Cluster 4-Digital Technologies), and with the European Institution of Innovation and Technology (EIT) Health.

Then, some important reflections on the **differences between EJP RD and what will be the RD Partnership have been illustrated**.

With regard to **funding**, while the EJP RD foresees a 70% reimbursement rate, there will be two possible reimbursement rates in HE:

- A reimbursement rate of 30% for the activities that are focused on funding of research (transposed to the EJP RD these would be the activities mostly of Pillar 1)
- A reimbursement rate of 50% if the Partnership is broader and implements also other activities, with a good balance between funding and those other activities.

This entails a lower reimbursement rate when compared to the EJP RD and calls for the importance of the **good balance and alignment with the national policies**. However, like in the EJP RD, there will be the possibility to apply for different reimbursement rates with the agreement of the whole Consortium, and to share the total budget that is reimbursed by the EC in a different way among the partners.

Furthermore, there will be a **longer-term strategy for HE with an up to 7-year timeframe.**

With regard to the participation of different organisations there are no main differences with the EJP RD, meaning that what has been done under EJP RD can continue but that there is also the possibility of different configurations with different types of stakeholders to be brought under one umbrella.

Highlights
In general, it has been stated that the **different funding framework of HE might stimulate additional/new bridges between RD activities, leveraging the regional, national, European or international potential in order to optimise the given budget and balance the planned activities**.

A **Strategic Research and Innovation Agenda (SRIA)**, which is a public document, has to be mandatorily prepared and validated in advance in each Partnership.

Monitoring will continue to be an important factor in HE, with 3 levels:

- Key Impact Pathways overarching for the whole HE
- Specific Common Indicators for all Partnerships
- Internal mandatory monitoring, established by each Partnership with own indicators that have to be in line with the internal objectives and established before the start of the Partnership.

Moreover, it has been reported that the discussion around the RD Partnership started in 2021 and that the launch of the Partnership is expected for 2024. The EC (lead Directorate General for Research and Innovation DG RTD, associating relevant Directorates Generals), initiated the discussion with potential partners through meetings (in April and July 2021), involving the MS and other possible partners.

A co-creation and consultation process via structured workshops is planned in 2021 to **build on the lessons learned through the EJP RD, the Rare 2030 Foresight and the experience of the ERNs**.

Highlights

The **objectives of the RD Partnership** that were **proposed in 2019** in preparation of the **Candidate Partnerships for HE** have been:

- To contribute towards the objectives of the International Rare Disease Research Consortium (IRDiRC) to shorten the average time to a correct diagnosis to 1 year; have 1000 new therapies for RD and methodologies to assess the impact on patients by 2027. This objective can be now updated in the light of the Rare 2030 Foresight Recommendations that put even more ambition on the diagnostic part, shortening the time for diagnosis to 6 months
- To further develop the ecosystem for discovery research and development of new diagnostic tools and therapies for RD, providing an effective "pipeline" from research to healthcare to ensure that research and innovation results are reaching the patients as quickly as possible and that healthcare needs can better feed into research prioritisation. This is indeed what has been started in EJP RD, and what has now to be considered also from the angle of the public/private partnerships and interactions
- To collect and share all relevant RD data at EU and international level efficiently utilising data collected by the ERNs. For this point ERNs, national RD registries, national hubs, national data centres and national cohorts are of extreme importance
- To boost the research collaboration in the EU, the Associated countries and in Third Countries enabling unprecedent pooling of resources and expertise
- To provide evidence for fit-for-purpose regulatory framework taking account of the latest science and of the establishment of EU/international standards, largely facilitating research and innovation. The collaboration with regulatory bodies should take advantage of the expertise that was already accumulated and of the structures and infrastructures that have been (or could be) created to interact with the regulators
- To reinforce the EU as an effective "hub" for RD research and innovation in the international context of RD.

Building upon the most relevant Recommendations of the Rare 2030 Foresight for the RD policies, the following hints should be transposed in the HE RD Partnership:

- A European policy framework guiding the implementation of consistent NP/NS for RD, monitored and assessed by multistakeholder bodies on a regulatory basis
- Earlier, faster and more accurate diagnosis of RD through better and more consistent use of harmonised standards and programmes across Europe, new technologies and innovative approaches, driven by patient needs
- A highly specialised healthcare ecosystem, with political, financial and technical support at European and national levels, that leaves no person living with a RD in uncertainty regarding their diagnosis, care and treatment

- Guarantee the integration of people living with a RD in societies and economies by implementing European and national actions that recognise their social rights
- A culture encouraging meaningful participation, engagement and leadership of people living with a RD in both public and private sectors
- RD research maintained as a priority across basic, clinical, translational and social research
- Data used to its maximum to improve the health and well-being of people living with a RD
- Improve the availability, accessibility and affordability of RD treatments by attracting investments, fostering innovation and collaboration across countries to address inequalities.

Highlights
Overall, **the planned broad objectives for the HE RD Partnership are complementary and in line with the outputs of the Rare 2030 Foresight study.**

Looking at the different stakeholders, directly or indirectly involved in the EJP RD, it has been shown that, 85% of the European RD research community is involved in the project; this is a good starting point, although it emerged that the industry is not yet a full part of the Consortium, as it was expected to be. Another critical point emerged in EJP RD is the different participation of the countries, that is based mainly on the national capacities.

Highlights
These capacities are not necessarily lacking in many countries and the **integration of the national activities and capacities into the future Partnership** should become an objective of the RD Partnership, as well as the involvement of the industry.

Furthermore, EJP RD qualifies as a single-entry point providing solutions for all: researchers, clinicians, patients, policy makers and funders, international Partners. The solutions span from funding to research support services, trainings at all stages, access to resources and tools, access to extensive network and expertise, clinical studies support services, support for registries, joint funding and strategy, optimisation of investments in research, access to support for national RD communities, holistic impact evaluation, multiple collaboration opportunities. While maintaining all these elements for the creation of an optimal research ecosystem, the **HE wants to address even more ambitious goals.**

Considering the current achievements in the RD field and the future opportunities, the **following scenarios for the HE RD Partnership** have been presented:

<u>Research support and collaboration (funding)</u>

Achievements	Future goals
• Relative stable funding support	• Continue to support basic,

for multinational research and widening efforts.	translational and clinical research as 95% of RD remain without treatment and are disregarded in terms of research • Ensure long-term commitment and integration of research in national strategies • More targeted programming.

The goal towards research support and collaboration is not only to increase the budget but also to **determine the scientific strategy for the coming years**. Indeed, the longer-term of the RD Partnership (in respect of the EJP RD) will hopefully allow a deeper commitment and alignment of the national strategies with the Partnership.

Exploitation of research and health data

Achievements	Future goals
• Attainment of the RD ontology, of "transferable data standards", of FAIR standards • Progress in the development of the Virtual Platform • Creation and implementation of ERN registries • 1+Million Genomes project • National initiatives to create data hubs and European Health Data Space (EHDS) • Improvement of the Solve-RD undiagnosed infrastructure (a model that could be implemented at national level).	• Build the linkage between health and research data and exploit the central position of the ERNs to facilitate the collection, access and use of data • Build and ensure sustainability of the connection between national and higher levels • Ensure the sustainability and curated knowledge resources needed as reference for automated data interpretation • Accelerate diagnosis by supporting relevant codification and tools (in relation with Orphanet efforts and other initiatives).

The achievements in this field can be considered as the building blocks that need to be exploited to the maximum in order to **create the linkage between health and research data**; an infrastructure built around the work of the **ERNs** could be a desirable goal in order to have a more **stable system of data sharing**. This entails also a better connection and integration with the national systems, and a strengthening of the resources that they provide (e.g., the curated data knowledge and interpretation, Orphanet ontology, etc.).

Participation of patients

Achievements	Future goals
• Patients' involvement in the	• Support patients' inclusion and

governance of the EJP RD • Progressive inclusion in RD research • Fostering of "Proof-of-concept" for PAO funding.	guarantee and equal weight of their voice at all levels • Provide for patient-needs driven research and novel and more inclusive funding models.

The "Proof-of-concept" for PAO funding is not yet sustainable and it requires more effort and/or a **more specific and stable model for PAO funding**.

Expansion of research capacity, translation and EU competitiveness

Achievements	Future goals
• Exploitation of ERNs extensive (clinical) research expertise • Stimulation of the pre-clinical research community • Improvement of tools and infrastructures to support pre and clinical research • Growing of interest from industry and appetite for new funding/collaborative models.	• Link the pre-clinical and clinical (building RD research networks) • Transform the Proof-of concept support model into regular support to accelerate the development-ready research transfer to investors • Integrate industry into multistakeholder collaborative models and create new complementary funding/support.

The stimulation of a pre-clinical research community has already been done in EJP RD or in clinical research infrastructures funded by the EC. **Linking the preclinical and clinical research is of great interest for the RD Partnership**, to be built around the clinical research networks, taking into account different models. With regard to industries, it is to underline that their integration does not necessarily imply their presence inside the Partnership, as the creation of parallel initiatives could be also envisaged.

Regulatory

Achievements	Future goals
• Innovation of Clinical Trials methodologies and patient-reported outcome measures (PROMs) • Example models like C-PATH (outside the EJP RD) • Fostering of interest of regulators and industry payers.	• Exploit the capacity of relevant clinical expertise (ERNs) coupled to methodological excellence in support of evidence-based research to accelerate the validation by the regulators.

Stable collaboration between RD community and regulators/policy framework and national participation

Achievements	Future goals
• Development of NP/NS for RD (not for all countries and with a certain heterogeneity) • Proof-of-concept of NMGs organisations • Visibility of national potential in research, education, innovation, healthcare.	• Build solid bridges between national, EU and international levels • Maximise the national potential and provide tailored solutions • Anchor RD in national strategies (as a holistic concept) if not already done.

This area reflects the most the content of the present strategic meeting. In this context, the EU can scale up research capacities and moreover, **build the solid bridges between all the above-mentioned building blocks (and achievements), to leverage and maximise the potential** and obtain specific and tailored solutions.

Finally, there are different strong **reasons for a European Partnership on RD**, in accordance with what has been underlined in the Rare 2030 Foresight study:

- To invest in basic research to continue the groundwork for innovation, both at MS and at EC level, with calls supporting international excellence, and to coordinate research strategies and funding priorities, incentivising this area
- The EU level is the only relevant level to pool knowledge, data, patients, experts, funds, allowing for a unique and high European added value for research (including public health, social research and healthcare transformation)
- The creation of Clinical Research Networks on RD to advance medical research and care, powered by Digital Technology and Data, facilitating collaboration, providing the building blocks for data sharing and clinical studies.

This means that **EU can scale up research capacities across a wide range of RD activities, keeping in mind a holistic, patient-centred approach**, in accordance also with the specific impacts and sustainable development goals of the United Nations (e.g., goal 3 "improving health and well-being", goal 9 "build resilient research infrastructures and foster innovation", or goal 17 "increase Partnerships").

Some of the performance goals elaborated also under Rare 2030 that could be useful as indicators in the fields of research and treatment are the following:

<u>Research</u>

- Greater incentives for all stages of research, to optimise competitiveness and excellence in basic, clinical, translational, social research
- More investments in pre-competitive infrastructures to advance needs-led research, fostering research capability of ERNs and building bridges with Clinical Research Networks for RD

- Creation of a European research ecosystem attracting more private investments and enabling more public-private partnerships.

Treatment:

- 1000 new therapies available by 2030, in line with IRDiRC goals
- Treatments approved in the EU for 500 different RD and for 50% of the overall population of RD people
- Therapies to be 3 to 5 times more affordable than current available treatments.

Highlights
Summarising, a RD Partnership under HE is needed: • To make sure that people living with a RD are not left behind • To leverage further the collaboration across stakeholders, including industry • To translate faster the research results into societal and economic benefits • To build the EU strategy by joining national forces and strengths, as every investment at national/regional level adds up to the one of HE and industry • To trigger structural changes, as well as health and digital investments by expanding the capacity of the ERNs, the national and EU infrastructures and the European Health Data Space, envisaging also that the Digital Transformation of today can help the RD community.