# EJP RD
# European Joint Programme on Rare Diseases

H2020-SC1-2018-Single-Stage-RTD
SC1-BHC-04-2018

Rare Disease European Joint Programme Cofund

Grant agreement number 825575

# Del 2.12
# 5th Scoping Paper

**Organisation name of lead beneficiary for this deliverable:** MUW

**Due date of deliverable:** month 63

**Dissemination level:** Public

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# Executive summary

The European Joint Programme on Rare Diseases (EJP RD) is an international programme bringing together over 130 institutions from 35 partner countries, aimed at creating an optimal ecosystem for research into rare diseases (RD) and the implementation of the outcomes of that research into clinical practice. EJP RD brings together patient and expert input, and disseminates breakthroughs in research, care, education, and medical innovation in the field of RD. The principal goal of the organization is to support the rapid implementation of results in research focused on RD and RD patients into clinical use – according to the "bench to bedside" principle, across all partner countries.

Work Package 2 (WP2) "Integrative research and innovation strategy", under Pillar 0 "Coordination, Transversal Activities & Communication" of the EJP RD is tasked with mapping Research and Innovation (R&I) needs for RD using a wide array of sources (e.g. the RD Operating Group and Policy Board, patients and caregivers, clinicians, International Rare Diseases Research Consortium (IRDiRC), European Reference Networks (ERNs), European infrastructures, bodies, projects).

With the five-year framework of the EJP RD coming to an end, a summary and review of the global progress of the project, and its contribution to the development of a long-term RD strategy is conducted. As with previous annually published deliverables, the aim is to inform the RD community, comprising all RD research stakeholders, and the general public about the progress achieved throughout the project, underlining the R&I needs to allow for rapid identification, adjustment, and implementation. The series of the scoping paper deliverables has contributed and continues to do so to the promotion and implementation of informed actions, and to the standardization of rare disease procedures among all Member States (MS).

This document is a successor to Deliverable 2.11 (D2.11) – the Fourth Scoping Paper, as a guiding tool for all stakeholders of the RD community – an instrument aimed at facilitating the response to the pressing R&I needs. Regular publication of such results allows for up-to-date and targeted initiatives of the RD community.

This document presents the key information published in the confidential D2.7 "Fifth Summary document on Research and Innovation (R&I) Needs." The key conclusions of the Strategic workshop "Alignment of national rare diseases strategies/activities with EJP RD" which took place on 5 July 2023 in Brussels, summarized in the confidential D2.26 "Second Report from strategic workshop" are also outlined, with particular emphasis on the clinical aspect of RD care.

A section of this document is devoted to a brief discussion of the experience of the EU13 MS – as outlined in EJP RD WP2-led surveys, and as reflected in government-sanctioned strategies and plans, and the conclusions of multilateral debates in the domain of RD.

Insufficient R&I infrastructure and RD strategy financing, including the need for a legislation-based answer to the question of efficient, equitable, and ethical reimbursement strategies, as well as educational programme gaps leading to social isolation of RD patients and caregivers in EU13 countries remain a significant challenge to be tackled in by all MS. However, many breakthroughs have been made in the field of R&I by researchers based in these MS. Great synergies can arise from cross-border cooperation, knowledge, and capital flows.

Identified mapped needs outline six key aspects to be addressed:

1. developing sustainable RD strategies at the European level: National Mirror Groups action; National Plans and Strategies for RD development; country-level need identification and resource use optimization; enhancing cross-border capital and knowledge flows, as well as training opportunities; European-level fund sourcing for health networks; new economic models for development and commercialization of orphan drugs; new, equitable reimbursement strategies;

2. extensive network development – 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; conducting cross-border clinical trials – pairing EU13 and EU15 countries; enhancing cross-border capital and knowledge flows, as well as training opportunities; European-level fund sourcing of health networks;

3. gathering, managing, and utilising high quality data in clinical practice: ensuring consistent high quality of clinical trials and resulting data; ensuring data FAIRification; improving cross-border data sharing; innovative uses of big data – machine learning and artificial intelligence (AI) in newborn screenings, diagnostics, and clinical practice;

4. digital harmonization and optimization on the European level: creation, implementation, continued quality monitoring, and improvement of coherent strategy at a European level for electronic health records, registries, e-infrastructures, open e-networks, virtual biobanks, protocols for data collection, data repositories;

5. strengthening the patients: holistic patient-centred approach; engaging patients and patient organizations in drug development and clinical trials; patient's voice in managing data and ethical dilemmas stemming from digital technologies; paediatric population focus;

6. closing the gap between EU13 and EU15 countries: clinical trial infrastructure development in EU13 countries; conducting cross-border clinical trials – pairing EU13 and EU15 countries; training opportunities for EU13 healthcare professionals; economic models for development and commercialization of orphan drugs and reimbursement strategies adapted to financial capabilities of EU13 countries;

**HIGHLIGHTS AND NEXT ACTIONS**

● This is the ultimate mapping effort, which aims to encapsulate all needs identified throughout the series of confidential Summary Documents on R&I Needs and outlined in their publicly disseminated counterpart series – Scoping Papers, during the five years of the EJP RD project framework. The final mapping of R&I needs, published in M53, included syntheses from earlier years and an assessment of EJP RD initiative alignment with the R&I needs mapped.

● The key mapped needs of the RD community remain the coordination and alignment of funds – with the underlining of need for new reimbursement strategies, governmental and private capital initiatives, also in the cross-border setting, supporting the translation of research results into therapies, particularly in the paediatric population, and the overarching goal of reaching a holistic R&I ecosystem, with the input of all stakeholder groups.

● There remains the need for continued evaluation of feedback from horizontal domains connected to R&I needs, such as diagnostics and healthcare, competitiveness and innovation, and regulatory, and ethical issues.

● The upcoming "European Rare Diseases Research Alliance" ERDERA initiative under Horizon Europe represents the next step towards sustainable research ecosystem and an all-encompassing, multi-stakeholder approach to RD.

● In an optimal vision of the future, the fulfilment of which requires continued need mapping and response, in line with the vision and goals of IRDiRC all people living with a rare disease will receive an accurate diagnosis and care within a year of seeking medical attention, if the disorder is known in literature. The availability of therapies will be made a reality, with 1000 novel therapies authorized by then, and methodologies will simultaneously be developed to assess the impacts of diagnoses and treatments on the patient's wellbeing and quality of life (QoL). Individuals with previously undescribed disorders will enter a coordinated diagnostic and research pipeline.

## List of abbreviations

| | |
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| AI | Artificial Intelligence |
| ATMP | Advanced Therapy Medicinal Product |
| AWP | Annual Work Plan |
| D/Del | Deliverable |
| EC | European Commission |
| EHR | Electronic Health Records |
| EJP RD | European Joint Programme on Rare Diseases |
| EPTRI | European Paediatric Translational Research Infrastructure |
| ERDERA | European Rare Diseases Research Alliance |
| 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 |
| IMI | Innovative Medicines Initiative |
| GDPR | General Data Protection Regulation |
| IRDiRC | International Rare Diseases Research Consortium |
| JTC | Joint Transnational Call |
| MS | Member State |
| NMG | National Mirror Group |
| NBS | Newborn Screening |
| QoL | Quality of Life |
| R&I | Research & Innovation |
| RD | Rare Diseases |
| SMEs | Small and Medium Enterprises |
| TRANSFORM | European Alliance for Transformative Therapies |
| WP | Work Package |

# 1. Introduction and Objectives

The following is the final, 5th entry in the Scoping Paper series, issued annually as part of activities undertaken by WP2 "Integrative research and innovation strategy", organized under the transversal Pillar 0 "Coordination, Transversal Activities & Communication" of the EJP RD. The main objective of the Scoping Paper series was to publicly disseminate the results of work carried out under the scope of WP2, providing an accessible summary of the annual updates enclosed in the confidential, consortium-access only "Summary Documents on Mapped Research and Innovation Needs". The Scoping Paper series allows for the assessment of the initiatives

undertaken during a given year on the mapping of needs in the field of R&I on new forms of holistic care for rare diseases.

The state of the aforementioned mapping of R&I needs (in accordance with Task 2.2 "Mapping of Research and Innovation Needs") was updated and submitted by 2023 within D2.7 "Fifth Summary Document on Mapped Research and Innovation Needs", 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 "Final List of Prioritization Criteria" and D2.2 "Prioritization scheme including decision-making process" – the result of initiatives carried out under the scope of Pillar 0 – provide reference to mapping needs and priorities. WP2 is specifically focused on the development of the EJP RD R&I Strategy with the participation and input of all related stakeholders.

WP2 of the EJP RD has identified the importance of joint exchange of knowledge and research results while searching for efficient models for sustainable R&I processes, overcoming the difficulties of cross-border data collection, standardization, and unification (Findable, Accessible, Interoperable and Reusable – FAIR principles) between partner countries. The fulfilment of this need is visible in the regular updates on the mapping of R&I needs in a mapping series via report publishing and public-level dissemination.

This document functions as a summary of the initiatives undertaken over the past 5 years, the conclusions, results, and planned future actions in relation to institutions and the RD community, drawing from the sources cited below. A comprehensive review of objectives set, the scope of activities of various entities, and their connections is provided.

It focuses on presenting the identified needs of all RD stakeholders – primarily patients, researchers in academic centres, the medical community, planners of research infrastructures, and legislators of MS, with particular attention to EU13 countries. A holistic approach to the system dedicated to servicing the RD community requires solution recommendation and implementation at a supra-national, European level – the biggest issues dealing with cross-border data management.

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). The results and conclusions function as a guidance for the National Mirror Groups (NMGs) and under the Horizon Europe program.

**The most important annual goals and activities in the Fifth Scoping Paper (D2.12):**

● Summarize the R&I needs scrutinized, updated, reported, and answered across the series of deliverables "Summary Documents on Mapped Research and Innovation Needs" (D2.7, D2.6, D2.5, D2.4, D2.3) focusing on D2.7 (confidential)

● Support a mid- and long-term RD R&I strategy in collaboration with the IRDiRC

● Support the creation of optimal conditions for research and a holistic approach to RD care

● Recognize the difficulties of EU13 countries meeting their RD needs and work towards ameliorating the relative financial, and infrastructural shortcomings through international partnership coordination, and adjustment of financing, and national activities

● Summarise the policy, educational, and clinical takeaways of the Brussels workshop on 5 July 2023 in the field of integrative R&I strategy "Alignment of national rare diseases strategies/activities with the European Joint Programme on Rare Diseases"

● Support future RD R&I programmes and their agendas – Strategic Research and Innovation Agenda (SRIA) for the future European Partnership on Rare Diseases ERDERA under Horizon Europe

D2.12, prepared by MUW, is the result of close cooperation with the leaders of Task 2.2 (ISCIII, ISS). It should be emphasized that, like previous documents on this scope (D2.10, D2.9, D2.8, D2.7), WP2 is devoted to the development of an EJP RD research and innovation strategy in conjunction with all related stakeholders.

The overall objective of the deliverable D2.12 – the Fifth Scoping Paper is to summarize several deliverables of WP2, and therefore contribute to an overarching assessment of initiatives undertaken by WP2, and the wider EJP RD.

Public dissemination is aimed at stakeholders at a national and international level to influence activities at all scopes and improve cooperation in the field of RD – signalling to the RD community needs and relevant WP2 initiatives.

## 2. Sources for preparation of the Fifth Scoping Paper

This document functions as an update to D2.11 "Fourth Scoping Paper," drawing primarily from the confidential D2.7 "Fifth Summary document on Mapped Research and Innovation Needs."

The contents of D2.1 "Final List of Prioritization Criteria" and D2.2 "Prioritization Scheme, including decision-making process - Guidelines for Prioritization" will be briefly outlined in the following subsections, as they build the foundation underlying the functioning of the EJP RD – an assumption flexible adaptation of the project to real needs in the field of research and innovation, based on mapped key priorities at a given moment. A

more detailed reference to D2.1 and D2.2 is provided in previously published deliverables D2.8 "First Scoping Paper" and D2.9 "Second Scoping Paper".

This document will also provide an overview of the policy, educational, and clinical takeaways presented and discussed during the hybrid mode Brussels workshop on 5 July 2023 in the field of integrative R&I strategy "Alignment of national rare diseases strategies/activities with the European Joint Programme on Rare Diseases". An outline of gathered insight regarding alignment with EJP RD and NMGs, national and European RD strategies – with particular focus on bridging the gap between EU15 and EU13, rare disease education, the role of research infrastructure – including the future role of AI infrastructure in diagnosis and treatment optimization, and the challenges regarding multi-centre (multinational) clinical research, orphan product development, and reimbursement of therapy.

The experience of Poland as a EU13 country, with both key issues related to infrastructure and financing persisting, but also significant policy breakthroughs made in recent years, reflected in the contents of the Polish National Plan for RD[1], as well as the conclusions and recommendations of the report following the conference of 1 February 2023 "Healthcare Policy Summit – Rare Diseases 2023"[2] were used in the process of recommendation formulation.

## 3. Summary results

This section aims to outline the activities carried out within the individual tasks of WP2 based on the objectives set in the former Scoping Paper and Annual Work Plan (AWP). The needs of the RD community remained at the centre of focus of this year's initiatives, allowing for drawing of conclusions and their inclusion in formal deliverables.

It is noteworthy that the actions presented below have considered the needs and opinions of a wide stakeholder group – with the crucial input of patients. Emphasis has been placed on both areas such as diagnostics, holistic care, and treatment, as well as legislation, ethics, competitiveness, and innovation.

Within WP2, Task 2.1 focuses on the "Priority scheme for EJP RD activities". Prioritization is crucial due to the fundamental problem of resource allocation and the lack of physical and economic ability to meet all identified and mapped needs simultaneously. D2.1 and D2.2 provide a scheme for prioritization to evaluate needs

[1] Council of Ministers of the Republic of Poland (2021) "Plan dla Chorób Rzadkich". Available at: https://chorobyrzadkie.gov.pl/sites/choroby_rzadkie/files/2023-08/za%C5%82.%202%20uchwa%C5%82a%20plan%20dla%20chor%C3%B3b%20rzadkich.pdf

[2] Instytut Rozwoju Spraw Społecznych, Gierczyński J. et Al. (2023) "HEALTHCARE POLICY SUMMIT CHOROBY RZADKIE 2023 Raport z konferencji naukowej, która odbyła się w dniu 1 lutego 2023 r. w Warszawie w trybie hybrydowym". Avaialble at: https://www.researchgate.net/publication/369538705_HEALTHCARE_POLICY_SUMMIT_CHOROBY_RZADKIE_2023_RARE_DISEASES_2023

based on criteria of scientific evidence aspects, demands of the RD community, regulatory and societal concerns, and financial and technical feasibility.

**D2.1 "Final list of prioritization criteria"**

This deliverable acknowledges the need for sustainable prioritization to order mapped needs and actions that either contribute to EJP RD objectives or stand in need of further exploration. A set of four general (applicable to all EJP RD activities) prioritization criteria are developed to allow for prioritization based on the input of stakeholders (patients, research community members, policymakers, European Reference Networks (ERNs), constituting the NMGs) - obtained through a survey. The four general criteria comprise aspects of scientific evidence, demands of the RD community, regulatory and social concerns, financial and technical feasibility.

The criteria, applied via a prioritization scheme (developed in D2.2) would fulfil the following set objectives of the prioritization activities, consisting of:

- the support and evaluation of the decision-making process by which to prioritize the mapped needs and activities that contribute to the achievement of the EJP RD objectives
- the facilitation of the future planning of activities under EJP RD's AWP
- the applicability in the event of a deviation – spontaneous or envisioned – from EJP RD's plans (under guidance of the Coordination Team)
- the further improvement of criteria, indicators and methodologies used in the prioritization process, following the assessment of the decisions made.

**Categories of criteria used in the prioritization process:**

(i) Scientific evidence aspects: the justification of undertaken initiatives on scientific data and the knowledge impact of such actions – a positive effect on RD research, applicability to a wider range of RD, and technological innovation.

(ii) RD community demands: the level of interest expressed by the wide RD community (patients, researchers, clinicians, health care providers, industry, and other stakeholders which are involved in the RD wider ecosystem). NMGs play a key role in respect to the gathering (through surveys, questionnaires, and consultations) of data regarding perceived relevance of EJP RD actions in impact on RD patients and caregivers QoL, future, and applicability in clinical practice.

(iii) Regulatory and societal concerns: the society's value and vision regarding RD, including possible reluctance to certain therapeutic approaches, and the monitoring of differences between EU-level and national legislation that may impact on clinical trials, reimbursement, insurance, and patient choice of treatment site.

(iv) Financial and technical feasibility: the evaluation of actions in a cost to benefit analysis, and an execution capability analysis, as well as the assessment of financing and allocation of resources in research for personalised treatments for different RDs,

according to financing capacity (including self-sustainability, and other, external sources of funding), the possibility of obtaining positive results, and their translation perspectives into clinical applications.

**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, ii) the community's outlook on the proposed initiative, and its usefulness, iii) the societal vision, and regulatory facilitations in the introduction of the innovation, iv) validation of economic and technical feasibility.

• Access to consistent data quality (P2): i) the potential to strengthen research at all levels via the creation or validation of relevant tools, e.g. creating common databases, ii) collaborating with the RD patient community to exchange experiences, sample research, assess treatment results, iii) compliance with the General Data Protection Regulation (GDPR), standardization regulations on data exchange between RD centres and privacy regulations, iv) social burden assessment based on the annual cost of living of a RD patient, calculation of the economic burden – the cost of current therapies or palliative care per patient or 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 RDs by building common resources and validated analytical tools, ii) active participation of patients in population and epidemiological studies, 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, healthcare providers, and regulatory agencies, iii) exchanging information between patients and agencies on research methodologies, negotiating 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. Guidelines for prioritization."**

D2.2 develops on the selected prioritization criteria specified in D2.1 to provide guidelines for their correct application where necessary and presents 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. The importance of subsequent validation is underlined. Therefore, the two deliverables D2.1 and D2.2 should be applied in conjunction.

Prioritization is defined in the document as "the process of deciding what should be built and when, based on what will bring most value to the user (in wide sense) and what is feasible." The purpose of prioritization of mapped needs is to optimize the use of existing resources to achieve the objectives of the EJP RD for the benefit of all stakeholders – especially RD patients, the group at the centre of EJP RD's focus.

Such optimal use of limited resources requires transparent and non-arbitrary decision making. Therefore, a dual approach to these two closely related processes, and their interactions should be ensured: prioritizing and making decisions.

**D2.7 "Fifth Summary document on Mapped Research and Innovation Needs"**

Summary documents on mapped R&I needs are developed annually and function as reference for the Policy Council and ExCom for their prioritization. The summary document taken as a reference in this Fifth Scope Document is the " Fifth Summary document on Mapped Research and Innovation Needs " (D2.7). This is a confidential, consortium-access only report, finalised in 2023. The Fifth Summary Document aims to provide a final update of the series devoted to mapping R&I needs, and to compile the progress in the field made through the five-year lifetime of the project – reflected in previous deliverables D2.3, D2.4, D2.5, and D2.6.

The ultimate document in the series includes two sections:

- Section I: Alignment of EJP RD activities with R&I needs mapped in the first three years of the programme [D2.3, D2.4, D2.5]. This section is dedicated to the assessment of the degree of covering of needs by EJP RD activities, under IRDiRC goals

- Section II: Summary Results for the current mapping of Research & Innovation Needs (continuing with the series, year 5). Two additional subsections are included: Paediatric and Permanent needs.

**The sources for Section II are outlined below (for the additional subsections, mapping utilises a combination of these sources):**

• Patient's perspective – from EURORDIS' information gathered through actions and barometer consultations conducted, and the conclusions of the NORD summit.

• Joint Transnational Calls (JTC) - the topics already approached in the Calls

• IRDiRC's international research strategy – information from the Scientific and Constituent Committees, Task Forces, and the State of Play of RD initiatives.

• Directorate-General for Research and Innovation of the European Commission and Horizon Europe – the issues outlined and debated, and the conclusion of the R&I Days in September 2022 – including progress in the Horizon Europe programme 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), European Paediatric Translational Research Infrastructure (EPTRI), 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

Priority areas requiring action are outlined by EURORDIS in the *third strategic objective*, part of the complex strategy for the period until 2030. Three areas of greatest focus are identified – answering the new challenges arising from development and implementation of health digital technologies, and resulting data gathering and management needs, the strive for the development of a holistic life-long approach to RD patients, and the support of their inclusion in society. These are supplemented by objectives of strengthening research and knowledge in the field of RD, early diagnostics, supporting both development of and access to already available transformative or curative treatments, the integration of care, and cross-border health care, including the reconciliation of national and European healthcare pathways.

The importance of data management, as an area originating multiple needs, has been repeatedly outlined in the R&I need mapping series. RD patients are highly willing to share data to foster advances in health and research. Advances in data standardisation – including the use of adequate RD standards, nomenclatures, and ontologies (ICD-11, ORPHA codes), improving data safety, optimisation of electronic health records (EHR), and ensuring they are harmonised and interoperable across European borders will allow for these benefits for R&I to be realized. This requires both an allocation of appropriate resources (at both the national and European levels), and development of robust standards to ensure data safety – secure, ethical, and responsible use and sharing. A need for improving stakeholder digital literacy in the field of health – particularly in reference to especially vulnerable categories such as genetic data also arises.

Patient needs were also reflected in the topics undertaken during the 2022 National Organization for Rare Disorders (NORD®) "Rare Diseases and Orphan Products Breakthrough Summit". The importance of accelerated and equitable access to treatments was underlined – with needs visible at every stage of therapy development from initial research, through clinical trials, to access to personalised therapies and the question of reimbursement. Equitable representation in research, involvement of

patients in all steps of clinical trials, accelerated approval of medicinal products, and equitable access to them, including innovative reimbursement strategies to tackle the costs concurrently growing with the advancement in advanced therapies are areas where the RD community demands action. Apart from the costs of new gene and cell therapies, the complex connected ethical aspects, relevant to genetic modification and testing, must also be acknowledged and tackled.

Diagnostics unsurprisingly remains an undeniable area of need – with postulates of newborn screening (NBS), shortening of the diagnostic pathway, and equitable access.

The needs of RD patients are only exacerbated by geopolitical instability – with the most severe, fast-evolving, and long-term challenges visible due to the war in Ukraine. Accessibility of medicines, supplies, basic needs, medical care and consultations, psychological support, and possibility of leaving the country are all key areas in which the conflict has caused disruptions. Moreover, the loss of contact with registered RD patients has been observed.

New needs have emerged not only in Ukraine, as due to displacement of refugees, strain has also been placed on the accepting country and infrastructure. Specific RD patients' needs – secure and disability-adopted housing, basic need fulfilment, psychological support, medical resources are stressed in reports from Moldova, Poland, and Romania.

## 2. Input from ERNs, related infrastructures, collaborating networks, and other initiatives

ERNs have a critical connection to national healthcare systems – the need for expansion with greater representation in terms of both countries and diseases was highlighted during a high-level ministerial conference in February 2022 in Paris. Data management within ERNs has also been identified as the origin of many needs. ERICA organized a multi-party workshop with the objective of developing a data management strategy for ERNs. The discussed topics included innovative healthcare and clinical data use in research, registry formation (according to the principle of sustainability – to ensure funding for long-term viability), ensuring quality data and its FAIRification, data sharing, governance, and management, while tackling safety and privacy issues. The role of the EJP RD Virtual Platform (with specific requirements for data holders and users) was underlined as a response to the need of improved collaboration and patient's involvement in the data collection process.

The Innovative Medicines Initiative (IMI) recognizes, by launching responsive projects, needs relating to data gathering, sharing, and re-use. The promotion of participation in studies and facilitation of recruitment are also parts of the project line-up. The screen4Care initiative launched by IMI aims to shorten the diagnostic time by promoting NBS – genetic testing and genomic technologies – and implementing AI algorithms to analyse health records.

The ESFRI Stakeholders Forum in 2022, a platform for the engagement of RD stakeholders and the exposure of their interests and needs, in its constitution outlined four points relevant to RDs:

- Increasing of stakeholders' involvement in need identification. Cooperation between research institutions.
- Addressing the visibility and sustainability of smaller research institutions and their resources (e.g. academic communities).
- Increasing expert access and mobility. Awareness raising. Scalable, sufficient, long-term investment coordination.
- Acknowledging at national level of distributes and federated resources.

These needs are supplemented by those remarked by the EU Council for RI and innovation – long-term sustainable investments in the European RI ecosystem, training and capacity building (with recognition of career development and gender balance), increased private capital investments in European innovative enterprises, and finally the recognition and reducing of the innovation gap between MS – with promotion of tailor-made local innovation policies.

## 3. Feedback from the WP2's Survey on National Plans and Strategies

The importance of integration of actions undertaken at national and European levels cannot be underestimated and requires enhancing of coordination and strategic planning at both scopes.

Within Task 2.5 "Translation/impact of prioritization on national and EU strategies" of WP2, aimed at gathering data on National Strategies and Plans for RDs, a survey was distributed yearly as part of the EJP RD complementary actions performed at national level. In 2023 the survey has been spread to 36 countries and answered by 25 (including all EU13 countries), a 69% participation rate. The results were further discussed during the Strategic workshop "Alignment of national rare diseases strategies/activities with EJP RD" on 5 July 2023, which will also be outlined in this document.

It is worth noting that according to the survey results, 24 of the responding countries (96%) have a National Plan or Strategy for RD that is either active, approved but not active, expired, under renewal, under approval or under development – countries which have undertaken any action in this direction, with the only exception of one country.

## 4. Joint Transnational Calls (JTC) and R&I needs on RD

The JTC2023 call, launched in December 2022, involves the first topic from the "Clinical" category – "Natural History Studies addressing unmet needs in Rare Diseases". The objective was defined to be the collection and analysis of comprehensive patient data to define targets for future therapies, while taking into consideration innovation, safety, and efficacy. The proposals were expected to cover

areas such as disease prevalence estimation, diagnostic, prognostic, and therapeutic biomarker/indicator identification, and relevant endpoint identification.

All JTCs followed the same process of preparation with collaboration of funders, participation of experts, and engagement of patients. Briefly, the past topics of JTCs will be outlined:

The topic for the EJP RD JTC2022 was "Development of new analytic tools and pathways to accelerate diagnosis and diagnostic monitoring (including undiagnosed cases) of rare diseases" in the category of "Diagnostics and Patomechanisms."

The topic for the EJP RD JTC2021 "Social sciences and Humanities Research to improve health care implementation and every day with a rare disease" in the category of "Social Sciences and Humanities" relayed on social sciences and humanities research that improved healthcare and daily life aspects of RD patients.

The topic for the EJP RD JTC2020 was "Development of new analytic tools and pathways to accelerate diagnosis and diagnostic monitoring (including undiagnosed cases) of rare diseases" in the "pre-clinical" category.

The topic for the EJP RD JTC2019 was "Research projects to accelerate diagnosis and/or explore disease progression and mechanisms of rare diseases" in the category of "Diagnostics and Patomechanisms."

## 5. IRDiRC's contributions to the delineation of R&I needs

The "State of Play Rare Diseases Research Initiatives 2019-2021", published by IRDiRC classifies RD research initiatives in relation to five thematic needs – shortening of the diagnostic journey, new therapy development, clinical research fostering, stimulation of stakeholder engagement, and those focused on access to care and impact assessment methodologies.

The document points to the relative fewer observational clinical studies being conducted (as compared to basic or preclinical research), with natural history studies – at the focus of JTC2023 – being further underrepresented. Health economics and biorepositories are two fields of study that require further initiatives. There exists a potential identified insufficiency (although it could result from the relative frequency of these RD) of clinical trials directed at renal, skin, immune, ophthalmic, embryogenesis, and endocrine RD.

IRDiRC also points to the need for harmonisation and homogenisation of definitions and concepts in the field of RD, including that of a "rare disease" itself, due to the divergence of FDA and EU views on this matter. This process should include industry and emerging country involvement.

One new Committee was launched – the Regulatory Science Committee addressing regulatory issues, and four new task forces were validated by IRDiRC's Consortium Assembly:

- Funding Models to Support the Spectrum of RD Research and Development
- Framework to assess impacts associated with diagnosis, treatment, support, and community integration that can capture changes along the rare disease patient and family journey
- Functional Analysis
- Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations

The IRDiRC Conference series and the International Congress of Research on Rare and Orphan Diseases-RE(Act) Congress in March 2023 underlined the importance of topics such as: (i) diagnostic, Whole Genome Sequencing, AI, new technologies, (ii) therapeutic development and precision medicine, (iii) regulatory science, (iv) clinical research, (v) gene and cell therapy and (vi) system thinking towards access.

## 6. Information from the Directorate-General for Research and Innovation, and Horizon Europe Programme (2021-2027)

R&I needs identification and response is a crucial part of development of the Strategic Research and Innovation Agenda (SRIA) for the future European Partnership on Rare Diseases ERDERA under Horizon Europe.
During the "European Research and Innovation Days" in September 2022 it was underlined that a strong R&I ecosystem in Europe would contribute to the transformation of healthcare systems and their digitalization, providing greater resilience. The RD related R&I would be embedded in a wider beneficial framework – constructed with pressure placed on knowledge dissemination, communication, engagement of relevant stakeholders at all levels of the R&I process, promotion of an ambitious open science policy, good practices sharing, and impact monitoring. This complex environment would function based on principles of trust and education – with training and increased mobility of young researchers. These goals cannot be feasibly achieved without the support of private sector entities, investments (entrepreneurs, innovators, industry – SMEs and large companies) and their entry into partnerships. Once again, the topic of the gap in the field of R&I between EU13 and other MS was tackled, with a need for performance balancing visible.

The implementation of innovative technologies – AI alongside the need for analysis of large data sets to allow data driven decision-making, blockchain, and metaverse in the R&I setting was also discussed.

## 7. Needs on research & innovation for paediatric population

The challenges and needs of RD patients are exacerbated in the paediatric population. The EPTRI Manifesto on paediatric research points to the lacks in available treatments for children and young patients, with many products lacking adequate

study in paediatric populations. These areas are to be fostered within EPTRI's research plan.

It should be noted that many innovative Advanced Therapy Medicinal Products (ATMP) benefit from early application – in the prenatal stage or in children. This further exacerbates the need for rapid diagnostic and screening measures. EURORDIS has also noted the importance of extensive NBS programmes.

The same document by EPTRI identified barriers to advancement, impeding paediatric treatment research:

- Insufficiency of preclinical information (cell line models, biomarkers and molecular targets, animal juvenile models)
- Lack of studies covering paediatric ages and considering effect of development and growth
- Lack of children-directed innovative study design (modelling, AI application, tools translating R&I into implementable treatments)
- Fragmentation of knowledge and expertise
- Low capacity of data-sharing and interdisciplinary technology development
- Limited participation of patients and caregivers in all phases of R&I
- Ethical and legal issues regarding paediatric research
- Limited market and resulting limited industry interest
- Insufficient interest in fulfilment of children's fundamental rights

Four recommendations were issued for the inclusion of paediatric research under the Horizon Europe plan by EPTRI:

- Securing public funding for paediatric research – to study new paediatric drugs and treatments.
- Exploring a dedicated paediatric research partnership – within the innovative health initiative, ERDERA, as well as the international consortium for personalised medicine.
- Covering existing gaps in paediatric research topics during all R&I phases – under Horizon Europe initiatives e.g. EU4health
- Prioritize unmet paediatric needs in the development of the European pharmaceutical strategy.

The European Paediatric Regulation, through the introduction of the Paediatric-use marketing authorization (PUMA) answers some of the needs by facilitation of processes, market protection, branding, and reductions of fees of products developed exclusively for children.

## 8. Feedback from other domains (horizontal) connected to R&I needs

Apart from needs in the scientific field, the series of R&I needs mapping aimed to bring attention to the transversal needs of the RD community in the categories of diagnosis and healthcare, regulatory action and ethics, and EU competitiveness and innovation. These categories will be shortly outlined.

(i) Diagnosis and healthcare

The gap between medical R&I and implementation in community healthcare is identified as a significant issue. Initiatives should be aimed at closing this gap. There exists a need for the creation of a RD framework to allow for the cooperation of MS within the ecosystem to address the mapped needs and inequities, and to allow for cross-border healthcare provision. Emotional and occupational needs of RD patients, families, and caregivers are also recognized. Access to treatment should also allow for improving autonomy and QoL of all stakeholders. Socio-health aspects of RD cannot be disregarded when devising educational programmes and resources.

At the centre of all actions should be the needs of the person/patient and their access to medical and social care – a holistic approach to RD.

Seven recommendations were formulated by the European Alliance for Transformative Therapies (TRANSFORM) to aid in the achievement of an ideal ecosystem, as demanded by the community:

- Creating a dynamic, patient-centric innovation ecosystem
- Ensuring that regulatory requirements remain appropriate to allow for ATMP development
- Enabling the use of real-world evidence to dispel uncertainty over ATMPs
- Realizing healthcare tariffication systems that support timely ATMP access
- Sharing best practices and recommendations in fields of NBS, testing, and diagnostics
- Promoting new access pathways for sustainable healthcare systems
- Improve infrastructure and cross-border access to transformative therapies

(i) Regulatory action and ethics

Alongside new innovations in RD R&I, new regulatory challenges emerge. The aforementioned IRDiRC's Regulatory Scientific Committee functions to provide expertise to answer regulatory questions, identify new regulatory challenges, and promote regulatory harmonisation – the need for which is particularly apparent in the data gathering and management areas. Data use transparency and correct use are essential, as well as ensuring an adequate scope for data re-use. Ethical challenges associated with big data must be examined by appropriate organizations – the Research Ethics Committee in the case of IRDiRC.

Challenges also involve the alignment of national legislation with European-level regulations, with unalike implementation – e.g. of the GDPR. The increase of patient and caregiver digital healthcare literacy is a companion need.

(ii) EU competitiveness and innovation

Data-related topics remain crucial in this aspect, and they have been addressed in high-level ministerial meetings at the European level. Collaboration and sharing of

data have proven essential and a European framework is essential to allow for this beneficial exchange and accumulation of information. Cross-border cooperation is also required in investments, innovation, training, and funding.

The unmet treatment needs have brought multiple initiatives aimed at tackling them. The EU-funded research initiative REMEDI4ALL (Repurposing of medicines for all) focuses on promoting the repurposing of medicines, bringing down times and costs of drug development by focusing on already approved, discontinued, shelved or investigational therapeutics. The IMI2 and the "Eubopen" projects instead focus on innovative drug discovery calls.

**Strategic workshop - Alignment of national rare diseases strategies/activities with EJP RD – 5 July 2023**

The strategic workshop titled "Alignment of national rare disease strategies with the European Joint Programme on Rare Diseases (EJP RD)" was conducted in a hybrid format, both online and in stationary mode in Brussels, on July 5, 2023. A detailed, publicly disseminated report D2.26 "Second Report from strategic workshop" is available.[3]

Several sessions of the workshop were aimed at addressing critical issues related to Rare Diseases (RD) strategies, alignment with the European Joint Programme on Rare Diseases (EJP RD), and the specific challenges faced by EU 13 countries.

Four sessions were conducted, with short summaries presented below. For a detailed coverage of the sessions, refer to D2.26.

- Session I – "Rare Diseases (RD) strategies/plans - Alignment with EJP RD activities and National Mirror Groups (NMGs)"

This session was devoted to the presentation of the results of a survey assessing the alignment of national RD strategies and plans with EJP RD activities over the five-year time framework of the programme. The vital role of NMGs in coordination and provision of support to initiatives in the RD field was underlined. Emphasis was placed on the situation in EU13 countries – with funding, bureaucratic hurdles in application procedures, and national contact point insufficient support underlined in the survey responses.

- Session II – "From national to European RD strategies"

[3] EJP RD, MUW (2023) "Del 2.26 Second Report from strategic workshop "Alignment of national rare diseases strategies/activities with the European Joint Programme on Rare Diseases" with national policy makers 5th July 2023". Available at: https://www.ejprarediseases.org/wp-content/uploads/2024/02/EJPRD_P0_D2.26_PU_Second-Report-from-strategic-workshop.pdf

The existence of significant barriers and needs particular to EU13 countries was acknowledged. Solutions to target the R&I and strategy gap in the field of RD between EU15 and EU13 countries were explored. There remains a notable absence of a systematic approach aimed at enhancing underrepresented countries' engagement in EU programmes – particularly in taking on coordinating roles or central responsibilities. The issue of underrepresentation of EU13 countries in European-level strategies has been identified to warrant further action within the ERDERA initiative under Horizon Europe, with an entire WP to be dedicated in ERDERA to ensuring increasing the engagement of stakeholders from these countries in future RD activities.

- Session III – "Capacity building to ensure equity and optimize outcomes for RD patients"

The third session focused broadly on improving outcomes for RD patients – a task requiring a multi-sectoral and multi-domain approach. A coherent and comprehensive RD European education strategy, aimed at all RD stakeholders, including healthcare practitioners and society at large, is necessary to empower RD patients, families, and advocates. Infrastructure, including highly specialized centres, plays a key role in the R&I process – translating outcomes into clinical practice, and in improving diagnostic times. Genetic testing and AI solutions were shown to be prospectively significantly beneficial, although presenting important ethical and safety considerations. AI could bypass some conventional limitations in RD R&I – optimizing clinical trials and reducing costs, with prospective use also in diagnostics.

- Session IV – "The future of clinical research and orphan product development – challenges and opportunities for EU13 countries"

EU13 countries were demonstrated to be facing significant challenges and opportunities in the aspects of clinical R&I, and orphan medicinal product development, and reimbursement. New drug introduction is impeded by unmet needs, inequities in the availability and affordability of treatments, and inadequate adoption of the full range of scientific and technological developments into clinical practice. A promising novel therapeutic product was presented, developed in a EU13 country, aimed at the treatment of Epidermolysis Bullosa.[4] A panel discussion assessed the idea of multi-centre, cross-border clinical trials, leading to the dissemination and flows of knowledge and capital across MS borders as an answer to the issue of unequal access to reimbursement therapy, with compassionate use discussed as a potential alternative.

Overall, concluding the workshop, several recommendations were issued, and fields of interest for future action identified, with an ultimate goal of ensuring that comprehensive, effective, and equitable care is provided to all RD patients, also in underrepresented countries, achieved through the synergies of regional, national, European, and international strategies dedicated to the RD community. Advances in

[4] A rare disease related to a defect of attachment of skin layers, causing the skin to be fragile and to blister easily.

personalized medicine must be fostered, promoting the integration and optimization of care pathways with the consideration of social and daily needs of patients. Improving access to diagnostics, treatment, and psychosocial support is essential – it requires enhancing cross-border knowledge sharing and training capacities, the continued digitalization of healthcare and data-related challenge tackling, devising new sustainable care models, tackling scientific, legal, financial, and regulatory barriers in access to both standard and advanced care products, as well as continued facilitation of global strategic collaboration through infrastructure and data sharing (accessible diagnostics ecosystem and coordination). The role of innovative technologies – AI and genetic testing – must be recognized, with effective diagnosis and treatment with AI to be addressed in European and national RD plans and strategies in MS, and ethical and data-related challenges tackled.

# 4. Conclusions and next actions

This ultimate Scoping Paper, published in the final year of the programme hopes to take stock of R&I needs mapped and achievements made in the five-year programme framework, but also, what seems even more crucial, to define new directions and provide a draft of a map for future action in the field of RD – to be undertaken by successor programmes under the next partnerships.

Regulatory challenges remain yet to be addressed – with a pressing need for unification of laws in fields of data privacy, security, and standards – particularly its interoperability and cross-border data exchange, which is needed for dissemination of clinical trial, natural history, and treatment outcome knowledge. The case-research and clinical trial infrastructure should be strengthened with the possibility of legal submission of data to a general database accessible for Member States. Research and work on new therapeutic measures should be registered when conducted in a Member State.

There is also an urgent need to adopt legislation on genetic testing, comprehensively regulating genetic diagnostics – with the genome data requiring appropriate protection. Proper supervision of genetic laboratories is necessary. Legislation regulating the medical usage of AI should be adopted with insights derived from consultations with AI experts, clinicians, and patients. The potential breakthroughs in RD care derived from AI should be acknowledged with programmes devoted to promoting its development. The overhauling of current reimbursement strategies should be considered by Member States and at a European level.

The rapid translation of research results, research progress and promotion into clinical practice – both in diagnosis and in treatment, as well as adopting a holistic approach to the patient should continue to be promoted. The creation of multidisciplinary, academic centres will allow for providing holistic care for patients with RD, as most RD patients at some stage of their disease, and sometimes from the beginning, require multispecialty care. This must be supplemented by continued computerization and digitization of healthcare, simultaneously enhancing patients' and clinicians' access to telemedicine services to allow for consultation with other centres in Member States.

It is necessary to equalize the level of benefits for the RD community between EU-13 and other Member States. Funding dedicated to the construction of high-quality R&I and clinical infrastructure for EU13 countries will increase access to diagnostics and care for RD patients. The proper coordination to align funding and national actions with supra-national priorities and initiatives is essential. This must be supplemented by 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. Cross-border clinical trials should be promoted to allow for compensation of fund or infrastructure insufficiencies in EU13 countries – with additional, special assistance to create and improve international collaboration efforts during clinical trials.

Apart from needs in the scientific (R&I) field, the transversal needs of the RD community in the categories of diagnosis and healthcare, regulatory action and ethics, and EU competitiveness and innovation should be of persistent interest to future RD efforts.

The increasing diversity and complexity of actions, and the deepening cooperation of international and national institutions to raise the societal and stakeholders' awareness of the achievements and challenges facing patients must be noted. This creates opportunities to reduce barriers and obstacles to accessing diagnostics and treatment and to improve patients' quality of life. The field of RD is increasingly considered as relevant by society and policies. The voice of the patient is gaining importance.

In conclusion, the continuation of work conducted during the framework of the programme within the next European Partnership for RD (ERDERA) is essential to foster collaboration to achieve the set out goals and act towards a sustainable ecosystem for R&I and the clinical implementation of results, to provide a holistic approach to RD care in developed clinical academic centres, together creating adult and paediatric R&I and clinical networks, useful for the conducting of multi-centre clinical trials.