Draft proposal for a
European Partnership under Horizon Europe
Rare Diseases

Version 18 February 2022

About this draft

In the course of 2021, Commission services asked potential partners to further elaborate proposals for the 2023/24 candidate European Partnerships identified during the strategic planning of Horizon Europe (HE). These proposals have been developed by potential partners based on common guidance and template, taking into account the initial concepts developed by the Commission and feedback received from Member States during early consultation1. The Commission Services have guided revisions during drafting to facilitate alignment with the overall EU political ambition and compliance with the criteria for Partnerships.

This document is a stable draft of the partnership proposal, released for the purpose of ensuring transparency of information on the current status of preparation (including on the process for developing the Strategic Research and Innovation Agenda). As such, it aims to contribute to further collaboration, synergies and alignment between partnership candidates, as well as more broadly with related R&I stakeholders in the EU, and beyond where relevant.

This informal document does not reflect the final views of the Commission, nor pre-empt the formal decision-making (comitology or legislative procedure) on the establishment of European Partnerships.

In the next steps of preparations, the Commission Services will further assess these proposals against the selection criteria for European Partnerships. The final decision on launching a Partnership will depend on progress in their preparation (incl. compliance with selection criteria) and the formal decisions on European Partnerships (linked with the adoption of the Strategic Plan, work programmes, and legislative procedures, depending on the form). Key precondition is the existence of an agreed Strategic Research and Innovation Agenda / Roadmap. The launch of a Partnership is also conditional to partners signing up to final, commonly agreed objectives and committing the resources and investments needed from their side to achieve them.

The remaining issues will be addressed in the context of the development of the Strategic Research and Innovation Agendas / Roadmaps, and as part of the overall policy (notably in the respective legal frameworks). In particular, it is important that all Partnerships further develop their framework of objectives. All Partnerships need to have a well-developed logical framework with concrete objectives and targets and with a set of Key Performance Indicators to monitor achievement of objectives and the resources that are invested.

Aspects related to implementation, programme design, monitoring and evaluation system will be streamlined and harmonised at a later stage across initiatives to ensure compliance with the implementation criteria, comparability across initiatives and to simplify the overall landscape.

In case you would like to receive further information about this initiative, please contact:

Partners (main contact):

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European Commission, DG R&I D2, RTD-RD-PARTNERSHIP@ec.europa.eu
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[1] https://www.era-learn.eu/documents/final_report_ms_partnerships.pdf

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1. General information

1.1. Draft title of the European Partnership

Rare Diseases Partnership

1.2. Lead entity

A number of Member States (MS), Associated Countries (AC) and other interested countries[2] formed in Spring 2021, under the hospices of the European Commission (EC), a group of representatives to prepare this Partnership. This group created a sub-group composed of a few volunteers, the so-called "Drafting Group" or "Writing group", who developed the proposal document in collaboration with the Commission services.

The lead entity for the Partnership will be agreed upon at a later stage.

Contact for now: the Drafting Group: writing-group@rd-partnership.org

1.3. Commission services

Unit D.2 (Health innovations and ecosystems) in the Directorate General for Research and Innovation of the European Commission is in the lead for this Partnership, in particular its team working on Rare Disease Research.

A specific functional mailbox was set up to as a contact point for this Partnership in the Commission: RTD-RD-PARTNERSHIP@ec.europa.eu

1.4. Summary

The aim of the Rare Diseases (RD) Partnership is to improve the health and well-being of 30 million persons living with a rare disease in Europe, by making Europe a world leader in RD research and innovation and delivering concrete health benefits to rare disease patients (through better prevention, diagnosis and treatments).

To leave no one behind, RD Partnership will deliver a RD multi-stakeholder ecosystem by supporting robust patient need-led research, developing new therapies and diagnostic pathways, by utilizing the power of health and research data and spearheading the digital transformational change in RD research and innovation (R&I).

Finally, the Partnership will structure the European Research Area (ERA) on RD by supporting the coordination and alignment of national and regional research strategies, including the establishment of public-private collaborations, through research activities all along the R&I value chain, ensuring that the journey from knowledge to patient impact is expedited, thereby optimising EU innovation potential in RD.

This will be enabled by a tripartite mission to be accomplished by 2031:

[2] Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, the Faroe Islands, Georgia, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the United Kingdom, Lithuania, Latvia, Malta, Morocco, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Turkey, USA (full list of RD Partnership participating countries to be added once interest confirmed)

- Bring supporting R&I resources and support from across Europe under one roof so that every high-quality RD research project will benefit from cross-disciplinary expertise, goal-oriented study planning and efficient execution.
- Enable every consenting patient living with a rare disease to be findable and enrolled in a suitable clinical study which is necessary for having access to regulatory and FAIR-principles[3] compliant data; generating advances in prevention, diagnosis, understanding of diseases and developing treatments.
- Make Europe a global leader in rare disease research through providing a suitable infrastructural and regulatory support as well as significant increase in investment to spur innovation, leading to job creation and optimising EU competitiveness in R&I.

2. Context, objectives, expected impacts

2.1. Context and problem definition

2.1.1. Policy Context

On 16 December 2021, the first-ever Resolution[4] on *"Addressing the challenges of persons living with a rare disease and their families"* was adopted by the United Nations (UN) General Assembly. The resolution recognises the challenges faced by people living with a RD and their families, being inequity, social exclusion and discrimination driven by a lack of public knowledge.

Political agendas around the world are committed to address the UN Sustainable Development Goals (SDGs). Persons living with a rare disease constitute a vulnerable group facing challenges linked to different pillars of the SDGs. Addressing the research needs in the field of rare diseases via the RD Partnership will support the EU's commitment to the UN's SDGs calling for universal health coverage for all at all ages by 2030, leaving no one behind, in particular contributing to SDG 3 (Ensuring healthy lives and promoting well-being at all ages). The RD Partnership will also contribute to the SDG 9 (Industries, innovation and infrastructures) to empower solutions to improve the health of persons living with a rare disease, SDG 10 (Reduce inequalities) to reduce social and health inequalities of the rare disease families and SDG 17 (Partnerships for the goals) as international collaboration is key in rare diseases research to reduce the fragmentation of resources, knowledge and expertise.

EU healthcare and research policies and actions in this field is legally underpinned and guided by the 2000 EU Regulation on Orphan Medicinal Products (OMPs)[5]. Before the introduction of this orphan drug legislation, even in the research community there was limited interest on rare diseases. Furthermore, important policy actions continued with the 2008 Commission Communication on Rare Diseases, the subsequent Council Recommendation on an action in the field of rare diseases and the Directive on the application of patients' rights in cross-border health care.

Rare disease research is since long a priority supported by EU Framework Programmes (FP) for Research and Innovation (R&I) and illustrated by the set-up of the International Rare Disease Research Consortium (IRDiRC) in 2011 and successful coordination of national research funding

[3] Findable, Accessible, Interoperable, Reusable for humans and machines
[4] https://www.rarediseasesinternational.org/un-resolution/
[5] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN

strategies by implementing joint transnational calls for research actions via the successive ERA-Nets. A major milestone was achieved in Europe with the launch of the European Joint Programme on rare diseases (EJP RD) (2019-2023), as a prime example of Member States working together in a coordinated manner.

From the European research policy perspective, the RD Partnership will contribute to the ambition of the European Partnerships in Horizon Europe[6] (2021-2027) to constitute a key implementation tool of Horizon Europe in order to maximise its impact and will contribute significantly to achieving the EU's political priorities[7] for 2019-2024 of the von der Leyen Commission and beyond. In particular the Partnership on Rare Diseases aims to contribute to: '*2. An economy that works for people'*, '*3. A Europe fit for the digital age'* and '*5. A stronger Europe in the world'*. Furthermore, the updated European Research Area[8] agenda, has set up as one of its objectives to: 'Make EU research and innovation missions and partnerships key contributors to the ERA'.

The current political landscape offers the opportunity to align the rare disease policy with the scientific, technological and societal shifts. EU institutions recognise the need for action:

1. The European Court of Auditors (ECA) Report (07/2019) on the implementation of Directive on patients' rights in cross-border health care recommended to assess the results of the rare disease strategy (including the role of the European Reference Networks) and decide whether this strategy needs to be updated, adapted. It provides an additional impetus for an updated framework for rare diseases by 2023 to improve support to facilitate rare disease patients' access to health care;
2. The EU communication[9] on the impact evaluation of the orphan and paediatric medicines regulations showed that both regulations have stimulated research and development of medicines for rare diseases but there is inadequate development in areas where the need for medicines is greatest (more than 95% of rare diseases still have no approved treatment option);
3. The European Parliament in its Resolution of 10 July 2020 on the EU public health strategy in the post COVID-19 era calls for an EU action plan on 'rare and neglected diseases'[10];
4. France, Czech Republic and Sweden have recognised their upcoming presidencies of the EU Council as a platform of discussion to bring rare diseases forward as a priority in this same 2022/23 timeframe[11]. The EU presidency of France will organize a High-Level Conference on Rare Diseases Healthcare Pathways and Research on 28 February 2022 in Paris and the EU presidency of Czech Republic will organise a European Expert Conference on the European Rare Disease Policy Framework and the Revision of the OMP Regulation.

[6] https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/european-partnerships-horizon-europe_en
[7] https://ec.europa.eu/info/strategy/priorities-2019-2024_en
[8] https://ec.europa.eu/info/research-and-innovation/strategy/strategy-2020-2024/our-digital-future/era_en
[9] https://ec.europa.eu/health/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en
[10] https://www.europarl.europa.eu/doceo/document/TA-9-2020-0205_EN.html
[11] https://www.fhf.fr/Europe-International/Politiques-europeennes/Presidence-francaise-de-l-Union-europeenne-Evenements

The European Commission actively contributed to the ECA report and in reply to it, expressed its commitment to assess the progress made as regards the implementation of its strategic approach to rare diseases. Following that, policy may be revised but only where appropriate and relevant. As confirmed by the Directorate-General in charge of Health and Food Safety (DG SANTE) of the Commission, the focus for healthcare related policies on rare diseases should be on the full implementation of the current EU action, including the new Pharmaceutical Strategy for Europe (adopted on 25 November 2020) and the review of the Regulation on Orphan Medicinal Products.

2.1.2. Scale and causes of the problems / bottlenecks; Associated research and innovation needs; Strategic opportunities

In the European Union, a disease is considered as rare when it affects not more than 5 persons in 10,000 - as defined in the EU legislation on OMPs[12]. Each rare disease affects a small number of patients in each country but, when considered all together, the 6000+ rare diseases are affecting a minimum of 4% of the population in each country[13], 30 million in Europe and 300 million people worldwide. Most RDs are of genetic origin, but they can be also infectious, tumoral, due to poisoning or be autoimmune or idiopathic. In 70% of cases, rare genetic disorders appear during childhood. These diseases are chronic, complex, progressive, disabling, and life-threatening. Due to the low prevalence of each disease, medical expertise is rare, knowledge and data are scarce and fragmented, care services often inadequate and research limited. Despite their great overall number, persons living with a rare disease are often left behind in our health care systems and when it comes to benefits of research including diagnosis and treatment development. Therefore, rare diseases are recognised as a field where European and international collaboration is indispensable to improve diagnosis and develop new treatments[14].

In the 1990's rare diseases were nearly invisible in our health and social care systems. A milestone in RD policy was reached with the OMP regulation coming into force, having boosted substantial research funding on RD until today. RD are recognized today as a public health and human rights priority in large part due to a policy framework in Europe[15]. For years, many stakeholders in Europe, with the support of the European Union, have contributed to building a progressively growing RD ecosystem including information and codification, patient empowerment, care and research. New avenues for the RD community were open since the launch in the last two decades of important RD initiatives: the establishment of the resource platform Orphanet[16] and of the patients' organisation EURORDIS (1997); the adoption of a European legislation on medicines for rare diseases (2000) and children[17] (2007); the Commission Communication on Rare Diseases[18] (2008); the adoption of the Council Recommendation on European Action in the field

[12] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN
[13] Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* **28**, 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0
[14] https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/rare-diseases_en
[15] Quote from Executive summary of Rare2030 Foresight in Rare Disease policy- Recommendations (Feb 2021)
[16] https://www.orpha.net
[17] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32006R1901
[18] https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

of Rare Diseases[19] (2009); the establishment of the International Rare Diseases Research Consortium (IRDiRC)[20] (2011) by the European Commission and the US National Institutes of Health (NIH); the recent implementation of the European Reference Networks (ERNs) (2017) set up thanks to the Directive on patients' rights in cross-border health care (2011); the launch of the European Platform for Rare Disease Registration[21] (2018) set up by the European Commission; the creation of the European Joint Programme on Rare Diseases (EJP RD) (2019) under the EU R&I FP Horizon 2020 (H2020); the evaluation and ongoing revision of on the legislation for medicines for rare diseases and for children (2020)[22] and initiatives to evaluate and improve the European Orphan Medicinal Product landscape (2021) and, last but not least, the new clinical trial Regulation applying as of 1 February 2022, thus further contributing to an increased empowerment of patients.

At national level too, many European countries adopted national plans (NP) and/or national strategies (NS) to tackle rare diseases[23], including policies for research on rare diseases.These EU and national policy actions were supported by many projects under different EU funding programmes such as the EU Health Programmes and the R&I FPs, as the so-called ERA-Net scheme (networking of national research funding agencies): E-Rare-1[24], E-Rare-2[25] and E-Rare-3[26], predecessors of EJP RD[27]. Also, the recent acceleration of new technologies, use of big data, implementation of FAIR principles, innovation beyond omics and artificial intelligence (AI), introduce additional challenges and opportunities. Out of necessity rare diseases have become pioneers in tomorrow's transformations and creative solutions for research and health care[28; 29; 30; 31]. The RD research community continually brings forward innovative concepts and models created for the needs of small patient populations but with benefits for all.

However, despite these significant developments in the RD field over the past years, the reality is that for a significant proportion of the 30 million patients in Europe, unmet needs remain. About 95% of the known rare diseases lack effective treatment options; about 50% of RD patients - mostly ultra-rare patients "the orphans of the orphans" - do not have a confirmed molecular

[19] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
[20] https://irdirc.org/
[21] https://eu-rd-platform.jrc.ec.europa.eu/_en
[22] https://ec.europa.eu/health/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en
[23] http://www.europlanproject.eu/NationalPlans?idMap=1
[24] https://www.era-learn.eu/network-information/networks/e-rare
[25] https://www.era-learn.eu/network-information/networks/e-rare-2
[26] https://www.era-learn.eu/network-information/networks/e-rare-3
[27] https://www.ejprarediseases.org/
[28] http://download2.eurordis.org/rare2030/Rare2030_recommendations_Exec_Summary.pdf
[29] https://pubmed.ncbi.nlm.nih.gov/33426479/ "The case for open science: rare diseases"
[30] https://rd-connect.eu
[31] https://solve-rd.eu

diagnosis[32,33]; the average time for diagnosing a known rare disease is still more than 4 years[34; 35; 36; 37]; it is estimated that the disease mechanisms for many rare diseases are still unknown, which makes diagnosis a challenge and the development of a treatment or cure even further away. Furthermore, 52% of patients and carers say their disease has a severe or highly severe impact on daily life[38]. These needs of RD patients require further coordinated joint research and innovation efforts of the public and private sector, and a contribution from citizens and users in co-creating solutions. Due to the scarcity of patients with a specific rare disease, and expertise and knowledge, research on rare diseases cannot be done in isolation and only coordinated, multinational actions can bring expected results.

During the last decade several initiatives coordinated by different actors involved in the continuum of R&I from basic discovery and clinical development to marketing innovative products, have identified several R&I gaps and needs that should be addressed to allow speeding-up the translation of the research results into benefits for the people living with a rare disease.

The Expert Group on Orphan incentives[39] study in their main recommendation for research, have re-iterated the huge need to improve the R&I ecosystem for basic research and clinical research to catalyse the company take-up of the research results into fast and cost-effective development of orphan medicines; Without solid understanding of disease aetiology, underlying disease mechanisms, biomarkers and targets, coupled with a strong research pipeline, no OMP development can take place. While dispersed and small patient populations make research in rare diseases challenging in itself, the fact that the RD ecosystem is not already fully functional for R&I hampers further research activity and company take-up. Research is often not 'development-ready' and securing funding for research is difficult.

In February 2021, the two-year Rare 2030[40] foresight study funded by the European Parliament and led by EURORDIS-Rare Diseases Europe concluded its recommendations that describe a roadmap for a new rare disease framework by establishing measurable goals for the first time. In line with the UN Sustainable Development Goals (SDGs), such goals set a common direction for all EU Member States to make tangible change for all their citizens living with a rare disease. The most relevant recommendations for RD research are summarized here:

- Patient-led rare disease research maintained as a priority - across basic, clinical, translational and social research and data used to its maximum to improve the health and well-being of people living with a rare disease;

[32] Wise AL, Manolio TA, Mensah GA, et al. Genomic medicine for undiagnosed diseases. Lancet. 2019;394(10197):533-540. doi:10.1016/S0140-6736(19)31274-7
[33] Smith HS, Swint JM, Lalani SR, et al. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: A Scoping Review of the Literature. Genet Med. 2019 Jan; 21(1):3-16.
[34] Rare Disease UK. The Rare Reality – an insight into the patient and family experience of rare disease. January 2016. https://www.raredisease.org.uk/media/1588/the-rare-reality-an-insight-into-the-patient-and-family-experience-of-rare-disease.pdf
[35] https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf
[36] https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf
[37] https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf
[38] Rare Barometer survey (May 2017): http://download2.eurordis.org.s3.amazonaws.com/rbv/2017_05_09_Social%20survey%20leaflet%20final.pdf
[39] https://od-expertgroup.eu/
[40] https://www.rare2030.eu/recommendations/

- Improve the availability, accessibility and affordability of rare disease treatments, by attracting investments, fostering innovation and collaboration across countries, to address inequalities;
- Earlier, faster and more accurate prevention and diagnosis of rare diseases through better and more consistent use of harmonised standards and programmes across Europe, new technologies and innovative approaches driven by patient-needs;
- A culture encouraging meaningful participation, engagement and leadership of people living with a rare disease in both the public and private sectors.

The International Rare Diseases Research Consortium[41], established in 2011 by the European Commission and the US National Institutes of Health, is a global consortium of 59 organisations (research funders, patient advocates, industry representatives) involved in RD research. IRDiRC has achieved its initial goals to stimulate the research-funding environment and hence catalyse the development of 200 new therapies and means to diagnose most rare diseases by 2020, four years ahead of schedule. In order to work towards this bold and ambitious vision, IRDiRC has set three goals. *Goal 1:* All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline; *Goal 2:* 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options. *Goal 3:* Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

IRDiRC addresses the RD challenges through collaborative actions such as establishing and providing access to harmonised data and samples, streamlining ethical and regulatory procedures, performing the molecular and clinical characterisation of RDs, boosting translational, preclinical and clinical research and providing recommendations to research funders how to effectively address the RD research challenges.

A major milestone was achieved in Europe to structure the RD research landscape, with the launch in 2019 of the European Joint Programme on rare diseases (EJP RD) as a prime example of Member States working together and also with other stakeholders on a more integrative and cross-sectorial approach to tackle health challenges. Moreover, EJP RD contributes directly to the ambitious goals of IRDiRC, as the network of European stakeholders.

The ambition of the RD Partnership is to build on the successes of EJP RD and provide solutions for tackling the **identified main R&I bottlenecks** that hinder the efficient development of better diagnosis, therapy and care fostered by research in the RD field are:

1. Need for further coordination & alignment of research funding & optimal integration with national rare diseases plans/strategies. E.g.

- Need for better alignment between national and EU research programme policies and strategies in the RD field;
- Insufficient financial and expert resources to address the relevant research questions for

[41] https://irdirc.org/

the huge number of rare diseases to understand the causes, natural history and pathways to treatment for RD;
- Unsatisfactory use and exploitation of research and health data due to lack of standards and interoperability;
- Fragmentation of research resources and data in different countries;
- Lack of a coordinated research pipeline to address the high number of unsolved RD;
- Need for further improvement to engage unrepresented groups and underrepresented countries into rare disease research.

2. Huge gap in translation of research results to deliver cost-effective solutions for people living with a rare disease; innovative actions needed to bridge the current gaps that are e.g.

- Basic research and clinical development are the backbone of development of orphan medicinal products[42]. However, there is a big gap in knowledge and expertise of basic / clinical researchers to what companies and investors need as development-ready research to be taken up by companies and investors;
- Lack of an operative multistakeholder approach to meet the needs and ambitions of all stakeholders involved in the development of rare disease treatments, from basic researchers to private companies to patients living with a rare disease[15];
- Difficult commercial landscape for drug development due to the often-low number of patients, lack of enough scientific knowledge and heterogeneous national market authorisation procedures and health care reimbursement conditions which lead to low interest of private companies to invest in RD research;
- Slow pace of adoption of data standards, leading to low regulatory grade generated clinical data, as well as validated innovative cost-effective methodologies that aid in the scientific evaluation of the efficacy and safety of new therapies and biomarkers;
- Lack of innovative solutions and methodologies to tackle currently undiagnosable RDs that could be translated into clinical practice.

3. Fragmentation of knowledge & data, lack of a holistic R&I ecosystem, e.g.

- Immaturity of existing collaborations to facilitate research and innovation in social and human science field of RD;
- Lack of European clinical research networks that leverage and expand the research capacities of ERNs;
- Underdeveloped possibilities to connect the clinical and research expertise of ERNs to wider research capacities outside of ERNs in Europe and in the rest of the world;
- Need of improvement to include patients at all levels of research to reach fruitful and sustainable partnerships between researchers and patients, co-leading the way for systematic patient-centred research;
- Difficult professional environment to attract and train new generations of RD specialists (researchers, physicians, patients) due to the high level of competition for resources with more common diseases.

An overarching issue of the above identified bottlenecks would be that the substantiated research

42 Orphan medicine incentives. How to address the unmet needs of rare disease patients by transforming the European OMP landscape (June 2021) European Expert Group on Orphan Drug Incentives

R&I activities on rare diseases should create value for patients. The patient should experience less suffering as a result of research outcomes, through better prevention of rare diseases, better diagnosis and better treatment. How the Partnership can achieve these aims through research, involving multi-stakeholder collaborations (alignment with National Plans, pharmaceutical companies, other industry partners and the ERN centres) should be closely monitored.
To reach this ambition, all stakeholders in Europe - the EU Member States and beyond - have to collaborate and strengthen the ecosystem for faster translation of research results from "bench to bedside", pooling of resources and expertise, sharing data of rare diseases and utilise the clinical research data of ERNs.

It is with this purpose in mind, that the Partnership should drive the research to cost-effective translation and bringing innovation to address the unmet medical needs of the rare diseases community, while coordinating national research efforts and establishing a holistic research and innovation ecosystem of knowledge, data, disciplines, people, sectors.

Investing in RD research does not only benefit the RD community but brings scientific, organisational and societal solutions that can be exploited in other medical fields and common diseases. The response to the Covid-19 crisis is a recent example of this: the development of RNA vaccines, such as the Pfizer vaccine, owes a lot to innovation in gene editing - techniques developed and refined with the aim to find cures for rare diseases. The experience with the European Reference Networks on rare diseases, on the other hand, has prompted the European Commission to launch the COVID-19 Clinical Management Support System to support healthcare professionals dealing with COVID-19 cases across Europe. The initiative has helped create rapid connections among healthcare professionals and hospitals across Europe to share data and improve the management of COVID-19 cases.

In addition, the specificity of RDs (limited number of patients that suffer from one of the 6000+ known rare diseases, their willingness to share their data [95% compared to 37%-80% of the general population][43] and the scarcity of knowledge and expertise) as well as the maturing structuration of RD ecosystem are valuable enabling factors for trans-national data-driven solutions (e.g. EU Health Data Space and European Open Science Cloud) that will improve life of all EU citizens.

2.1.3. Experience and outcomes of previous R&I Partnerships

Over the period 2007 to 2020, the EU has supported this field extensively through its Framework Programmes (FP) for Research and Innovation with more than €1.8 billion were attributed to over 320 interdisciplinary, multinational research and innovation projects bringing together the complementary expertise needed, which no individual research institution and country could possess alone. (see report[44]). RD research was supported by EU R&I funding FPs for a long time (already with FP4, 1994-1998, until FP7, 2007-2013) and continued to be supported in Horizon 2020 (2014-2020) in various ways, with most of the funds directed towards collaborative research projects (consortia) under the Health research policy area. The EU-funded RD research projects include basic and translational research to understand the causes and characteristics of rare

[44] https://op.europa.eu/en/publication-detail/-/publication/2ab5235e-7fbe-11eb-9ac9-01aa75ed71a1/language-en/format-PDF/source-193764078

diseases; proof-of-concept of pre-clinical and clinical validation of new therapies and new diagnostics tools and technologies; clinical research (clinical trials, natural history and cohort studies). These projects span across all medical areas i.e., neurological, immunological, metabolic diseases or rare cancers. In addition, the EU invested in specific programmes and actions that support strategy building, serve as basis to coordinate actions at national, EU and international level, and provide the necessary tools/innovation to advance rare diseases research.

Apart from IRDiRC already mentioned, the key programmes and initiatives supported by the EU and on which the RD Partnership will be built or will collaborate with are:

a) European Reference Networks (ERNs)[45], their registries and their clinical research coordination platform ERICA[46]

In 2017, 24 European Reference Networks (ERNs) were established under the Directive on patients' rights in cross-border health care with the aim to tackle complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resources. They provide the opportunity for patients and professionals across Europe for access to the best expertise, timely exchange of life-saving knowledge and translation of cutting-edge research results and innovations into the clinical practice. Within the objectives of ERNs set in the legislation, research is a key component, beyond the care provided to rare disease patients. Most ERN members participate in clinical research, more than 50% in translational research, and 50% in pre-clinical research. Therefore, ERNs comprise a valuable network for rare disease research along the whole pipeline from basic to preclinical to translation and implementation into clinical practice. All 24 ERNs are represented by at least one partner in EJP RD, while the whole ERN community is meant to benefit from EJP RD activities.

The ERN registries are supported via the EU Health Programme and also cooperating with EJP RD for their development (including FAIRification). These registries, linking health and research data, and meant to be interoperable by design between them and with other resources, are capturing a growing number of RD patients providing the critical mass of information necessary for the implementation of the foreseen RD Partnership data related activities.

ERICA: a "coordination and support action" (2021-2025) is meant as platform to strengthen research and innovation capacity by the integration of ERN research activities.

b) Orphanet

Orphanet[47] is an EU-funded multilingual knowledge base on rare diseases and orphan drugs as well as a network of 42 countries in Europe and beyond. Orphanet provides re-usable data essential for research on the platform www.orphadata.org and standards for rare diseases codifications notably via the Orphanet nomenclature (the ORPHAcodes), including a structured vocabulary for rare diseases, the Orphanet Ontology of Rare Diseases (ORDO). These resources contribute to improving the interoperability of data on rare diseases across the globe and across the fields of health care and research. The integral role played by Orphanet in the research and care spheres has led to its recognition as an IRDiRC Recognised Resource and integration in the French node

[45] https://ec.europa.eu/health/ern/networks_en
[46] https://erica-rd.eu/
[47] https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN

of ELIXIR. Orphadata, Orphanet's data download platform, and the Orphanet Rare Disease Ontology, are ELIXIR Core Data Resources. The ELIXIR Core Data Resources serve as a mark of the highest quality in infrastructure service provision and play a critical role in the long-term preservation of life science data. Orphanet and the ORPHA nomenclature are also cited as key resources in every European legislative text on rare diseases and as key measures in many national plans/strategies for rare diseases[48].

c) Solve-RD - solving the unsolved rare diseases

Solve-RD[49] (2018-2022) is an EU-funded research project which aims at solving unsolved rare diseases for which the molecular underlying cause is not yet known. Solve-RD currently brings together more than 300 clinicians, scientists and patient representatives of 51 sites from 15 countries and builds upon a core group of four ERNs which annually see more than 270,000 RD patients. The project developed an interoperable data and analysis infrastructure, re-analysed genomic data of unsolved RD patients with latest bioinformatic tools and managed to solve and already diagnose > 10% out of the 22.000 unsolved patient cases.

d) RD-Connect

RD-Connect (2012-2018) was a European multidisciplinary project (under FP7) that created an integrated global infrastructure for RD research. The RD-Connect project provided the infrastructure to develop three new platforms to improve the study and analysis of Rare Diseases: (i) Genome-Phenome Analysis Platform[50] to analyse and share genomic data; (ii) Registry & Biobank Finder[51], a directory of RD biobanks and patient registries; (iii) Sample Catalogue[52] to browse RD biosamples stored in biobanks.

e) The 1+ Million Genomes initiative (1+MG)

This latter initiative brings together 23 European countries with the goal to have at least 1 million sequenced genomes accessible in the EU and establish a federated data infrastructure providing European transnational solutions for access/sharing of genomic data. The first pilots for the 1+MG infrastructure include use cases on cancer and rare diseases.

EU has also supported the coordination between research funders across Europe and beyond with several initiatives like E-Rare, EJP RD and IRDiRC. The RD Partnership will build on the experience and outcomes of these closely related European and international initiatives.

f) E-Rare

The general goal of E-Rare (ERA-Net for research programmes on rare diseases) was to coordinate existing programmes and to prepare joint and strategic activities to overcome some limitations imposed by scattered funding and fragmentation between national research programmes. The E-

[48] 2018 State of the Art report http://www.rd-action.eu/rare-disease-policies-in-europe/
[49] https://solve-rd.eu/
[50] https://platform.rd-connect.eu
[51] https://rd-connect.eu/what-we-do/phenotypic-data/rb-finder-for-registries/
[52] https://samples.rd-connect.eu

Rare consortium was created in 2006, renewed in 2010 and finished in a final instalment from 2014-2020. Funding by different EU programmes was critical to the success of E-Rare. In the end, it comprised a network of 28 partners - public bodies, ministries, and research funding organisations - from 20 countries: EU Member States[53], 3 Associate States and 2 non-European countries. In the 13 years period of E-Rare, 10 Joint Transnational Calls were organised of which one (JTC2015) was directly co-funded by the EU. The 152 funded projects with 140 M€ covered a wide range of rare diseases in all medical domains, covering the whole research pipeline and addressing different types of studies such as diagnostics, therapy, biomarkers, natural history or gene discovery. The funding activities of E-Rare were integrated in 2019 in Pillar 1 of EJP RD.

g) The European Joint Programme co-fund on Rare Diseases (EJP RD)

Member States expressed the wish that the RD Partnership builds upon the EJP RD co-funded by national public research entities and the EU R&I funding programme Horizon 2020. While E-Rare was mainly a scheme for joint calls, EJP RD (2019-2023) has a hybrid nature, with such calls and in-house research activities, offering a framing structure for the RD research ecosystem.
EJP RD is a prime example of cooperation across Member States and also with other stakeholders on an integrative and cross-sectorial approach to tackle health challenges. It builds upon established collaborations between research funders, ministries, research institutes and universities, ERNs, EU research infrastructures, foundations and patient organisations.

EJP RD integrates more than 130 institutions from 35 countries. Its main objective is to create a research and innovation pipeline "from bench to bedside" ensuring rapid translation of research results into clinical applications and uptake in health care for the benefit of patients. The programme brings together research funders, ministries, research institutes and universities, hospitals (all 24 ERNs are part of EJP RD), EU research infrastructures, foundations and patient organisations. EJP RD is based on all efforts made in the field of rare disease during last 15 years. It integrates existing infrastructures, trainings, funding programmes and tools, expands them and develops new essential ones. In this way, a harmonised (and centralised) multistakeholder RD research ecosystem has been created.

EJP RD is organised around 5 main axes:

1. Collaborative Research Funding (including Joint Transnational Calls (JTCs)),
2. Coordinated Access to Data, Tools & Services (Virtual Platform),
3. Capacity building (training) & empowerment,
4. Accelerated translation of research results & clinical studies,
5. Centralised coordination and transversal activities (strategy, sustainability, ethics & regulatory, communication).

Examples of impact and results of the EJP RD thus far

Governance and alignment. The EJP RD put in place a governance that allows the EJP RD strategy be aligned with the national strategies of the 35 countries involved, that of the European

[53] EU Member States (Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Spain, The Netherlands), three Associate States (Switzerland, Israel and Turkey) and two non-European countries (Canada and Japan).

Commission and other major players such as industry. The inclusion of industry representatives (IMI, EUCOPE) in the EJP RD Policy Board enhanced the interest of industry for EJP RD actions. Close collaboration with policy makers allowed on increased awareness of the RD research ecosystem and new possibilities for negotiation of financing of RD research in countries not yet involved in funding activities (by joining EJP RD JTCs implemented in Pillar 1). Several National Mirror Groups have been established to ensure national coordination of and with all rare diseases stakeholders to facilitate the alignment between national and EJP RD activities, to contribute to EJP RD objectives and benefit from it. The alignment with national strategies is now visible, for example in France (e.g., implementation of federated Virtual Platform, standards, ontologies, and methods used, as mandatory for the alignment of national resources such as RD registries and databases, cohorts and the Health Data Hub that will host RD data) or in the Netherlands.

Collaboration with ERNs. One important short-term outcomes achieved by the EJP RD is the establishment of strong collaboration with the ERNs. The inclusion of ERNs in the EJP RD allows for progressive empowerment of the ERNs in their research capacities and close alignment of the EJP RD activities (e.g., development of the Virtual Platform) with the requirements of the users. Mapping of ERNs strengths, gaps and research needs enabled the implementation of dedicated support (e.g., for ERN registries implementation, FAIRification of their resources) and research projects (e.g., use cases for multi-omics pathways). The collaborative work to make ERN registries FAIR-enabling at the source laid the basis for improvement of data sharing and conditional re-use to increase health data secondary use for research purposes. It was also expanded to the related Informed Consent Form (ICF), which resulted in adaptation of the original ICF template, that was developed for healthcare, to make it research-targeted (i.e., enabling the re-use of healthcare data for research purposes) while allowing for customization to include ERNs and national specificities, and help their endorsement by national or local ethics committees.

Research. EJP RD completed two Joint Transnational Calls focusing on acceleration of diagnosis and/or exploration of disease progression and mechanisms of RDs (2019) and effective therapies for RDs (2020). 40 multinational projects were funded for € 55 million, including € 8.7 millions of EU funding. A dedicated call for projects on social science and humanities research, to improve health care implementation and everyday life of people living with a rare disease, was launched for 2021. The fourth call (2022) is dedicated to the development of new analytic tools and pathways to accelerate diagnosis and facilitate diagnostic monitoring of rare diseases.
Additional funding activities resulted in financing of:
(1) 3 RD Research Challenges projects, focusing on public-private collaboration to develop therapeutic solutions for patients;
(2) 19 networking events to support knowledge sharing in the rare disease community;
(3) 3 demonstration projects to validate new innovative methodologies for RD clinical trials;
(4) 33 training (short-term fellowships) for young clinicians and 15 transversal workshops for ERNs.

Virtual Platform. The building blocks of the Virtual Platform (VP) were developed, and the VP will continue to mature over the remaining years of the EJP RD. The Commission's European Platform on Rare Disease Registration (EU RD Platform) is a reference structure. The metadata model linking resources were validated and extended with the latest standards, the prioritised RD resources were made ready for linkage, the data model linking records inside the resources is being optimised to consider consent and reuse conditions, the pilot tools to query resources and discover

data are in the testing phase before deployment. Additionally, 70 new biological pathways have been created and some are exploited through bioinformatic networks, using multi-omics data, to accelerate the diagnosis of rare diseases.

Training. During the first 3 years, more than 1500 trainees were enrolled in the education and empowerment activities: nearly 750 people were trained (researchers, clinical staff and patients) in 28 courses. 25 ERN secondments for research fellows and 13 ERN networking events were assigned. The first two runs of the EJP RD Massive Open Online Courses (MOOCs) fostering RD diagnosis were created and opened as free training to all interested parties through a specialised platform allowing to train almost 513 persons. The training activities were expanded and adapted to the needs of the EU13 countries[54], thereby offering additional opportunities to train new experts and improve the training programmes by making them more inclusive. Similarly, dedicated widening measures applied in the JTCs allowed inclusion of research teams from underrepresented countries in high quality research consortia and successful funding of their research projects.

Support. The support services for multinational clinical trials and the innovation management, implemented with the European infrastructures ECRIN and EATRIS, supported 3 requests for support for clinical trials, 4 research projects for translational support and search for sponsors, while 15 applications of JTC2020 profited from mentoring service. It was also featured as reference service for all RD projects funded by the European Commission. The work of EJP RD on demonstration and innovation in methodologies for clinical studies in small populations resulted in direct collaboration with the European Medicines Agency. The pathways for validation of novel proposed methodologies are now being considered, which will improve the design of clinical studies and accelerate the delivery of new treatment options on the market.

Collaborations with other programmes and projects. Finally, recognised as major European player in the field of rare diseases, EJP RD was competitively selected as a Driver Project for the Global Alliance for Genomic & Health (GA4GH), which is the forefront international standards creation organisation for the genotype-phenotype data domain. EJP RD is not only contributing to the establishment of global standards for responsible genomic data sharing, but also is driving new developments in the field that stem from the joint actions and enhanced capacity of its multiple stakeholders working together. Moreover, EJP RD started the collaboration with the Critical Path Institute, notably with its RDCA-DAP - The Rare Diseases Cures Accelerator-Data and Analytics Platform, which is an FDA-funded initiative that provides a centralised and standardised infrastructure to support and accelerate rare disease characterisation, with the goal of accelerating therapy development across rare diseases. The expertise of EJP RD in data modelling and standardisation led to a joint proof-of-concept testing the query of data provided by both parties through EJP RD metadata models, ontologies and standards. This is paving the interoperability between EJP RD and RDCA-DAP resources. In year 2, EJP RD also initiated direct collaboration with European initiatives like the 1+Million Genomes (1+MG) project and the European Health Data Space (EHDS), ensuring alignments and recognition of RD needs. Furthermore, the collaboration between EJP RD and conect4children (c4c) IMI project ensure the basis for optimised, standardised and well-trained infrastructure for clinical trials in paediatric populations (often RD patients). EJP RD also collaborates with health data-oriented projects: RD-CODE from which interoperability tools (mapping services) are adapted for their use in the VP; OD4RD

[54] Group of 13 EU countries: Bulgaria (BG), Croatia (HR), Cyprus (CY), Czech Republic (CZ), Estonia (EE), Hungary (HU), Latvia (LV), Lithuania (LT), Malta (MT), Poland (PL), Romania (RO), Slovakia (SK), Slovenia (SI)

(Orphanet data for rare diseases) which will leverage the ORPHAcodes training material to increase the interoperability of data between the healthcare sector and ERN registries, X-health and TEHDAS in which EJP RD promotes the standard and data models adopted in EJP RD.

The multistakeholder RD research ecosystem that EJP RD has built produces benefits for patients in several ways; (1) patients/patient representatives engaged in preclinical research projects, e.g. represented in ERN activities through the European Patient Advocacy Groups (ePAGs), and possibly educated through trainings; (2) the services for multistakeholder networking, finding RD resources, improving data sharing and FAIRification of data for reuse of data, support for translational research and clinical studies resulting in improved research outcomes.

Positive Mid-term review EJP RD

The mid-term review evaluation of EJP RD in 2021 performed by the EC and involving independent, external experts, indicated that the project was considered as unique in the world gathering stakeholders across many different sectors, and that it is likely to be impactful in the long term. This review highlighted EJP RD specific strengths, that are the joint secure data management platforms, dissemination, the unifying handling of ethics principles across different areas in Europe, comprehensive education and training programme and the way in which the RD area can inspire common, chronic disease areas, even if the scale and role of genetics may be different. The industrial potential is also evident. The reviewers thought that a major achievement of EJP RD is getting this group of diverse stakeholders to work together in one project and indicated that the project and its achievements are unique in the world. Synergies with the Coordination and Support Action for ERNs, ERICA, was also recommended.

2.2. Common vision, objectives and expected impacts

2.2.1. Ambition, Vision, Mission

The RD Partnership will be organised around the following *ambition, vision, and mission.*

AMBITION:

To improve the health and well-being of 30 million persons living with a rare disease in Europe, by making Europe a world leader in RD research and innovation, and delivering concrete health benefits to rare disease patients, through better prevention, diagnosis and treatment. The Partnership will support the EU commitment to UN 2030 Agenda's Sustainable Development Goals: (i) Good health & wellbeing (SDG3), (ii) industries, innovation and infrastructure (SDG9), (iii) Reduced inequalities (SD10) and (iv) Partnerships for the goals (SDG17).

VISION:

To leave no one behind, the RD Partnership will deliver a RD multi-stakeholder ecosystem by supporting robust patient need-led research, developing new treatments and diagnostic pathways, by utilizing the power of health and research data and spearheading the digital transformational change in RD research and innovation.

Finally, the Partnership will structure the European Research Area on RD by supporting the coordination and alignment of national and regional research strategies, including the establishment of public-private collaborations, through research activities all along the R&I value chain, ensuring that the journey from knowledge to patient impact is expedited, thereby optimizing EU innovation potential in RD.

This vision will be enabled by a tripartite mission to be accomplished by 2031.

MISSION:

- Bring supporting R&I services from across Europe under one roof so that every high-quality RD research project will benefit from cross-disciplinary expertise, goal-oriented study planning and efficient execution.
- Enable every consenting patient living with a rare disease to be findable and enrolled in a suitable clinical study, by boosting generation of regulatory-level and FAIR-compliant data from diversity of sources, with the ultimate goal to fasten advances in prevention, diagnosis, disease knowledge and treatment.
- Make Europe a global leader on rare disease research through a significant increase in investment to spur innovation, leading to job creation and improving EU competitiveness in R&I.

In a nutshell, the mission for the Partnership is to provide a suitable infrastructural and regulatory-compliant environment enabling an improved European competitiveness in RD research and health care.

2.2.1.1. General and specific objectives

The proposed General Objectives (GO), which correspond to long-term IMPACTS, are:

- GO1: Optimal generation and translation of knowledge into meaningful and accessible health products and interventions that respond to the needs of patients living with a rare disease across Europe and globally.
- GO2: Unlock the full potential of healthcare and research data in the digital era.
- GO3: Timely, equitable access to innovative, sustainable and high-quality healthcare by virtue of a highly integrated research and healthcare system.

- GO4: More effective outcomes from different types of collaborations: public-public cooperation (EU public funding and policies with national and regional public funding and policies) as well as cooperation with civil society (e.g., patients) and the private sector (industry, SMEs, NGOs).

The proposed Specific Objectives (SO), which correspond to mid-term OUTCOMES of the Partnership, are:

- SO1: Deploy outcome-oriented investments along the R&I value chain, to advance high quality, patient needs-focused R&I.
- SO2: Better understanding of RD burden and analysis of the potential effectiveness of existing interventions to tackle this RD burden.
- SO3: Interoperable, federated, evolving and scalable RD infrastructure of data, samples, resources and tools with necessary critical mass for meaningful RD research & innovation.
- SO4: Active utilisation in all Member States & Associated countries by all stakeholders of high-value, ethically and regulatory compliant data tools and services tailored to needs of RD research community.
- SO5: Decreased number of undiagnosed patients as well as reduction in the duration of the diagnostic odyssey of patients.
- SO6: Increased capacity of RD stakeholders across Europe through quality training and skills development.
- SO7: Improved success rates of therapeutic development and diagnostic improvement.
- SO8: Meaningful empowerment, engagement, and leadership - as equal partners - of people living with a rare disease.
- SO9: Effective alignment of national RD strategies with EU objectives, leveraging shared resources and maximising MS and Associated Countries contributions.
- SO10: Effective transcontinental collaboration.

The following Tables 1 and 2 respectively introduce visual representations of - for Table 1 - the articulation between the Vision for the Partnership, UN Sustainable Development Goals (SDGs), General Objectives (GOs), Specific Objectives (SOs) and Operational Objectives (OOs), as well as - for Table 2 - some potential targets proposed for each Specific Objective of the Partnership by the end of the initiative.

Table 1. Summary of the Vision for the Partnership and links between UN Sustainable Development Goals (SDGs), General Objectives (GOs), Specific Objectives (SOs) and Operational Objectives (OOs)

The Specific Objectives are interlinked as they may respond to more than one expected General Objective expressed as long-term impacts (see also the table 2 of objectives above). The proposed SOs correspond directly to the expected outcomes that Rare Diseases Partnership should achieve or contribute to, in line with its mission, and within its lifetime or at the latest at 2031 horizon.

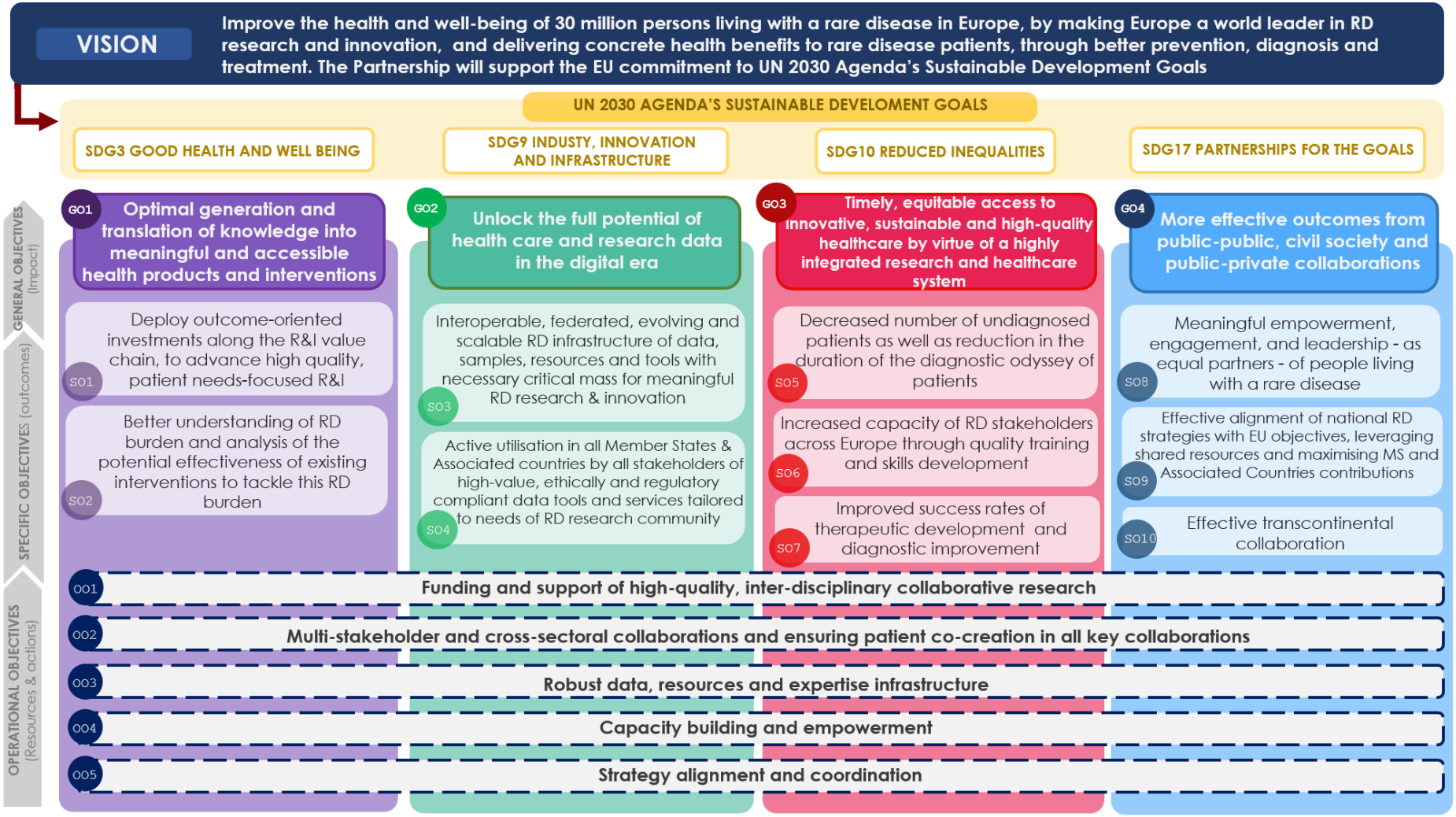


Table 2. Proposed targets to be reached by the end of the Partnership for each Specific Objective

In this table, some potential targets are formulated to be reached by the end of initiative, for each Specific Objective:

Specific Objective	Potential targets by the end of the initiative (tentative) (assuming 2027 is mid-term, 2031 is end of the term)
SO1: Patient-need led relevant research enabled by outcome-oriented investments strategically deployed along the R&I value chain	• Public Early-stage investment coordinated with later stage investment by private sector and philanthropy • Increased participation of patients/patient organisations as co-designers of research • Patients/patient organisations are research partners/co-researchers in consortia in all research proposals under the Partnership by 2027 • Patient-Cantered Outcome Measures (PCOMs) and Patient-Reported Outcome Measures (PROMs) guidelines developed and applied across all 24 ERNs and related JTC and multinational European consortia by 2028 • PCOMS/PROMs utilized in every trial and regulatory application issued from the Clinical Research Network (CRN) and increased adoption at relevant national clinical networks • All eligible research projects funded in RDP to be enrolled in the Mentoring programme • Higher number of successful basic research projects transitioning to preclinical development
SO2: Better understanding of RD burden and impact assessment of interventions	• Research projects funded to understand RD (burden) in all the partner countries, including capturing a current picture of the patient journey, and challenges that could be addressed by R&I • Social research projects led by RD patients (5 examples) • Socio-economic assessment of the disease burden
SO3: Interoperable, federated, evolving and scalable RD infrastructure of data, samples, resources and tools with necessary critical mass for meaningful RD research & innovation	• National RD registries and relevant ones under JTCs linked in the Virtual Platform discoverability network and the EU RD platform • Regulatory quality standards agreed and implemented for clinical research datasets • At least (50) multinational research projects using data and/or samples identified through and benefiting from the RD Partnership data infrastructure • Reach critical mass of FAIR data resources that have enabled continuous federated learning applications, such as for improved diagnosis or treatment options.

Specific Objective	Potential targets by the end of the initiative (tentative) (assuming 2027 is mid-term, 2031 is end of the term)
SO4: Active utilisation in all Member States & Associated countries by all stakeholders of high-value, ethically and regulatory compliant data tools and services tailored to needs of RD research community	By mid-term (2027) • Increased number of RD research sites, across MS and Associated Countries, using the RDP infrastructure • Number of patients with RD enrolled in partnership-associated registries doubled (from the beginning until the end of the RD Partnership) • On-boarding support and guidance provided for partner countries with less developed data infrastructures
SO5: Decreased number of unsolvable cases as well as reduction in the duration of the diagnostic odyssey	• At least 20 multi-national collaborative projects on innovative diagnostic approaches funded • Improved identification of undiagnosed cases in ERNs' registries and their inclusion in research pipeline • Improved fraction of patients with genetically confirmed hereditary diseases • Increased bioinformatic research capacity for omics analysis • Development and validation of multi-omics diagnostic and prognostic research approaches for selected disease groups
SO6: Increased capacity of RD stakeholders across Europe through quality training and skills development	Attractiveness of careers related to RD enhanced through: • Adaptive and inclusive mechanism established for knowledge exchange and capacity development • Targeted mobility programmes for under-represented countries to exchange expertise and forge new research collaborations • All Early Career Researchers in funded projects have the possibility to undertake suitable training courses/certification • RD online/hybrid certifying training hub enabling multidisciplinary and didactic capacity building through customised training paths used by each RD research stakeholders' type • Train the trainers programmes enabling capacity building in EU national languages • Increased number of researchers trained in Transdisciplinary patient-centric research including understanding of regulatory implementation/exploitation issues • Increased awareness on the needs of translational and clinical research

Specific Objective	Potential targets by the end of the initiative (tentative) (assuming 2027 is mid-term, 2031 is end of the term)
SO7: Reduced failure rates of therapeutic development	• Increase the number of academic projects transitioning to industrial development in the EU • Increased number of therapeutic targets identified through the multidisciplinary CRN Framework and JTCs-funded research projects • Increased number of investigational medicinal products implemented into clinical research and developed in Europe • More structural use of early health technology assessment in early clinical development: all call topics that support applied research for novel therapeutics / solutions encourage inclusion of HTA analysis
SO8: Equitable engagement and leadership - as equal partners - of people living with a rare disease	• Equitable engagement of patient representatives on all governance structures within the partnership • Patient representative on steering committees of all funded RD clinical studies • Patient Organisations Partners in research Studies • Patient Organisations as leaders in research studies • Patient organisations involved in interactions with regulatory and HTA (EUNetHTA) institutions for agreement on PCOMs and PROMs
SO9: Effective alignment of national RD strategies with EU objectives, leveraging shared resources and maximising MS and Associated countries contributions	• By end of the Partnership all partner countries have an active National Mirror Group • RDP used as platform to support policy debates linked to RD research (drug regulation, diagnostics, medical devices)
SO10: Effective transcontinental collaboration	• The findings and the recommendations raising from IRDiRC activities will be integrated into the RD Partnership actions to further stimulate international collaboration and interoperability • The resources integrated into the Virtual Platform will be accessible for researchers across the world to foster research and collaboration • Maximisation of transcontinental collaboration within all funding opportunities of the RD Partnership will stimulate collaboration and promote research with international research stakeholders • The European Clinical Network for Rare Diseases will be interoperable with RD clinical networks from other EU countries and other continents, more particularly the US RDCRN. • Increased collaboration of global industry with EU academia

Today, 95% of RD remain without treatment and are disregarded in terms of research, thus increased, outcome-oriented funding directed towards (high) unmet medical needs is needed to reduce this gap. Moreover, with patients as co-leaders of the Partnership, the strategic and operational objectives are assured of alignment with their needs. Specifically, it will **enable patient-need led relevant research** by providing a seamless funding pipeline for basic to applied RD research, **coordinated along the value chain**. Attention will be given to robust SSH research to better understand the **burden of RDs and the impact of new interventions**. The **investment in outcome-oriented research projects**, actively monitored and steered towards translational opportunities will ensure their outputs meet regulatory requirements and **patients' needs** thereby **reducing failure rates of therapeutic developments**.

To accelerate the **generation of therapeutic options and curative treatments** for persons living with RD it is necessary that **every consenting patient is findable and enrolled in a suitable clinical study**. This can only be achieved through an integrated approach where clinical settings will regularly inform research activities, such as the design of studies or the selection of endpoints that are useful for clinicians, relevant for patients and directly applicable in clinical trials. Moreover, innovative technology will be used to empower patients in the processing of their data. The Rare Diseases Partnership will build the **linkage between health and research data** by stimulating the *ab initio* adoption of standards for FAIR data and metadata and exploiting the already existing capacities of ERNs, EJP RD Virtual Platform and national resources to create an **interoperable, federated, evolving and scalable RD infrastructure of data, resources and tools** constituting a core facility of the future Clinical Research Networks that will be further deployed so that **high-value, ethically and regulatory compliant data**, tools and services **are actively used by all stakeholders at national level**. The RD partnership will thus support a critical mass of findable, accessible, interoperable, reusable (FAIR) resources enabling innovation. Gathering of clinical, research and patients' expertise, coupled with effective data and services coordinating centre, and supported by relevant public and private commitments, will directly **boost innovation in RD diagnostics and therapeutic space.**

Training and education are consistently identified as key drivers for improvement of research and health care outcomes in RD. For this reason, they are placed as transversal, high priority elements of the Partnership. Given the complexity of the RD domain, persistent themes are to include development of skills in trans-disciplinary and trans-sectorial collaboration, patient-focused research orientation, and improving awareness of ethical, regulatory and implementation related aspects of research and innovation. Significant attention will also be paid to training on application of high value data resources and tools - including cutting edge approaches such as Artificial Intelligence (AI) - to ensure FAIR data generation and management and encouragement of re-use of data and support digital innovation in the RD space.

Bringing national, EU and international stakeholders (public or private) into the heart of the actions of the RD Partnership will be key to not only maximise their potential and contributions but also to revitalise national strategies, based on common EU values and SDGs and leveraging on global collaboration. The long-standing cooperation with the International Rare Diseases Research Consortium, as well as structural engagement of other relevant initiatives (e.g., RDI and CZI) will be pivotal to guarantee effective transcontinental collaboration.

2.2.1.2. How will the RD partnership address these objectives?

The RD Partnership will address these objectives by the following actions and resources **(Operational Objectives, OO)**:

1. Funding and support of high-quality, inter-disciplinary collaborative research,
2. Multi-stakeholder and cross-sectoral collaborations, such as public-private (industry and academia) and academia-healthcare, and ensuring patient co-creation in all key

collaborations,
3. Robust data, resources and expertise infrastructure,
4. Capacity building and empowerment,
5. Strategy alignment and coordination.

For more details on foreseen actions and resources, see section 3 Planned Implementation.

2.2.1.3. Link with broader policy objectives and SDGs

The objectives of the RD Partnership have been consciously designed to align with broader policy objectives of relevance to the RD field (as well as complimentary domains). As an example, Rare 2030 Foresight Study actively designed recommendations of actions that lead to the preferred vision for RD research amongst other complementary actions in the field of rare diseases. RD has long been a priority area for European action, but as RDs are very much a global challenge, and global strategies are often required to address the many gaps and inequities, it is important that this Partnership contributes meaningfully to the UN SDG agenda. Four key SDGs are particularly relevant here:

SDG 3 – Good Health and Well-Being

'Good health and well-being' have multiple dimensions. RD and advancing excellent and patient needs-centred research is a prerequisite for many of these. A collaborative and cohesive framework, extending from basic science to effective treatments, appropriate access to health care and person-centred social support, is necessary. Robust, specific and comprehensive national RD plans are needed to structure all of these actions in European and national systems (and often also across continents). For this reason, the Partnership will ensure a 'joined-up' approach, both to stakeholders and also to policies and strategies, in order to contribute to better health and wellbeing, specifically the following components: understanding the burden of RD on patients, families and societies at large; bringing more (and more accurate) diagnoses to patients, faster; enabling the most promising research to result in effective therapeutic or care products patients can access. In this way, the RD Partnership is contributing actively to the goal of giving all patients access to Universal Health Coverage.

SDG 9 – Industries, Innovation and Infrastructure

Advancing research in RD requires collaboration across stakeholder groups as well as geographies, and industry engagement is an essential component. The Partnership will work with industry and industry associations to maximise collaboration in the pre-competitive space, to support more needs-led innovation (through better understanding of the needs of RD populations, through partnership with patients at all stages of research, and by accelerating the translation of innovation into patient benefit). The Partnership will, through engagement with the digital and technology sectors, ensure a strong focus on evolving, refining and implementing resilient data infrastructures to support research and better health, in order to develop and promote the use of high quality, ethical, and regulatory-compliant tools across all sectors of the research ecosystem.

SDG 10 – Reduce Inequalities

Patients living with RD experience multiple inequalities compared to individuals with more common disorders. They may have a disease without a diagnosis or have difficulty accessing the expertise to make a diagnosis, they may have a disease without a therapeutic intervention or have difficulty accessing a therapy where they live, they may experience difficulty taking up education or employment opportunities because of their RD. This Partnership will make a meaningful contribution to addressing this goal, particularly by reducing the uncertainty and anxiety of often-avoidable diagnostic odysseys and increasing the prospects of more (and more effective) therapies in future. By ensuring a focus on connecting the national, European and global levels, and fostering renewed momentum on plans and strategies for RD, it will support greater research-

relevant benchmarking, which will illuminate inequalities for often marginalised and vulnerable RD populations whilst also supporting a greater national awareness of the extent of inequalities and needs in the health and social domains, thus enabling actions.

SDG 17 – Partnership for the Goals

The RD Partnership is assembling a broad consortium of stakeholders, to address the myriad and complex challenges posed by RD: research funders, ministries, patients and patient representatives, research institutes and universities, clinicians (through ERNs), EU research infrastructures, foundations, industry, regulatory agencies, HTA bodies and more. This level of collaboration (spanning geographical boundaries and bridging governmental, civil, and private sectors) is necessary to develop innovative tools and approaches and disseminate these effectively through training and capacity-building. The RD Partnership will also ensure an open approach to building new collaborations and welcoming new actors. A key strength here is the emphasis on meaningful patient partnerships, in policy making and priority-setting as well as research and development.

Furthermore, the activities planned within RD Partnership will indirectly address additional SDGs, including Reducing Poverty (1), Quality Education (4), Gender Equality (5) and Decent Work and Economic Growth (8). In addition to this strong alignment with the UN SDGs, the global outreach of the Partnership is fully in line with the spirit of the UN Resolution 'Addressing the challenges of persons living with a rare disease and their families' adopted on 16 December 2021[55].

At the European level, the Partnership's objectives and activities are well aligned with multiple strategic priorities of the European Commission relevant for research activities.

General Objective 1 (GO 1) *'Optimal creation and application of knowledge into meaningful health products and interventions for patients living with rare disease across Europe and globally'* compliments several of the priority intervention areas for Horizon Europe[56]: not only 'non-communicable and rare diseases', but also 'health throughout the life course,' 'tools, technologies and digital solutions for health and care including personalised medicine' and 'health care systems'. Although the Partnership is first and foremost centred on research, it is acknowledged that a very close collaboration between health care and research is necessary in RD. The GOs of this Partnership (particularly GO 3 *'Timely, equitable access to innovative, sustainable and high-quality health care by virtue of highly integrated research and health care system'*) are very complimentary to the priorities of the *Health* Cluster of Horizon Europe (as it is detailed in the specific section of this proposal dedicated to the *"Necessity for a EU Partnership"*): (i) Staying healthy in rapidly changing society; (ii) Tackling diseases and reducing disease burden, (iii) Ensuring access for patients to innovative, sustainable and high-quality health care, (iv) Unlocking the full potential of new tools, technologies and digital solutions for a health society and (v) Maintaining an innovative, sustainable and globally competitive health-related industry.

General Objective 2 (GO2): *'Unlock the full potential of clinical and research data in the digital era'* is very much aligned with the European Digital Strategy[57] (strengthening digital sovereignty

[55] United Nations Resolution on 'Addressing the challenges of persons living with a rare disease and their families.': https://digitallibrary.un.org/record/3953832

[56] https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en

[57] https://digital-strategy.ec.europa.eu/en/policies

and setting standards across this 'Digital Decade') as well as the European data strategy, with data-driven innovations bringing better and more personalised medicines and evidence-based policy (which is much-needed in RD). GO4 *'More effective outcomes from public-public, civil society and public-private collaborations'* will support implementation of the Industrial Strategy[58]. Furthermore, the RD Partnership's emphasis on integrating and building capacity in all EU MS and associated countries aligns well with the Horizon Europe component on *'Widening participation and strengthening the European Research Area'*.

2.2.1.4. Impact

The main goal of the RD Partnership is to have a **differential impact on the health status of rare disease patients**. This is linked to significant contribution to the objectives set by the International Rare Diseases Research Consortium being that every person living with rare disease has access to diagnosis, most suitable treatment and care within less than one year of coming to medical attention. By applying a "holistic" approach to the RD ecosystem, encompassing all stakeholders and ensuring more effective outcomes from public-public, civil society and public-private collaborations, the RD Partnership will directly (or indirectly) **contribute to the reduction of undiagnosed cases** and, at the same time, open the door for the **development of new therapies**.

To **unlock and use efficiently clinical and research data** has been on the agenda for long time. The RD Partnership aims to be a driver to the final act of this process so that by the end of the programme active utilisation in all involved countries by all stakeholders of high-value, ethically and regulatory compliant data tools and services tailored to needs of RD research community leads to **shortening of time to diagnosis and treatment**. Ultra-rare disease patients will be positively affected by the programme, especially from supporting and funding personalised medicine and the development of advanced therapies.

The program will also **reduce inequities between different types of RD** by targeting disregarded rare diseases through meaningful empowerment, engagement, and leadership of patients, building of new or expanded networks and supporting dedicated research. This will be complemented by the effective alignment of national and EU RD policies to ensure better understanding of RD burden and implement relevant measures.

Finally, the integration of needs, information and expertise under all type of public, private, patient, and society combinations will impact the innovation capacity of the academic and industry fields in Europe. Their closer interaction under the Partnership will enable new and productive ideas impact on outcomes from the projects and actions supported from the RD Partnership. All of them will benefit, not only RD patients but also other health and social fields. Of special importance is the fact that the activities supported by this European action will prompt the generation of new research collaborations, will trigger the start of new industrial adventures and, with no doubt, will increase leadership in the European innovative capacity.

2.2.1.5. Qualitative & quantitative justification of the vision & ambition & what will be different from what we have now?

The RD Partnership will contribute to close the gap between research and health care by providing the necessary support, advance research, infrastructure and innovation needed to leave no person living with rare disease behind.

[58] https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-industrial-strategy_en

This ambition is based on the following facts:

- Today between 27 and 36 million Europeans suffer from rare diseases, with a number of unmet needs and with a considerable variation in access to authorised medicinal products (depending on where they live in Europe).
- Many do not have a recognised disease with a diagnosis. Many patients experience delay to diagnosis; IRDiRC goal 1 is exactly about improving diagnosis.
- many patients and carers have reduced or stopped professional activity as a result of their disease and do report difficulty with activities of daily living[59]); integration of person-centred care is key.
- 95% of rare diseases are still without authorised treatment, but the treatments that are available for the 5% are not necessarily transformative or curative, R&I also needs to be directed into those areas where there are no authorised treatments at all, linking with the discussion on "unmet medical needs" in the frame of the envisaged revision of the OMP legislation.

Barriers to development of novel or improved therapeutics and access for patients include:

- Lack of a diagnosis; lack of knowledge of the underlying pathophysiology and potential therapeutic targets within a disease/ disease group; lack of data sharing between transnational academic and industry partners to pair pathophysiology data with potential therapeutics; lack of identifiable patient populations for biomarker studies or trials; high risk-to-investment return ratios for private companies in RD therapeutic development, with concomitant lack of alternative R&I pathway to the patient; unsuitability of regulatory approval processes for Orphan Medicinal Products; high reimbursement costs for Member States when marketing authorisation obtained.
- The need to improve the R&I ecosystem for pre-competitive research and company take up of research results. Although various initiatives, such as the ERNs and EJP RD have enabled an acceleration of collaboration and clustering of knowledge on rare diseases, RD research is still dispersed across many different institutions, the gap between basic, pre-clinical and clinical research persists. The respective expertise rests with a few specialists, who also operate at different geographical locations. This implies that research activity lacks scale and visibility among patients who would like to participate, researchers and companies with potential commercial interests for development. In addition, research is often not 'development-ready', and securing funding for research is difficult.
- The strong R&I foundations for many rare diseases is lacking. Often knowledge of the disease mechanisms is still very partial and models to study some rare diseases do not exist. In fact, when basic research is insufficient or is lacking entirely, it is too risky for a company to take up a therapy development project. It may not be financially viable for a company to invest in the primary research over and above other R&I costs incurred in drug development. Conversely, an R&I ecosystem that produces a high level of available research results, and their smooth translation to clinical settings, will significantly improve the case for investing in new therapeutic options, regardless of whether these are classical small molecules, advanced therapies or even lifestyle interventions.
- The process for developing and bringing medicines to the market is complex, costly, and requires early on collaboration of many stakeholders (researchers, industry, patients,

[59] 7/10 patients and carers have reduced or stopped professional activity as a result of their disease and 8/10 report difficulty with activities of daily living. Rare Barometer Voices Sample

medical professionals, investors, funding bodies, regulators and HTA/reimbursement bodies). The small number of patients affected by a given rare disease may mean that it attracts relatively less attention and funding in the research community, makes research and clinical trial studies more difficult and riskier, regulatory approval more difficult to achieve and, overall, the investment case less attractive. There is need to engage and boost the regulatory science, including robust framework, and development of Real-World Evidence (RWE) as well as early and direct engagement with regulators to facilitate generation of regulatory-compliant research results.

On the other hand:

- A relatively stable joint support for multinational research projects through competitive funding has been developed and expanded since 2006 by E-Rare and EJP RD initiatives. Many countries indicate this investment as the only RD-specific funding they provide and recognise the importance of maintaining such support. This is even more specific for under-represented countries (such as the EU13 countries) for which dedicated widening measures have been put in place to accelerate their participation in research projects.
- The exploitation of research and health data for the benefit of RD community is being facilitated by recent developments of EJP RD Virtual Platform of data, tools and resources, deployment of ERN registries, Solve-RD proof of concept for solving the undiagnosed RDs cases, as well as joint efforts for common data sharing framework and re-use of genomics data of 1+ Million genomes initiative. All that backed by the European efforts to develop the European Health Data Space. It is also important to underline that today the support for data repositories and tools for RD research is foreseen in 81% of RD national plans/strategies, however only 31% indicates at the same time specific support to FAIR data. This confirms that strong alignment between national and EU efforts is possible and urgently needed.
- The collaboration with EU Research Infrastructures like EATRIS and ECRIN allowed the first proof-of-concept for translational/clinical studies support services dedicated to rare diseases with the objective of acceleration of the uptake of RD research results, their further de-risking and investment by industry. At the same time, the interest of industry for rare diseases and collaborative research models is also growing.
- The capacity generated by the ERNs, coupled with methodological expertise in support of evidence-based research and innovation in clinical studies initiated under EJP RD provide a solid base for further development of research driven by regulatory requirements. Close collaboration with initiatives like Critical Path Institute bridging public, private and regulatory bodies is also key.
- The foundations of patients-involvement in governance, research and decision-making have been put (notably at all levels of the EJP RD) and should be further expanded.
- Finally, most EU countries have today a national plan or strategy for rare diseases that were motivated by the EU Council Recommendation of 2009 on an action in the field of rare diseases. These often require renewal or update. The implementation of National Mirror Groups initiated under EJP RD can facilitate gathering of RD stakeholders at national level, identification of needs and definition of new measures to revive national plans and align them with IRDiRC goals as well as with new objectives and recommendations provided by Rare 2030 foresight.

Table 3. What will the RD Partnership bring in comparison with what exists today?

Research support & collaboration	
What exists today (based on EJP RD, ERNs, Solve-RD, national plans/strategies)	**What will be different (what the RDP will bring)**
Relatively stable funding support for multinational research Widening efforts Opportunities for public-private collaboration	Strong and continued support of basic, translational and clinical research as 95% of RDs remain without treatment and are disregarded in terms of research. Ensured long-term commitment (integration in national research policies) & (if needed) more targeted programming Public-private collaboration as part of the RD Partnership including Public Early-stage investment coordinated with later stage investment by private sector and philanthropy Accelerated patient-centred research via the support of dedicated research projects within the EU Clinical Research Network for Rare Diseases (CRN) Sustainable and integrative support services to accompany all funded projects to guarantee generation of meaningful and exploitable outputs
Exploitation of research & health data	
RD Ontology, "transferrable" data standards, FAIR standards, VP model in development ERN registries, EU RD Platform and other RD-Ready resources, 1+Million Genomes, national initiatives to create data hubs and EHDS Solve-RD undiagnosed diseases infrastructure/model Biological pathways building methods, exploiting omics data, to accelerate RD diagnostics and therapy target identification with some case-studies proof of concept	Established Data Exploitation Hub within CRN core support structure catalysing the FAIRification of existing and newly collected research and clinical data, plus biosample information, to regulatory-level quality standards Extended Data types exploitation including RWE, biomarkers, COAs/ PCOM and mHealth/ Telehealth data, for novel analyses methods (including AI and ML) offering standardised deep phenotyping Deployed standardised deep phenotyping clustering services and Omics analysis tools for diagnostic acceleration and therapeutic development

	CRN core support structure coordinating the diagnostic research needs of the CRN to unravel novel pathologies and to feed the RD research pipeline from diagnosis to therapy Health & research data possibly linked or made interoperable at EU and national level • exploiting the central position of ERNs and the services of the EU RD platform to facilitate collection, access & use of data, along with cloud and hub functionalities, in co-creation with the EC services • leveraging on existing infrastructure/model to build the link of the national and European RD data infrastructures • supporting relevant codification and tools to accelerate diagnosis Sustainable data ecosystem maintaining: • the connection between national & higher levels (EU, international) • the curated knowledge resources that are a reference for automated data interpretation (new technologies, AI/ML) • FAIR-based VP specifications & stewardship guidance, by which data resources can natively make computable knowledge and data (FAIR digital objects) available for secure, federated AI and Machine Learning technologies.
Participation of patients	
RD Patients represented in the governance “Proof-of-concept” for PAO funding in research projects	Involvement of patients at all levels of governance and execution Engagement of RD patients and/or representatives as equal partners in all stages of the research process Patient involvement in all three stages of the funding process to ensure that research is patient-centred: i) strategic decision-making with the identification and prioritisation of research topics, ii) co-planning research activities, iii) decision-making on the allocation of funding to research projects Novel & more inclusive funding models provided to ensure sustainable patients participation

Research translation & EU competitiveness	
ERNs extensive (clinical) research expertise Stimulated pre-clinical research community Tools & infrastructures to support pre & clinical research Growing interest from industry & appetite for new funding/collaborative models	Fully integrated and mutually synergistic pre-clinical & clinical RD research pipeline The proof-of-concept support services models of EJP RD transformed into regular support to accelerate the development-ready research transfer to investors Industry integrated into multistakeholder collaborative models Accelerator hub creating new, complementary funding/support to expedite research results into products
Capacity building	
Relevant training offer covering different types of stakeholders and topics provided within EJP RD and partner organisations Proof-of-concept for an online education course fostering knowledge on RDs “Train the trainer” concept validated National/regional training and education capacities to be leveraged	Training as integrative part of the research pipeline: - To educate new generations of clinicians/researchers - To upscale expertise of stakeholders - To empower patients Sustainable and accredited online education programme Training and education capacities expanded to national level reducing knowledge and expertise gap
Regulatory	
Innovation in space of CT methodologies & PROMs Example models like C-PATH Interest of regulators, industry, payers	The capacity of relevant clinical expertise (ERNs) coupled to methodological excellence exploited in coordination with regulators, to support evidence-based research accelerating the entry into market for the patients’ benefit

Policy framework & national participation	
National RD plans & strategies (sometimes outdated, sometimes including RD research, heterogenous,) Proof-of-concept for National Mirror Groups organisation Visibility (to some extent) of national potential (leverage) in research, education, innovation, health care Expansion of ERNs to new sites (often from underrepresented countries) translating to new patient populations, researchers, academic and clinical partners availability to Partnership	Solid bridges between national, EU & international levels National leverage potential is maximised & tailored solutions provided RDs are anchored in national strategies (as a holistic concept covering all aspects of society e.g., education, R&I, healthcare, legislation)

2.2.2. Collaboration with other partnerships and Union programmes

The RD Partnership ambition is to improve the health and well-being of people living with a rare disease by making Europe a world leader in innovation to address the unmet needs of 30 million persons living with a rare disease in Europe (see section 2.2.1 Ambition, Vision, Mission).

To do so, the RD Partnership will leverage relevant activities in Europe complementary to the RD Partnership and will conversely generate content that may benefit other EU initiatives.

Three main collaborations' targets are envisioned at this stage:

- (1) Collaboration with European Partnerships under Horizon Europe,
- (2) Collaboration with European Union programmes, projects and initiatives,
- (3) Collaboration with other large European or international initiatives.

Synergies with different types of activities in the Partnership and funding support will be further identified with the aim to support and enhance specific actions (including possible co-funding, parallel funding or subsequent funding), as well as to ensure relevant dissemination and exploitation of results from this Partnership. For instance, regional funds can support the uptake of evidence-based results, services-innovations and other innovations identified through the RD partnership.

For each collaboration opportunity, "opportunity topics" cover diagnosis, treatment, care, research, data and European and national infrastructures that set out the roadmap for the next decade of rare disease policies and will be also applied as guidance within the RD Partnership (and its future Strategic, Research and Innovation Agenda).

The indicative list of partners' profiles sought for the RD Partnership (as identified in January 2022) is available in Section 2.4 – Partner composition and target group.

EU Partnerships

Key collaboration opportunities have been identified with several **EU Partnerships** that are either already starting or are planned to start within next months or before the start of the RD Partnership candidate in three main areas: (i) the Health Cluster (ii) the Digital, Industry and Space Cluster, (iii) partnerships with cross-sectoral themes.

Strong collaboration will be initiated with **four European Health Partnerships**[60]: the Innovative Health Initiative (IHI)[61], Fostering a European Research Area for Health Research (ERA4Health)[62], as well as the European Partnerships on Personalised Medicine (PM) and Transforming Health and Care Systems (THCS).

Aside from the Health cluster, collaboration is also foreseen with **cross-sectoral Partnerships** such as the EIT Health, Innovative SME and European Open Science Cloud (EOSC).

Finally, to ensure best uptake and alignment in data, computing and machine-learning research areas, **two Partnerships lying under the Digital, Industry and Space Cluster** have been identified as potential candidate for partnerships, one on High Performance Computing (EuroHPC) and one on Artificial Intelligence (AI), data and robotics.

Relevant Partnerships with whom collaboration activities are foreseen have been identified and are listed in *table 4 "Collaboration with pre-identified EU Partnerships" (see below).*

EU Programmes and Initiatives

[60] https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/european-partnerships-horizon-europe/candidates-european-partnerships-health_en
[61] https://www.imi.europa.eu/about-imi/innovative-health-initiative
[62] https://ec.europa.eu/info/sites/default/files/research_and_innovation/funding/documents/ec_rtd_he-partnerships-era-for-health.pdf

The RD Partnership will strive to align not only at the EU Partnership levels but will also take advantage of pre-existing and to-be funded EU Programmes and EU projects to maximise the use of resources and alignment. The RD Partnership will namely build synergies with Horizon Europe initiatives (such as European Innovation Council (EIC), Missions, in particular the Cancer Mission). The RD Partnership will also build synergies with the EU4Health Programme and the Digital Europe Programme (DEP). EU programmes such as the ESF+ (European Social Fund Plus, invest in education, employment and social inclusion), InvestEU and ERDF (European Regional Development Fund) will also systematically be considered to develop the best uptake and development of the RD Partnership activities. At this stage several EU programmes and projects were pre-identified for potential collaboration (*see table 4, and 5 below*).

Other European and international programmes and initiatives

In addition to EU-funded partnerships and programmes, collaboration will also be developed with overarching European or international major initiatives. A first tentative list is included in *table 6 below.*

Table 4. Collaboration with pre-identified EU Partnerships

EU Partnership	Objectives	Pre-identified Opportunity topics	
Health Cluster			
Innovative Health Initiative (IHI)	A collaborative platform bringing the several industry sectors (pharmaceuticals including vaccines, diagnostics, medical devices, imaging and digital sectors) together with academic partners for precompetitive research and innovation in areas of unmet public health need, to accelerate the development and uptake of people-centred health care innovations. Since some projects under the Innovative Medicines Initiative (IMI), predecessor of IHI, are still running / will deliver a legacy useful for the RD Partnership, synergies will be sought with them too.	Innovative & needs-led research and development Optimising data for patient & societal benefit Earlier, faster, more accurate diagnosis Integrated & person-centred care	*This collaboration is expected to address the objectives GO1, GO4 and SO1, SO4, SO7, SO9-10*
ERA4Health	The partnership aims to establish and implement a strategic research agenda and joint funding strategy between major European public funders to advance health research and develop innovation. As well as to develop new approaches that overcome known challenges in multinational clinical research. This will be achieved in close collaboration with ongoing initiatives to support the conduct of multinational non-commercial studies. This would lead to establishing appropriate mechanism(s) for identifying topics and funding sources, and for launching (joint) calls for large, multinational IICSs on various health interventions addressing important public health needs.	Innovative & needs-led research and development Long-term integrated European & national plans and strategies	*This collaboration is expected to address the objectives GO2, GO4 and SO1, SO7, SO9-10*
Transforming Health and Care Systems	Improving health and care models in an ageing, data-driven and digital society, shifting to holistic health promotion and person-centred care approaches through health policy and health systems research (including guidance on how to transform health systems; developing new solutions for health and care; strengthening innovation and its successful transfer to health care systems).	Long-term integrated European & national plans and strategies Access to high quality health care Integrated & person-centred care	*This collaboration is expected to address the objective GO3 and SO1-5, S09-10*

EU Partnership	Objectives	Pre-identified Opportunity topics	
Personalised Medicine	To align national research strategies, promote excellence, reinforce the competitiveness of European players in Personalised Medicine and enhance the collaboration with non-EU countries.	Innovative & needs-led research and development Long-term integrated European & national plans and strategies	*This collaboration is expected to address the objectives GO1, GO4 and SO7, SO9-10*
Digital, Industry and Space Cluster			
High Performance Computing	The EuroHPC will establish an integrated world-class supercomputing and data infrastructure and support a highly competitive and innovative HPC and Big Data ecosystem.	Optimising data for patient & societal benefit Innovative & needs-led research and development	*This collaboration is expected to address the objectives GO2, GO4 and SO1, SO3, SO4*
AI, data and robotics	The partnership on AI will help structuring the European AI community, develop a strategic research agenda and federate efforts around a topic that holds great potential to benefit our society and economy.	Optimising data for patient & societal benefit Earlier, faster, more accurate diagnosis Innovative & needs-led research and development for diagnosis/outcome and pathophysiology biomarkers	*This collaboration is expected to address the objectives GO2, GO4 and SO1, SO4, SO5*

Other Partnerships (across other themes)			
Innovative SMEs	The initiative aims to support the transnational market- oriented research projects initiated and driven by innovative SMEs. Innovative SMEs shall take the lead and exploit commercially the project results, thus improving their competitive position. Research organisations, universities, other SMEs, large companies and other actors of the innovation chain can also participate.	Available, accessible and affordable treatments Innovative & needs-led research and development	*This collaboration is expected to address the objectives GO1, GO4 and SO1, SO3, SO4, SO7*
European Open Science Cloud (EOSC)	The co-programmed partnership aims to improve the storing, sharing and especially the combining and reusing of research data across borders and scientific disciplines. The Partnership brings together institutional, national and European initiatives and engages all relevant stakeholders to co-design and deploy a European Research Data Commons where data are Findable, Accessible, Interoperable, Reusable (FAIR).	Optimising data for patient & societal benefit	*This collaboration is expected to address the objectives GO2, and SO3, SO4*
European Institute of Innovation & Technology Health (EIT Health)	Backed by the European Union EIT Health will be delivering solutions to enable European citizens to live longer, healthier lives by promoting innovation, improving health care for citizens and strengthen the health economy in Europe.	Innovative & needs-led research and development Optimising data for patient & societal benefit Available, accessible and affordable treatments Long-term integrated European & national plans and strategies	*This collaboration is expected to address the objectives GO1, GO3, GO4 and SO1, SO4, SO6-10*

Table 5. Alignment sought within Horizon Europe and with other pre-identified EU programmes (2021-2027)

Identified Programme	Objectives	Pre-identified Opportunity topics and expected nature of collaboration
Horizon Europe **For example (but not only) HORIZON-HLTH-2022-DISEASE-06-04-two-stage)**	The EU's key funding programme for research and innovation with a budget of €95.5 billion	• Mutual awareness and information, for example with projects resulting from the 2022 call for the "Development of new effective therapies for rare diseases • Integrated & person-centred care • Optimising data for patient & societal benefit
European Innovation Council – (EIC)[63]	It aims to identify and support breakthrough technologies and game changing innovations to create new markets and scale up internationally.	• Innovative & needs-led research and development • Optimising data for patient & societal benefit
Digital Europe Programme	A new EU funding programme focused on bringing digital technology to businesses, citizens and public administrations.	• Innovative & needs-led research and development • Optimising data for patient & societal benefit

[63] https://eic.ec.europa.eu/index_en

Identified Programme	Objectives	Pre-identified Opportunity topics and expected nature of collaboration
EU4Health[64] (for example, from the 2021 Work Programme (WP): • **EU4H-2021-PJ-06** • **EU4H-2021-PJ-14** • **EU4H-2021-PJ-17**)	EU programme of €5.3 billion complementing EU countries' policies with four main goals: 1) to improve and foster health in the EU, 2) to tackle cross-border health threats, 3) to improve medicinal products, medical devices, and crisis-relevant products, 4) to strengthen health systems, their resilience and resource efficiency. Under these 4 general goals, 10 specific objectives are pursued and several of them are relevant for the RD Partnership. Action grants for example relevant in the 2021 WP: • Action grants for developing a pilot project for an EU infrastructure ecosystem for the secondary use of health data for research, policy-making and regulatory purposes. • Action grants supporting training activities, implementation, and best practices. • Action grants to organise and collect data to understand the safety, quality and efficacy of therapies applied in the field of assisted reproduction and based on haematopoietic stem cells.	• Integrated & person-centred care • Long-term integrated European & national plans and strategies • Partnership with patients • Optimising data for patient & societal benefit • Strengthened health systems allowing for uptake of results • Improved environment for development and uptake of medicinal products and medical devices
European Regional Development Fund (ERDF)	It aims to strengthen economic, social and territorial cohesion in the European Union by correcting imbalances between its regions. It will enable investments in a smarter, greener, more connected and more social Europe that is closer to its citizens.	• Integrated & person-centred care • Long-term integrated European & national plans and strategies

[64] https://ec.europa.eu/health/funding/eu4health-2021-2027-vision-healthier-european-union_en

Table 6. Collaboration with pre-identified other initiatives, projects and organisations

Identified Initiative / Programme/ Organisation	Objectives	Pre-identified Opportunity topics and expected nature of collaboration
1+MG / B1MG	The '1+ Million Genomes' (1+MG) initiative brings together 22 EU countries, and Norway with a goal to have at least 1 million sequenced genomes accessible in the EU.	• Innovative & needs-led research and development • Earlier, faster, more accurate diagnosis • Long-term integrated European & national plans and strategies
Accelerating research & development for advanced therapies (ARDAT) (IMI project, 2020-2025)	IMI project which aims at delivering the knowledge, tools and standards needed to speed up the development of Advanced Therapy Medicinal Products (ATMPs).	• Innovative & needs-led research and development • Tools to accelerate development of advanced therapies Expected nature of collaboration: • Complementary activities and integration of results into new RDP activities • Deployment/ Implementation activities
conect4children - Collaborative network for European clinical trials for children (c4c) *(IMI project **(2018-2024)** that will be replaced by a sustainable legal entity from 2023)*	Better medicines for babies, children and young people through a pan-European clinical trial network	• Innovative & needs-led research and development • Optimising data for patient & societal benefit • Earlier, faster, more accurate diagnosis Expected nature of collaboration: • Strategic – access to the broader paediatric community • Services for applicants and funded projects that recruit babies, children, young people • Foundational work on data standards, site standards, global interoperability
C-PATH: RDCA-DAP	Accelerate data sharing and drug development in Rare Disease. FDA funded initiative.	• Innovative & needs-led research and development • Optimising data for patient & societal benefit Expected nature of collaboration: • Strategic, to facilitate global collaboration and alignment in innovative & needs-led research and development

Identified Initiative / Programme/ Organisation	Objectives	Pre-identified Opportunity topics and expected nature of collaboration
Darwin	EMA coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use, from real world health care databases across the EU	• Innovative & needs-led research and development • Optimising data for patient & societal benefit Expected nature of collaboration: • Strategic to facilitate EU regulators collaboration and alignment in innovative & needs-led research and development
European Health Data & Evidence Network (EHDEN)	IMI project that aims to build a large-scale federated network of data sources standardised to a Common Data Model.	• Optimising data for patient & societal benefit Expected nature of collaboration: • Strategic to accelerate data standardisation and training
European Health Data Space (EHDS)	European Health Data Space, initiative by the EC to promote better exchange and access to different types of health data, to support health care delivery, health research and health policy making purposes.	• Optimising data for patient & societal benefit • Long-term integrated European & national plans and strategies • Access to high quality healthcare
European Platform on Rare Disease Registration (EU RD Platform)	To cope with the fragmentation of RD patients' data contained in hundreds of registries across Europe. To act as a knowledge generation centre benefiting healthcare providers including ERNs, researchers, patients, and policy makers in the common effort to improve diagnosis and treatment for RD patients.	• Expanded ERN registries and further developed ones will be linked to the EU RD platform • Optimising data for patient & societal benefit • Innovative & needs-led research and development • Long-term integrated European & national plans and strategies
ERICA (Coordination and Support Action under Horizon Europe, 2021-2025)	Builds on the strength of the individual ERNs and create a platform that integrates all ERNs research and innovation capacity.	• Innovative & needs-led research and development • Integrated & person-centred care
GenoMed4ALL	H2020 project on transforming the response to Haematological Diseases by seizing the power of Artificial Intelligence	• Innovative & needs-led research and development • Earlier, faster, more accurate diagnosis Expected nature of collaboration: • Application of Artificial Intelligence on federated data

Identified Initiative / Programme/ Organisation	Objectives	Pre-identified Opportunity topics and expected nature of collaboration
GO FAIR	Stakeholder-driven and self-governed initiative that aims to support implementation of the FAIR data principles via Global and Open FAIR implementation networks.	• Innovative & needs-led research and development • Optimising data for patient & societal benefit Expected nature of collaboration: • Convergence of FAIR implementation between and within communities • Collaboration with the Rare Disease GO FAIR network and its network of patient organisations
GA4GH	The Global Alliance for Genomics and Health fosters common technical standards, seeking to enable responsible genomic data sharing within a human rights framework.	• Innovative & needs-led research and development • Earlier, faster, more accurate diagnosis Expected nature of collaboration: • Participate in the development and implementation of international data standards • Strategic – building partnerships with similar non-European initiatives
Gaia-X	Gaia-X represents the next generation of data infrastructure: an open, transparent and secure digital ecosystem, where data and services can be made available, collated and shared in an environment of trust.	• Optimising data for patient & societal benefit
Orphanet Data for rare Diseases (OD4RD) – Direct Grant	Contribute to standardized RD data generation by the maintenance and implementation of ORPHAcodes in Health Care Providers hosting ERNs RD codification best practices, assistance and tools Optimising data for primary and secondary use	• Optimising data for patient & societal benefit • Innovative & needs-led research and development Expected nature of collaboration: • Strategic to increase interoperability between primary healthcare data and registries and other research-oriented data repositories; • increase data readiness; • accelerate Real-World Data generation

Identified Initiative / Programme/ Organisation	Objectives	Pre-identified Opportunity topics and expected nature of collaboration
Patient Focused Medicine Development (PFMD)	Not-for-profit collaborative initiative benefiting patients and health stakeholders by designing a patient-centred health care system with patients and all stakeholders.	• Partnership with patients Expected nature of collaboration: • Patient Engagement Open Forum as community and capacity building platform for patient engagement in RD
Screen4care: Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies (IMI project, 2021-2026)	IMI project that aims at shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies	• Innovative & needs-led research and development • Earlier, faster, more accurate diagnosis • Partnership with patients Expected nature of collaboration: • Development of joint strategies
Joint Action Towards the European Health Data Space – TEHDAS JA	TEHDAS JA, funded under the EU Health Programme, helps EU MS and the EC to develop and promote concepts for the secondary use of health data to benefit public health and health research and innovation in Europe. It aims at enabling European citizens, communities and companies to benefit from secure and seamless access to health data regardless of where it is stored	• Optimising data for patient & societal benefit • Integrated & person-centred care • Access to high quality health care
X-eHealth	EU-funded project that aims at developing the basis for a workable, interoperable, secure and cross border Electronic Health Record exchange Format in order to lay the foundation for the advance of eHealth sector.	• Optimising data for patient & societal benefit • Earlier, faster, more accurate diagnosis

2.2.3. Investment required

Building upon the experience of the EJP RD co-fund where the EU (via Horizon 2020) and Member States jointly co-fund activities, the RD Partnership is primarily a co-fund where EU public (Horizon Europe) and national (sometimes even regional) public Ministries/agencies jointly finance the activities. In addition, cooperation with private actors (NGOs, charities, industry etc.) might also be sought on specific aspects, while overlapping with initiatives such as the Innovative Health Initiative (IHI) will be avoided.

The RD Partnership's ambition will only be possible with a strong political engagement and high investments from stakeholders (participating countries, public and private funders, European Commission). Based on the EJP RD experience, it is important to underline that the ambition of gathering all stakeholders under one umbrella to accelerate research for the benefit of patients was a challenge whose success could not be taken for granted. After three years of existence, the EJP RD has demonstrated that such venture is possible and that it can be achieved only by collaborative and comprehensive efforts. This is also reflected through the applied funding model where the joint effort of the national funding bodies providing in cash contribution and the reimbursement rate of 70% of the European Commission allow for an internal distribution of funds compensating constrained input by participating research performing organisations, hospitals and not-for-profit bodies that do not have the capacity to bring major funding as a contribution to the partnership. Yet, such model is necessary to ensure meaningful participation of all stakeholders and break the barriers preventing patient organisations and under-represented countries to participate.

This concept paper presents RD Partnership with its full ambition of making a sustainable change for the RD community and beyond. This is fully relevant to the national commitments: the span of the proposed structure and aims allow for leveraging of national contributions at different levels and for different type of activities (funding, data sharing and infrastructure, training, innovation, in house research activities, etc.) making sure that each country can maximise its already existing efforts in the RD space and, whenever possible, engage further.

It is also important to underline that the possible inclusion of industry as full beneficiaries in the partnership, besides being unique (for a co-funded type of partnership), is considered as major gamechanger in building integrative RD ecosystem and advancing RD Partnership goals. This inclusion needs to happen in full synergy with other initiatives such as the Innovation Health Initiative (IHI) Partnership.

A tentative assessment of the budget required to fulfil the proposed ambition is presented below. The "*Overall summary of the estimated costs of the Rare Diseases Partnership*" table includes a column indicating an estimation of what (which part of the activities and thus overall ambition) could be achieved if the relevant commitments from participating countries, beneficiaries, and the EC (both possible reimbursement rate and overall committed budget) are not reached.

For the Competitive research funding and support:

- Competitive Joint Transnational Calls (JTC) to fund multinational projects (annual implementation):

An estimation of 25 000 000 € per JTC of national investment is expected, and thus 175 000 000 € for the proposed 7 years duration of the Partnership. How much of this investment will be seen as eligible for EC co-funding remains to be clarified as current administrative practice would probably only allow for the first 3 calls to be fully included in the reimbursement calculation. Part of the top up will be assigned to the funding of patient organisations in the selected projects for funding for all the calls planned in the Partnership.

The expenditure with the engagement, management, and monitoring of the JTCs (i.e., JTC

secretariat personnel, evaluation meetings organisation, payments to experts, travels (for funders and evaluators), and for project and monitoring meetings organisation) is estimated to be around 500 000 €/JTC, and thus 3 500 000 € for the 7 years duration of the partnership.

- Networking:

The funding of new or expanded networks established in the 7 years duration of the partnership is estimated to 2 500 000€. The costs of management are expected to be around 300 000€.

- "In house" funding of clinical research with CRN:

The overall estimated budget to cover CRN research projects that will be funded through internal calls is of 168 000 000 €. This represents 80% of the total estimated costs of the Clinical Research Network (CRN). Total expected costs of CRN are estimated at 30 000 000€ per year.
These calls will be supported by direct use of EC funds, complemented by in-kind contributions of involved research performing organisations and possible in-cash and/or in-kind contributions of industry.

For European Clinical Research Network (CRN) for Rare Diseases:

- RD Clinical Research Infrastructure (including data exploitation hub):

The costs of a common support infrastructure for CRN are estimated to 42 000 000 € for the 7 years (representing 20% of the total estimated costs of CRN). This comprises the costs of the support services, infrastructure (e.g., maintaining and enlarging the VP to include national registries and data sources, developing innovative analysis resources and providing cloud computing and data exploitation facilities, and providing a data quality assurance service within CRN) as well as the management costs.

For Transversal activities:

- Data integration and coordination services:

The cost is estimated at 15 000 000 € to support all funded projects to be generated within the RD Partnership.

- Mentoring services:

The costs of the mentoring services include the management of the service by a dedicated team: 210 000 €.

- Acceleration hub:

The overall budget being it in-cash and/or in-kind contributions needs to be evaluated together with the industry partners. As example, for funding to advance 30 therapies to trial readiness, the budget of around 100 000 000 € would be needed. For the management of the acceleration hub, the costs would be 1 176 000 € + 100 000 € for subcontracting to support IP.

- Ethics and legal support:

Costs for daily management of ethics/legal evaluation and support coordination, independent ethics advisor (for the whole programme) and relevant meetings: 1 666 000 € for the proposed 7 years duration of the Partnership.

- Central coordination and management:

Central coordination personnel costs are estimated to be around 5 300 000 € (including senior

project managers, communication managers, financial officer, assistant, IT manager and coordinator), plus 500 000 € for communication, dissemination and other costs for 7 years.

- Capacity building:

The overall estimated budget to cover all training activities that will be developed under the RD Partnership is of 5 000 000 €. This includes the development, the management and the (online or face to face) organisation of the trainings.

Out of the total cost, around 1 000 000 € will be dedicated to the implementation of national "Train the trainers" model.

Governance and strategy

- National Mirror Groups (NMGs):

The costs of the National Mirror Groups are divided as follow:

- Central coordination of the NMGs (part of the Coordination office) to support the processes and NMGS: 588 000 €
- National coordination of the NMG + organisation of meeting at national level (with one Face to Face (F2F) meeting of each NMG per year) – considering 27 participating countries: 8 542 800 € (316 400 € per country)

- Monitoring of the RD Partnership:

Management of the monitoring of partnership operational, specific and general objectives through adapted monitoring system in line with the requirements of Horizon Europe: 854 000 € for the 7 years (including costs of the adapted monitoring system).

- Sustainability/Exit strategy preparation:

All activities related to prepare the sustainability/exist strategy of the RD Partnership (to be integrated at the central coordination level) including possible subcontracting for market studies, legal advice, etc.: 500 000 €.

- IRDiRC secretariat

Support for IRDiRC Secretariat (personnel and Task Forces support): 1 764 000 € for the personnel + 840 000 € for Task Forces implementation for the 7 years duration of the Partnership (considering 4 Task Forces per year).

- Governance Meetings

Organisation of relevant meetings and/or workshops of the Governing Bodies (including National Alignment Board) and support to IRDiRC: 3 675 000 € for 7 years for governing bodies, and IRDiRC meetings.

Overall summary of the estimated costs of the Rare Diseases Partnership:

	Cost	Achievable with limited budget (estimation)
Competitive research funding and support		
Competitive Joint transnational calls	178 500 000 €	YES
Networking	2 800 000 €	Possibly
"In house" funding of clinical research within CRN	168 000 000 €	NO
Total	**349 300 000** €	
European Clinical Research Network for Rare Diseases		
RD Clinical Research Infrastructure	42 000 000 €	NO
Total	**42 000 000** €	
Transversal activities		
Data integration and coordination services	15 000 000 €	Partially and only if funded as part of research projects
Mentoring services	210 000 €	Partially and only if funded as part of research projects
Acceleration hub	101 276 000 €	Only if funded outside of the RD Partnership (e.g., as part of IHI)
Ethics and legal support	1 666 000 €	Limited service
Central coordination and management	5 800 000 €	Limited service
Capacity building	5 000 000 €	NO
Total	**128 952 000** €	
Governance and strategy		
National Mirror Groups	9 130 800 €	NO
Monitoring of RD Partnership	854 000 €	Limited service
Sustainability/exit strategy preparation	500 000 €	NO
IRDiRC Secretariat	2 604 000 €	NO
Governance Meetings	3 675 000 €	Limited service
Total	**16 763 800** €	
Total	**537 015 800** €	

As shown in the table above, with a limited budget, RD Partnership would not be able to achieve its goals and ambition, and the proposed activities will merely focus on the funding of joint transnational calls with some limited support services. The holistic and integrative approach to research offered by the RD Partnership vision and including full involvement of all stakeholders, maximization of national contributions and encompassing all elements required to reach the expected impacts will be hampered and unachievable.

Some basic information on the EJP RD budget to be considered when envisaging commitments to the Rare Diseases Partnership:

EJP RD has been initiated with an overall budget of 94 500 000 € of which 55 000 000 € corresponds to EC contribution. The remaining 39 500 000 € corresponded to 23 600 000 € of national in-cash contributions for the joint transnational calls and 15 900 000 € of in-kind contributions to other activities foreseen in the programme (research & infrastructure building, training, support services). It is important to note that although it is expected that in-kind contribution will remain the same (or eventually slightly decrease), by the end of the project the in-cash contributions committed to specific joint transnational calls is expected to increase. The initial amount of 23 600 000 € for JTC 2019 and 2020 was increased to 45 500 000 € of national contributions. It is also expected that around 40 000 000 € more will be invested in the remaining joint calls that were not accounted in the initial estimation. IMPORTANT: these amounts also include contribution of third countries not receiving EC reimbursement. In addition, the initial commitment was lower since most funders could not commit to more than one or eventually two years of successive funding (due to the lack of national long-term funding decisions).

Some lessons learned:

- Even if the overall in-cash contributions are expected to be higher than initial ones, they are dependent on the national funding decisions that often are limited to 1-2 years plans. Considering that for 15 years most involved countries recognises that E-Rare/EJP RD is their only (or major) line of investment in rare diseases research, it would be essential that longer-term commitments are envisaged for the RD Partnership.
- The commitments going beyond the first years of the project might be subject to lower or no reimbursement from Horizon Europe, since the research projects financed within these calls will run beyond the lifetime of the EJP RD Partnership itself. It would be important to inquire how these successive commitments could be accounted in the total commitment of the programme and respective reimbursement amount.
- The in-kind contributions of 10-30% (as in EJP RD) are often a maximum possible commitment from the participating institutions that are limited by their internal budgets and personnel they can dedicate to the project. Their capacity to increase such institutional / organisation budgets is currently non-existent as it is directly bound to the overall, often ministerial or regional, financial investment in research. It is doubtful that specific budget dedicated to rare diseases can be singled out as part of this global approach to funding of research performing institutions.

2.2.4. Transformational changes in the broader research and innovation ecosystem

While the European Union has fostered tremendous progress in the past decade to improve the life of people living with a rare disease in Europe, it is undeniable that the world we live in today is different than the one we knew back then. This new generation faces a new context, with new challenges but also new opportunities. It has taken a generation to get where we are. Now it's time to shape the future for Europe to indeed be a place where no one is left behind.

"In ten years' time, we will be living with a rare disease. In ten years, we may also be parents of a child living with a rare disease. By 2030, we want to live in an inclusive society that recognises all our needs and challenges. We want to live in a society that acknowledges that our conditions are more than collections of physiological symptoms but rather require a holistic approach to be fully understood and, more importantly, addressed. We want to have access to the right diagnosis without having to go through the all-too-common diagnostic odyssey and to be given the

appropriate treatment wherever we live and whatever our socio-economic status may be." – Rare 2030 Foresight in Rare Diseases Policy, Feb 2021.

The RD Partnership aims at taking the challenge pointed by the new generation by contributing to improvement of health and well-being not only of people living with rare diseases but also in a broader context of more efficient and innovative research & health care systems, enhancing EU competitiveness and reducing inequities among EU countries for vulnerable populations. More specifically, RD Partnership will induce transformational changes at three levels:

1. Impact on EU competitiveness

Through the establishment of comprehensive research and innovation ecosystem for rare diseases therapies, connecting local, regional, national and international levels, the RD Partnership will contribute to a step change in the way new treatments are developed. A unique system comprising high level expertise of ERNs and the European clinical research RD community at large, efficient and regulatory-exploitable natural history studies, generation of endpoints and biomarkers, supported by relevant, standardised data and samples infrastructure and competent personnel, will reinforce EU's attractiveness for companies fostering clinical research/ trials and development of treatments and diagnostics. Providing such favourable environment will lead to higher and more regular investments and job creation of high-quality jobs, improving trade balance of the EU.

2. Rare diseases as precursors of transformation towards precision medicine

Out of necessity, rare diseases have become pioneers in tomorrow's transformations and creative solutions for research and health care. The community continually brings forward innovative concepts and models created at the margins of the health care system but with benefits for all. RD Partnership has the power to leverage and create cross-country, cross-systems, cross-languages capacities required to achieve the critical mass needed to innovate in small-populations space. The innovation in genetic or chemical profiling, finding commonalities among ultra-rare diseases, addressing the methodological and regulatory compliant challenge of clinical studies with few, and heterogenous patients' profiles that will be performed to accelerate diagnosis and treatment delivery for persons living with rare diseases, will be transposable and open the venues for personalised or simply more cost-effective approaches to common diseases.

3. Contribution to the reinforcement of equity among EU countries for vulnerable populations

RD Partnership will reinforce the social justice for vulnerable populations by providing environment conducive to earlier diagnosis, faster and more accurate treatments and care. The reinforced inclusion and connection between EU-wide and national research and capacity building structures will support less developed sites and knowledge sharing thereby reducing inequalities between countries. The trainings targeted to patients, patient representatives, professionals and society as a whole will contribute to more knowledgeable and prepared RD community and society and enhance education around rare diseases and their challenges, as well as leadership of patients. RD Partnership will reduce the inequities between rare disease patients, by also supporting those with 'undiagnosed' rare disease, where collaboration across sectors is key to provide those with 'hard to diagnose rare disease' with more innovative diagnosis tools, professionalism, understanding and support. Finally, by investing in dedicated research and approaches to measure socio-economic impact and burden of rare diseases, RD Partnership will bring key numbers and possible solutions that can be translated at national and EU level to provide equal treatment to all citizens.

2.2.5. Phase-out / Exit strategy

The guiding principle is that the whole Partnership is greater than the sum of its parts. This

principle will be implemented in the development of the exit strategy by considering how each service relates to the context provided by the RDP and how the RDP will transition away from this Framework Programme as a whole and as components. Each service will have a defined exit and sustainability strategy and stated relationship to the overall Portfolio. The overall exit strategy will describe a range of scenarios including what will happen if a service is sustained in a successor to the RDP, or included in mainstream services, or sustained outside a successor to the RDP (e.g., funded by national governments) or if the service is not sustained. The exit strategy will specify how each service will adapt the scope and scale of its services to the available resources – this may include shrinking the service extent or limiting accessibility of the service. Services may be successful and develop a life of their own beyond the RD Partnership as companies, spin-offs etc. In that case, the exit strategy will specify how the service relates to the other services including Access Rights for Results developed by the RD Partnership and how services transition out of the Partnership. The connections between each service and the Partnership as a whole will be mapped from content and administrative perspectives. This will inform decisions about the place of each service in the ecosystem, including when and how to support any spinouts. The sustainability strategy will describe which stakeholders will be supporting a services operation, maintenance and further development, how the stakeholders will support sustainability – deployment of material, financial, and human resources, and how validated estimates of market size justify the scale and scope of the services to be sustained.

Sustainability will be supported by evaluation of individual services and the Partnership as a whole. The added value of the integration provided by the Partnership will be embedded in the descriptions of the sustainability of the services. Evaluation will include metrics (KPIs, outcomes, and metrics) and narrative (e.g., case studies, lessons learnt). Furthermore, the Partnership will support mechanisms, such as stakeholder workshops, to match maturity level with possible sustainable strategies for products of RD partners.

Internal mapping of the services and their roles will be combined with mapping the RDP's role in the broader health/medical context. Mapping will inform relationship building. This external stakeholder management already includes ongoing discussions with national and international initiatives in RD and will facilitate identification and selection of options for the exit strategy and sustainability.

Member States as main beneficiaries and co-funders of the RD Partnership will be in the position to best utilise its results and integrate in their research and innovation ecosystem, but also in the RD health care settings, for example but not necessarily uniquely within health care units which are ERN members.

It is also planned that industry partners will be key members of the RDP: multiple companies will share the work. Each company will benefit from a relationship that develops from scoping and planning, through development and management, and on to sustaining outcomes. Quantitative information about this involvement (metrics) and qualitative information (e.g., lessons learnt) will inform the relationship with each company during the RDP and the transition beyond this Framework Programme.

Thus, the sustainability and exit strategy can utilise, but not necessarily be limited to, the following models or their combinations:

- Member States commitment:
    1. Integrating RDP results, tools and services in the R&I ecosystem and health care settings for rare diseases;
    2. Using local funding on a country-by-country basis;

3. Developing formal infrastructure, perhaps including the European Research Infrastructure (ERIC) mechanism[65], where one or more of the established European Research Infrastructures would commit to operate and possibly further develop one or more services to a pre-agreed extent;
4. Combined commitment of Member States together with industry partners.

- European Commission commitment via established European infrastructures such as European Platform on Rare Disease Registration developed and hosted by the EC Joint Research Center (JRC). Such institutions could operate and possibly further develop the service to a pre-agreed extent.
- Contractually defined in-kind contributions by [international] experts to a service hosted at some national institution(s) or hosted by an established consortium such as Orphanet.
- Contributions from the private sector (including but not limited to companies in the pharma, devices, medical technology, and diagnostic sectors) through:
  1. fees for service;
  2. In-kind contributions of material or staff costs relating to specific development programmes, either sponsor initiated or investigator initiated;
  3. Contributions from corporate responsibility / philanthropic functions;
  4. Membership fees.
- Results with translation potential can be sustained via private investments or by using general public private partnerships mechanisms. This can include seeking investments via various seeding mechanisms (e.g., mentoring services and monitoring process to be presented to a board of "investors" including private actors), achieving investments or collaboration agreements with SMEs or large companies beyond the scope of the project during / after project lifetime. Spin-offs can be created based on outputs of the project (e.g., new commercial or non-profit entities). International, national, and regional incubator mechanisms such as EUREKA (Σ!), European Institute of Innovation & Technology (EIT) Health, or SEMIA can also be foreseen.
- Partially or fully self-sustaining paid service delivery for further exploitation of generated results. These options could be managed by one of the Beneficiaries or by a dedicated legal entity.

Development of Phase out / Exit strategy

Accordingly, the development of the exit strategy for the Partnership will be based on a hybrid of work by the overall coordination and each service. The RD Partnership Coordination Office will establish a standard methodology for defining the exit strategy and review the strategies suggested by each service to promote consistency and synergy. This process will not be a static, one-off exercise but will extend throughout the life of the RDP. An external consultancy may be used to support this work. The exit strategy will be scoped and built with a view to understanding what is sustainable and how services can be sustained. The management and maintenance of the RDP will consider how appropriate self-reliance can be developed and when centralisation of management and resources are needed. Regular review of the Partnership's activities will constantly look for and revise the opportunities for sustainability.

[65] https://ec.europa.eu/info/research-and-innovation/strategy/strategy-2020-2024/our-digital-future/european-research-infrastructures/eric_en

2.2.6. Strategic Research and Innovation Agenda (SRIA) development

SRIA drafting process:

During the development of this Concept Paper, more than 180 experts from 24 countries and EC, representing all types of expertise and background were gathered and actively participated in the writing work. This allowed pre-identification of important topics and key considerations (e.g., specific research topics that require attention, processes to put innovation in practice, economic evaluation, expansion beyond RD community, development and regulatory acceptance of ATMPs, and many more) that go beyond the overarching nature of this document. Thus, it is expected that comments captured at this stage and such extensive support will be further used to develop the SRIA (following the steps indicated below).

The process of developing the agenda will involve several stages:

Preparatory/initial phase:

- Set-up a dedicated expert team to guide and oversee the development and implementation of the SRIA (if needed, involve external experts specialised in strategy and performance management).
- Identify the key stakeholders to include in the SRIA framework development process (develop a stakeholder map).

Writing & consultation process:

- Initial reflection and analysis of gaps and opportunities conducted within the RD community and with the EC (including based on the open public consultation).
- The early ideas about scope, impact, outputs should be consulted by the core partners with several test audiences - research and health care communities, umbrella patient organisations, EU infrastructures, industry, relevant EU initiatives and multinational research consortia etc.
- The preliminary draft should be open for public consultation for at least one month and, if required be supported by a public webinar. Both the consultation and information about the webinar and its outcomes should be broadly disseminated. In addition, all input received should be made available on the dedicated consultation website.
- The above-mentioned results should be used for the SRIA revision.
- It is expected that the draft will continue to evolve as more information about the scope of other European programmes, partnerships and European initiatives become available to more precisely delineate the type of activities that should be prioritised in RD Partnership.

Validation phase:

- Following stakeholder and expert interaction, the final SRIA will be submitted for approval of the General Assembly & European Commission (after the signature of the Grant Agreement).
- The SRIA will be reviewed at the occasion of the Partnership interim evaluation.

2.3.Necessity for a European Partnership

Rare diseases were nearly invisible in our health and social care systems in previous decades. Today, they are recognised as a public health and human rights priority, in large part due to a policy framework substantially defined by the Commission Communication on *"Rare Diseases: Europe's Challenges"* (COM(2008)679) and the Council Recommendation of 8 June 2009 on *"An action in the field of rare diseases"* (2009/C 151/02) setting the roadmap for a number of

legislative acts and policies, such as the EU Regulations on Orphan Medicinal Products[66], the Paediatric Use of Medicines[67] and Advanced Therapies[68], and the Directive 2011/24/EU on patients' rights in cross-border health care. In addition, previous research and innovation initiatives in the field of RD at EU level allowed to raise the interest of a wide range of stakeholders (e.g., Research Funding Organisations, Research Performing Organisations, EU Research Infrastructures, Patient advocacy groups, etc.), as well as to perform significant advancements. However, there are still relevant challenges to be tackled.

The Rare Diseases Partnership represents the ideal forum to bring the EC and national public (including research funders) as well as private partners together to address those challenges through a concerted research and innovation initiative. Indeed, the RD Partnership is to be conceived as a collaborative space where MS/AC and the European RD ecosystem will be able to contribute to enhancing research in this field and perform networking activities, in a coordinated manner. In this view, the Partnership will contribute to achieving the EU's political priorities as well as those of countries according to their specific needs. This will reduce fragmentation and avoid duplication of efforts and investments, which are transversal needs.

2.3.1. Addressing the objectives of Horizon Europe

Through the implementation of Horizon Europe (FP9), the EC intends to maintain Europe at the forefront of research and innovation. In particular, the overarching goals of this EU research & innovation framework programme are:

- To fuel EU's scientific and technological excellence and to strengthen the European Research Area (ERA).
- To tackle policy priorities, including green and digital transitions and SDGs.
- To boost Europe's innovation capacity, competitiveness and jobs.

In line with the central aims of the EU's policies and programmes relating to social cohesion and inclusiveness and the health, well-being, rights and security of its citizens, one of the Key Strategic Orientations (KSOs) set by Horizon Europe's Strategic Plan 2021-2024 is the creation of a more resilient, inclusive and democratic European society. In this view, the investments under Horizon Europe - Cluster 1 (Health) will be instrumental to develop stronger health systems, improve medical technologies and develop the knowledge and innovations that underpin the health and well-being of all citizens[69].

For instance, within Cluster 1 (Health) of Horizon Europe, the proposed RD Partnership will pay special attention to addressing the targeted impact "**Tackling diseases and reducing disease burden"** aiming at enabling health care providers to better tackle and manage rare diseases and at reducing the disease burden on patients effectively, thanks to better understanding and treatment of diseases, more effective and innovative health technologies and improved patient safety. In this view, the Partnership is wholly dedicated to achieving this targeted impact.
At the same time, through its General and Specific Objectives, the proposed Partnership will also contribute to addressing other targeted impacts of Cluster 1 (Health), namely:

- **Staying healthy in a rapidly changing society.** One of the key elements to achieve this impact is the availability and accessibility of real-world health data, which can lead to anticipatory

[66] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
[67] Regulation (EC) No 1902/2006
[68] Regulation (EC) No 1394/2007
[69] European Commission Directorate-General for Research and Innovation (2021). Horizon Europe: Strategic plan 2021– 2024. Luxembourg, Publications Office of the European Union

actions and will require appropriate support by research and data infrastructures. In this view, the proposed Partnership aims at unlocking the full potential of clinical and research data in the digital era.

- **Ensuring access to innovative, sustainable and high-quality health care.** Research and innovation can provide decision-makers with new evidence, methods and tools to implement successfully innovative solutions into their health care systems. In turn, this will help to improve the governance and resilience of health care systems as well as to allocate resources according to people's needs and preferences while delivering fiscal and environmental sustainability to make sure those needs can be met in the long-term. In this view the proposed Partnership aims at driving timely and equitable access to innovative, sustainable and high-quality health care by virtue of highly integrated research and health care system, in particular decreasing the number of unsolvable cases/misdiagnoses during the diagnostic odyssey.
- **Unlocking the full potential of new tools, technologies and digital solutions for a healthy society.** Research and innovation are needed on the large spectrum of tools and technologies for biomedical research, prevention, diagnosis, therapy and monitoring. The RD Partnership aims at optimising the creation and application of knowledge into meaningful health products and interventions that respond to the needs of patients living with rare diseases across Europe and globally, hence improving their quality of life, diagnosis and therapy development. Moreover, to provide high-quality health care and reduce health inequalities, end users' engagement in multidisciplinary, cross-sectorial cooperation with key stakeholders could help address specific unmet needs for health tools, technologies and digital solutions with limited commercial interest but also designing and developing suitable health products and services tailored to needs of specific population groups including the ones related to sex/gender or other aspects. In this view, the proposed Partnership aims at fostering research collaboration in the EU, with the Associated and Third Countries, and stakeholders in the RD ecosystem, thus enabling unprecedented pooling of resources and expertise.
- **Maintaining an innovative, sustainable and globally competitive health-related industry.** Research and innovation are needed to develop new cross-sectorial business models where health-related industry cooperates early with health care systems in the development of value-added products and services to enable an optimal uptake and deployment of innovative solutions, as well as to achieve the triple aim of improving the patient experience of care (including quality and satisfaction), improving the health of populations, and reducing the per capita cost of health care in the long-term. The RD Partnership will foster comprehensive public-private collaborations with industry, SMEs, charities and foundations aimed at achieving more effective outcomes to make Europe a global leader in rare disease research, leading to job creation and optimising EU competitiveness in R&I and health care innovation.

While the strategic plan 2021-2024 of Horizon Europe (HE) applies primarily to Pillar II (Global Challenges and Industrial Competitiveness) of the Programme, effective links with Pillars I and III, and the widening participation and strengthening the European Research Area (ERA) part, will ensure an integrated approach that enhances the effect of HE overall. This part of the Programme will optimise the impact of Pillar II by contributing to the objectives of the entire framework programme. It is going to reduce the innovation divide and geographical disparities, build the necessary capacity to allow successful participation in the R&I process and promote networking of and access to excellence. In this view, the proposed Partnership will contribute, in general terms, to the expected impacts of widening participation and strengthening ERA.

2.3.2. Supporting a meaningful collaboration among countries

Even though there are an estimated 27 to 36 million EU citizens (between 6 and 8% of the EU population) affected by one of the 6000 to 8000 recognised rare diseases (many of them life threatening or chronically debilitating)[70], usually there are very few cases for each individual RD in each Member State. Therefore, collaboration at the EU and international level for research is largely recognised as essential to progress in the development of more efficient and sustainable workflows in the health systems, diagnostic means and pipelines, high quality evidence-based treatments, cure and care, channels for collaboration of the different stakeholders and mutual benefits for all the actors in the RD ecosystem, to make a real difference for RD patients and their carers, and the society at large[71]. Indeed, no country alone has the knowledge, experience and capacity to investigate or treat all types of RD.

A co-funded Partnership is the best instrument to support a meaningful collaboration among countries. The EU added value of aligning such activities lies in a more efficient use of existing (human, infrastructures, financial) resources as well as knowledge, data and best-practice transfer between countries and within the RD ecosystem, thus providing access of direct benefit to patients from the provided European co-funding.

Indeed, by cooperating and exchanging life-saving knowledge and research at European level through the already known ERNs, patients across the EU can have access to the best expertise available. Furthermore, with the implementation of the proposed RD Clinical Research Network, as expressed in this proposal, the scope will be further enhanced with the transversal perspective, with collaboration also targeting the international scenario in an overarching approach. Previously under-represented countries in EJP RD will also be positioned to engage with this mechanism, and measures will be taken to boost and to monitor their participation in the CRN activities.

Even though research and innovation have the power to uncover the knowledge and develop the technologies to serve individual and societal well-being, economic prosperity (while preserving equity) and environmental sustainability, this ambition can only succeed through an extensive collaboration of Member States and internationally. Indeed, reaching meaningful impacts requires a portfolio approach encompassing a broad range of activities, including strategy, networking, excellence research funding, rapid translation, data sharing, training, piloting, demonstration, prioritisation and support for innovation and dissemination. In this view, e.g., the COVID-19 pandemic has shown the importance of effective coordination among EU Member States in the area of health, opening the door to a strong European Health Union, where, among others, countries work together to improve prevention, diagnosis, treatment and aftercare for any disease. Activities funded by the EU4Health Programme, such as in its Work Programme 2022, will support the capacity building in Member States, allowing also for an improved uptake of the Partnership's results.

The EU-funded EUROPLAN project[72] (2012-2015) as well as recent work of the EJP RD have led to the conclusion that there are observable differences between MS/AC in what respects to the implementation of RD National Plans or Strategies, in different facets. According to that, 70% of countries informing have an approved NP/NS, therefore, a gap has been identified to that respect. Regarding the funding for research projects on RD, less than 60% of countries promote national calls and only 50% promote transnational calls. Less than 50% foresee investments for networking to share knowledge on RD. Some additional public funding initiatives (apart from NP/NS) existed in less than 70% of countries for research and/or networking in the field of RD. Private funding initiatives to that respect were identified in less than 50% of countries. An advisory body of

70 Directive 2011/24/EU on patients' rights in cross-border health care
71 In this view, see for example the Special report 07/2019 of the European Court of Auditors "EU actions for cross-border health care: significant ambitions but improved management required"
72 http://www.europlanproject.eu

national experts for EU R&I policy existed in 52% of the countries, but this was not specific for RD. More than 20% of the NP/NS do not foresee the support for data repositories and tools dedicated to RD research. Half of the plans or strategies do not yet support FAIR data in the country. Holistic approaches for RD diagnostics and therapeutics are promoted by the NP/NS in 81% of the countries, but still 19% not including this is a high percentage, also considering that the alignment with IRDiRC goals should have started years ago. Regarding capacity building and empowerment, less than 80% of the NP/NS promote and/or support training activities. Rapid translation of the research results in clinical studies and health care are promoted by less than 50% of the NP/NS, and only 36% identified other initiatives to this respect. More than 60% of the NP/NS do not promote the development of innovative methodologies tailored for clinical trials in RD. Regarding EU13 countries, some main obstacles and barriers have been identified for the development, improvement and translation of RD research results: funding (in general), specifically the access to national resources for funding of research and development of RD projects, lack of options for exploitation of research results at national level, and some other.

A Partnership approach would indeed help filling the above-mentioned gaps, especially by ensuring that a set of common targeted objectives are shared by all countries involved in the Partnership and put in place with a transversal approach, for a concerted action aimed at achieving specific impacts. As a consequence, IRDiRC's goals would be implemented more broadly and concretely in the different countries. Therefore, the Partnership, which will be aligned with IRDiRC strategy, can be considered as instrumental to put those goals in the front page in the different countries, thus bringing to a real cohesion, alignment and maximisation of national efforts with the ultimate goal of responding to the relevant identified needs.

Maximising the impact on the patients' health and/or health systems level (also taking advantage of the experience of previous initiatives and their outcomes, like all those of the EJP RD) requires building a long-term strategy and annual programming for the wide range of activities. To this end, the proposed Partnership will implement a long-term strategic research and innovation agenda based on its GO and SO (as mentioned in Section 2.2 of this proposal) which is difficult to do within the framework of biannual work programmes. This will encourage a stronger commitment by all actors in the longer term and support a better realisation of the full potential of the European collective investment in research and innovation in the RD field.

The proposed RD Partnership will also catalyse the transfer of good practices to the national and regional level, including leveraging the power of national/European data sources, in particular by making nationwide or regional RD discoverable and actionable for international RD research. In this regard, the role of **National Mirror Groups** will be extremely important to ensure meaningful collaboration with and between countries, since they will bring together the national representatives of the RD Partnership and other relevant RD stakeholders (see Section 3.3 of the proposal), thus ensuring national coordination for the best contribution of countries to common objectives, and then the RD Community at large. In a nutshell, NMGs will serve as intermediates between the Partnership and national and regional stakeholders in the field.

Last but not least, the proposed Partnership will benefit from the experience of many of its members that already have a deep knowledge of European collaborations in the RD field, by participating e.g., in so called ERA-Net schemes and co-funds, research and innovation collaborative projects and joint programming initiatives.

2.4. Partner composition and target group

The RD Partnership will be able to rely on an existing network of initiatives launched and expanded under FP7 and Horizon 2020 such as EJP RD, research projects involving ERNs, ERICA, Solve-RD, as well as the Innovative Health Initiative, and research infrastructures. The new partnership will build upon the cumulative experience of these networks in planning and executing research activities, as well as results they already generated. This will enable the efficient launch of the RD partnership and shorten the ramp-up phase.

The Partnership will rely on:

- Partners from public and private sectors who will participate in the planning and implementation of actions (funders, research community, networks and infrastructures, patients and end-users);
- Stakeholders from public and private sectors providing advice/input for priority setting, project implementation or deployment of results (science, patients and end-users perspective, etc.) or securing alignment with national or global plans and initiatives (ministries of research and health, National Mirror Groups);
- Extended community of beneficiaries of grants based on competitive calls issued by the Partnership and directly involved in the in-house research projects/demonstrators to be implemented under the Clinical Research Network.

Type and composition of partners

According to the Treaty on the European Union, the EU shall encourage cooperation between Member States and "lend support to this action"[73]. Rare diseases are a prime example of a research area that can strongly profit from defragmentation of the research ecosystem and from coordination on a European and international scale[74]. This consolidation (breaking the silos between sectors and communities) and building bridges to new groups of countries in Europe and beyond will lead to a more efficient use of resources, including data, infrastructures, know-how and scientific and medical progress in complex areas of unmet need.

Breaking the silos between communities

The Partnership needs to involve all types of actors along the health and research value chain in priority setting and in funded projects:

- Research funders – EC, national authorities, charities/ foundations/ funds, i.e., leading organisations that fund, manage and implement strategically planned focused health research programmes;
- Research and innovation communities – across life science and technology/data disciplines
    - researchers from academia, health institutes, research institutes and university hospitals, often members of the ERNs, and various industry sectors to ensure the best opportunity for generating new scientific ideas and successful R&I activities;
    - research infrastructures and networks (clinical trials, knowledge, data, biobanks, translational platforms, etc.) who act as neutral brokers and efficiency enablers;
- Users: patients and citizens, health care professionals and health care providers (such as clinical centres of excellence) to provide input into the strategic design and implementation of activities, ensuring that it addresses the needs of persons living with rare diseases, their physicians and caregivers.

[73] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12008E168:EN:HTML
[74] Council Recommendation 2009/C 151/02, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

- EU-wide and national policy makers, regulatory authorities, HTA bodies (EUnetHTA[75]), and health care payers to provide early input to the activities increase likelihood that the results of actions will meet regulatory requirements necessary for uptake and thus for reaching societal impacts.

EJP RD created a strong community, mostly consisting of public sector researchers from different academic and medical disciplines, research infrastructures as well as RD patients and representatives of rare diseases affecting humans from birth to adulthood. The RD Partnership will step-up the integration of perspectives currently underrepresented in order to address research needs of the wide spectrum of rare diseases:

- The RD Patient community - To fully realise the patient-need led research, the partnership will involve patients at all levels of governance and execution. Patients and/or representatives will be active partners in planning and prioritising research activities, engaging in projects and facilitating patient engagement across all activities including development and deployment of results.
- The private sector - the Partnership will enable full industry engagement in R&I and deployment activities to accelerate the generation and uptake of regulatory compliant research results and translate them into innovation for the benefit of patients. It will also help identifying and addressing challenges of implementing tools and knowledge in an industrial context.
- Charities and foundations - philanthropic as well as patient led research foundations are not only funders of research. They also provide wealth of in house scientific and medical expertise and in-depth knowledge of programmes and stakeholders in the field.

<u>Building bridges between countries</u>

More than 130 beneficiary institutions from 35 countries participate in the EJP RD and up to 32 funding organisations from 23 countries participated already in its Joint Transnational Calls (JTCs). Currently, more than 1600 ERN Full Members and Associated Partners cover the whole EU region and Norway, besides, through the national networks and pathways they extend to other national centres engaged into RD activities. Moreover, Orphanet is also a long-standing pan-European network. The RD Partnership will gradually bring on board additional players to attract and increase the critical mass of resources, know how, talents and excellence, but also to erase white spots on the RD research map and offer equal opportunities to patients across Europe.

To achieve this goal, the partnership will create mechanisms to onboard:

- Under-represented EU13 countries (to pursue the objective already set in EJP RD) to secure balanced representation from all EU countries.
- Associated and non EU countries. In EJP RD, already 7 associated countries (Armenia, Georgia, Israel, Norway, Serbia, Switzerland, Turkey), the UK and Canada were represented.
- Third Countries members of the IRDiRC who are interested in funding collaboration.

In addition to expanding the partners' base, the RD Partnership will strengthen international collaboration. This collaboration will directly contribute to achieving the objectives of delivering for patients as well as strengthening the European capacity: coordination contributes to more effective planning and use of resources, synergies and collaboration contributes to building capacity and excellence. Connecting programmes across the globe is the only way of addressing

[75] Creating, facilitating and promoting sustainable Health Technology Assessment (HTA) cooperation in Europe, Joint Action funded under EU Health Programme: https://www.eunethta.eu/

some of the most complex unmet needs especially for the very rare diseases.

The linkage with international partners will be ensured at different levels.

- First, the operation of the IRDiRC Scientific Secretariat within the RD Partnership will provide strong links to international collaborators as well as a joint management of research and innovation strategy. This will be particularly relevant to drive and support the participation of members from the US National Institutes of Health who are also members of the IRDiRC Consortium Assembly and participate in its activities. These interactions will stimulate the European added value in the field of international collaboration to advance faster toward the vision and goals defined by IRDiRC.
- Secondly, through the already established collaboration with partners like Canada, Australia (Western Australian Department of Health) also expressed interest to participate as so-called Associated Partner contributing to and aligning with research and training activities.
- Finally, the RD partnership intends to pursue efforts in expanding the collaboration and integration of other countries willing to join with their knowledge and resources to achieve shared benefits for rare diseases patients.

3. Planned Implementation

3.1. Activities

Aiming for effective generation of knowledge and its consequent translation into meaningful diagnostic and therapeutic interventions, the implementation of the RD Partnership will focus on creating an efficient, highly integrated operations and support environment for the RD research community. Building on previous experience such as in EJP RD, key drivers will further implement and deploy recently developed infrastructures and services. Activities will be coordinated across organisational, regional and sectoral boundaries, and outcomes-oriented funding will be deployed that advances high-potential research towards the clinic.

The RD community recognises that, out of necessity, people living with a rare disease are often the most motivated stakeholders to make progress on their disease when not only the number of patients living with the disease is low but also knowledge, expertise and funding available are lacking to do more. RD Partnership recognises that patient engagement is key, especially in rare disease research. A structured framework for patient engagement in research adds scientific and societal values and leads to better science with outcomes most relevant and impactful for patients hence benefitting the entire RD community. Robust patient-need driven research requires engaging patients in the three stages of the funding process: i) strategic decision-making with the identification and prioritisation of research topics based on unmet needs, ii) co-planning research activities including co-development of Real-World Evidence (RWE), Patient-centred/relevant outcome measurements (PCOMs/PROMs) including Patient reported outcomes (PROs) (e.g., patient representative/ organisation as research partner/co-researcher in consortia) and iii) decision-making on the allocation of funding to research projects including review, evaluation and monitoring. A flexible and coherent patient engagement framework will be developed to support adaptation at national levels and to promote sharing of best practices, re-using and extending existing resources such as the 'IMI-Paradigm toolbox for Patient Engagement in medicines development' and the 'Short Guide on Patient Partnerships in RD Research Projects' developed within the EJP RD. The framework will also take inspiration from national initiatives for citizen engagement (such as the approach of the Dutch Research Council (NWO) to solicit questions from the general public to define the Dutch Research Agenda) and will promote engagement by relevant groups such as children and young people (e.g., c4c and its resources). Several patient engagement reference groups (PERGs) will be developed to reflect the needs to engage specific diseases and expertise based on the development of activities. Representatives of the PERGs will be integrated into the Multistakeholder Strategic Steering Board (MSSB) to advise on the inclusion of specific recommendations facilitating a cohesive patient engagement approach throughout the Partnership.

To ensure maximum co-ownership and transparency to allow all relevant stakeholders have a voice in the RD Partnership, an effective governance framework (*see section 3.3 Governance*) has been designed to facilitate lean, responsive and effective development of the operational strategies and support services.

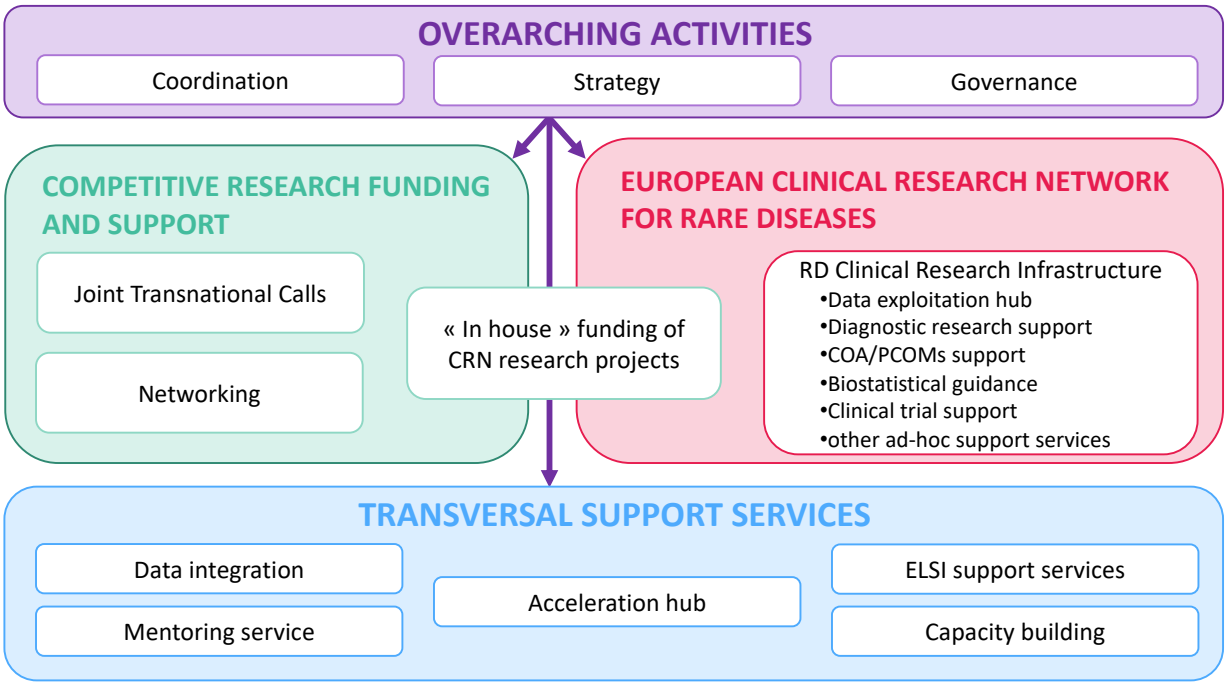
All RD Partnership activities will be organised within a coherent structure guided by five major transversal themes:

- RD **funding and support** that give rise to high-quality, inter-disciplinary research collaborations creating robust and FAIR data generated with future development towards the patient in mind to contribute to – among other knowledge gaps - better understanding of the drivers and characteristics of specific RD and RD clusters, and the underlying factors exacerbating the diagnostic journey.
- Actions, support and **cross-sectoral collaborations** that must contribute to structurally identifying and accelerating promising research results through the early validation stages

and towards clinical development of innovative products and interventions.

- Further advance the state of the art in **infrastructure, services and support** so that clinical and translational research are highly productive.
- **Capacity building** of all stakeholders to support new generations of researchers, decrease knowledge and competences gaps between countries and empower patients.
- Fully **integrated strategy and coordination** to support effective public, public-private and civil society partnerships.

The above thematic directions will be implemented through a set of building blocks, **transversal actions and support tools, services and resources**, so that the above is achieved with maximum efficiency and effectiveness at all levels.



The RD Partnership implementation concept

Competitive research funding and support

Ensuring that every high-quality RD research project will benefit from cross-disciplinary expertise, goal-oriented study planning and efficient execution is part of the RD Partnership mission. This should be done by bringing the high value supporting services from across Europe under one roof and as stated above, requires coordination of key funding, support and infrastructural components.

The RD Partnership aims to implement an innovative and comprehensive approach to research funding and support including **three major types of funding**:

- Funding of transnational, collaborative and patient-needs driven research projects via open, competitive joint transnational calls involving national/regional research funding organisations.
- Funding of networks (networking events/workshops) fostering building of new, or expansion of existing networks, with specific attention to sharing of knowledge and building connections between patients, researchers and clinicians around

disregarded rare diseases.
- Funding of "in house" collaborative and patient-needs driven research projects to be implemented under the strategic themes identified within the European Clinical Research Network for Rare Diseases.

Competitive Joint Transnational Calls (JTCs)

The funding of transnational collaborative research is critical to enhance the cooperation between scientists working on rare diseases across Europe and beyond, and thus reduce the fragmentation of research in this field and avoid duplication of efforts. Most questions concerning best care of patients can only be answered with a cross-sectorial, transnational collaboration in research, deployment and successful implementation.

RD partnership will expand upon the experiences and lessons learned from the many funding bodies involved in the organisation of JTCs on rare diseases in E-Rare and the EJP RD as well as the fruitful collaboration between funders and community infrastructure providers. It is foreseen that seven JTCs for research projects will be launched combining national/regional funding maximised by inclusion of different types of funders. These will possibly have broad topics to enable the widest participation of funding organisations and embrace basic, pre-clinical, translational as well as public health, social sciences and humanities research topics. To meaningfully support the *Widening participation and strengthening the European Research Area* objectives of Horizon Europe and to decrease the inequalities in RD research capacity between countries, the inclusion of researchers from underrepresented countries will be actively encouraged, through the implementation of dedicated measures like for example the possibility of enlarging the research consortia at several stages of the application procedure, or prompting of young principal investigators as consortia coordinators.

The Multistakeholder Strategic Steering Board will be used to support the Board of funders in choosing topics for the Joint Transnational Calls.

Networking

To encourage sharing of knowledge on rare diseases between patients, clinicians and scientists a networking support scheme will be implemented based on the experience made in EJP RD. The scheme will provide financial support by direct use of EC funds to third parties for fostering organisation of workshops or conferences to support new networks or strengthening existing networks, to enable exchange of knowledge and stimulate new collaborations. It is expected that these new or improved networks may lead to future collaborative research efforts, e.g., by applying to research funding within the RD Partnership (e.g., JTCs), to COST actions or Marie Skłodowska-Curie Actions (mobility and training calls). The networking scheme can also be used as a preparatory step for setting up clinical research consortia. To reduce the inequalities between different RDs, specific attention will be given to so-called disregarded rare diseases. The outcomes of an IRDiRC taskforce on disregarded diseases (expected in 2023) will be used as starting point.

"In house" funding of clinical research within European Clinical Research Network for Rare Diseases

Regular calls for focused research projects will be launched within a new infrastructure to be developed in the RD Partnership: the **European Clinical Research Network for Rare Diseases (CRN, see below)**. The calls are expected to cover the following themes:

- Innovative diagnostic research approaches
- Discovery and validation of biomarkers and surrogate endpoints for rare diseases
- Identification and validation of rare disease-specific patient centred outcome measures
- Real world evidence generation for rare disease outcomes with standard of care therapies
- Clinical trial evidence generation for novel and re-purposed drugs and medical devices

These calls will be supported by direct use of EC funds, complemented by in kind contributions of involved research performing organisations and possibly in cash and/or in-kind contributions of industry.

The Multistakeholder Strategic Steering Board will be used to support the CRN's strategic decisions and promote most promising collaborations including public-private partnerships wherever possible and useful to maximise the clinical impact of the programme.

European Clinical Research Network (CRN) for Rare Diseases

Since 2017 clinical and research expertise for rare diseases in Europe is organised in 24 thematic consortia, the European reference networks (ERNs). The ERNs have started to gather a critical mass of RD patient data through ERN-wide registries in a standardised and FAIR-compliant way in close collaboration with the EJP RD. The emerging EJP RD Virtual Platform will support the FAIRification of the ERN registries and various European research resources in a federated data and knowledge ecosystem, in cooperation with the EU RD platform and the European Health Data Space initiative. While this federated data ecosystem is expected to facilitate clinical and translational research initiatives of the ERNs and the European RD clinical research community at large and related resources, further methodological and operational support will be required to maximise their existing capacities in identifying and enrolling suitable patient populations in diagnostic and therapeutic studies. To materialise this critical next step, we propose to set up a **European Clinical Research Network for Rare Diseases** with a common support infrastructure that will provide services to multinational research consortia formed by the ERNs and other RD clinical research groups in Europe and Associated countries. All structures and processes to be implemented in the CRN will be **complementary to the existing ones** and will serve the key goal to **accelerate patient-centred research** and generate **impactful results**. Thorough consideration would be taken to ensure strong synergies and avoid overlaps with the current system of the ERNs under the directive on patients rights in cross-border healthcare and ERN activities recently or currently funded from other EU funding instruments, including the 3rd EU Health Programme (2014-2020), the EU4Health Programme (2021-2027) or the Connecting Europe Facility (2014-2020).

To guarantee optimal but agile coordination of the CRN as integrative part of the RD Partnership, a **CRN Coordination Office** will be installed as part of the RDP Coordination Office to ensure seamless implementation of shared support services such as:

- Administrative, legal and financial assistance;
- Communication and dissemination activities;
- Coordination of the involvement of the CRN expert service teams and advisory boards;
- Development of collaborations with complementary initiatives to maximise efficiency, avoid duplications, facilitate the operation of the CRN encompassing all the relevant expertise from other initiatives, including, but not limited to EU RD Platform at JRC, EU PERMED, C4C, 1+MG, the EHDS, EOSC, IHI, member states (NMGs);
- Development of partnerships to co-fund the activities of the CRN beyond the timeframe of the RD Partnership, in relation with the industry and philanthropy organisations.

RD Clinical Research Infrastructure

The implementation of a joint support infrastructure will ensure the harmonised development of the projects funded through the CRN, secure the use of state-of-the-art methodologies, avoid the emergence of redundant structures, and guarantee efficient use of the available resources. The services delivered will be tailored towards the needs of the research projects.

The thematic focuses of the service structures will reflect the anticipated main lines of research. In addition to a few core support structures, ad hoc expert teams or Advisory Boards will be formed to serve specific needs, for example support in definition and refinement of topics for internal calls for projects that will drive the in-house research performance. We currently anticipate the following services:

Core support structures:

- A **Data Exploitation Hub** will be established to orchestrate the findability, accessibility, interoperability and re-usability of existing and newly collected patient data, plus biosample information, increasingly emphasising regulatory-level quality. In case of the expansion of the ERN registries and further developed or new registries under the RD Partnership, those should to be integrated/linked to the EU RD platform. The infrastructure, standards and tools provided by the EU RD Platform will be implemented. This approach aligns with the design of advanced data-heavy international projects, and suitable technologies exist (e.g., the Gates Workbench, as used by ICODA, C-Path, IMI, etc.). This lightweight coordination and hub function will operate transversally across the CRN, whilst most data operations will sit within the various themes and projects undertaken by the CRN, using established interoperability tools, standards and FAIR principles. This architectural arrangement will help the RD Partnership to move towards regulatory-level data, by providing centralised quality assurance support, in collaboration with the EMA. Particular efforts will be undertaken to maximise the secondary use of medical and healthcare data facilitated by the EHDS for clinical research: it will explore different approaches, from research consortia as EHDS data users to more integrative approaches requiring stronger alignment on governance, infrastructure and data standards and legal provisions. Metadata data and data models, semantic and technical interoperability will have been explored during the EJP RD and EHDS Pilot phase and will continue during the RDP.
- **Coordinated diagnostic research support structure** taking advantage of available data sharing, analysis and standardised deep phenotyping clustering services and Omics tools for diagnostic innovation projects.
- **Clinical Outcome Assessment / Patient-Centred Outcome Measures support structure**. This service should provide methodological guidance and practical support on COA and the development and validation of specific PCOMs for rare diseases.
- **Biostatistical guidance** on study design and assistance in data analysis for both interventional and non-interventional studies. Services could include help with innovative trial designs customised for rare disease populations including clinical trial simulation for most efficient planning, the most efficient use of registry cohort data as standard of care control arms, and innovative data analysis methods including AI approaches.
- **Clinical Trial Support Infrastructure**. The CRN will leverage the expertise of the existing European clinical trial infrastructures (ECRIN for adult, c4c for paediatric trials) to empower the research consortia to conduct clinical trials.

Ad-Hoc Support Services (to be developed on demand, depending on the needs of the future research projects), e.g.:

- expert advice on the identification and validation of **biomarkers and surrogate endpoints**.
- **telehealth and telemetry systems experts** will provide state of the art guidance on the development and/or utilisation of wearables, devices, mobile health technologies and medical devices.

Transversal research support services

Financing of research is key but does not guarantee that funded projects will generate meaningful and exploitable outputs. Thus, to increase the utilisation and further translation of research results, RD Partnership will deploy dedicated support services that will accompany researchers all along and beyond the lifetime of the funded project. Again, based on the pre-identified gaps and needs, four main types of support are foreseen:

- Data integration and coordination services
- Mentoring service targeting optimisation of translation and uptake of research outputs
- Acceleration hub opening possibilities for follow up funding for new discoveries with high potential for application into health care.
- ELSI support services

Data integration and coordination services to:

- Facilitate access to data sources and resources through the EJP RD Virtual Platform that will open a unified route to discover, query and eventually access patient registries, biobanks, genomics and multi-omics repositories, knowledge bases, resources (such as animal models and cell lines libraries), omics deposition and analysis platforms, as well as translational & clinical research supporting material and services, in a coordinated manner. The VP will be expanded to connect with national RD registries and other national data sources but also with ENCePP resource database at EMA.
- Provide guidance and support to users for distributed implementation of data management, standards and tools adoption, data discovery/sharing/analysis and bio-sample related services, in concert with the central VP access methods.
- Maximise the exploitation of data generated by the RD Partnership-funded research projects as widely and responsibly as possible by stimulating adoption of FAIR principles 'by design' (Findable, Accessible, Interoperable and Re-usable for humans and machines) encompassing applicable ethics, regulatory and data protection provisions, machine readable interoperability standards, as well as through incentivised connections with relevant data platforms integrated into the Virtual Platform and supported by FAIRification services for researchers.
- Extend the FAIR steward service developed by the EJP RD to help researchers to make research results FAIR, which will be a prerequisite to get research projects funded.

Mentoring service

The **mentoring service** to support researchers that was developed in the EJP RD in collaboration with EATRIS and Telethon Italy will be expanded in the RD Partnership. The aim is to increase the impact of projects by providing tailored expertise along each step of the translational pathway. This expertise is delivered early on at the project proposal phase so that the route to patient impact can be planned out. This greatly reduces the barriers between promising science and accessible treatments. Examples of the service are support for translational feasibility, regulatory compliance, HTA advice, quality assurance and control and intellectual property strategy. Regular exchange and engagement with the industry and regulators will be part of the mentoring services to ensure that research is designed and executed according to high methodological and scientific standards and is amenable to further development at the end of each research stage. Furthermore, Patient Engagement Reference Group, will be involved in the service to ensure that research is designed in a patient-focused and patient-relevant manner. Finally, to ensure that leading clinical, biological, technological and regulatory expertise are close at hand for truly multi-disciplinary,

patient-focused R&I, the expertise services provided by the CRN and other clinical communities and infrastructures (e.g., for clinical trials ECRIN and, for children and young people c4c) will be solicited at regular timepoints to consider the pipeline of funded studies and maximise the opportunities for planning and securing funding for trials.

Acceleration hub

A key tactic to deliver the expected long-term impacts of RD Partnership will be to deploy public-public and public-private investments along the research and development pipeline in a coordinated, connected and seamless manner within the Acceleration Hub. This will be supported by working closely with the Innovative Health Initiative (IHI), so that new discoveries with high potential for application into health care will be structurally scouted, evaluated and supported for accelerated validation and development towards clinic. Moreover, research funding charities, professional / learned societies and philanthropies will be actively encouraged to both present projects and act as co-funders in projects and programmes that are relevant to their mission.

As part of the collaboration with IHI, the application-focused activities of the Acceleration Hub will feature the following high-level coordination between the RD Partnership Board of Funders and IHI, to ensure that funding of basic, early preclinical, late preclinical and late development stages of RD research is coordinated and covered adequately, in order to reduce the funding gap that characterises the "valley of death" translational gap. Modelled on previous Accelerator concepts such as the anti-microbial resistance accelerator of IMI, it will be proposed to implement the RD Accelerator concept considering the specificities of RD, so that funding is targeted and fit to task for the field and supporting RD innovations in therapies and diagnostics.

Finally, in order to ensure smooth, fast and effective structuring of the contracts and agreements necessary to facilitate productive multi-sector collaboration, dedicated alliance management and legal capacity – with specific expertise in public-public and public-private collaboration - will form part of the operating team of RD Partnership.

ELSI support services

A team of ethics/regulatory/legal/societal experts will provide advice on any pertinent ELSI and regulatory issue related to the research projects and RD Partnership activities (more specifically CRN), to ensure compliance with ethics and regulatory requirements and GDPR. The service will include multiple levels of support involving:

- Dedicated ethics review process of RD research projects/activities to accelerate/facilitate the implementation of such projects;
- Contribution to the development of relevant documents from the ELSI and regulatory point of view including patient consent and data protection, e.g., of adaptable informed consent and assent documents, Transfer Agreements models (Data & Material transfer specificities according to national/local rules and provisions;
- Dedicated communication & support channel to ensure ELSI office is efficiently connected with members of the RD Partnership.

Capacity building

The training and capacity building must be considered as integral part of the overall RD ecosystem strategy. Accelerating research, diagnosis and development of treatments is also very much dependent on the appropriate education of new generations of researchers, clinicians, patient representatives and policy makers but also constant improvement of the capacities of the experienced ones. RD Partnership will integrate training components as part of its support

activities for:

- Funded research projects, with focus on training of young researchers;
- Researchers/clinicians involved in the Clinical Research Network;
- Patients and patient representatives to ensure and accelerate their informed engagement at all levels;
- Overall society and stakeholders, comprising general student and clinician population interested in RDs, to support access to RD education, including at national level using "train the trainers approach" and assistance in national organisation.

Some pre-identified top priority topics for developing new trainings include but are not restricted to i) Data & tools: analysis, standards, management, quality, use, sharing (as per the Virtual Platform); ii) Regulatory literacy & requirements; iii) Translational research and technological transfer; (iv) Innovative trial designs; (v) Innovative diagnostic and therapeutic tools and developments; (vi) Patient Centred Outcomes Measures.

Strategy and coordination

High level, multistakeholder strategy, and governance

Ensuring the development and deployment of R&I strategy and recommendations at all levels (national, EU and international) is essential for the efficient and agile advancement of the RD Partnership towards expected outcomes and impacts.

The overall and annual planning of the RD Partnership will be driven by the pre-established SRIA to be developed and validated by all stakeholders (*see section 2.2.6 Strategic Research and Innovation Agenda (SRIA) development*), possible updates of which will be overseen by the Multistakeholder Strategic Steering Board and National Alignment Board (*see section 3.3.3 ADVISORY BODIES*). The latter will also be key to the implementation of the activities fostering alignment of and with national and regional policies and strategies.
To that end, the RD Partnership will support the deployment and operations of National Mirror Groups (NMGs) in all participating countries. The NMGs will advocate and be the linkage to national/regional RD programmes, infrastructures, centres of expertise and strategies. They will be conducive to the revitalisation of National RD Plans/Strategies and critical in identifying and sharing of best practices to bridge health care to research and strengthening incentives for the underrepresented countries to be set up under RD Partnership umbrella.

Today IRDiRC is a main contributor to global RD research strategic agenda. Thus, RD Partnership will continue the previous engagement in supporting IRDiRC not only by contributing to its goals but also at operational level. The Scientific Secretariat of IRDiRC will be part of the RD Partnership coordination team, to manage efficiently the work of the consortium, maximise the alignment and capture opportunities for joint, international actions, e.g., the development of collaboration between the EU Clinical Research Network for Rare Diseases and its equivalent in US or on other continents or countries.

Coordination

It has been recognised that highly competent **central coordination and management of the consortium** armed with relevant tools and expertise is vital for the successful day-to-day delivery of operations and achievement of the project's goals. RD Partnership aims to take advantage of experience and tools already acquired through EJP RD to establish active and proficient coordination office that will accompany RD Partnership partners by providing operational and strategic support including (other services may be identified at later stage):

- Experienced, skilled, and dedicated coordination team
- Adapted tools for central, secure management
- Legal support to accelerate engagement with other initiatives or organisations
- Robust monitoring of the partnership (as a whole, of its components and alignment with national actions, contribution to expected impacts and SDGs)
- Communication and dissemination services
- RD connector (hub) to increase matchmaking between researchers-clinicians-patients and industry
- Central Helpdesk (being central entry point to reach out to experts and services of the RD Partnership).

3.2. Resources

The Rare Disease Partnership's ambition is to improve the health and well-being of people living with a rare disease and make Europe a world leader in innovation for this group of diseases. Addressing the unmet needs of 30 million persons living with a rare disease in Europe supports the EU commitment to the UN 2030 Agenda's Sustainable Development Goals. Such a high ambition will only be possible with a strong political engagement and high involvement of stakeholders with binding commitments both in cash and/or in-kind. Members (beneficiaries) of the Rare Diseases Partnership will be requested to sign a Grant Agreement (GA) and to work actively towards achieving the overall aims of the Partnership.

The financial support from public and private research and innovation funders to joint transnational activities will be an important source of funding for ground-breaking competitive and "in-house" research and innovation projects, leveraging the funds committed by EC. These investments represent the core of financial contributions to the RD Partnerships. Investments in a range between hundred thousand and millions of euros are expected (depending on the capacity of each beneficiary). On the other hand, beneficiaries will be eligible to receive reimbursements, for e.g., travel and accommodation for joining meetings, for personnel costs for managing the joint transnational activities. For most Research Funding Organisations, the latter financial support is important to participate in the Partnership. The European Reference Networks, Academia, EU Infrastructures, patient organisations, and relevant national/regional organisations/institutions will participate mainly through the provision of in-kind support to the Rare Diseases Partnership, and all together can contribute with several millions of euros.

The RD Partnership aims to set a robust, flexible, and attractive multi-annual financial and funding model that will allow the support of not only ground-breaking research and innovation, but also financing of other activities, such as networking schemes to share knowledge, support services, and infrastructure required to maximise the outcomes of research projects as well as training and education. It will take advantage of the knowledge and lessons learnt from EJP RD and IRDiRC, and bring together research and innovation funders and research performers (ERNs, universities, and other research organisations), industry, EMA, and patients/patient organisations, with the support of co-funding from the European Commission.

The type of partners and overall budget and commitment by founding members other than the EC will be determined by several factors:

- The multiannual financial framework 2021-2027.
- Scope of the Strategic Research and Innovation Agenda.

- EC co-funding rates applicable to the RD Partnership.
- The possibility of using structural funds as national/regional commitments in joint transnational activities: models for synergies with structural funds required.
- The possibility of synergies with another EU funding programme, e.g., EU4Health and Digital Europe, and with other Partnerships such as the Innovative Health Initiative, the ERA4Health Partnership and European Partnership for Personalised Medicine.
- The definition of in-kind contributions from associated countries outside the EU, and their eligibility to match with EU funds.
- Details of the governance structure and operational model.

Types and levels of contributions:

- Financial contributions will be provided essentially by funding agencies/bodies, ministries, industry, and the European Commission, but we also aim at having direct investments from charities (e.g., Telethon French Fondation Maladies Rares, Bill and Melinda Gates Foundation, Chan Zuckerberg Initiative). These investments will be dedicated to a large extent to joint transnational calls, but also to support Clinical Research Network projects as well as the training and research support services.
- In-kind contributions will be provided by: funding agencies/bodies and ministries, industry, patient organisations (e.g., EURORDIS, national patient associations), European Research Infrastructures (e.g., EATRIS, ECRIN, BBMRI, etc.), Regulatory Agencies (e.g., EMA), European Reference Networks, as well as national or regional universities, and academic institutions, etc. The expected in-kind contributions may include, for example, personnel costs in relation to bringing skills and expertise, management capacities, co-creation, and execution of training and education programmes. The costs of the use of infrastructures (e.g., sequencing or bioinformatics capacities and tools), facilities required to host meetings or workshops can also be accounted for. Finally, national investment in complementary research activities to be implemented at the national level and fully aligned with the ones of the RD Partnership should be envisaged.

RD Partnership should promote activities/resources linked to market

One of the most ambitious goals for the future Partnership on rare diseases will be to strengthen collaboration with the industry. Besides important strategic contributions, the participation of industry partners as full beneficiaries of the Partnership will open multiple opportunities in terms of joint activities and resource contribution. Direct co-funding of research activities (e.g., research projects within Clinical Research Network), possible in-kind contribution with expertise to improve the translatability of pre-clinical studies, or provision of tools or platforms required to run the studies should also be possible. Finally, joint, parallel, or subsequent funding and research activities to be launched in collaboration with the Innovative Health Initiative or individual industry partners are under discussion. Such alignment will be central to optimal creation and application of knowledge into meaningful health products and interventions that respond to the needs of patients living with a rare disease across Europe and globally.

Generating sufficient research to address unmet needs requires an increase in the scale and continuity of funding for basic research and early development above and beyond the duration of the Partnership. As stated above, more funding can be achieved by incorporating more actors in the financing structure but also adoption and/or collaboration with funding programmes or funders that will contribute to covering gaps in the funding pipeline. The pre-clinical research is often linked to a high risk of failure and is mostly approached by academics but also SMEs that target

innovation in research as a business model. Thus, to increase the capacity of smaller actors, such as SMEs, to undertake R&I in rare diseases, an adapted support is needed. Therefore, the Partnership will offer the possibility to finance SMEs (next to academia) by incorporating next to the public funding side for instance, the European Investment Bank (EIB), which is already investing in the rare disease space and other important health initiatives, such as the EU Malaria Fund. The Partnership will also engage collaboration with other programmes that target specifically innovative SMEs. These may include:

- The European Innovation Council (EIC) where the funding and support are organised into three main funding schemes: the **EIC Pathfinder** for advanced research to develop the scientific basis to underpin breakthrough technologies; the **EIC Transition** to validate technologies and develop business plans for specific applications; and the **EIC Accelerator** to support companies (SMEs, start-ups, spinouts and in exceptional cases small mid-caps) to bring their innovations to market and scale-up. In each case, the direct financial support to innovators is augmented with access to a range of Business Acceleration Services.

- The Innovative SMEs Partnership offers regular calls for proposals resulting in collaborative research and innovation activities that should result in a faster time to market, de-risking investment, supporting business growth, contributing to EU and global priorities, and supporting access to markets and knowledge.

The establishment of the collaborations and synergies mentioned above will be an important source of financial and in-kind resources for Rare Diseases R&I. It will help take the Rare Diseases Partnership projects to the next level in the development chain by maximising and speeding the development of diagnosis, therapies, and medicinal products, and accelerating their availability in the market.

RD Partnership will bring together other investments and synergies

The new Horizon Europe framework programme opens the possibility for the **use of structural funds** (ex. ERDF, ESF+) as national/regional commitments to Partnerships or as complementary funds (ex. for partners involved in activities other than calls or for the National Mirror Groups). Such a funding source, in addition of the synergies it brings with it, will be significant and may lead to a stronger involvement of widening countries and regions around Europe, both directly in the activities of the Rare Diseases Partnership and commitments in Joint Transnationals Calls.

The **Widening Programme** represents another possibility of strengthening researchers and research institutions in widening countries, contributing to the convergence with the best performing countries. Within this programme, the **COST** actions and **Teaming** represent very interesting opportunities.

- **COST actions**: to build networks of researchers and provide financial support for connecting and collaborating with the aim of participating in Rare Disease Partnership Joint Transnational Calls (JTCs) and/or other activities that require a “consortium”.

- **Teaming**: with the Team up of an institution in a High Performing Country with another from a Widening country, centres of excellence in rare diseases can be established in the latter. The widening country may also take advantage of the availability of structural funds (ERDF) to support its national contribution required for Teaming.

The use of **structural funds and the widening programme** could be an important source of funds, improving the capacities for the widening countries while directly contributing to the

Partnership's financial and in-kind income. In addition, the alignment and contribution to the European Research Area objectives are also essential.

The **EU4Health programme** should represent an important source of complementary synergies and funds. Collaboration and alignment with this programme are crucial, especially regarding the work of the ERNs, their integration in national health care systems (supported by a Joint Action) and the ambitioned Clinical Research Network.

Another essential alignment will be with the **Digital Europe Programme (DEP),** as it can be a source of funds to innovate and further develop relevant tools and data infrastructure based on the already existing Virtual Platform of the EJP RD and connected data resources.

For **broader investments,** the RD Partnership will take advantage of the long-standing and strong collaboration with IRDiRC to expand its international span and target funding partners (e.g., charities, funding organisations, and industry), from countries outside Europe.

Finally, venture philanthropists such as the **Bill and Melinda Gates Foundation, Scott R. MacKenzie Foundation and Chan Zuckerberg Initiative** will also be approached as potential investment and collaboration partners either to finance participation of research teams from USA (and possibly beyond USA) in the Rare Diseases Partnership JTC, or to co-fund research projects to be developed within Clinical Research Network, or actions dedicated to patients' participation and patient-driven research.

3.3. Governance

An initiative such as the RD Partnership needs to establish clear roles and responsibilities in order to meet the objectives, build trust from the wider rare diseases community and mechanisms to prevent and solve potential conflicts. The management structure aims at transparent decision-making process with well-defined responsibilities in Pillars, WPs and tasks. It will provide efficient and adaptive structure, necessary to capture and deal with emerging strengths and weaknesses. It will manage the strategy planning, annual work plans and allocation of resources. It will be responsible for interactions with external stakeholders. The EC will provide terms of reference and guidance for the governance of the partnerships under Horizon Europe, during the SRIA development and the grant agreement preparation phase.

It is developed according to the principles of subsidiarity and should stimulate co-decision of each partner and cocreation of knowledge, be it at the EU-level, the national level or at the level of the scientific community. The management structure of the RD Partnership will be defined to:

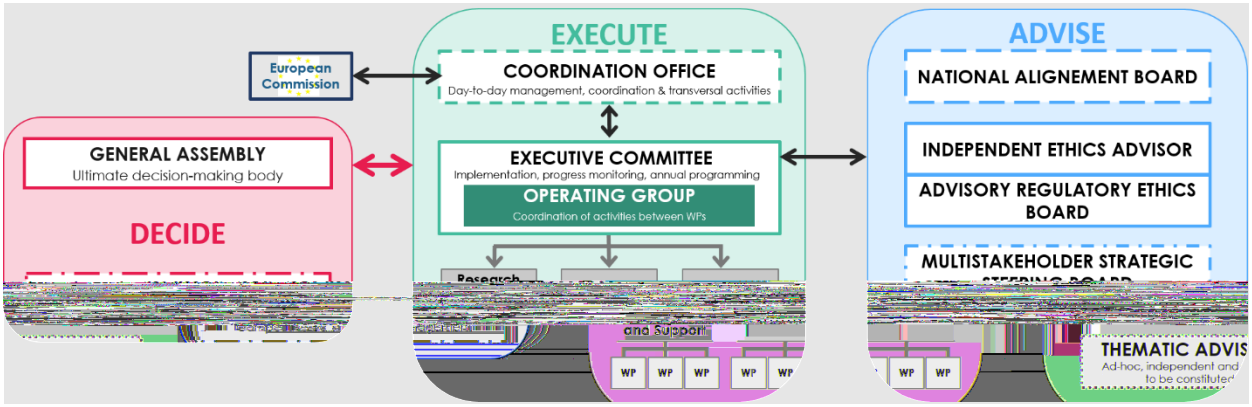
- Plan, organise and monitor the effort to achieve the RD Partnership's objectives within constraints of time schedule and budget.
- Clearly define the decision-making procedures and bodies.
- Run performance control procedures leading to the expected quality of achievements and deliverables described in the work plan.
- Continually inform the partners on the project status and progress.
- Drive the project implementation in accordance with administrative, financial and legal issues defined by the European regulations and national specificities.
- Guarantee that the rights and obligations of the partners are kept compliant with the Grant Agreement signed with the European Commission and the Consortium Agreement.
  A Consortium Agreement will be signed between the partners to specify the project

governance, the internal organisation of the consortium, the management of the project and any other critical aspects such as liability and confidentiality.

The proposed organisational structure of the consortium is as follows:

- **Decision-making bodies;**
- **Executive bodies;**
- **Advisory bodies**.

A particular attention will be paid to the composition of different Boards and Committees. The fair representation of funders, ERNs, patients, EU infrastructures and industry should be ensured correspondingly to the role agreed with them.



3.3.1. Decision-making bodies

3.3.1.1. General Assembly (GA)

Composition: GA will be composed of representatives of ALL beneficiaries of the RD Partnership (one representative per beneficiary).

Role: GA will be the ultimate decision-making body dealing with extraordinary decision requiring vote of all members like inclusion of new ones or exclusion of a non-performing partner. The GA will validate the strategic propositions proposed by the Executive Committee such as the annual work plan, the budget, etc. In particular, the GA will:

- Approve the initial 7-year work plan before submission of the proposal.
- Approve the initial Strategic, Research & Innovation Agenda (SRIA) and its updates.
- Approve the annual work plans.
- Be consulted on the annual summary reports.
- Monitor and approve the achievement of the most significant milestones.
- Approve ethical, legal and data management frameworks developed.
- Support the Executive Committee in developing a long-term sustainability plan for the RD Partnership.

Voting procedure: The GA will strive to reach consensus and if consensus cannot be reached, the GA will vote on different options. GA Quorum and voting arrangements will be elaborated on in the Consortium Agreement.

Meetings: at least once a year.

3.3.1.2. Board of funders (BoF)

Role: In order to ensure the independence of competitive joint transnational calls management, the final decisions on call topics and implementation of calls will be taken autonomously by the Board of Funders.

Composition: Funders are the funding bodies contributing to the joint transnational calls (JTCs) and the European Commission which is contributing with EU funding via the Horizon Europe funding programme. While the full composition of the Board of Funders may be known from the beginning of the Partnership (and updated if new funders join), its configuration will be variable every year, depending on the decisions of funding bodies to participate in each of the competitive calls. BoF will be chaired by the leader of the Work Package in charge of JTCs. The European Commission will be full member of the Board of Funders when EU funding is activated. The EC proposes that the BoF would have a prominent role in the governance and steering of the whole Partnership as the body of highest strategic level (to be discussed and /agreed upon at a later stage with the EC services and MS).

The EC will provide terms of reference and guidance for the governance, voting rights and decision making of the Partnerships under Horizon Europe, at a later stage during the SRIA development and/or grant agreement preparation phase(see section 3.3.1.4).

Voting procedure: BoF quorum and voting arrangements will be elaborated on in the Consortium Agreement (EC services will be consulted).

Meetings: *Ad hoc* meetings before and after the launch of each competitive call for proposals.

3.3.1.3. Necessity of implementing a "firewall" for the Joint Transnational Calls

It is planned that the RD Partnership will not only implement JTCs, but also run in-house activities, which means that in the same consortium there will be funding agencies and also entities which are potential beneficiaries of the calls. In order to avoid conflicts of interest, a so-called "firewall" will need to be put in place, building upon EJP RD experience.

To provide a firewall between the call organisation and the beneficiary Research Performing Organisations (RPOs), ensuring that there is no risk of a conflict of interest and/or unfair advantages for applicants to the calls, the Board of Funders will apply the following rules and processes:

For the definition of call topic:

- Establishment of clear rules of participation for RPOs and firewall separating two phases of call topic development:
  - Phase 1: general topic definition open to all RD Partnership partners and consultation with RD community at large (including outside of RD Partnership). The Multistakeholder Strategic Steering Board (MSSB) will also be consulted for general strategic orientation of the call topic definition.
  - Phase 2: locked and involving only participating funding organisations (BoF): decision on the choice of topic (if several proposed) and/or refinement of topic details, eligibility rules, etc. In case of involvement of experts from participating RPOs their participation to the call (as well as participation of their direct collaborators) is forbidden. Each expert signs a confidentiality agreement.
- Decision on the topic description and the call documents will be made solely by the representatives of the funders (BoF).

In addition:

- Call will be published on Participant Portal and on the RD Partnership website and kept open for at least 60 days.
- Proposal evaluation will be implemented in a two-step procedure according to the Horizon Europe rules including the evaluation criteria and scoring system.
- Proposal evaluation will be done by independent experts who have no conflict of interest

with the evaluated proposals. If possible, exclusion of experts from participating institutions will be privileged. Usually, experts from several countries do not evaluate projects with their national component, depending on the national funding agencies rules. Employees of organisations that have submitted proposals in the calls will not evaluate proposals which include their organisation as applicant.

- Funding decisions will be made solely by the funders based on the ranking list established in the evaluation procedure by independent experts according to rules agreed upon.
- An independent observer will follow up the evaluations and submit an assessment report to the EC and to the consortium of funders involved.

Entities that participate in the above-mentioned activities will not be allowed to be applicants to the open calls. Only the representatives of funders will participate in or attend the meetings related to the above-mentioned activities. For the specific case of the beneficiaries which both have a status of Research Funding Organisation (RFO) (Programme Manager) and Research Performing Organisation, additional measures will be taken in order to avoid any possible COI. The separation between funding and research activities will be ensured by the nomination of dedicated persons that will be allowed to represent these institutions on the Call Steering Committee. These representatives will not be allowed to apply to the call. This extends to other members having a primary appointment in the same component (unit) of a multi-component organisation to which the representative is directly affiliated. Any other person from such RPO- RFO beneficiary institution participating directly or indirectly (through the possible third parties) in the RD Partnership project will not be involved in: the decision on topic of the call; the description and preparation of call documents; the preparation of the pre-announcement; the call evaluation process; the final decision on the projects to be funded.

3.3.1.4. Management of the in-house research activities implemented through internal calls for projects

As for the joint transnational calls, the definition of the topics for internal calls fostering in-house research projects to be implemented within CRN, will be done through structured consultation/discussion with the Multistakeholder Strategic Steering Board (MSSB). Furthermore, the EC proposes that the Board of Funders (including the EC) will have a prominent role in the governance and steering of the whole Partnership as the body of highest strategic level (to be discussed and agreed upon at a later stage with the EC services and MS). When required, a dedicated *Ad hoc* group issued from MSSB, potentially expanded to specific industry partners if co-funding by industry is foreseen, will be created to finalise the topic(s) definition. In order to avoid any COI during the implementation and management of the internal calls, the call secretariat will be issued from one of the research funding agencies that not only does not perform research itself but also has the capacity to ensure transparent and high-quality management of the whole process. These internal calls are being discussed and their implementation modalities are not yet set.

All submitted proposals will be evaluated by an independent evaluation committee composed of relevant experts outside of the RD Partnership. The projects recommended for funding by the above-mentioned committee will be implemented directly as part of the RD Partnership.

3.3.2. Executive bodies

3.3.2.1. Coordination Office

Composition: The Coordination Office is composed by the Coordinator (Coo) and the Coordination Team (Coo Team).

The Coordination Team will be under the responsibility of the Coordinator and will include Project

managers, Communication manager, Financial and administrative manager, and assistant. The team of Project managers should include the following competencies: patient engagement, data management, legal competencies, impact and monitoring follow-up.

Role: The Coordinator, with the support of the Coordination Team, will be in charge of the day-to-day overall scientific, administrative and financial management of the project and will be the primary contact point for the European Commission. In particular, the Coordinator will:

- Ensure the implementation of the Grant Agreement signed with the EC;
- Prepare the Consortium Agreement to be signed by the partners, with the support of the Executive Committee;
- Update and maintain the Consortium Agreement and submit amendment requests to Grant Agreement;
- Oversee deadlines and milestones of activities, and quality control of deliverables;
- Propose contingency action plans to the Executive Committee and oversee their implementation;
- Report on the implementation of the initiative and challenges encountered to the Executive Committee, the Consortium, General Assembly and the European Commission;
- Chair the Executive Committee and act as the scientific secretariat for their meetings;
- Ensure cooperation and alignment across WPs and Pillars;
- Ensure technical and financial reporting to the European Commission and budget management;
- Organise the General Assembly Meeting once a year;
- Ensure transversal activities of the RD Partnership;
- Follow-up the impact and monitoring of the RD Partnership;
- Supervise and host the Scientific Secretariat of IRDiRC;
- Represent the RD Partnership at the EU and international level;
- Together with the Executive Committee manage the project reserve budget;
- Implement the engagement strategy of the RD Partnership.

The Coordination Team will be responsible also for the day-to-day operational management of the RD Partnership and the Scientific Secretariat of IRDiRC. The financial and administrative officer will provide financial advice support to all partners. The Communication Manager will coordinate the internal and external communication of the RD Partnership. Members of the Coordination Team will continuously support the Operating Group, Executive Committee and all other partners of the consortium in fulfilling their obligations according to the work plan. The Coordination Team will also comprise the CRN Coordination Office.

3.3.2.2. The Executive Committee (ExCom)

Composition: The ExCom will consist of the Coordination Office, Pillar Leaders and all WP Leaders. It will be chaired by the Coordinator. The ExCom will set down its rules for procedures (Terms of Reference) in advance of the official start of the RD Partnership.

Role: The ExCom will:

- ensure the implementation of the RD Partnership according to the overall 7-year plan of the initiative and the individual annual work plans.
- monitor progress according to the milestones as set out in the 7-year plan and the annual work plan.
- be responsible for the overall quality control of deliverables and reports.
- be in charge of adopting solutions to problems encountered during the implementation and can refer to the General Assembly if no agreement can be found or if the solution will imply major deviations from the work plans agreed by the GA. In this case, the Coordinator is in charge of duly informing the European Commission about expected

deviations.

- oversee how resources are spent and propose changes if needed.
- be the entity preparing the basis for the decisions to be taken in the GA based on input from the Operating Group (see below) and WP leaders.
- inform the GA about connections established with sister initiatives at national, EU- and international level and can ask for the GA's assistance to establish contacts if needed.

Meetings: every two months, starting month 1 (physical or web conference), adapting the number of meetings to the necessary the following years.

3.3.2.3. The Operating Group (OG)

Composition: Since it is expected that the ExCom will be a relatively large body, a more restricted group is necessary for the efficient administration of day-to-day activities. The Operating Group is part of the ExCom and will be composed of the Coordination Office and all Pillar leaders. The representation of funders, ERNs, patients, industry and EU infrastructures should be ensured via the Pillar leaders. Pillar leaders are nominated for the lifetime of the project. However, in case of change, attention will be taken to keep fair representation of respective groups in the OG.
Role: The OG will be responsible for close communication and coordination of activities between different Pillars and WPs. The OG will reflect on progress and engage in a collective brainstorming on future directions and visions for the RD Partnership. Regular (twice a month) conference calls will ensure close follow up of activities, continuous alignment and adequate reactivity in case of urgent situations and risk management. The OG will participate in the preparation of the Executive Committee meetings and will be the driving force for the elaboration of the Annual Work Plans.

3.3.2.4. Pillar Leaders (PL)

Role: Pillar leaders (PL) will support the coordination and interaction of Work Package Leaders (WPL) within their respective Pillars, as well as across the Pillars.

Three Pillars are defined in the RD Partnership:

- Funding and Support of Research Activities
- Clinical Research Network (CRN)
- Transversal Activities

The tasks of the PLs are to:

- Ensure the coordination of activities across the WPs in the Pillar to deliver a coherent set of results both within the Pillar, and with respect to the outputs generated under the other pillars. This will ensure that the overall outcomes of the RD Partnership are coherent and complementary and together generate a robust and harmonised rare diseases platform and ecosystem;
- Ensure good communication with the Coordination Office;
- Ensure coordination and collaboration across Pillars and promote knowledge transfer within and across Pillars (via the Operating Group activities);
- Ensure that tasks are not duplicated and promote complementarity and synergies. The main forum for this process will be the ExCom meetings;
- Organisation of regular management meetings (telephone conferences and/or personal meetings) with the respective WP leaders to ensure that work within the WPs is in line with the annual work plans and contributes to the development of annual work plans for upcoming years;
- Participate in the OG and ExCom meetings and teleconferences;
- Feed into the development of the annual communication plan.

3.3.2.5. Work Package Leaders (WPL)

Role: Work Package Leaders will be in charge of implementing the tasks of the WPs as agreed in the annual work plans, cross-coordinating with other WPLs, informing the PL about any deviations to the annual work plan and developing contingency plans. The WPL will be supported by a number of Task and Subtask leaders who are responsible for the implementation of a specific task within the work package. The tasks of the WPL therefore are:

- Manage implementation of the WP and tasks, and ensure good communication within the WP in order to ensure efficient flow of information;
- Ensure that work within the WP is in line with the annual work plans;
- Identify any bottlenecks or obstacles, as well as links, synergies and overlaps across WPs, and report them to the Pillar Leaders.
- Formal reporting of progress to the Pillar Leaders and the Coordinator for discussion at the Executive Committee meetings, and contributing the sections of the annual report for their WP;
- Draft the WP descriptions for upcoming annual work plans;
- Participate in the Pillar and ExCom meetings and teleconferences.

3.3.3. Advisory bodies

3.3.3.1. National Alignment Board (NAB)

Composition: The National Alignment Board (NAB) will be composed of Representatives of each National Mirror Groups and Representatives of the European Commission Directorates: DG Research & Innovation, DG Joint Research Centre (JRC), DG SANTE, DG CNECT. A chair will be selected by and within the member of the NAB.

Role: The National Alignment Board will ensure that national/EU activities, strategies and needs are considered when taking decisions at the RD Partnership level and when designing the annual work plans.

The members of the RD Partnership are aware of the importance of continuous feedback and dialogue with relevant national stakeholders. This is necessary to translate efficiently the specific needs and strategy represented by countries or European Commission as well as the outcomes of the RD Partnership.

Meetings: At least once a year

3.3.3.2. National Mirror Groups (NMG)

Composition: Participating countries will have to constitute NMG, bringing together the national representatives of the RD Partnership and other relevant RD stakeholders. It is expected that NMG will include representatives of the ministries of research and health, National plan/strategy for RD, national nodes of the European Reference Networks, patient organisations, relevant national authorities, industry representatives, national representatives of EU infrastructures, national funders and research institutions (whether participating to the RD partnership or not) and HTA/reimbursement representatives. NMG will also include the relevant national partners of the RD Partnership, in particular NAB and GA member that will report NMG views and positions during NAB and GA meetings.

Role: The role of the NMG will be to ensure national coordination, contribute to the objectives of the RD Partnership and benefit from it.

Meetings: The RD Partnership will propose standard Terms of Reference for the functioning of NMG, but it will be up to each NMG to establish their own procedures depending on the national ecosystem.

3.3.3.3. Multistakeholder Strategic Steering Board (MSSB)

Composition: The Multistakeholder Strategic Steering Board (MSSB) will be composed of patient organisations, academic institutions, public and private funders, regulatory bodies, including EMA and Health Technology Assessment (HTA) representatives at the EU level (e.g., EU-Innovation Network), EHDS representatives, IRDiRC and MS represented by the chair of the NAB.

Role: The MSSB will give the strategic direction to the research and support activities foreseen in the RD Partnership through different and adapted funding mechanisms. This includes the strategic orientations for the Clinical Research Network. It will ensure that patient needs are key drivers for funded research and support activities, revising the priorities to maximise the impact of funding, targeting under-represented diseases, meaningful topics yet underexplored, and ensuring high-quality, open and re-usable results and translation in clinical impact. It will thus ensure that a holistic approach of RD research is implemented, responding to unmet needs of the patient journey, from social, organisational and scientific determinants of rare diagnosis inequalities until the research and development of applicable and accessible solutions improving patients' lives.

Meetings: Every six months

3.3.3.4. Thematic Advisory Boards (TAB)

Establishment procedure: Based on the needs, the RD Partnership will set up Thematic Advisory Boards. The creation of such TAB will have to be submitted to and validated by the ExCom. A dedicated procedure will be established in the RD Partnership to create such group(s), including a minimum set of necessary information before the creation of such Board:

- Define the task/request to be submitted to the TAB;
- define the expertise necessary in the TAB;
- define what is expected as result of the work of the TAB;
- define the deadline to finalise the work of the TAB.

Composition: Thematic Advisory Boards will be constituted of members selected based on their relevant expertise and knowledge to answer the submitted question. A balance between the internal members of the RD Partnership and external experts/international stakeholders will be kept in its composition.

Role: Thematic Advisory Board(s) will be established to answer to a specific question and thus will have a limited lifetime in the frame of the RD Partnership.

Meetings: to be defined for each Thematic Advisory Board when established

The EC will provide terms of reference and guidance for the governance of the partnerships under Horizon Europe, regarding the necessity for the inclusion of a permanent scientific Advisory Board, during the SRIA development and grant agreement preparation phase.

3.3.3.5. Advisory Regulatory and Ethics Board (AREB)

Composition: The Advisory Regulatory and Ethics Board (AREB) will be composed of internal RD Partnership ethics/regulatory/legal experts, including members with recognised expertise among involved partners.

Role: The AREB will be set up in order to ensure compliance of the RD Partnership as well as of the projects funded within the RD Partnership and their activities with ethics, regulatory and legal requirements. It will ensure compliance with all European and international relevant provisions, including, but not limited to, patients' rights, data protection and confidentiality. The board will provide advice and support to the partners on the ethics, regulatory and legal aspects of the activities and will have an active role in the ethics review and monitoring of the funded projects if needed. The ELSI Support Service will directly operate under AREB.

The Independent Ethics Advisor will supervise the actions of AREB and will be in charge of advising on and monitoring ethical/legal/regulatory issues of the RD Partnership, of the Data Management Plan as well as of the projects funded within the RD Partnership to ensure that the ethics management of the projects is carried out within the Horizon Europe framework.

3.3.4. European Commission (EC)

The EC services have initiated the preparation of the RD Partnership with the Member States - forming a group of national delegates nominated by representatives in the Programme Committee under the Health Cluster for Horizon Europe - and are following the whole preparation of the programme. Since this group and its sub-group ("drafting group" set with a few volunteer MS) agreed to build upon the EJP RD work and to accept the useful offer of the EJP RD coordination team to organise a preparation Workshop (1-2 December 2021) and further preparation work, EC services are also included in the working groups and meetings organised by EJP RD coordination team in the preparatory phase of the Partnership, while also keeping its official channels to communicate with MS representatives involved in Horizon Europe.

During the lifetime of the RD Partnership, representatives of relevant EC Directorates (DG Research & Innovation, DG SANTE, DG JRC, DG CNECT - and whenever deemed useful - EU agencies or Joint Undertakings such as EMA, HaDEA, ERC, EIC and IHI) will be part of the NAB allowing the EC to have direct access to the strategic questions and discussions of the RD Partnership and allowing a perfect alignment of RD Partnership and EC activities. Depending on the needs, EC representatives will also be included in the *Thematic* Advisory Boards. Representatives of DG R&I staying in the lead for this Partnership under Horizon Europe, it will remain the main point of contact for the Partnership, while other DGs and agencies will be involved when relevant and possible.

The overall strategic objectives, impacts and outcomes of the RD Partnership are established based on the Sustainable Development Goals (SDGs) of United Nations, along IRDiRC goals and EU policies and legislation, including expected impacts of the Health cluster of Horizon Europe, establishing per se that the objectives of the RD Partnership are defending the EU public interest. The monitoring of those objectives will be closely followed up by the RD Partnership and regularly presented and discussed with the GA.

3.4. Openness and transparency

Establishment of the Partnership and recruitment of partners

Full inclusivity of the RD Partnership will be ensured through the active participation of the whole multistakeholder RD research ecosystem including i) Research funders (EC, national authorities, charities/foundations/funds, private sector), ii) Research and innovation communities – across life science and technology/data disciplines (like research institutes and universities, hospitals (through participation of current and any future ERNs and CRNs), EU research infrastructures, iii) research outputs users (like patients and citizens, patient organisations, health care professionals, researchers); iv) EU-wide and national policy makers, regulatory authorities (EC, national authorities, EU agencies and industry organisations).

Geographical coverage: all EU and EEA MS and associated countries were approached during the preparatory phase of RDP, to ensure the widest possible geographical approach. Particular emphasis will be placed on broadening participation to include countries traditionally underserved and underrepresented in RD research. Global international collaboration will be further ensured through IRDiRC, and by introducing the expertise of other global actors to specific activities.

Patient-centredness and responsiveness to patient-need led research: The principles of patient-need led research necessitates a robust and relevant Patient Engagement Framework which aims to integrate patients and/or representatives: (1) As members of Patient Engagement Reference Groups (PERGs) including representatives from ultra-rare diseases, 'disregarded'

diseases and paediatric patients to leave no-one behind, (2) as equal partners in all stages of the research process from planning and prioritising research activities, engaging in implementation (as a beneficiary and research partner), monitoring and dissemination of projects' results.

Alignment of European and national RD research policies and activities according to the identified needs and priorities of every MS/Associated Country will be ensured through the National Alignment Board (NAB) and National Mirror Groups (NMGs). NMGs, already established in some countries under EJP RD, will ensure a two-way link with the Partnership, feeding national needs and expertise into the Partnership's activities, priorities, and outputs and in turn, disseminating the results of the Partnership to the 'grass-roots' researcher level. In this way, excellence of RDP will reach a very large number of researchers.

Alignment with the relevant other EU Partnerships, programmes, projects, initiatives (EU-wide and global) will ensure the complementarity and synergies on the one hand and avoidance of duplication of efforts on the other hand, for the RDP.
The precise nature of inclusion (i.e., direct inclusion as beneficiaries and linked third parties into RDP activities or indirect inclusion through the established RD research networks, consultancy, advisory and dissemination activities) will be determined by several factors (e.g. EU and national contributions, EU co-funding rate, the definition of in-kind contributions). The Partnership will actively engage with complimentary fields, such as personalised medicine and digital health: relevant projects, programmes and initiatives will be identified through preparatory and ongoing mapping and active reach-out, and this will be repeated across the course of the Partnership.
Once established, an **open and ongoing approach to recruitment of partners** will be ensured. Inclusion will be based on the identified aims and priorities of the RDP, which will be revisited at regular intervals to factor in novel developments in the field and national priorities. This regular prioritisation process will involve the whole RDP, including the National Alignment Board and will feed the annual planning process. Where possible and required, the Advisory axis of the RDP (including not only the National Alignment Board, Independent Ethics Advisor, and Advisory Regulatory Ethics Board, but also Thematic Advisory Boards according to the identified needs and priorities) will be consulted. Dissemination (e.g., workshops and webinars), consultancy and advisory activities will be open to a broader collaborator base and the general public, where possible. Ultimately, the Executive axis of the RDP (the Executive Committee, the Coordination team, and the Operating Group of the RDP) will be responsible for an active outreach and liaison with potential partners, identification of cross-cutting activities, and reporting to the General Assembly for annual planning and decision-taking process.

Dissemination awareness-raising and capacity building activities will include a range of measures and tools targeted at different groups and stakeholders, such as websites, newsletters, awareness-raising initiatives (such as RD Day events), webinars, publications (open source whenever possible), guidelines and presentations at conferences and related events. The (expanded) NMGs will also be key tools for dissemination to the wider national RD communities. In terms of capacity-building, the emphasis will be on 'training the trainers' to embed trainings in national ecosystems. This will all be supported by a continuous emphasis on mapping and addressing the informational and capacity-building needs of the multistakeholder community, with subsequent adjustment of dissemination, awareness-raising, and capacity-building activities. A strong focus on dissemination will also support the inclusion of new partners and actors: in particular, the General Assembly and National Alignment Board meetings - which will balance the involvement of RDP partners and new external groups and stakeholders - will provide information on RDP progress and developments, whilst supporting an open prioritisation of tasks, exchange of ideas and development of future prospects.

The basis for each **Annual Work Programme (AWP)** will be the initial multiannual work programme laid out in the Grant Agreement. This will be revised and defined in more detail across the broad annual programming process, which will centre on meetings of the National Alignment

Board and General Assembly. As these meetings unite both RDP partners and external stakeholders, prioritisation of tasks for finalisation of each AWP will benefit from broad input. The Executive Committee will be responsible for the operational design and redaction of the AWP which will be subsequently presented, discussed, and agreed by all RD Partnership members. The ultimate decision-making body for the AWP will be the General Assembly of the RD Partnership.

4. List of abbreviations

Abbreviation	Full Form
1+MG	1+ Million Genomes initiative
AI	artificial intelligence
AREB	Advisory Regulatory Ethics Board
ATMP	Advanced Therapy Medicinal Product
AWP	Annual Work Programme
B1MG	Beyond One Million Genomes project (EU-funded viaHorizon 2020)
BoF	Board of Funders
c4c	conect4children, EU-funded under IMI (Horizon 2020)
CEF	Connecting Europe Facility (EU funding programme, 2014-2020)
COA	Clinical outcome assessment
CoE	Center(s) of Expertise
COI	conflict of interest
COMP	Committee for Orphan Medicinal Products
Coo	Coordinator
Coo Team	Coordination Team
COST	European Cooperation in Science and Technology
CP	Concept paper
C-PATH	Critical Path Institute
CRN	Clinical Research Network
CZI	Chan Zuckerberg Initiative
DARWIN EU	Data Analysis and Real-World Interrogation Network (EMA project)
DEP	Digital Europe Programme
DG CNECT	Directorate-General for Communications Networks, Content and Technology of the European Commission
DG JRC	Directorate-General Joint Research Centre, European Commission
DG RTD	Directorate-General for Research and Innovation, European Commission
DG SANTE	Directorate-General for Health and Food Safety, European Commission
DIGITAL	Digital Europe Programme
EATRIS	European infrastructure for translational medicine
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Genome-Phenome Archive
EHDS	European Health Data Space
EIC	European Innovation Council
EIT	European Institute of Innovation and Technology
EIT Health	European Innovation and Technology Health
EJP RD	European Joint Programme on Rare Diseases
ELSI	Ethical, legal and societal issues
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (Database of the European Medicines Agency)

Abbreviation	Full Form
EOSC	EU Open Science Cloud
ePAG	European Patient Advocacy Groups
ERA	European Research Area
ERA-NET	funding instrument designed to support public-public co-funds / partnerships under EU Research and innovation funding programmes
ERA4Health	European Research Area for Health Partnership
E-RARE	ERA-NET for research programmes on rare diseases
ERC	European Research Council
ERDF	European Regional Development Fund
ERIC	European Research Infrastructure Consortium
ERICA	European Rare Disease Research Coordination and Support Action
ERN	European Reference Network
ESF+	European Social Fund Plus
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
EU13	13 new EU Member States since 2004
EU4Health	EU4Health 2021-2027 - a vision for a healthier European Union (https://ec.europ a.eu/health/funding/eu4health_en)
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
EUnetHTA	European Network for Health Technology Assessment
EUPATI	European Patients' Academy
EU RD Platform	European Platform on Rare Disease Registration (https://eu-rd-platform.jrc.ec.europa.eu/_en)
EuroHPC	European High-Performance Computing Joint Undertaking
EUROPLAN	European Project for Rare Diseases National Plans Development
EURORDIS	European Organisation for Rare Diseases
ExCom	Executive Committee
F2F	face to face
FAIR	FAIR Guiding Principles for scientific data management and stewardship: Findable, Accessible, Interoperable, Reusable
FDA	Food and Drug Agency
FFRD	French Foundation for Rare Diseases
FP	Framework Programme for Research and Innovation
FP4	Fourth Framework Programme for Research and Innovation (1994-1998)
FP6	Sixth Framework Programme for Research and Innovation (2002-2006)
FP7	Seventh Framework Programme for Research and Innovation (2007-2013)
FP9	Ninth Framework Programme for Research and Innovation (2014-2020) - Horizon Europe
FTE	full-time equivalent
GA	General Assembly
GA	Grant Agreement
GA4GH	Global Alliance for Genomics and Health
Gaia-X	Gaia-X European Association for Data and Cloud

Abbreviation	Full Form
GO	General Objective
GO FAIR	GO FAIR Initiative (https://www.go-fair.org/)
GPAP	Genome-Phenome Analysis Platform
H2020	Horizon 2020 (8th Framework Programme for Research & Innovation)
HE	Horizon Europe (9th Framework Programme for Research & Innovation)
HOPE	European Hospital and Health care Federation
HPC	High Performance Computing
HTA	Health Technology Assessment
ICF	informed consent form
ICT	information and communications technology
ICODA	International COVID-19 Data Alliance
IHI	Innovative Health Initiative (Joint Undertaking under Horizon Europe)
IICS	investigator-initiated clinical studies
IKAA	in-kind contributions on additional activities
IKOP	in-kind contributions from Industry to operational activities
IMI	Innovative Medicines Initiative (Joint Undertaking under Horizon 2020)
InvestEU	InvestEU Programme (https://europa.eu/investeu/home_en)
IP	Intellectual Property
IRDiRC	International Rare Diseases Research Consortium
IT	Information technology
JARC	Joint Action on Rare Cancer
JRC	Joint Research Centre (Directorate-General of the European Commission)
JTC	joint transnational call
KPI	Key performance indicators
KSO	Key strategic orientation
MOOC	Massive open online course
MS	Member State of the European Union
MS/AC	Member States/Associated Countries
MSSB	Multistakeholders strategic steering board
MSCA	Marie Sklodowska-Curie Action
NAB	National Alignment Board
NIH	National Institutes of Health (USA)
NIH-RDCRN	National Institutes of Health-Rare Diseases Clinical Research Network
NMG	National Mirror Group
NP	National Plan
NS	National Strategy
NWO	Dutch Research Council
OG	Operating Group
OMP	orphan medicinal product
OO	Operational Objective
ORDO	Orphanet Ontology of Rare Diseases
P (P1, P2, P3...)	Pillar (Pillar 1, Pillar 2, Pillar 3...)
PAO	Patients' Advocacy Organisation

Abbreviation	Full Form
PARADIGM	Patients Active in Research and Dialogues for an Improved Generation of Medicines
PB	Policy Board
PCOMs	Partners for Change Outcome Management System
PERGs	Patient engagement reference groups
PerMed (or PM)	Personalised Medicine
PL	Pillar Leader
PM	person month
PPP	public-private partnership
PREMs	patient-reported experience measures
PROs	Patient reported outcomes
PROMs	patient-reported outcomes measures
PSIP	Partnership Specific Impact Pathway
R&I	Research and Innovation
Rare2030	Rare 2030 Foresight Study, EU-funded (https://www.rare2030.eu)
RD	Rare disease(s)
RDP	Rare Diseases Partnership
RDCA-DAP	Rare Disease Cures Accelerator-Data and Analytics Platform
RD-CONNECT	European project funded under FP7 (https://rd-connect.eu)
RDI	Rare Diseases International
RFO	Research funding organisation
RPO	Research performing organisation
RWE	Real World Evidence
Screen4Care	public-private project funded through the Innovative Medicines Initiative under Horizon 2020
SDG	Sustainable Development Goal(s) of the United Nations
SEMIA	Start-up incubator in France (https://www.startup-semia.com/)
SME	Small and Medium-sized Enterprise
SO	Specific Objective
Solve-RD	Solve-RD - Solving the Unsolved Rare Diseases, project funded under Horizon 2020 (https://solve-rd.eu)
SRIA	Strategic Research and Innovation Agenda
TAB	Thematic Advisory Board
UK	United Kingdom
UN	United Nations
US	United States
VC	venture capital
VP	Virtual Platform
WP (WP1, WP2...)	Work Package (Work Package 1, Work Package 2…)
WPL	Work Package Leader
X-eHealth	eXchanging electronic Health records in a common framework