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1. Executive Summary

The European Joint Programme on Rare Diseases (EJP RD) is a program that aims to create optimal conditions for research into rare diseases (RD). The main goal is to support and quickly implement the obtained results into clinical use. Sharing knowledge and results together while finding efficient models for sustainable development is of paramount importance in overcoming the problem of data fragmentation and the resulting difficulties.

All activities in the EJP RD have been specified in detail in the proposal approved by the European Commission. The description of the work planned for the 5 years of the project was exhaustive, therefore all activities were and are constantly planned, distributed (among partners and over time) and prioritized in advance, from the beginning to the end of the project.

Thanks to annual reports, it is possible to inform the RD community as well as outsiders about their progresses achieved throughout the project and to focus or adjust the activities performed so that they can respond to real needs at a given moment. The priority of EJP RD is to support and quickly implement the obtained results into clinical application, so as to ensure comprehensive research and innovation - the "bench to bedside" principle.

The presented document is another in the cycle after the Third Scoping Paper (D2.10), which, due to the procedures and activities described in the field of research and innovation (R&I) for RD, will be a tool for all communities dealing with this issue - including the European Programme for Rare Diseases.

It is a specific instrument for regular mapping and monitoring of the progress and needs in the field of research and innovation, which are intended to facilitate assistance to patients with rare diseases on many levels.

This document presents the key information published in Deliverable 2.6 (D2.6) "Fourth Summary document on mapped research and innovation needs" "The fourth document summarizing research and innovation (R&I) needs" of the EJP RD.

Regular publication of such results allows for up-to-date and targeted activities for the rare disease community. The elaboration of these results is based on the outcomes of the mapping of research and innovation needs carried out under Work Package 2 (WP2) "Integrative research and innovation strategy" in the published documents D2.1, which contains the final list of priority-setting criteria, and D2.2 containing the priority diagram for EJP RD activities. Each year, this document contributes to ensuring well-targeted annual work plans as well as a coherent long-term strategy for the EJP RD. In addition, it contributes to the promotion and implementation of informed actions, and to the standardization of rare disease procedures among all Member States (MS).

Building on the Rare 2030 project, activities to support and promote all rare disease strategies and plans should be expanded. This framework should include holistic care for a rare disease patient, i.e., the possibility of research, diagnosis, access to the latest forms of treatment and qualified medical staff in one place. In order to standardize and interoperate data, actions are needed to create platforms (including the EJP RD Virtual Platform), the need for which was already observed in previous years.

Identified mapped needs are a combination of diagnostic and treatment paths with a focus on the five aspects:

1. quality improvement through harmonization and optimization procedures, registries, e-infrastructures, open e-networks, virtual biobanks, protocols for data collection, infrastructures, data repositories;
2. providing sustainability: resources optimization and sharing; European funding of health networks; economic models for development and commercialization of orphan drugs;
3. strengthening the patients by e.g., holistic patient-centred approach, Innovative ways for engagement in drug development and clinical trials;
4. integration and enhancement of the data quality with innovative use of them as well as RWD, AI & big data
5. extension of clinical and pan-European multi-stakeholder networks of EU research, patient and healthcare organizations; collaboration with ERNs on national integration; Open Science (open access to publications, data, and to research. It is worth mentioning that the mapped R&I needs in previous years are in line with the vision and goals of IRDiRC. In an optimal vision of the future, all people living with a rare disease will receive an accurate diagnosis, care, and available therapy within a year of seeking to medical attention. To achieve this, three goals have been defined: all patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature and all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline, 1000 novel treatments for rare diseases will be authorized, the majority of which will target conditions for which there are no approved treatments, methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

HIGHLIGHTS AND NEXT ACTIONS

- This penultimate mapping has started to complete all needs identified throughout the series during these years. The final product of this series of mapping on R&I needs, due in M53, will include syntheses from earlier years and the contribution of EJP RD activities carried out to address the needs discovered.

- The key headings of the needs of the RD community are coordination and alignment of funds and governmental initiatives, innovation in the translation of research results, and the reach of a Holistic R&I ecosystem.

- Continued evaluation of areas outside of science, such as diagnostics and healthcare, competitiveness and innovation, and regulatory and ethical issues (such as the renewal of European initiatives and alignment at the national level, or the acceleration of innovation ecosystems).

- The upcoming European Partnership on Rare Diseases represents a step in the right direction toward a sustainable research ecosystem and an all-encompassing approach to RD.

2. List of abbreviations

BoMS	Board of Member States
EC	European Commission
EJP RD	European Joint Programme on Rare Diseases
ELSI	Ethical, Legal and Social Issues
EMA	European Medicines Agency
ERICA	European Rare Disease Research Coordination and Support Action Consortium
ERN	European Reference Network
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
FAIR	Findable, Accessible, Interoperable and Reusable
GDPR	General Data Protection Regulation
IRDiRC	International Rare Diseases Research Consortium
JTC	Joint Transnational Call
MAA	Marketing Authorisation Application
MS	Member State
NMG	National Mirror Group
OR	Orphan Regulation
PaOs	Patients Organizations
R&I	Research & Innovation
RD	Rare Diseases
RWD	Real-World Data
RWE	Real-World Evidence
SMEs	Small and Medium Enterprises
TEHDAS JA	Towards the European Health Data Space Joint Action
VUS	Variants of Unknown Significance

3. Introduction and Objectives

The main goal of the Scoping Papers series, which are issued annually as part of WP 2 "Integrative Research and Innovation Strategy" of the EJP RD, is to publish the results of a work carried out on particular tasks in WP 2, especially the summary of the "Mapping of Research and Innovation Needs".

The above mentioned mapping of research and innovation needs (Task 2.2) is updated and submitted annually by 2023 as a confidential and more extended document for Consortium members only (including Commission services) based on Documents in Tasks 2.3 ("Scientific programming of joint transnational calls"), 2.4 ("Management of the medium, longer-term research strategy questions and dedicated linkage with Task Forces of IRDiRC") and 2.5 ("Translation/impact of prioritization on national and EU strategies").

WP2 deliverables D2.1 and D2.2, which are the result of activities developed under the cross-cutting EJP RD Pillar 0, were key to create the map of needs and priorities. WP2 is specifically geared towards the development of the EJP RD Research and Innovation Strategy with all related stakeholders.

The joint exchange of knowledge and results while searching for efficient models for sustainable development is of great importance as it is the only chance to overcome the barrier of disinformation and the difficulties of collecting and sharing data between partner countries. For this reason, it is so important to publish this type of report. Work Package 2 (WP2) of the EJP RD identifies and regularly updates the mapping of research and innovation (R&I) needs in a mapping series, under the EJP RD activity.

This document is a compilation and summary of the most important issues contained in the sources cited below. It presents the activities undertaken over the past 3 years, (and especially over the past year), the conclusions, results and planned activities in relation to institutions and the RD community. Moreover, it shows the objectives set, the scope of activities of various entities, and their connections.

It focuses on presenting the identified needs of patients, stakeholders, academic centres, researchers, the medical community, research infrastructures and member states, including attention to underrepresented countries. The purpose of the aforementioned is to improve the functioning of the entire system dedicated to the RD community by recommending solutions and implementing them at the European level. In addition, it also considers EC comments on the Mid Term Review.

This document, in accordance with the description of activities, will be delivered to the leaders of Tasks 2.3, 2.4 and 2.5. for additional comments (complementary actions). In addition, the results and the developed model of activities should be promoted and implemented by the National Mirror Groups (NMG), after their creation, and under the Horizon Europe program.

Creating and publishing the Scoping Paper allows for the assessment of the work done during a given year on the mapping of needs in the field of innovation and clinical research on new forms of rare disease treatment. The document also allows for revisions and adaptations based on the current circumstances and demands. The fourth edition of the document summarizing mapped needs in the field of research and innovation (D 2.6), was released this year.

The most important annual goals and activities in the Fourth Scoping Paper (D2.11):

- Summarize the R&I needs scrutinized, updated and reported in D2.6 (confidential)
- Supporting a mid- and long-term RD research and innovation strategy in collaboration with the IRDiRC.
- Creating optimal conditions for research and a holistic approach to RD care
- Equal opportunities for the possibility of meeting the EU-13 countries' RD needs through coordination and adjustment of financing and national activities. Defining a prioritization model for EJP RD activities in the framework of the annual planning and in relation to WP3 (Sustainable Development) and WP4 (Ethical, Regulatory, Legal and IPR Framework)
- Currently, the result of close cooperation with the leaders of Task 2.2 (ISCIII, ISS) and the EJPRD Coordination is the preparation by MUW 2.11 deliverable which is the fourth public Scoping Paper. It should be emphasized that, like previous documents on this scope (D2.10), WP2 is devoted to the development of an EJP RD research and innovation strategy in conjunction with all related stakeholders.

The overall objective of this delivery document D2.11 of the Fourth Scoping Paper is therefore to support the progress of the EJP RD contributing to the medium- and long-term strategy of the project, through a summary of several deliverables of WP2.

Moreover, it aims to influence national activities as well as improve international cooperation in the field of rare diseases by making public the present achievements of WP2 and the most pressing needs of the RD community.

4. Sources for the preparation of the Fourth Scoping paper

The development of this document is mainly based on update D2.10 "Third Scoping Paper; D2.6 "Fourth Summary Document on Mapped Research and Innovation Needs" and on the mid-term reivews comments of EJP RD.

Briefly recall the results of D2.1 "Final List of Prioritization Criteria" and D2.2 "Prioritization Scheme, including decision-making process - Guidelines for Prioritization ", the content of which is described in the subsections below. In line with the assumptions of EJP RD, which assume flexible adaptation of the project to real needs in the field of research and innovation, based on mapped, key priorities at a given moment. They were cited in greater detail in previous deliverables, "The First Scoping Paper" and "Second Scoping Paper".

5. Summary results

This part shows the activities carried out within the individual tasks of WP2 based on the objectives set in the former Scoping Paper and Annual Work Plan. In the previous year important initiatives were organized. Thanks to them, conclusions about the needs of the RD community were drawn and included in the formal documents.

It is noteworthy that actions presented below have taken into account the needs and opinions of patients, as well as an increasing emphasis on other non-scientific areas such as diagnostic and healthcare, regulatory and ethics, competitiveness and innovation.

Within WP2, Task 2.1 focuses in particular on the "Priority scheme for EJP RD activities". Broadly defined prioritization is crucial due to the lack of physical and economic ability to meet all mapped needs at one time.

D2.1 "Final list of prioritization criteria":

This deliverable describes the objectives of the prioritization activities, consisting of : i) supporting and evaluating the decision-making process to prioritize the mapped needs and activities that contribute to the achievement of the EJP RD objectives (ii) facilitate future planning activities under the Annual Work Plan (iii) prioritizing choices and actions in the event of a deviation from, or the need for, planned activities (iv) further improvement criteria, indicators and methodologies used in the prioritization process, after assessing the impact of the decisions made.

According to the approved EJP RD proposal, such prioritization criteria should be used to structure the mapped needs and activities that contribute to the objectives of the EJP RD or require further research. This document defines a set of broad criteria. Such criteria can be applied to all EJP RD activities.

In fact, the EJP RD proposal defines four general criteria: aspects of scientific evidence, postulates of the RD community, regulatory and social concerns, financial and technical feasibility.

Furthermore, the criteria should be defined on the basis of data collected through a survey of rare disease stakeholders from the research community, European Reference Networks (ERNs), patients and policy makers that would constitute National Mirror Groups (NMGs).

Categories of criteria used in the prioritization process:

(i) Aspects of the scientific evidence: use of scientific data that can have a positive effect on the course of the disease as well as the use of technological innovations in this area.

(ii) Rare Disease Community Requirements: To interest the EJPRD community as well as patients, their families, healthcare providers, industry, IT and other groups about rare diseases. Playing a key role by Mirror Groups (NMG), which will regularly conduct surveys on the importance of the planned activities for their quality of life and future.

(iii) Regulatory and Social Concerns: This involves monitoring differences between EU and national legislation that may impact on clinical trials, reimbursement, insurance, and patient choice of treatment site.

(iv) Financial and technical feasibility: assessment and individual approach to financing and allocation of resources in different rare diseases according to capacity and possibility of obtaining positive results - spending prioritization and need mapping.

The above-mentioned four categories of prioritization criteria can be used for each of the four pillars:

- Experimental approach (P1): i) the innovation potential of the research should be assessed, ii) the community's opinion on the proposed action and its usefulness, iii) the evaluation of results from credible sources concerning the given population data, or regulatory facilitations in the introduction of the innovation data, iv) validation of the actual possibilities - " profit and loss balance "- availability of technical means, economic impact, etc.

- Access to consistent data quality (P2): i) the potential to strengthen research at the highest level by creating or validating relevant services, e.g. creating common databases, ii) collaborating with the rare disease patient community to exchange experiences, sampling research, assessing treatment results, iii) compliance with the GDPR, standardization regulations on data exchange between rare disease centers and privacy regulations, iv) social burden assessment defined on the basis of the annual cost of living of a RD patient, economic burden based on the cost of current therapies for palliative care per patient / year.

- Building the capacity to perform or contribute to the positive impact of research (P3): i) increasing the capacity to carry out research and introducing new technologies in RD therapy, increasing the capacity to share relevant research on rare diseases by building common resources and validated analytical tools, ii) active participation of patients in population and epidemiological studies to increase the capacity to analyze results , iii) increasing the ability to provide relevant data through better communication with regulatory and societal stakeholders; iv) increasing the capacity to translate basic research into cutting-edge therapies through links with commercial and non-profit funders.

- Access to consistent quality data that can support industry participation and development planning (P4): i) tools contributing to the exchange and dissemination of clinical research results and technical innovation, ii) understanding between rare disease communities, patients, Community and regulatory agencies, iii) exchanging information between patients and agencies on research methodologies, details of reimbursement policy, iv) development alternative non-profit drug development models, increasing user and RD community awareness of cost definition. Mechanisms of innovative therapies, discussion and development of new cost reduction and payment models.

D2.2 "Prioritization Scheme for EJP RD actions, including decision-making process

D2.2 "Priority setting flowchart for EJP RD activities, including the decision-making process - Prioritization guidelines": is a prioritization flowchart to streamline and standardize the decision-making process. This flowchart provides detailed information on the different steps in the prioritization and decision-making process. In this process, selected priorities specified in Document D2.1 are used.

It is this scheme that enables clear information on the different steps in the prioritization process. It provides guidelines for the correct application of the prioritization criteria (as expressed in D2.1) where necessary, and their subsequent validation to advance decision making. Therefore, this document (D2.2) should be read and used in conjunction with the D2.1 product content.

The purpose of prioritization in this context is to optimize the use of existing resources to achieve the objectives of the EJP RD for the benefit of patients. Such optimal use also requires decision making which should be transparent and avoid arbitrariness.

Therefore, a dual approach to these two closely related processes and their interactions should be ensured: prioritizing and making decisions. The purpose of this document is to provide guidance on the use of both processes in the EJP RD activities when needed.

In short, "prioritization" can be defined as the process of deciding what and when to build, based on what will bring the most value (in a broad sense) to the user and what is feasible.

D2.6 "The fourth document summarizing research and innovation needs".

Summary documents on mapped research and innovation needs are generated annually and sent to the Policy Council and ExCom as a basis for prioritizing the research and innovation needs of the EJP RD. The Summary Document taken as a reference in this Fourth Scope Document is the "Fourth Document Summarizing Research and Innovation Needs" (D2.6). This is a confidential report that was finalised in 2022. The Fourth Summary Document aims to continue and update the series of mapping research and innovation needs and to compile all the needs mapped in recent years [Del 2.3, Del 2.4 and Del 2.5].

This year, the mapping of research and innovation needs has been divided into two sections:

- Section I: Mapping research and innovation needs from previous years is dedicated to start wrapping up the results of the previous series of the Summary documents on R&I needs. The detected needs have been categorized and summarized according to the EJP RD concept and considering the alignment with the IRDiRC's vision and goalsi

- Section II: Summary of R&I needs mapping results, with multiple sources to ensure that all relevant information is included.

These sources are detailed below:

• EURORDIS- A patient perspective, mainly through information in the form of activities and barometer consultations.

• EJP RD Strategic Policy Workshop - July 2021 (M31). D 2.25 " First Report from strategic workshop with national policy makers ", containing initiatives, activities, conclusions and recommendations from the workshop and have become a contribution to discussions on the research and innovation needs.

• Joint Transnational Calls (JTC) along with the topics

• International IRDIRC research strategy. Information from the Scientific and Founding Committees and Task Groups, as well as EJP RD arrangements.

• Directorate-General for Research and Innovation of the European Commission and Horizon Europe. The issues outlined and discussed and the lessons learned during the Research and Innovation Days in June 2021 - including progress in the Horizon Europe program for 2021-2027 - contributed to the mapping.

• Other sources: European Rare Disease Research Coordination and Support Action Consortium (ERICA) for ERNs information, European Strategy Forum on Research Infrastructures (ESFRI roadmap), advances in the Orphan drug regulation, the United Nations' Resolution on RD, initiatives, partnerships or Joint Actions (JA), like the TEHDAS JA (Towards the European Health Data Space Joint Action), and other sources such as scientific literature search or reports.

1. Feedback obtained from patients

EURORDIS is running the Rare 2030 Action campaign. The European Union and its members are being urged by the EURORDIS to adopt an action plan for rare diseases (R&I).

The document should relate RD strategies and plans at the national and European levels and be comprehensive.

The goals were defined at the document titled "A Working Proposal: Europe's Action Plan for Rare Diseases" and concentrated on ways to stimulate European leadership in R&I, to reduce premature deaths from RD along with the economic, social, and psychological burden of RD and delays in diagnosis. Aside from the foregoing, this document demonstrates the added value of RD use cases in digital technologies and data analytics, as well as the importance of focusing on the rarest diseases through international collaboration.

The Rare Barometer involved three thousand seventy-seven hundred patients and caregivers in 70 countries, representing 978 rare diseases. The results of the study were published in a document entitled "The future of rare diseases: leaving no one behind!" with the main conclusions of neediness of the integrated approach to research, diagnosis, treatment, health and social care, taking into account technological advances, regulatory framework, and the patient organization's role in research.

Due to the epidemiological situation in the world, the patients' needs still require broadly understood attention.

It is crucial to remember the effects of the COVID-19 pandemic crisis on RD patients at all levels, including research and innovation, clinical, social, and psychological. Research on the actual impact is therefore anticipated (and required) in the upcoming years.

1. Input from the ERNs, related infrastructures and collaborating networks

The European Rare Disease Research Coordination and Support Action consortium (ERICA) leveraging all the innovation and research potential of the ERNs, by setting goals (enhancing networks, achieving effective data collection strategies and high quality clinical trials) that also represent needs which realization will help patients receive better diagnosis and treatment.

The other relevant needs identified by Board of Member States (BoMS) on ERNs (29 April 2021) are:

- standardisation and FAIRification (including the EJP RD Virtual Platform) due to diversity of registries' designs and the platforms used across the ERNs.
- research on and development of innovative sustainability models in order to search for sources of financing in MS.
- building knowledge and capacity through training modalities for ERNs participants, including on-line training platforms.
- collaboration and optimisation of synergies.

There are discussions on adding three potential new ERNs: on rare gynaecological and obstetric diseases, on rare infectious diseases, and on rare mental diseases.

Besides of above a report on barriers to share data across borders was published in February 2022 by the Joint Action "Towards European Health Data Space" (TEDHAS JA). Four themes grouping the barriers were identified: Data, Infrastructure, Trust and transparency, and Legal.

2. **Feedback from the WP2's Survey on National Plans and Strategies and the workshop "Alignment of national rare disease strategies with the European Joint Programme on Rare Diseases (EJP RD)":**

The need for a good connection and alignment with collaboration and knowledge-sharing, especially strengthening the underrepresented countries and national resources improvement remain critical points for R&I in EU-13 countries.

The constitution of National Mirror Groups (NMG) is still a step to fulfil. Balance between open science and market values represents a need if a business-like approach is adopted.

3. **Joint Transnational Calls (JTC) and R&I needs on RD:**

The 2022 JTC call, launched in December 2021, involves the topic "Development of new analytic tools and pathways to accelerate diagnosis and facilitate diagnostic monitoring of rare diseases". The topic for the EJP RD-JTC 2021 relayed on social sciences and humanities research that improved healthcare and daily life aspects of RD patients.

4. **IRDiRC's contributions to the delineation of R&I needs:**

The conclusions of IRDIRC's 25th Consortium Assembly Meeting affirms that improvement of discourse, communication and activity dissemination within global stakeholder collaboration will facilitate attainment of the goals for 2027.

Improvement of natural history methodologies and economic evaluations also are presented as needs for untreated RD. To the previous and currently ongoing 9 Task Forces set by IRDIRC they added the two new ones in order to tackle specific needs of the RD community. Connected with regulatory issues and methodologies on drug repurposing and deficiencies in research on Disregarded Rare Diseases.

5. **Information from the Directorate-General for Research and Innovation, and Horizon Europe Programme (2021-2027):**

The need of robust infrastructures for data sharing (including the FAIRification of data) and reinforcement of the connection between the private and the public sectors were highlighted as key issue. Public Procurement of research and innovation is assisting the healthcare sectors to develop solutions for urgent and unmet needs.

According to Horizon Europe Programme - the partnership proposal for RD was ready to be published in the EC page in February 2022, showing not only the state of the preparation, but also next steps for the development of the Strategic Research and Innovation Agenda.

6. **Feedback from other domains (horizontal) connected to R&I needs: Diagnosis & Healthcare, Regulatory & ethics, EU competitiveness & innovation**

The "H-CARE Survey" conducted by EURORDIS shows that there are still several needs to fulfil in the healthcare pathway for RD patients. Healthcare experiences of RD patients are declared as worse than those with chronic diseases. From a patient perspective, (especially after the covid-19 pandemic), the most critical need for improvement is in the areas of clinical follow-up, empowerment and psychological support. Furthermore, the results of the survey demonstrated the role and importance of multidisciplinarity and expertise by ERN's for identifying the gaps and improving patients' quality of life.

In the document called "Assessment of the EU Member States' rules on health data in the light of GDPR" it was stated that the application of the GDPR and national laws is heterogeneous, with several operational and legal issues.

This makes cross-border cooperation for research even more challenging in addition to healthcare provision.

The themes and their barriers (and thus needs) on Infrastructure, Legal and Trust and transparency issues, shown in the TEHDAS JA report, include the heterogeneity of national laws/rules on health and research data in addition to GDPR interpretations, with different derogations.

Besides, the lack of standardized data sharing agreements with private sector obstructs the public-private collaboration.

Orphan Regulation (OR) is still under construction, but report of feedback and impact obtained from the public consultation (published in November 2021) showed the most significant obstacles such as: the introduction of new drugs include insufficient development of unmet needs, the inequities in availability and affordability of treatments, and the inadequate adoption of scientific and technological developments.

Public consultation on how to improve access and uptake of new medicines in Europe was published in June 2021 (report from the conference on R&I days). There is a need for accelerating innovation ecosystems and new entrepreneurships, which can be fulfilled by contacting research institutions, academia, industry (SMEs) and investors.

Training researchers is very important for progress in diagnostic and to raise the competiveness and the need to implement innovation in rare disease treatment regimens. In addition, targeted training for researchers will improve their skills and competitiveness, enabling diversified career paths and mobility across sectors. Overall, European R&I policies aim to strengthen innovation cohesion and increase the competitiveness of the EU as a whole.

Based on the above-mentioned documents, in the fourth edition of the document summarizing research and innovation needs D 2.6, the current priority needs have been mapped, which include:

- Integrating and optimizing the healthcare pathways, social and daily needs of RD patients to achieve holistic care (including access to appropriate treatment, care and psychosocial support in a patient-centered manner).
- Digitization of healthcare, access to information, telemedicine, enabling and improving access to teleconsultation of patients with rare diseases around the world.
- Access to diagnostics and medications.
- Advances in personalized medicine.
- Efficient and equal healthcare delivery for patients with rare diseases.
- Capacity building for physicians, patients and families and sharing knowledge across borders.
- High-quality care, with new models of care, taking into account sustainable development.
- Accelerate orphan drug authorization processes, facilitate the regulatory pathway for potential therapies and drug re-use, including access following regulatory approval.
- Facilitate strategic global collaboration through IA tools / tools / platforms / data sharing and diagnostic and infrastructure platforms (accessible and coordinated diagnostic ecosystem).
- Identifying potential regulatory obstacles in basket testing. Building capacity to combine innovation, research and business (training for trainers, aligning with national programs, coaching).
- Facilitate the adoption and implementation of RWE in the healthcare decision. Marketing Authorization Applications (MAAs) based on RWE.

Identified synergies with regional, national, European and international RI and strategies for optimal use.

- Access to orphan drugs by small or underdeveloped countries.
- Increasing the attractiveness to the pharmaceutical industry thanks to clear criteria (financial and non-financial).
- Identifying barriers to access to standard care products.
- Facilitate and improve data sharing in health research (EC space / ecosystems, e.g. European Health Data Space (TEHDAS), European Health Research and Innovation Cloud (HRIC), OpenScience)
- Capacity building on the drug development path for therapy developers.
- Health economics research through dedicated calls and funding, and support from HTA, standards and evidence base.
- Identifying scientific, legal, and regulatory issues in emerging therapies and technologies, and assisting with research and development procedures.
- Develop legally and ethically sound contracts for the collection and sharing of health and genetic data, including appropriate consents (ELSI framework) for data sharing and available innovative technologies such as artificial intelligence.

6. Conclusions and next actions

The upcoming final year of the programme will take stock of what has been achieved so far but will also contribute to define new directions for action in the field of rare diseases.

For this purpose, a final mapping exercise will be carried out and the identified needs of the RD community throughout the years and proposals to meet them will be summarised in the next "Mapping Research and Innovation Needs". Further actions will be taken to improve coordination & alignment of funding and national actions also with innovation on translation of research approach.

The process of creation, promotion and cement of National Mirror Groups was initiated in previous years. The first half of 2022 was crucial for the work on the constitution of new national groups among the beneficiary countries of the EJP RD program. In addition, new contacts have been made in each beneficiary country to

start and help them build national mirror groups based on countries where they are already created and well-organized.

A development model with good practice is pertinent to realize this task. The First Report from Strategic Workshop with national policy makers, (Del 2.25) was finalised and contains highly relevant input collected from the workshop, related to key points on NMG building, policies, the forthcoming Partnership, needs, including specific-EU-13, and strategic actions among other. Another important activity that was already addressed during the "Strategic Workshop with National Policy Makers" is standardization and assistance in meeting the needs of the EU-13 countries for Rare Diseases.

Other domains beyond scientific requisites, such as diagnostics and healthcare, competitiveness and innovation, and regulatory and ethical concerns (e.g., renewal of European actions and alignment at the national level, or acceleration of innovation ecosystems), will continue to be evaluated.

Under individual WP tasks, it is worth highlighting the most critical actions planned for the following year.

- The subsequent use and implementation of the established prioritization criteria will be reviewed and updated considering the new developments, needs and changes in the rare diseases ecosystem.

- The last mapping of Research and Innovation needs will be prepared and composed of the previous series, with the addition of the activities and outcomes that EJP RD has carried out to tackle the detected needs. The documents constantly contain the main points, such as internal input from the EJP RD' operating group, International research strategy developed by the International Rare Diseases Research Consortium (IRDiRC), Yearly analysis of the state of play of funded research and drug development, overlaps and trends at international level, National and EU needs represented by the EJP RD Policy Board with a special attention to EU-13 needs.

- With the same procedures as previous ones and in line with identified research and innovation needs the additional call in 2023 JTC will be launched in December 2022 (after the decision of Board of Funders and refined JTC topics presented in the Fourth List of refined JTC topics).

- Cooperation between EJP RD and IRDiRC still guarantees alignments in objectives and results. The establishment of Task Forces (IRDiRC) helps avoid duplication of efforts in replying to specific needs or bottlenecks and aiming to issue recommendations or concrete actions to overcome the identified obstacle.

- The Management of the medium and longer-term research strategy questions and dedicated linkage with Task Forces of IRDiRC will be continued.

- To have an impact on the activities of EJP RD and undertake strategies at a national level is making a link with the National stakeholders or with existing Mirror Groups. The following step in this task is to continue collecting information from the countries through a dedicated survey, including from those countries not participating in previous surveys on national plans or strategies, with special attention to the needs and obstacles of EU-13 countries. The results and analysis will be compiled in the Fourth Analysis of the national state of play and alignment process with EJP RD. They will be presented with relevant policy makers at the second edition of the Strategic Workshop. After that, all discussions, feedback, actions, and further strategic plans as a result of a Strategic Workshop will be collected in a report, the D2.26 "Second Report from strategic workshop with national policy makers".

- The urgent aim in the following year will be to establish a National Mirror Group (NMG) in each beneficiary country, participating directly in the EJP RD. NMG should be responsible for identifying, discussing and bringing the nation's needs to the upper level. Thanks to them, each country gained a noticeable opportunity to speak up with a united and single voice. The additional value of the existing NMG is aligning each country's policies, strategies, and concrete actions with the outputs of the EJP RD. The EJP RD Coordination team will monitor the general activity of NMG in the final year of the programme, but leaving the functioning of each NMG and the content of the national meetings as an autonomic decision at the national level.

  The first subsequent action will be the transmission of the present Scoping Paper to the T2.3, T2.4 and T2.5 leaders for complementary actions, to the NMGs (if constituted), and within the forthcoming EC Framework Programme.

In relation to the above planned activities, building a European strategy from the essential elements of national ones appears to be a challenge during the program, but could be also a significant contribution in creating effective and coherent European system in the area of rare diseases.

In order to initiate this it is necessary to equalize the level of benefits for the RD community between EU-13 and other members. For this purpose, financial assistance is needed for 13-EU to build an appropriate research and scientific infrastructure, as well as to increase access to diagnostics and care for RD patients. Another important challenge is the unification of the law and the regulatory issue that would allow the free, lawful exchange of information on treatment outcomes, in order to create a general database. It is also important to exchange information and register research and work on new forms of therapy in RD conducted by members of EJP-RD.

Future action is fundamental to resolving all of these mentioned needs and problems. Taking into account prioritizing themes to be implemented under Pillar 0

("Coordination and cross-cutting actions" - the central coordination pillar that supports the activities of the four main pillars of the EJP RD) the proper coordination to align funding and national actions is essential as well as innovation in the translation of research results, research progress and promotion in diagnosis and treatment, and a holistic approach to the patient.

The diversity and complexity of actions and the deepening cooperation of the most important international and national institutions raise the environmental and stakeholders' awareness of the achievements and challenges facing patients. Moreover, this creates opportunities to reduce barriers and obstacles to accessing treatment and improve patients' quality of life.

In recent years, it has been observed that thanks to the involvement of national institutions and large research infrastructures in the program, the field of rare diseases is increasingly considered as relevant by society and policies. More and more national governments are developing federal programs, rare disease centers, collaborations with other actors working on rare diseases and rare disease groups.

The voice of the patient is gaining importance. Creating virtual platforms, data sharing, registries, etc., is a big step in access to diagnosis and knowledge, but it is still a regulatory challenge.

With reference to above, it is worthwhile to emphasize the most important issues from the end user's point of view, which should initiate the actions and, as a result, lead to meaningful changes :

- Legislation and unification of the law regarding the exchange of RD patients' databases
- Strengthening the case-research infrastructure and the possibility of legally submitting the results to a general database accessible to the Member States
- Additional, special assistance to create and improve international collaboration with clinicians and scientists for the development of ATMP
- Creating multidisciplinary, academic centers providing holistic care (diagnostics, counseling, psychological support, treatment, access to ATMP therapy) for patients with RD
- Workshops, internships for scientists and clinicians from the Member States to exchange information and own experiences in order to improve qualifications and standardize the treatment process.

- Computerization and digitization of healthcare, patients' access to telemedicine services, the possibility of consulting specialists from various centers of the Member States via IT AI.

In conclusion, it is also significant to underline the importance of the continuation of the program in the next European partnership for rare diseases, as collaboration can achieve the goals set and take a step towards achieving a sustainable ecosystem for research and a holistic approach to rare disease care.