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Fifth List of Research and Innovation Needs Requiring Medium- or Long-Term Approach and Related Task Forces

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1. Objectives and methodology

The deliverable 2.20 titled "Fifth List of Research and Innovation Needs Requiring Medium- or Long-Term Approach and Related Task Forces" is designed to accomplish a dual purpose.

Firstly, this deliverable aims to comprehensively outline the accomplishments of IRDiRC throughout the year 2023. With the impending transition of the IRDiRC Scientific Secretariat from EJPRD to ERDERA in September 2024, the paramount objective of the Scientific Secretariat is to ensure the successful completion of all ongoing activities registered under EJPRD. It is important to note that the acceptance and management of new Task Force proposals will be deferred until September 2024 when ERDERA will commence.

Furthermore, this deliverable aims to detail the ambitious medium- and long-term strategic research and innovation objectives of the ERDERA partnership, as the EJP RD programme comes to an end in August 2024.

2. Background

2.1. IRDiRC's Background

The management of the medium and long-term research strategy questions and their dedicated linkage with Task Forces of the International Rare Diseases Research Consortium (IRDiRC) is part of the WP2 – Strategy, Task 2.4 in EJP RD.

IRDiRC unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organizations, and researchers from all over the world to drive and promote international collaboration and advance rare diseases research strategy worldwide. It's overarching vision for 2027 is to "**Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention".** Many of the EJP RD organizations, including the European Commission are also members of IRDiRC and participate actively in different committees. Furthermore, the Chair and Vice-Chair of IRDiRC are members of EJP RD Policy Board. Finally, the Scientific Secretariat (SciSec) of IRDiRC is ensured by the coordination team of the EJP RD. Such strong connection is a mutual advantage and prevents duplication of efforts.

It is important to underline that EJP RD agreed that close collaboration and follow up of the IRDiRC goals and strategic recommendation is central to all EJP RD actions and thus no specific Scientific Board have been established within EJP RD. However, the EJP RD consortium has the possibility to analyse the RD landscape and propose relevant complementary actions that are of benefit for all RD community. This is being done in collaboration with EJP RD Policy and Governing Boards.

It was agreed that any research strategic question or need identified by the EJP RD Policy Board as requiring medium or longer-term approach will be studied in relation to the ongoing or future Task Forces planned within IRDiRC activities.

At present, each of the IRDiRC Scientific (Diagnostics, Interdisciplinary, Therapies, Regulatory) or Constituent (Funders, Patients Advocacy, Companies) Committees has the possibility to seize upon specific RD research need or bottleneck and propose a Task Force aiming at issuing recommendations to overcome the identified obstacle. These proposals are evaluated, prioritized, and submitted for final validation through unanimous vote by members of the IRDiRC Consortium Assembly (CA).

The setting up of a Task Force (TF) follows a well-established scheme in accordance with IRDiRC procedures, composed of the following steps:

i. From January to September of each year, IRDiRC Constituent and Scientific Committees identify actionable topics that can advance RD research and subsequently write an activity proposal following the IRDiRC activity proposal template, which includes the following elements: background of the topic, objectives of the activity, foreseen impact on the RD community, project plan and timeline, expected output/deliverable, required members expertise, planned potential collaboration with other organizations, and sustainability plan;
ii. The Scientific Secretariat provides support to the different Constituent and Scientific Committees in preparing their activity proposal document. In October of the same year, all activity proposals are submitted to the IRDiRC Operating Committee (OpComm) for preliminary review and provision of recommendations, including identification of potential synergies between proposals. In November of the same year, the Scientific Secretariat sends all the activity proposals to the Consortium Assembly for review, indicating which proposals are recommended by the OpComm. The Consortium Assembly is given three to four weeks to review all the submitted proposals. The OpComm-recommended activity proposals are presented during the December Consortium Assembly meeting, wherein, members of the Consortium can challenge the activity proposers and raise questions. An online vote is launched by the Scientific Secretariat for two weeks to the Consortium Assembly after the proposals are presented. Result of the online vote is released before the end December;
iii. Preparation and launch of Call for experts to constitute the Task Force are done by the Scientific Secretariat with the respective activity proposers during Q1 of the following year;
iv. Establishment of the Task Force is commenced in Q2;
v. Each Task Force has 12 to 18 months of work including regular conference calls, and an optional in-person workshop;
vi. Each Task Force produces their final recommendations and/or roadmap to be followed by the engaged stakeholders, generally through publications or toolkits (enquirers);

vii. The Scientific Secretariat, together with IRDiRC members and the Task Force members, continuously disseminate all IRDiRC activity outputs.

Usually, the IRDiRC SciSec is responsible for managing and overseeing the selected Task Forces. However, in case of actions or activities proposed that are considered of high importance, the involvement of additional partners on both EJP RD and IRDiRC side would be expected.

The establishment of an IRDiRC Task Force involves a significant emphasis on collaboration with the EJP RD program. Notably, a considerable number of individuals holding pivotal strategic roles within the EJP RD program, including Task Leaders, Work Package Leaders, and even Pillar Leaders, also hold membership in IRDiRC Task Forces, as delineated in subsequent sections of document D2.20. This interdependence underscores the robust partnership between EJP RD and IRDiRC, aligning with the overarching, enduring strategy of the EJP RD initiative and the IRDiRC consortium.

2.2. ERDERA Partnership proposal's development

The EJP RD will come to an end in August 2024, making it unsuitable for further defining research and innovation needs, especially regarding collaboration with IRDiRC. However, within the Horizon Europe framework, the European Commission has initiated a call for proposals to establish a new European partnership focusing on rare diseases. Collaboratively, representatives from Member States, a significant portion of the EJP RD consortium, and rare disease community representatives from Europe and worldwide have united to craft a successor program — the European Rare Diseases Research Alliance (ERDERA). This initiative aims to build upon EJP RD, offering broader scope and resources for advancing rare disease research.

The development process of ERDERA took place over a long period of time and brought together the rare disease community as a whole (researchers, clinicians, patients, patient organisations, Member State representatives, funders, industries, etc.) at various key stages.

The process of the development of the Partnership was divided into the following main phases:

i. The European Commission (EC) established the EC group of National representatives that is composed of colleagues from the Research Ministries (primarily) and National (regional) funding bodies, including a few experts nominated by the respective Ministries/funders.
ii. The 'concept paper' (an outline of the draft proposal) for the Rare Diseases Partnership was published in February 2022, after it was developed firstly by a core 'drafting group' of National representatives and subjected to the consultation/feedback of a large group of rare disease experts nominated by the countries, including experts selected by the European Joint Programme on Rare Diseases. The document is publicly available at the EC

website: https://ec.europa.eu/info/sites/default/files/research_and_innovation/funding/documents/ec_rtd_he-partnerships-rare-diseases.pdf. It provides an overview of the vision, the general and specific objectives, and the expected impacts of the RDP, including an indicative estimation of the required budget, and the proposed governance.

iii. The development of the Strategic Research and Innovation Agenda (SRIA) for the RD Partnership was kicked off on 30 June 2022 with the launch of the SRIA Task Force (TF). The SRIA is the key strategy document of a partnership for decision-making and must be formally approved by a partnership's decision-making body. For European Partnerships, the SRIA must be agreed with the Commission and the EU Member States prior to the launch of the initiative, as the key strategy document of the partnership for decision-making.

iv. The consortium has prepared the proposal of the RD Partnership that has been submitted at the deadline (September 2023) of the call topic to be included in the work programme 2023 of the Health cluster of Horizon Europe. The proposal included the SRIA, the description of the actions presents the activities for the whole duration of the partnership (and detailed activities for at least the first year of the Partnership - first annual work plan), the financial resources, including the institutions that will be the partners and their contribution and tasks in the Partnership.

v. Subject to the successful evaluation of the proposal, the next step would be the grant agreement preparation phase that will include the legal and administrative procedures for each partner to become a formal beneficiary to the grant agreement, followed by the signature of the grant agreement

3. List of IRDiRC Task Forces, Working Groups, and Initiatives launched in 2023

3.1 Funding Models to Support the Spectrum of Rare Disease Research and Development

a. Introduction

The successful development of therapies for any disease requires support from early stages (basic/fundamental research), through more mature preclinical, translational, or early clinical stages, then more mature clinical stages, and finally, post-marketing studies. How different funders decide when to fund at a given stage in a treatment's development is fairly opaque. Knowledge of the factors that contribute to this process might help other funders understand better how to facilitate the development of these treatments.

The former IRDiRC Chrysalis Task Force addressed some of these questions for companies but led to the realization that this knowledge was lacking for other types of funders. Furthermore, it is unclear how the decisions of one type of investor might impact the decisions of other funders or the funding ecosystem for rare diseases. A

better understanding of the landscape (and even a recognition of the variability) would likely ultimately benefit those living with rare diseases. Both successes and failures might be very informative.

b. Objectives

- Identify key motivating factors for different types of funders of rare disease research.
- Identify how different types of funders decide at which point in a research study's lifecycle they will provide support.
- Identify the key influencing factors for effective public-private partnerships at different stages of a treatment's life cycle.
- Identify models of public-private partnerships, including means of sharing information (with attention to tech transfer issues and regulatory requirements).

c. Output

- Summary of analysis from the collated literature review and Key Opinion Leader (KOL) interviews to identify factors to meet the objectives, and publication of this material as a SLOT analysis (strengths, limitations, opportunities, threats) of the current funding landscape.
- Publication of the results and analysis performed on the Orphan Drug Designation database.
- Funding model toolkit for rare disease research.

3.2 Preparing for genetic N-of-1 treatments of patients with ultra-rare mutations

a. Introduction

The N-of-1+ therapy approach is transforming the drug development landscape and has the potential to facilitate treatment of patients with ultra-rare diseases for whom no previous treatment has been developed. However, while the development of therapies specific to very few patients have a lot of promise, the largest challenge faced by these initiatives is that the drug development, regulatory frameworks and reimbursement systems were not designed for N-of-1+.

b. Objectives

The overall objective of this Task Force is to connect different N-of-1+ efforts to reduce duplication, achieve global consensus and create a roadmap towards development and implementation of N-of-1+ treatment.

- To produce a reference document summarizing the current state-of-the art, to raise awareness of the N-of-1+ concepts and challenges with all stakeholders
- To identify the major challenges hampering N-of-1+ therapy development and timely patient access, in order to allow for development of proposed solutions and create a better opportunity for strategic planning and delivery of N-of-1 therapies

c. Output

The output of this Task Force is a State-of-the-Art publication, that includes also the framework of the N-of-1 roadmap. A second publication on future perspectives is planned for Q2 2024. The group has been working on a collection of educational resources on N-of-1 therapies and research is under development with the scope of being publicly available on the IRDiRC website in Q1 2024.

3.3 A framework to assess impacts associated with diagnosis, treatment, support, and community integration that can capture changes along the rare disease patient and family journey

a. Introduction

This research project builds upon the work of the IRDiRC Working Group on Goal 3 who produced a framework of the patient journey identifying key areas for developing methodologies to assess the impact of diagnoses and therapies on rare disease patients and families. While there are some studies on the impacts of living with a rare disease and some that chronicle the natural history, there has been relatively little research measuring the impacts of "diagnosis/no diagnosis/misdiagnosis" as well as "availability/no availability" of therapeutic interventions and their efficacy.

b. Objectives

The objectives of this Task Force are to (1) Develop, operationalize, and test a comprehensive framework of holistic, multidimensional, and evolving life-long experiences of patients and families living with a rare disease; (2) Develop, operationalize, and validate multidimensional indicators and measures (qualitative and quantitative) of impacts associated with diagnosis, treatment, support, and community integration that can be used to capture changes along the patient "journey"; and (3) Investigate qualitative case studies to represent a number of parameters that could inform on impacts.

c. Output

The output of this Task Force will be a publication presenting and discussing the framework.

3.4 Functional Analysis

a. Introduction

With the introduction of high-throughput methods of large-scale mutagenesis, followed by the large-scale functional assessment of induced variation, and supported by computational methods, new horizons open up. Multiplexed assays of variant effect (MAVE) and the application of CRISPR/Cas9 or RNAi for gene disruption and multi-omics for the screening of functional biological impacts provide the means for proactive, large-scale, functional assessment of genome and their variation,

including the development of variant effect maps for basic and clinical research communities. However, there needs to be more guidance on applying these novel methods, required infrastructure, and standards to the field of rare diseases (RD) that are frequently characterized by ultra-rare or unique private mutations.

b. Objectives

- Foster further development, standardization, and quality improvement of the experimental and computational methods of functional assays and their uptake by the RD research community and clinical practice.
- Foster ecosystem building, infrastructure development and partnerships for the effective chain from fundamental research to clinical applications of functional assays.
- Foster equity in RD diagnostics and treatment through the application of indiscriminative multiplexed assays of variant effect and variant effect maps to the fundamental research and clinical practice in rare diseases).

c. Output

A position paper on framework for a robust and effective ecosystem of functional analyses in rare diseases.

3.5 Newborn Screening Initiative

a. Introduction

Given IRDiRC's goal of shortening the diagnostic odyssey for RD patients, a group of international experts has been brought together to provide insight into the current state of Newborn Screening worldwide, highlighting technological advances, as well as the many challenges, to implementing comprehensive screening programs.

b. Objectives

Newborn Screening has played a major role in the national screening programs implemented around the world. However, there are great differences between countries or regions in terms of number of diseases screened and the technologies used. The new emerging technologies, such as next-generation sequencing offer the opportunity to screen for genetic disorders through a single test, but can pose a challenge in the cost, complexity, and access to the appropriate equipment. In addition, there are certain ethical considerations to be considered, as well as potential social stigma. Different cultures may also view NBS in different lights which will often guide national policy that can differ greatly between countries. Taken together, these issues pose a serious challenge to implementing comprehensive NBS programs globally which ultimately impacts on our ability to identify and diagnose rare disease at an early stage. The scope of this initiative is to offer an overview of the current real technologies applied at worldwide level, as well as key considerations in terms of patients 'overview of the process, ethical and policy issues.

- Two special editions are in preparation: **Real World Applications and Technologies**
- **Policy, Ethics and Patient Perspectives**

c. Output

[…All papers are planned to be published in the Rare Disease and Orphan Drugs Journal (RDODJ).as two special issues (one special issue consists of minimum 5 papers).

Currently published and publicly available on the journal website:

Newborn Screening I – Real World Applications and Technologies

- A systematic review of real-world applications of genome sequencing for newborn screening
- Could federated data analysis be the catalyst accelerating the introduction of newborn genome screening for the detection of genetic disease?
- Next-generation sequencing-based newborn screening initiatives in Europe: an overview

Newborn Screening II – Policy, Ethics and Patient Perspectives

- Development of newborn screening policies in Spain 2003-2022: what do we actually need to reach an agreement?

- The Australian landscape of newborn screening in the genomics era

4. ERDERA Partnership's SRIA

The ERDERA Partnership Strategic Research and Innovation Agenda is a strategic document written by a task force composed of over 80 experts from the European and international rare disease community representing various fields of activity. It goes further than the concept paper in terms of the overall strategy and scope of the ERDERA with the definition of :

- The ambition and the vision of the proposal
- The operational objectives (OOs), the specific objectives (SOs), the general objectives (GOs), in line with the Horizon Europe impact pathway (that can be seen below)
- The key performances indicators planned to monitor the impact of the ERDERA partnership on the short, medium and long term.

The ERDERA Partnership builds on lessons learned from the EJP RD, that was achieved in Europe to structure the RD research landscape. The ERDERA will consolidate and extend the achievements of EJP RD to accomplish its vision : deliver a RD multi-stakeholder ecosystem by supporting robust patient need-led research, developing new treatments and diagnostic pathways, by using the power of health and research data and spearheading the digital transformational change in RD research and innovation.

The ambition of the ERDERA partnership is to contribute to and accelerate directly the goals set by the International Rare Diseases Research Consortium (IRDiRC).

In line with the Horizon Europe impact pathway, the General Objectives GOs) correspond to the long-term impacts to which ERDERA aims to contribute. The Specific Objectives (Sos) reflect medium-term timescale and correspond directly to the expected outcomes that the Partnership should achieve or contribute to, in line with its mission, and within its lifetime, or at the latest, at 2034 Horizon. Finally the Operational objectives (OOs) are considered as means and resources and are translated through the activities that will be implemented by the Partnership to accomplish the overarching So and GO levels.

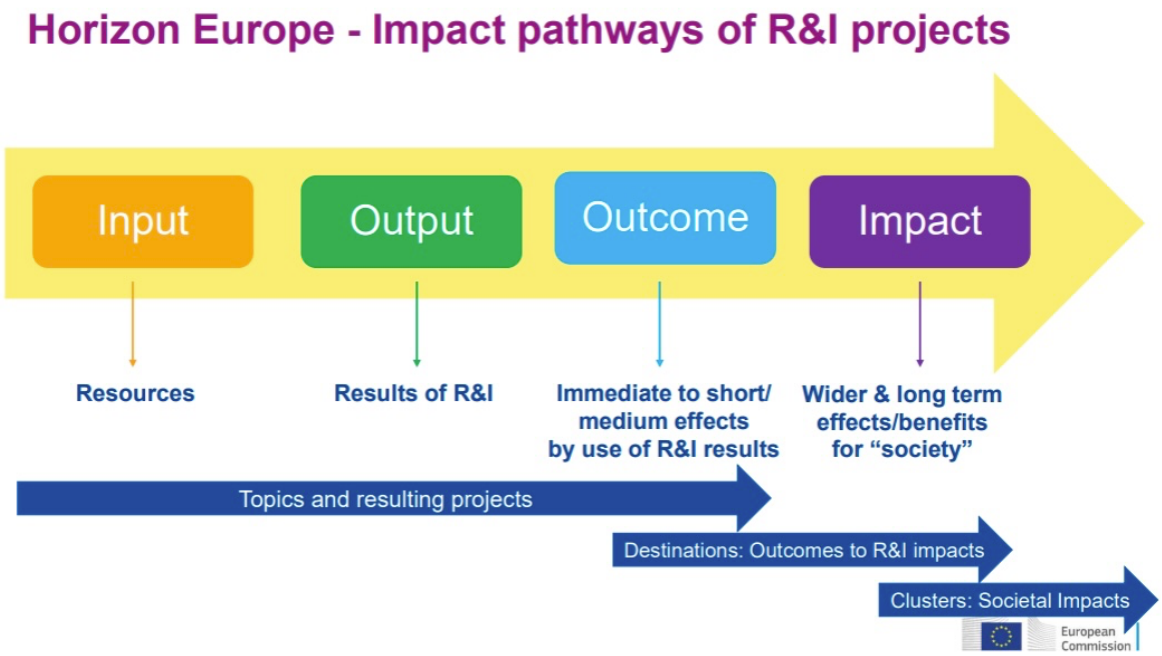

Figure 1: Horizon Europe - Impact pathways of R&I projects
Outputs : Operational Objectives (OOs)
Outcomes : Specific Objectives (SOs)
Impacts : General Objectives (GOs)

The ambition and the objectives of the ERDERA can be displayed through the following intervention logic : the Partnership Specific Impact Pathways (PSIP)

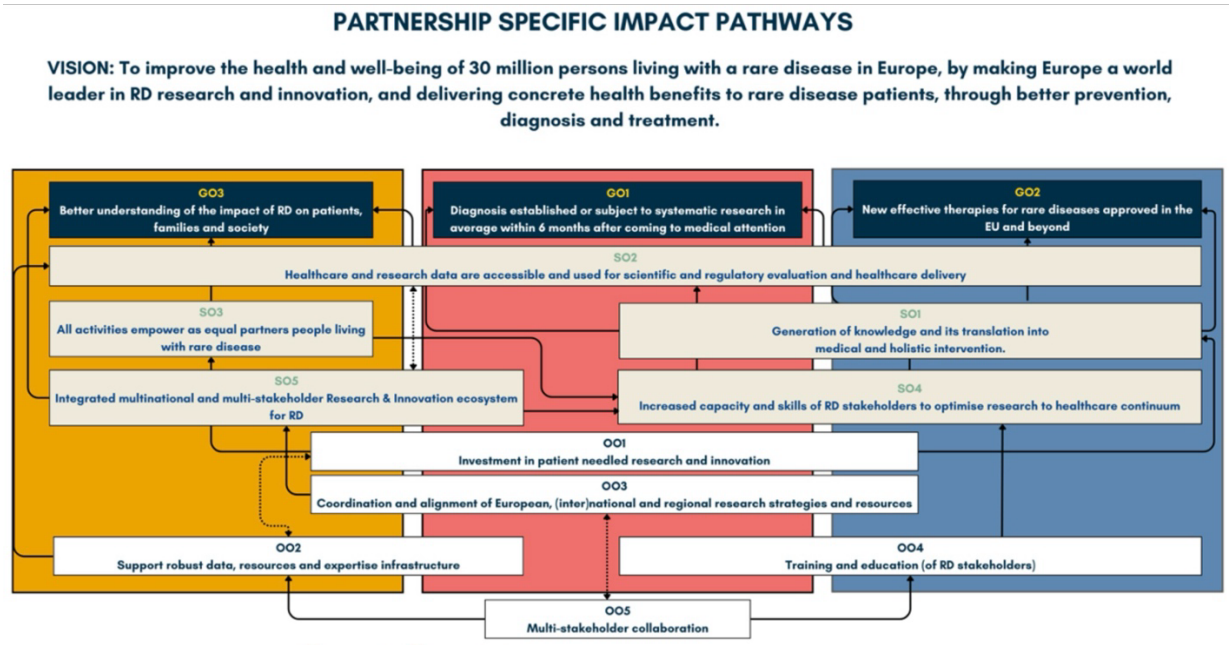

Figure 2: ERDERA PSIP

The General Objectives (GOs) of the European Rare Diseases Research Alliance have been inspired by and fully aligned with the goals of IRDiRC in order to improve the health and well-being of people affected by rare diseases by delivering concrete health benefits through prevention, diagnosis and treatment development.

ERDERA GO1 : Diagnosis established or enrolment in systematic research in average within 6 months after coming to medical attention

IRDiRC 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.

ERDERA GO2 : 1000 new therapies for rare diseases approved in Europe and beyond

IRDiRC goal 2 : 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options.

ERDERA GO3 : Better understanding of the impact of RD on patients, families and society

IRDiRC goal 3 : Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

ERDERA's goals and objectives (GOs, SOs and OOs) will be assessed based on their level of measurability and achievability using a comprehensive set of relevant and demanding Key Performance Indicators (KPIs), submitted within the proposal.

The ERDERA Partnership has been structured based on workstreams and Work Packages developed in an objective-driven manner to directly contribute to the predefined General Objectives. The ensuing figure illustrates the correlation between ERDERA's workstreams, their respective Work Packages, and their contribution to the overarching General Objectives.

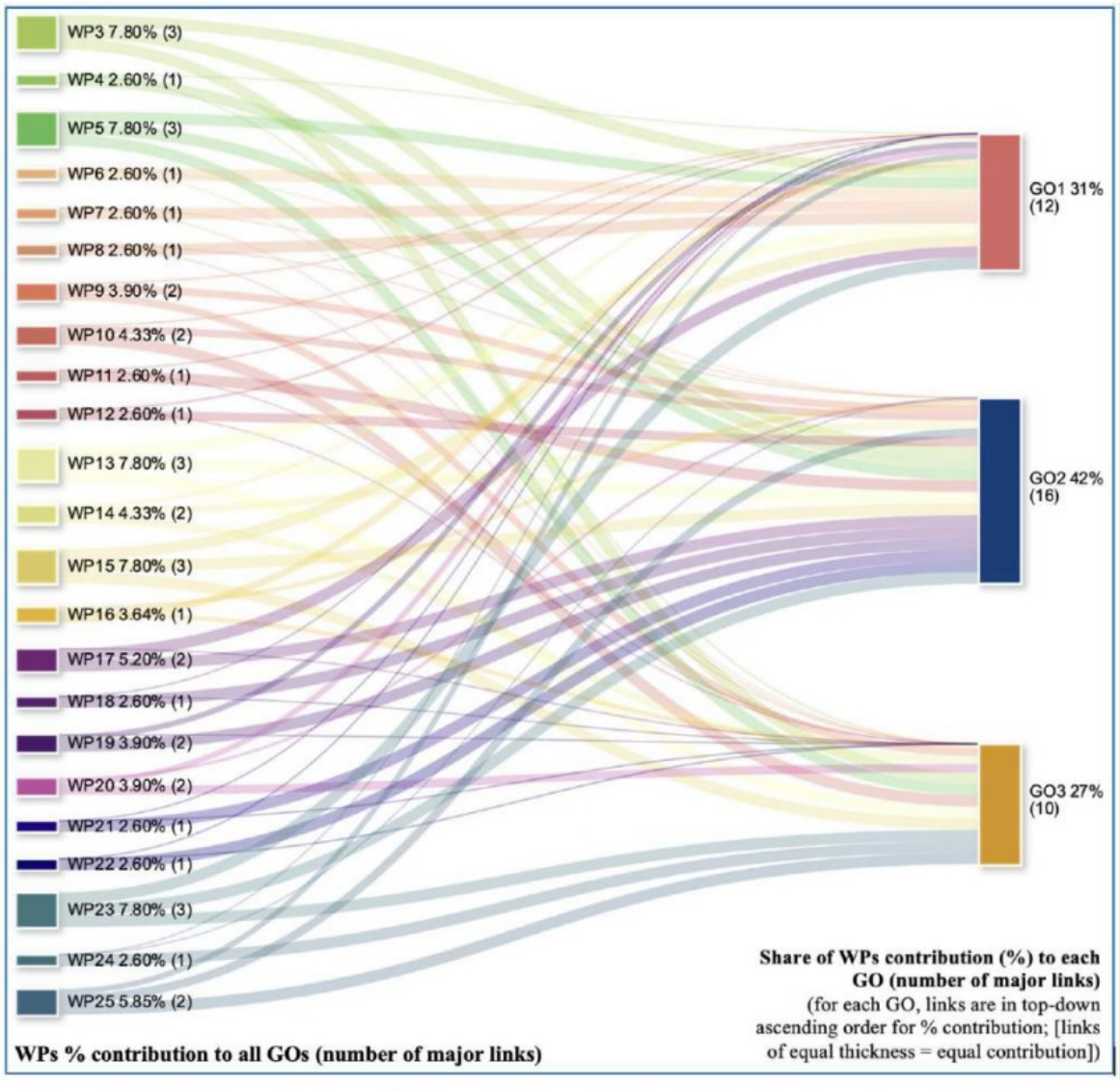

Figure 3: ERDERA Work Package relative contribution to the General Objectives based on the number of tasks involved

Synergies with other initiatives and collaborations (with other EU partnerships, with other EU programs and projects, and with overarching European and/or international major initiatives such as IRDiRC) are envisioned to reach the ERDERA's ambitions, to support its actions and to further define the research and innovation needs and how to address them.

Besides, for a further defining of these needs and solutions, especially regarding collaboration with IRDiRC, ERDERA consortium dedicated a full workstream to the

(Inter)national Capacity Alignment. Within this Workstream, the Work Package 25 will amplify the impact and the effectiveness of global collaborative efforts and drive transformative change at the international scale by aligning the research strategy of the ERNs, engaging with IRDiRC and supporting its scientific secretariat, establishing international strategic alliances an organizing joint workshops and conferences with Clinical Research Networks from all over the world.

Through this workstream and ongoing collaboration with all other ERDERA workstreams, the entire research and development (RD) community across the benefiting countries (ERDERA partners, IRDiRC partners, national key stakeholders, patient organisations, international organisations collaborating, etc.) will have the capability to develop a dynamic and evolving list of research and innovation needs.

5. Annex 1 – List of EJPRD Members/Institution Beneficiaries that are members of IRDiRC Committees and Task Forces 2023

5.1. EJP RD members in IRDiRC Constituent Committees

5.1.1 Funders Constituent Committee (11)

- AFM-Téléthon, France
- Agence Nationale de la Recherche (ANR), France
- Canadian Institutes for Health Research (CIHR), Canada
- Federal Ministry of Education and Research (BMBF), Germany
- Foundation for Rare Diseases, France
- Georgian Foundation for Genetic and Rare Diseases (GeRaD), Georgia
- INSERM, France
- Istituto Superiore di Sanità (ISS), Italy
- National Institute of Health Carlos III (ISCIII), Spain
- Fondazione Telethon, Italy
- The Netherlands Organisation for Health Research and Development (ZonMw), The Netherlands

5.1.2 Patient Advocacy Constituent Committee (1)

- EURORDIS, France

5.1.3 Diagnostics Scientific Committees (4)

- Academisch Medisch Centrum bij de Universiteit van Amsterdam (AUMC), The Netherlands
- Fundacio Centre de Regulacio Genomica (CNAG-CRG), Spain
- Vall D'Hebron Research Institute, Spain
- Vilnius University Hospital Santaros Klinikos, Lithuania

5.1.4 Therapies Scientific Committees (1)

- EURORDIS, Europe

5.1.5 Regulatory Scientific Committees (1)

- AFM-Téléthon

5.1.6 Interdisciplinary Scientific Committees (4)

Istituto Superiore di Sanità (ISS), Italy

- University Medical Center Groningen, The Netherlands

University of Cambridge, UK

- Vall D'Hebron Research Institute, Spain

5.2. EJP RD members in Task Forces in Year 2023

5.2.1 Funding Models to Support the Spectrum of Rare Disease Research and Development (2)

- Canadian Institutes for Health Research (CHIR), Canada
- Foundation for Rare Diseases, France

5.2.3 Preparing for genetic N-of-1 treatments of patients with ultra-rare mutations

- Leiden University Medical Center, The Netherlands
- EURORDIS, France

5.2.4 A framework to assess impacts associated with diagnosis, treatment, support, and community integration that can capture changes along the rare disease patient and family journey

- University of Tübingen, Germany
- Institute of Health Carlos III, Spain

5.2.5 Functional Analysis (2)

- Vilnius University Hospital Santaros Clinics, Lithuania
- Spanish Institute of Health Carlos III (ISCIII), Spain

5.2.6 Newborn Screening Initiative (4)

- Fondazione Telethon, Italy
- Spanish Institute of Health Carlos III (ISCIII), Spain
- AFM-Téléthon, France
- EURORDIS, France

6. Annex 2 – ERDERA's Strategic Research & Innovation Agenda

ERDERA

EUROPEAN **RARE DISEASES** RESEARCH ALLIANCE

Strategic Research & Innovation Agenda

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6.1. Summary of SRIA development process

The development of ERDERA's SRIA follows an established process that encompasses different writing, consultation, and consensus phases.
The **preparatory/initial phase**, started in February 2022 and included setting-up of a dedicated expert team (SRIA Task Force) to guide and oversee the development and implementation of the SRIA. This included identification of key stakeholders to include in the SRIA framework development process (develop a stakeholder map).
The SRIA Task Force brings together over 80 experts from the European and international rare disease community representing:

- **Various fields of activity:** preclinical, translational and clinical research; drug development and diagnostics innovation; biostatistics; data science; regulatory science; research funding, social sciences & humanities;
- **Different types of stakeholders representing:** research organisation/institutions; hospitals/university hospitals; EU research infrastructure; patients' organisations; foundations; funding bodies; regulatory & health technology assessment bodies, Member States representatives, European Commission;
- **Other relevant programmes, initiatives and networks:** EJP RD, Solve-RD, ERNs, Innovative Health Initiative, European Health Data space, DARWIN EU, CSA STARS, C-PATH.

The writing phase encompassed the initial reflection and analysis of gaps and opportunities conducted within the RD community and with the European Commission. The early ideas about scope, impact, outputs were agreed by the SRIA TF and several iterations took place between the SRIA TF and Member States/Associated Countries and European Commission directorates. The following items were developed by the SRIA TF:

- The definition of Operational Objectives (OOs), Specific Objectives (SOs) and General Objectives (GOs), in line with the Horizon Europe impact pathway (input → output → outcome → impact) and resulting in the Partnership Specific Impact Pathways (PSIP) scheme, which encompasses the connections among different levels.
- The definition of the overarching challenges followed the scope, outputs and outcomes for each of the objectives.
- The definition of Key Performance Indicators (KPIs) for each level.

The Preliminary SRIA draft was opened for public consultation in May 2023 and closed mid-June. It gathered 138 responses (see Fig 1).

The major outputs of the consultation were integrated in the current version of the SRIA and will be further processed. It is expected that this draft will continue to evolve until its finalization foreseen for Sep 2024 (final validation by the Governing Board and the European Commission after the Grant Agreement signature for ERDERA).

The full preparatory timeline is presented in Fig. 2.

Fig 1. Results of SRIA open consultation

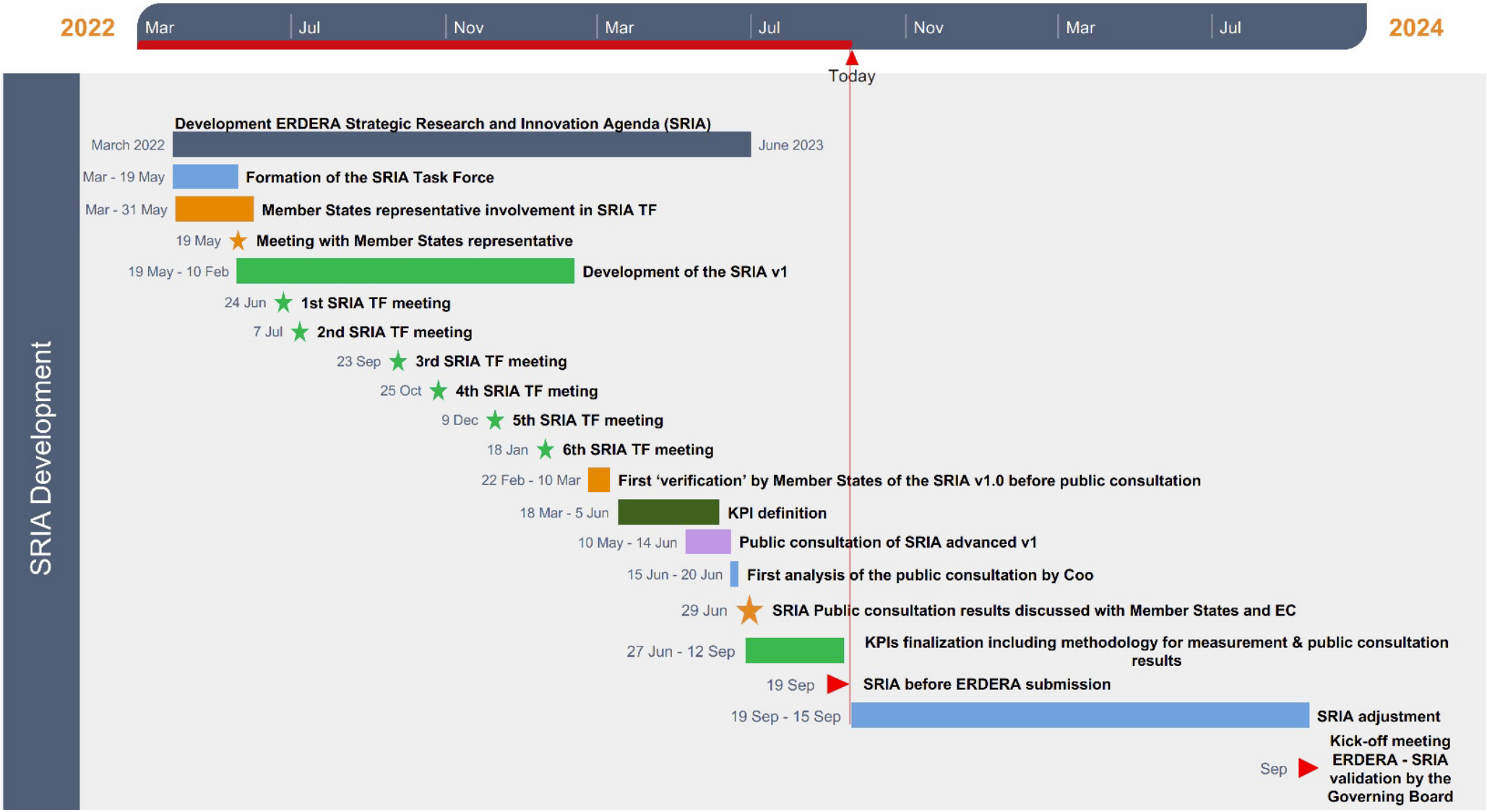


Fig 2. ERDERA's SRIA development process and timeline

6.2. Vision of the European Rare Diseases Research Alliance

6.2.1. Missions

The European Rare Diseases Research Alliance will be organised around the following ambition, vision, and mission.

AMBITION:

The European Rare Diseases Research Alliance (ERDERA) has the ambition to improve the health and well-being of the 30 million people living with a rare disease in Europe, by making Europe a world leader in RD research and innovation, to support concrete health benefits to rare disease patients, through better prevention, diagnosis and treatment. It will support the EU commitment to UN 2030 Agenda's Sustainable Development Goals: (i) Good health & wellbeing (SDG3), (ii) industries, innovation and infrastructure (SDG9), and (iii) Reduced inequalities (SDG10) as well as the EU political priorities (a Europe fit for the digital age, an economy that works for people, a stronger Europe in the world, Promoting our European way of life and democracy).

VISION:

To leave no one behind, the European Rare Diseases Research Alliance will deliver a RD multi-stakeholder ecosystem by supporting robust patient need-led research, developing new treatments and diagnostic pathways, by using 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 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 the end of the Partnership.

MISSION:

- Bring and share supporting R&I knowledge, resources and services from across Europe under one roof so that every RD research project would 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 and sharing of FAIR-compliant, regulatory-quality 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, by aligning the regional, national and European research and innovation priorities, leading to job creation and improving EU competitiveness in R&I.

6.2.2. Building on Lessons learned

The European Rare Diseases Research Alliance stems from joint actions between the EU Members States, Associated countries, European Commission and other relevant stakeholders. It builds on lessons learned from the European Joint Programme on Rare Diseases, EJP RD, a major milestone that was achieved in Europe to structure the RD research landscape. EJP RD was launched in 2019, as a prime example of Member States and other stakeholders working together on a more integrative and cross-sectorial approach to tackle health challenges. It gathered more than 130 institutions from 35 countries and built the foundations of RD ecosystem by integrating multinational RD funding, support services and data infrastructure (virtual platform of distributed FAIR data sources and services). The Partnership will benefit equally from the outputs but the ones that are key for the ERDERA of several other key programmes and initiatives supported by the EU (to only name few) as the European Reference Networks (ERN), their registries and their clinical research

coordination platform ERICA; IMI projects like Connect for Children (C4C) pan-European collaborative paediatric network for high quality clinical trials in children, and Screen4Care; Orphanet, the EU-funded multilingual knowledge base on rare diseases and orphan drugs including ORPHA codes ontology; EU-funded research projects such as Solve-RD, accelerating RD diagnosis pathway for unsolved rare diseases for which the molecular underlying cause is not yet known; RD-Connect, a European genome-phenome analysis platform including directory of RD biobanks and samples; the European Rare Diseases Registry Infrastructure implemented by JRC, projects such as X-eHealth and EHDEN that target millions of health data records, and the 1+Million Genomes initiative targeting 1 million sequenced genomes accessible in the EU including RDs as key use case. Finally, the national contributions will be essential to the European Rare Diseases Research Alliance to ensure long-term commitment, integration of resources and best alignment of the national plans and/or national strategies to tackle rare diseases.

The ERDERA will consolidate and extend the achievements of EJP RD so that other actors can contribute more easily and efficiently to the generation of evidence that leads to concrete benefits for patients.

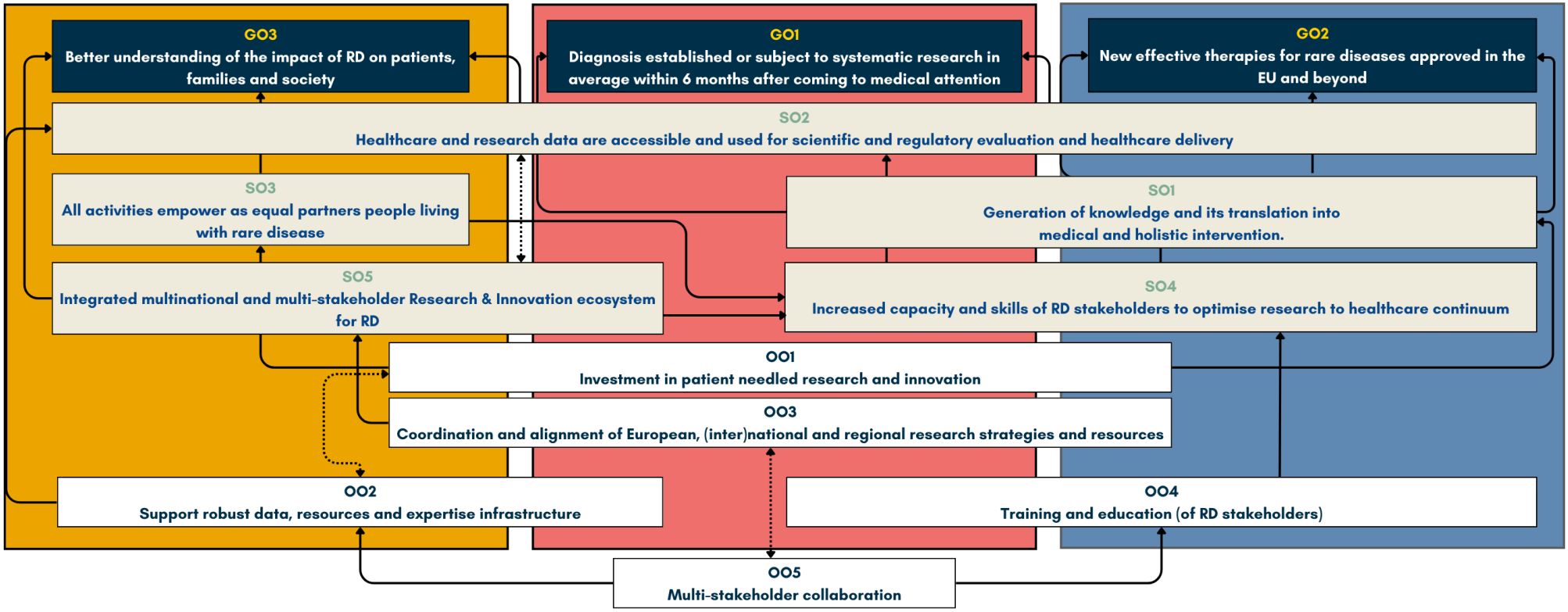
The ambition of the European Rare Diseases Research Alliance will build on, contribute to and accelerate directly the goals set by the International Rare Diseases Research Consortium[1] (IRDiRC). This is reflected in the General Objectives of the Partnership. The programme aims to provide solutions for 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 which are: 1/the need for further collaboration & alignment of research funding and optimal integration with national rare diseases plans/strategies; 2/ the huge gap in translation of research results to deliver cost-effective solutions for people living with a rare diseases (noting that the conduct of clinical studies is a burden that can be addressed); and 3/ the fragmentation of knowledge and data, lack of holistic R&I ecosystem. Research & Innovation activities on rare diseases should create value for patients by reducing suffering of people living with rare diseases through better prevention, better diagnosis and better treatment as a direct result of research outcomes. The European Rare Diseases Research Alliance should drive the research 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 and sectors.

[1] IRDiRC goals for the decade 2017-2027 are: 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 (Future of Rare Diseases Research 2017–2027: An IRDiRC Perspective. C.P. Austin et al. Clin Transl Sci. 2018 Jan;11(1):21-27. doi: 10.1111/cts.12500. Epub 2017 Oct 23)

6.2.3. intervention logic - Partnership Specific Impact Pathway (PSIP)

PARTNERSHIP SPECIFIC IMPACT PATHWAYS

VISION: 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.



6.2.4. General Objectives[2]

The General Objectives (GOs) of the European Rare Diseases Research Alliance are defined in line with the Partnership's vision and mission to improve the health and well-being of people affected by rare diseases by delivering concrete health benefits through prevention, diagnosis and treatment development. It was agreed that they should be inspired by and fully aligned with the goals of IRDiRC. Moreover, they are contributing to EU political priorities (cf. "Ambition") and to the Sustainable Development Goals (SDGs) of the 2030 Agenda for Sustainable Development adopted by the United Nations in 2015. In particular, they are affiliated with SDG3 "Ensure healthy lives and promote well-being for all at all ages", SD9 "Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation", and SDG10 "Reduce inequality within and among countries".

6.2.4.1. GENERAL OBJECTIVE 1: DIAGNOSIS ESTABLISHED OR ENROLLMENT IN SYSTEMATIC RESEARCH IN AVERAGE WITHIN 6 MONTHS AFTER COMING TO MEDICAL ATTENTION

Patients with undiagnosed diseases and their families often face an uncertain and unpredictable journey, called a diagnostic odyssey, which is particularly complex in the case of rare diseases as 50% of patients still do not have a final diagnosis, and when they do, it is on average after 4 years of the diagnostic journey.

The European Rare Diseases Research Alliance will contribute to shortening the diagnostic pathway for patients with rare diseases. For those disorders already identified in the literature the ambition is that a patient is diagnosed within a maximum of six-months after the first medical appointment with a specialist. For the undiagnosed disorders efforts will be made to build and/or strengthen the bridge between research and healthcare to provide to every undiagnosed patient the possibility to be included in a globally coordinated diagnostic and research pipeline.

6.2.4.2. GENERAL OBJECTIVE 2: 1000 NEW THERAPIES FOR RARE DISEASES APPROVED IN EUROPE AND BEYOND

95% of RDs are still underserved in terms of research and patients with rare diseases, although diagnosed, face a lack of viable long-term treatment options. To contribute to IRDiRC goals, and more specifically Goal 2 – "1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options", the European Rare Diseases Research Alliance, will accelerate the development of new therapies (especially for diseases without approved options) by providing the necessary support to research projects aimed at developing new treatments and by expediting clinical trial readiness of rare diseases, including contribution to regulatory fitness to enable regulatory approval.

[2] General Objectives correspond to the impact aimed to be achieved by the European Rare Diseases Research Alliance, i.e., the wider & long term effects on society (including the environment), the economy and science, enabled by the outcomes of R&I actions.

6.2.4.3. GENERAL OBJECTIVE 3: BETTER UNDERSTANDING OF THE IMPACT OF RD ON PATIENTS, FAMILIES AND SOCIETY

Rare diseases place a significant burden on patients and their families, on caregivers and on society in general. For 52% of them, rare diseases mean a serious impact on their daily lives. Understanding of the impact of RDs on people lives means also better evaluation of the societal and healthcare costs and capacity to implement more inclusive, holistic healthcare approaches. Through required means (funding, data collection) and processes (involvement of people living with rare diseases at all levels) the Partnership will contribute to capturing of RD impact and comprehensive understanding of patients and carers needs leading to, in the long term, improved and/or new processes that will facilitate the diagnosis and care pathways and translate into meaningful societal support.

6.2.5. Activities and resources (Operational Objectives[3])

Operational Objective 1: Investment in patient need-led research and innovation

The European Rare Diseases Research Alliance will implement annually competitive Joint Transnational Calls (JTC) to fund patient-needs driven, multinational, research projects, including the funding of dedicated support to patients' organisations. Specific measures will be applied for the JTCs in order to improve the participation and visibility of under-represented countries in the European Rare Diseases Research Alliance.

Other funding schemes will be used including support to expanding or establishing new networks for knowledge sharing targeting underserved Rare Diseases, and fund in-house research, through the Clinical Research Network (CRN)[4]. These latter funding schemes 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. Clinical trials conduct could benefit from these funding schemes; the resources expected for their implementation will need to be estimated.

Operational Objective 2: Support robust data, resources and expertise infrastructure

The state-of-the-art infrastructure, services and support will be further advanced so that clinical and translational RD research are highly productive.

The infrastructure of the clinical research network will be established by leveraging on and expanding and connecting existing resources and tools (e.g., EU RD Platform, EJP RD Virtual Platform, European patients' registries and biobanks, as well as other national data sources & capacities). This infrastructure will comprise dedicated support services that will include, but are not limited to, provision of distributed and cloud computing and data exploitation facilities, innovative analysis resources, quality

[3] Operational Objectives correspond to the actions, activities and resources that will be deployed by the European Rare Diseases Research Alliance to achieve its Specific and General Objectives.

[4] The Clinical Research Network has for objective to promote efficient implementation of clinical studies and preparedness for clinical trials. It connects various resources from the European Rare Diseases Research Alliance partners and collaborators, supported by an IT infrastructure. It conducts internal research projects that are selected through internal calls and are backed by dedicated services, including but not limited to diagnostic research support, biostatistical guidance, clinical trials methodologies and operations, and Clinical Outcome Assessment support. Its IT infrastructure utilizes existing resources and platforms and extends them to allow for data exploitation for in-house research projects and piloting of the CRN.

assurance services, research guidance on coordinated diagnostic, Patient-Centred Outcome Measures, biostatistical and multinational Clinical Trials. Other ad-hoc support services (e.g., for identification of biomarkers and surrogate endpoints and validation, mHealth expertise) can be developed according to the emerging needs of the CRN. Importantly, these integrative services will be expanded, developed and deployed to support all activities of the European Rare Diseases Research Alliance (beyond CRN). They will comprise data integration and coordination services and expanded mentoring services to support all funded projects. Ethics, Legal, Regulatory and Societal Impact support will also be implemented.

Operational Objective 3: Coordination and alignment of European, (inter)national and regional research strategies and resources

A fully integrated strategy and coordination will support effective public, public-private and civil society partnerships. National coordination and alignment will be ensured through maximisation of the national in-kind contributions in advance and all along the lifetime of the Partnership. The National Mirror Groups (NMGs) will be set-up and supported to organise coordinated interaction between the Partnership and national and regional stakeholders. They will catalyse the transfer of good practices to the national and regional level, including leveraging the power of national/European data sources, by making nationwide or regional RD discoverable and actionable for international RD research.

The cooperation with international partners will be ensured through (1) the operation of the IRDiRC Scientific Secretariat to provide strong links to international collaborators (such as the US National Institutes of Health) as well as a joint management of research and innovation strategy; (2) the maintenance of already established collaboration with Associated partners (like Canada, Israel and Australia) contributing to and aligning with research and training activities; (3) expanding the collaboration and integration of other countries willing to join with their knowledge and resources; and (4) Stimulating and supporting the development of trans-regional activities.

Operational Objective 4: Training and education (of RD stakeholders)

The Capacity building of all stakeholders will support new generations of researchers, clinicians, patient representatives and policy makers, decrease knowledge and competences gaps between countries, empower patients and constantly improve the capacities of the experienced RD stakeholders.

The European Rare Diseases Research Alliance will integrate training and capacity building components as part of its support activities for funded research projects and Clinical Research Network. Dedicated efforts will be made to train patients and their representatives on topics of relevance to ensure and accelerate their informed engagement at all levels. To support access to RD education for overall society and stakeholders, comprising general student and clinician population interested in RDs, including at national level, the Partnership will take advantage of already initiated by EJP RD massive open online courses and expand them to accredited education programmes.

Operational Objective 5: Multi-stakeholder collaboration

All types of actors will be involved, along the health and research value chain, in priority setting. These include research funders; research and innovation communities across life science and technology/data disciplines; users represented by patients and

citizens, health care professionals and health care providers; as well as EU-wide and national policy makers, regulatory authorities, Health Technology Assessment bodies, and health care payers. The European Rare Diseases Research Alliance will gradually bring on board additional stakeholders. Mechanisms will be created to onboard Under-represented, including EU13[5] countries, Associated and non-EU countries. The inclusion of industry as partners in the ERDERA is considered as major gamechanger in building integrative RD ecosystem and advancing European Rare Diseases Research Alliance. This inclusion needs to happen in full synergy with some other initiatives listed in annex 1.

The multistakeholder collaboration, that is at the root of the Partnership, requires an effective governance framework. The Terms of Reference and guidance for the governance of the partnerships under Horizon Europe, that will be provided by the EC, and learnings from other initiatives such as EJP RD, will be used to set the organisational and governance structure of the consortium that will comprise decision-making bodies; executive bodies and advisory bodies. A central coordination and management of the consortium will take advantage of experience and tools already acquired through EJP RD to establish active and proficient coordination office that will accompany European Rare Diseases Research Alliance partners by providing operational and strategic support. This will include the management of the monitoring of Partnership operational, specific and general objectives through adapted monitoring system in line with the requirements of Horizon Europe.

The detailed breakdown of resources to specific activities will be decided by the European Rare Diseases Research Alliance decision-making bodies when adopting annual work programmes, considering advice from the constituted advisory bodies. The description of specific activities and allocated resources will be provided in annual activity reports. The annual activity reports will also report on the Key Performance Indicators used to monitor progress towards reaching the European Rare Diseases Research Alliance objectives, with specific baselines and targets.

6.2.6. Synergies with other initiatives

To reach its ambition, the European Rare Diseases Research Alliance will leverage relevant complementary activities in Europe and will conversely generate content that may benefit other EU initiatives.
Collaborations are envisioned with (i) Horizon Europe European Partnerships, (ii) European Union programmes, projects and initiatives, (iii) large European or international initiatives, should they be public, public-private or private including no-for-profit.

Synergies will be sought with the aim to support and enhance specific ERDERA actions (including possible co-funding, parallel funding or subsequent funding), as well as to ensure relevant dissemination and exploitation of results from the European Rare Diseases Research Alliance. For instance, regional funds can support the uptake of evidence-based results from e.g., the funded research projects, the services-innovations and other innovations identified through the ERDERA.

[5] List of EU13 countries: Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia, Slovenia

For each collaboration opportunity, "opportunity topics" cover diagnosis, treatment, care, research, data and infrastructures that set out the roadmap for the next decade of rare disease policies.

Key collaboration opportunities have been identified with **several EU Partnerships** implemented in the Horizon Europe context in three main areas: (i) the Health Cluster (ii); the Digital, Industry and Space Cluster;(iii) partnerships with cross-sectoral themes. A close collaboration will be initiated with other European Health Partnerships, starting with: (1) the Innovative Health Initiative (**IHI**), (2) the **ERA4Health** - Fostering a European Research Area for Health Research, as well as (3) the European Partnership on **Personalised Medicine** and (4) the Partnership 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 SMEs** and European Open Science Cloud (**EOSC**). Finally, to ensure the 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, data and robotics**. These initiatives, and others with potential for collaboration, are listed in annex 1.

The European Rare Diseases Research Alliance 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 European Rare Diseases Research Alliance will namely build synergies with Horizon Europe initiatives, such as the European Innovation Council (**EIC**), the Marie Sklodowska-Curie Actions (MSCA); and Missions, in particular the **Cancer Mission**. The Partnership will also develop specific synergies with the **EU4Health** and the **Digital Europe** Programmes. Other EU support schemes such as the European Social Fund Plus (**ESF+**), the invest in education, employment and social inclusion (**InvestEU**) and the European Regional Development Fund (**ERDF**) will also systematically be considered to develop the best uptake and development of the European Rare Diseases Research Alliance activities. Several EU programmes and projects have been pre-identified for potential collaboration (see annex 1).

In addition to EU-funded partnerships and programmes, collaboration will also be developed with overarching European or international major initiatives such as the Rare Disease Moonshot launched in December 2022 or the Together4Rare initiative. Collaboration with non-for-profit organisations and charities who are paving the way in RD research collaboration will also be sought.

6.3. Specific Objectives[6] of the European Rare Diseases Research Alliance

6.3.1. Specific Objective 1: Generation of knowledge and its translation into medical and holistic intervention

6.3.1.1. Challenge

The journey from bench to bedside should be accelerated thanks to the generation of knowledge and its translation into medical and holistic intervention, but still faces the following challenges:

Insufficient support of RD research

More than 90% of RDs are not properly addressed in terms of research and accompanying sustainable R&I funding. From the scientific perspective this includes lack of knowledge of the underlying molecular disease cause, pathophysiology, lack of disease models and potential therapeutic targets within a disease/ disease group hampering diagnosis and development of suitable treatment options. From the funding perspective, the high risk-to-investment return ratios for private companies discourages their engagement in RD therapeutic development, and concomitant lack of alternative R&I pathways to the patient slows down the journey from the bench to bedside. A streamlined and optimized, jointly driven public-private pipeline is needed, supported by powerful data management.

Need for more innovative RD research models

One disease - one treatment equation is not a viable option for 7000 rare diseases. Standard research in common disease conditions explores cell, tissue and animal work in individual disease states in comparison with health, to identify disease pathways and potential therapeutic targets. In RDs very small numbers of patients affected with individual rare diseases make the use of such standard clinical development pathways often impracticable. Specific approaches and linked research infrastructure are not currently in place to explore innovative options like studying groups of RDs with common underlying pathophysiology, or decentralized studies leveraging on telemedicine, remote outcome evaluation, and data science, to expedite the research yield and identify new therapeutic agents or re-purpose existing therapies.

Dysfunctional regulatory components

On one hand, the generation of regulatory-compliant research results, and thus the translation and uptake of academia-driven research, is often compromised by lack of timely regulatory advice and interaction beforehand with regulators. On the other hand, there is a need to engage and boost regulatory science to provide a robust, more digital framework and accelerate implementation of novel technologies, innovative trial design or the use of Real-World Evidence (RWE) in study design and development.

6.3.1.2. Scope

To address the above challenges and enable accelerated translation of knowledge into health interventions and other services, under this specific objective the Partnership will enable patient-need led relevant science by providing a RD research

[6] Specific Objectives correspond to the outputs (direct results of the project) and outcomes (short/medium term effect of the projects results) that the European Rare Diseases Research Alliance aims to achieve.

support pipeline from basic research to clinical trial readiness. To better target underserved RDs activities it will investigate mechanisms underlying disease and disease progression, biomarkers and identification and validation of other tools to promote prevention, inform development of treatments, diagnostics, and other innovative healthcare solutions. Attention will be paid to Social Sciences and Humanities research to better understand the impact of rare diseases and the potential benefit of new interventions. Furthermore, the Partnership will explore research/diagnostic/therapeutic/data science approaches for multiple diseases with common aetiology/pathway/other characteristics, taking account of their impact on regulatory requirements and processes.

The integration across value chain will be addressed by combining research financed and performed by both public and private stakeholders and involving patients. This coupled with effective support services including state-of-the-art data infrastructure (SO2) and research pipeline coordination will directly boost innovation in rare disease diagnostics, therapeutics and other interventions such as prevention. The Partnership will aim to unite and strengthen the research ecosystem by creating infrastructures that address connectivity and maximize various public and private resources to support all steps of R&D, from discovery to late development, to post-marketing obligations and backtranslation. Thereby, the Partnership will increase reproducibility of results and accelerating discovery, translational research and development.

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. The Partnership will aim to support processes from preclinical to late development considering regulatory requirements. It will support development, regulatory acceptance, upscaling and deployment of innovative clinical trial methodologies (pooled design and analysis methods, AI, use of different sources of evidence, including RWE, data necessary to inform reimbursement decisions) for small and very small populations. Attention will be paid to demonstrate the value of new methodologies to standardize and benchmark them against existing regulatory and HTA evaluation and approval processes to help adapting them to rare disease specificity and engage regulatory acceptance.

Activities under this specific objective will be enabled by and will inform those of Specific Objective 2 (Data). Deployment of new methodologies in research, regulatory and HTA practice and health practice will rely on supportive activities under Specific Objective 4 (Capacity building). The integration of public and private resources into one research support pipeline will contribute to the strategy of Specific Objective 5 (Integrated multinational and multi-stakeholder R&I ecosystem for RDs).

6.3.1.3. Potential Outputs

- RD funding programme based on long-term (*7* years) funding commitment and robust prioritization strategy.
- At least *167M€* in invested in RD research, including on the impact of RD on patients, families and society.
- *16M€* invested in projects using secondary use of clinical data and reuse of research data for RD prevention, earlier diagnosis, treatment, and mitigating impact on the life of people living with a rare disease.

- All funded projects accompanied by sustainable and integrative support services to accelerate the development-ready research and to guarantee generation of exploitable output.
- Functional RD research funding accelerator hub[7] ensuring smooth transition and support all along value chain to expedite research results into products. Fully integrated and mutually synergistic non-clinical & clinical trial readiness RD research pipeline (including Clinical Research Network).
- The capacity of relevant clinical expertise coupled to methodological excellence exploited in coordination with regulators/HTA, to support evidence-based research accelerating the entry into market for the patient benefit.

6.3.1.4. Specific Outcomes

- Higher number of successful basic research projects transitioning to preclinical development.
- Increased number of academic projects transitioning to industrial development in the EU.
- Public Early-stage investment coordinated with later stage investment by private sector and philanthropy.
- Better and faster integration of novel technologies and methodologies along the RD healthcare pathway with a focus on specific subareas such as diagnosis, devices, trial readiness and integrated care.
- Increase in number of RD cases with a diagnosis.
- Increased integration of RD research and care.
- Increased number of investigational medicinal products implemented into clinical research and developed in Europe.

6.3.2. Specific Objective 2: Healthcare and research data are accessible, and used, for scientific and regulatory evaluation and healthcare delivery

6.3.2.1. Challenge

Projects and initiatives such as the EJP RD, JRC, ERICA, ERNs, RD-Connect, Darwin, C-Path, and Solve-RD, together with ELIXIR, 1+MG, BBMRI-ERIC, EOSC, and EHDS are gradually providing the foundations of a powerful, standards-based European RD data ecosystem. Herein, the RD community embraced the FAIR principles [Wilkinson et al.] to optimize how data can be used to reach tangible results.

[7] The acceleration hub aims at promoting innovation, encourage collaboration, and support the translation of scientific discoveries into real-world applications that benefit society. As a collaborative and interdisciplinary service, it brings together researchers, entrepreneurs, investors, and other stakeholders to accelerate the development and commercialization of scientific and medical innovations. It offers a range of resources and services, such as funding, mentorship, access to specialized equipment, training, networking opportunities, and regulatory guidance, that help researchers and entrepreneurs move their ideas from the laboratory to the market more quickly and efficiently. . Within the European Rare Diseases Research Alliance, the acceleration hub will have a large scope including, but not limited to, biotechnology, drug development, medical devices and digital health, and will leverage on its public-private collaborations.

Nevertheless, the full potential of healthcare and research data for research, innovation, regulatory purposes, and healthcare delivery in the RD domain remains untapped to significant extent. There are major challenges regarding the awareness and integration of the accessible resources and the skills to fully exploit the data ecosystem. Challenges include planning studies that use data from multiple sources, analysing and interpreting data from such studies (e.g., by explainable AI and interdisciplinary collaboration), and translating insights from data research into actionable results e.g., treatments for individuals, clinical guidelines, development of drugs and devices, increased technology readiness, and improved HTA and reimbursement decisions. Increasing the capability of data producers in applying standards for accessibility, quality and interoperability of data is still a challenge. Full exploitation of data for the global objectives depends on widespread adoption of these standards.

6.3.2.2. Scope

The Partnership will aim at strengthening selected ongoing and new actions to harness opportunities that well-managed healthcare and research data present for rare diseases. Opportunities include qualifying data pertinent to innovation for regulatory purposes, optimizing clinical trial readiness within the EU Clinical Research Network, RD diagnosis in EU wide initiatives (e.g., EU-wide undiagnosed program), understanding RD impact and burden, and exploiting patient-centred outcomes.
The European Rare Diseases Research Alliance will support the generation, pooling, integration and sharing of high-quality and interoperable RD data in an expanding ecosystem of distributed FAIR data sources, building on existing infrastructures encompassing the European Platform on Rare Disease Registration, the EJP RD Virtual Platform network, RD-Connect, and services not specific for RD (e.g., BBMRI-ERIC and ELIXIR). It promotes advanced data analysis and data interpretation methods and approaches that exploit this ecosystem. Approaches are as federated as possible and as centralised as needed to enable robust and flexible data use scenarios that promote collaboration among European countries and stakeholders, facilitate research, innovation and regulatory qualification of data, as well as better translate into tangible healthcare benefits for RD patients, contributing thus to the SO5.
The Partnership will also support the development of data-driven computational tools, statistical and artificial intelligence methods, as well as digital solutions to understand the diseases progression, to solve undiagnosed RD cases and implement new clinical studies/trials designs for small populations, this will be enabled by and will inform the activities of the Specific Objective 1. The involvement of RD patients and clinicians is essential to ensure that advanced computational data access, analysis and modelling tools are being developed, considering user needs, utility and sustained exploitation early on, with patient's health outcome improvement being the key driver. This will rely on supportive activities of SO3 and SO4 for patients' empowerment and capacity building of RD stakeholders.
Advancing RD data standards, harmonising data access services and deploying high performance data analysis capacities will be promoted within the Partnership in coordination with the activities of the SO5, through the collaboration with existing national, EU and international data initiatives and infrastructures.

6.3.2.3. Potential Outputs

- Exploitation of FAIR repositories of clinical and omics RD data on a European scale, extending to Patient Reported Outcome Measures (PROMs), longitudinal real-world observations, streaming data, and data from wearables.
- An EU-wide undiagnosed programme based on the effective detection of undiagnosed RD patients in national health systems and on an infrastructure of FAIR reference data (phenomics, genomics, multi-omics, etc.).
- A comprehensive data infrastructure based on FAIR principles, existing resources, data protection regulation, and quality standards including validated Patient Centred Outcome Measures (PCOMs) to support patient-centred research, as well as regulatory and HTA decision making.
- Promoting the regulatory qualification of RD data with the goal of accelerating the development and access of therapies, and measurements or methods that aid therapy development across rare diseases.
- A FAIR data-based framework exploiting patient-driven health and socioeconomic studies to inform policy decisions.
- Widespread use of data-driven computational tools and models, artificial intelligence methods and digital solutions that exploit the FAIR data ecosystem to advance trial readiness, to solve undiagnosed RD cases, to understand disease progression, develop and validate clinically meaningful trial outcomes, and implement innovative clinical study/trial designs for small populations.
- Collaboratively developed knowledge platform for open access, dissemination and sharing of scientific knowledge, including negative results and data.
- Data standards for making new types of data elements FAIR, including real world observations and evidence, patient reported outcomes, and data required to satisfy regulatory requirements.
- Demonstrations of the value of a critical mass of FAIR data for secondary use of clinical data and reuse of research data for RD prevention, earlier diagnosis, treatment, and mitigating impact on the life of people living with a rare disease.

6.3.2.4. Specific Outcomes

- Improved RD diagnosis (higher diagnostic yield, earlier diagnosis) through FAIR data use.
- Support for symptomatic patients without a satisfactory diagnosis.
- Improved trial readiness and therapeutic options through FAIR data use.
- Accelerated development of therapies across rare diseases, facilitated through regulatory-grade data that are FAIR for analytics supporting RD characterization.
- Increased accuracy of diagnosis and individualised treatments from clinical decision support using advanced data driven methodologies/analytics.
- Reduced time-to-use of therapeutic solutions in a clinical context by advanced data driven methodologies/analytics.
- Increased availability and usability of RD innovation.

- Demonstrated added value of digital health tools for RD.
- Researchers, patients and clinicians are increasingly re-using and sharing RD data to implement multinational research for delivering new concepts in RD pathophysiology, new diagnostics, novel drug targets, biomarkers and new disruptive approaches for clinical research.

6.3.3. Specific Objective 3: All activities empower, as equal partners, people living with rare disease

6.3.3.1. Challenge

Research on RD should create value first and foremost for patients. People living with a RD are often the most motivated stakeholders to make progress on their disease given the number of patients living with the disease is low and that knowledge, expertise and funding are scarce. At the same time, patients and carers are often a significant source of expertise related to individual rare diseases. Only by harnessing patient expertise, together with clinical and research expertise, can we address the challenges posed by RD.
Although patient engagement is recognised as a cornerstone of the RD ecosystem, obstacles remain to genuine and significant involvement of patients in research. More specific challenges arise for the 'undiagnosed' and ultra-rare diseases, where collaboration across sectors and geographic borders is indispensable but where research activity lacks scale and visibility among patients who would like to participate. Resources are not targeted to research on RD with the highest unmet needs and access for patients to interrogate limited existing research sources is not eased. Patient involvement is not systematic and/or capitalised on to generate data that support decisions making by regulators or payers.
Furthermore, there is currently insufficient patient participation at all levels of research to enable productive and sustainable partnerships between researchers and patients. This includes incentives (funding, regulatory) to enable equitable inclusion of Patients Living With a Rare disease (PLWRD) and/or representatives from the earliest point of research or participation of patients/patient organisations as co-designers of research. Coordinated cooperation in the development of the RD disease specific patient-centred outcome measures (PCOMs/PROMs), consideration of patient preferences, and co-development of Real-World Evidence (RWE) must also be stimulated. Thus, an organized framework for patient involvement in research, building upon what has been initiated by the EJP RD, is required to systematically support patient-centred research and deliver new innovations.

6.3.3.2. Scope

The European Rare Diseases Research Alliance will provide an inclusive pathway and adequate resources to empower PLWRD and/or representatives as equal partners. PLWRD will be involved at all levels of governance and execution of the European Rare Diseases Research Alliance, with training or induction as necessary. A structured, flexible and coherent framework for patient engagement in research will be developed which will be adaptable at national levels and will promote best practices, re-using and extending existing resources (such as PARADIGM, EJP RD PENREP[8], etc.).

[8] The EJP RD PENREP, Patient Engagement in Biomedical Research Project, working group is composed of

Patients and/or representatives will be active and equal partners in planning and prioritising research activities, engaging in projects and facilitating patient engagement across all research activities, encompassing implementation, monitoring and dissemination of projects' results.
Training for patients/patient representatives will be provided on a continuous basis to ensure and accelerate their informed engagement at all levels. Patients will also have a role in identifying training needs for researchers and clinicians working with people with rare diseases, so that training on patient involvement in research will be provided to funded projects.
Novel and more inclusive funding models will be developed to ensure sustainable patients' involvement in research projects and to ensure that availability of funding is not a barrier to patient participation at a national/regional level. PLWRD will be engaged in decision-making on the allocation of funding to research projects (including evaluation and monitoring).

The European Rare Diseases Research Alliance also aims to reduce inequities between different types of RD by targeting underserved RDs through meaningful empowerment, engagement, and leadership of patients or their advocates, building new or expanded networks and supporting dedicated research.
In developing this inclusive pathway, the ERDERA will take advantage of the existing infrastructures like Patient Advocacy Organisations (agnostic or RD specific), RD Patient National Alliances, the ERNs and their European Patient Advocacy Groups (ePAGs), charities, etc.

6.3.3.3. Potential Outputs

- Patient-informed decision making, on which unmet needs to investigate and prioritize in research is made.
- Patient representation in all governance structures within the European Rare Diseases Research Alliance.
- Patients/patients' representatives involved in all research applications and on steering/governing committees of all funded RD studies.
- Effective patient partnerships enabled through dedicated funding of patient organisations contributing to research projects.
- Agreed mechanisms to feedback research results in a consistent and systematic way to relevant patient groups.
- Awareness and adequate signposting of the infrastructures and resources available to support and guide patients in the RD Research landscape.
- Patient empowerment through capacity building and training activities resulting in proactive patient partnerships in research.
- Increased knowledge within PLWRD to further understanding of rare diseases.
- The training on patient involvement in research is coupled to every funded research project.

patients' representatives and research funders who aims to encourage fruitful, sustainable and enduring partnerships between scientists and patient organisations, co-leading the way for systematic patient-centred research.

- PCOMs/PROMs co-developed by PLWRD and applied across all relevant funded research and all 24 ERNs.
- Guidelines developed to support equitable patient inclusion to inform researchers, regulators and funders at the national and European levels.

6.3.3.4. Specific Outcomes

- Increased participation of patients/patient organisations as co-designers of research Innovative and disruptive approaches in funding and developing patient-centred research benefitting the whole health research ecosystem.
- Patient voices are considered when deciding about research priorities and strategies.
- A greater sense of shared ownership of the research process/outcomes.
- Trusted relationships to access resources, expertise and the support required to translate research into positive health impact.
- A better understanding of the real needs and preferences of patients informing research questions and driving new design interventions.
- Healthcare solutions assessed according to criteria that matter to patients and public contributing to achieving people-centred healthcare.
- Building legal requirements for equitable inclusion in all levels of engagement in research.

6.3.4. Specific Objective 4: Increased capacity and skills of RD stakeholders to optimise research to healthcare continuum

6.3.4.1. Challenge

The capacity building element is often underestimated when considering the long-term strategy for building strong rare diseases ecosystem. Despite several efforts deployed by the EJP RD, ERNs or EURORDIS to provide a wide range of knowledge sharing, training and educational activities for RD research stakeholders, there is still an unmet need for an integrated concept combining systematic and comprehensive knowledge transmission with targeted acquisition of specialized skills in order to increase the EU's RD research capacity in an efficient and sustainable manner.
Both raising new generations of RD researchers/clinical specialists/patient experts and continuous acquirement of new competences by RD stakeholders are main challenges augmented by fragmentation and lack of sustainability of existing training and education programmes. This is even more evident at national level where specialised curricula are incomplete or simply do not exist and the sharing of available knowledge is slowed down due to the language barriers. Furthermore, efficient capacity building is hampered by the absence of a central knowledge hub allowing on the visibility of existing expertise and contributing to better alignment of efforts deployed under different initiatives (including the bottom-up funding programmes of the European Commission that generate important volume of RD-related projects).

6.3.4.2. Scope

The Partnership will incorporate capacity building activities as **integral part of the rare disease research pipeline.** Alignment with the knowledge generating actions of the

initiatives (ERNs, C4C, STARS, etc.) will be sought. This will enable, on one hand, upgrading of scientific, technology (including FAIR approaches) but also regulatory knowledge of stakeholders participating in research projects financed through competitive calls but also those performing "in house" research activities as part of the Clinical Research Network of the European Rare Diseases Research Alliance. On the other hand, new generations of RD researchers will be equipped with state-of-the-art competences. Young researchers will be given the opportunity to train during interdisciplinary liaison programmes and secondment coupling clinical and non-clinical activities.
To unlock the access to RD top-level education to all, the Partnership will develop an accredited, comprehensive online education programme taking stock of highly performing pre-existing modules complemented by novel training units.
The model of "train the trainer" and innovative language AI technologies will be used to expand and deliver capacity building programmes in all countries participating in the Partnership.
Finally, the Partnership will provide a central platform for knowledge sharing by gathering and enabling access to relevant expertise (comprehensive catalogue & helpdesk) and ensuring connection with all existing RD projects and initiatives. This will provide novel opportunities for collaboration, improve the visibility of RD stakeholders and optimise the use of resources by enhancing the performance of previously disconnected activities.

6.3.4.3. Potential Outputs

- All researchers in funded projects have access to suitable training courses/certification.
- European Master graduation programme enabling training of new generations of RD researchers.
- RD stakeholders empowered and mastering methodologies required to generate and use good-quality data according to European standards.
- Increased participation of researchers from under-represented countries in education/training programmes.
- Train-the-trainer programmes enabling capacity building at national level, including under-represented countries.
- Central knowledge hub enabling mapping and access to existing expertise, resulting in improved knowledge transfer and forging new collaborations.

6.3.4.4. Specific Outcomes

- A new generation of researchers trained in transdisciplinary, patient-centric RD research interconnected with clinical care.
- The EU equity among countries for RD capacity building is increased.
- National/regional training and education programmes are aligned with European standards.
- Increased awareness of RD stakeholders of the needs of translational and clinical RD research.
- The EU RD capacity building is increased.

6.3.5. Specific Objective 5: Integrated multinational and multi-stakeholder Research & Innovation ecosystem for RD

6.3.5.1. Challenge

In the field of rare disease research (e.g., RD diagnostics, therapeutic development, trial readiness networks) cross-national, cross-disciplinary, cross-sectoral and multi-stakeholder collaboration lays the ground for scientific and technological progress that translate in innovative and relevant research results and improvements of care. However, the opportunities for integrating the different national, European and international collaboration in the diverse areas along the healthcare pathway have not been fully harnessed yet. The challenge can be divided around four main axes:
(1) Multi-stakeholder collaborations that still suffer from insufficient number of effective public-public and public-private collaborations that are translated towards application, due to lack of trust to open every tool to the most effective type of collaboration, backed by lack of awareness of needs of other actors in R&I value chain and persisting gaps in the funding pipeline. This includes also lack of a structured and continuous dialogue among regulatory agencies, payers and developers on common challenges.
(2) National-EU-international alignment, especially operative integration of national capacities as part of a multinational ecosystem. This involves lack of suitable governance models and federated solutions enabling data access/visiting across different data sources in different countries or of sustainable models for the collection of RWE and data on burden of disease (including societal costs), closely linked to the Specific Objective 2; but also insufficiently coordinated policies and R&I funding for RD in multiple countries.
(3) Collaboration between existing projects/programmes or initiatives that is subject to fragmentation and duplication of efforts which translates into lack of sustainability and innovation drop rate in EU.
(4) Participation and visibility of under-represented countries.

6.3.5.2. Scope

To address the above-mentioned challenges the Partnership will break the silos between communities by consolidating the already existing strong community, currently mostly consisting of public sector researchers, research infrastructures as well as RD patients and representatives, and stepping-up the integration of underrepresented perspectives, namely the industry, regulatory bodies and payers. This will be reflected by relevant governance and advisory structures but also overall Partnership organisation to ensure coherence and maximise impact of all actions. Contribution to RD Moonshot objectives will be essential. Furthermore, through dedicated onboarding mechanisms, the European Rare Diseases Research Alliance will gradually bring in 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 and beyond. The integration of the Scientific Secretariat of IRDiRC will be key to 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.
The proposed European Rare Diseases Research Alliance will also catalyse the transfer of good practices to the national and regional level, including leveraging the power of national/European resources, making them 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 European Rare Diseases Research Alliance and other relevant RD stakeholders.

By default, the Partnership will build on previous and currently operating actions in the RD field such as EJP RD, Solve-RD, ERICA, 1+MG, EHDS or the forthcoming JA on ERNs to help leverage the existing capacities. It will also ensure close alignment and (when possible) joint activities with other Horizon Europe partnerships (e.g., IHI, EIT Health, Innovative SMEs, ERA4Health and partnerships on Personalised Medicine and Healthcare Systems) as specified in the Synergies with other initiatives section.

6.3.5.3. Potential Outputs

- Structured and enabling environment for multistakeholder and multinational governance and consultation upstream (researchers, industry, patients, regulators), to define common and concerted objectives, considering the constraints of each and aligned with the needs of patients.
- ERDERA used as multistakeholder platform for dialogue to support technical questions, but also social challenges and policy debates linked to RD research (drug regulation, diagnostics, medical devices).
- By end of the Partnership all partner countries have an active National Mirror Group supporting alignment of goals, strategies and shared best practices.
- Efficient mechanisms to identify, onboard and deploy high value (national) resources, services and tools that are valuable to the RD community.
- Effective transcontinental collaboration through integration of IRDiRC recommendations, accessibility to European Rare Diseases Research Alliance resources and shared research, clinical and development opportunities.
- Set-up complementarities and synergies with other relevant programmes and initiatives.
- Integrative solutions and research pipelines for RD subareas such as diagnosis or trial readiness that integrate and leverage the existing European and national RD research actions.
- Structural involvement of regulatory bodies (medicines, diagnostics, reimbursement agencies) in all actions involving research.
- Enable novel collaborations between funders, regulators, payers, and other sectors through provision of frameworks and models for multi-stakeholder collaboration.
- Improved trial readiness of clinical research sites.

6.3.5.4. Specific Outcomes

- RD patient benefits from research results that were enabled through the multi-national and multi-stakeholder Research & Innovation ecosystem for RD.

- National resources and capacities are supported, optimised and fully integrated in the overall RD ecosystem and their use maximised for the benefit of people living with rare diseases.
- Sustainable national RD research strategies, aligned with and benefiting from EU and international collaborations in all participating countries.
- Successful implementation of transcontinental collaboration.
- Improved coordination of EU initiatives and enhanced EU leadership in RD field.

6.4. Performance Indicators

These Performance indicators are designed to measure the outputs, the outcomes of the European Rare Diseases Research Alliance Objectives (General Objectives, Specific Objectives, Operational Objectives).

European Partnership [European Rare Diseases Research Alliance]			**Monitoring and evaluation framework**, version1 [18/09/2023]		
Overall vision: 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.					
Objectives		**What is a measure of success?**	**Which is the data source | and methodology used** [project data, study, ….] **| Unit of measurement**	**Who is responsible for monitoring and providing the data/ information When will it be collected?**	**Baseline and target**
General objectives (linked to impact indicators)	GO1	Rate of diagnosed rare diseases cases	CRN & national RD diagnostic centres (Standard annotations (e.g., through 'semantic tags' for diagnosed and undiagnosed) | The increase of acceleration of undiagnosed cases | (measured percentage)	**Responsible:** CRN diagnostic research leaders (WP6-8) & Monitoring task leaders in coordination with national RD diagnostic centres. **Assessment frequency:** Y3 and Y7.	**Baseline:** 10-12,5% increase in (genomic) diagnostic rate**. Target: Y3:** 15%. **Y7:** 20%
	GO1	Time to diagnose patients with a rare disease.	ERN registries | Improvement in the time to diagnoses of patient seeking medical attention for an unknown condition | qualitative	**Responsible:** Data Services Hub, Monitoring task leaders. **Assessment frequency:** Y7/Y10.	**Baseline:** 4 years. **Target: Y7:** Time to diagnose decreases . **Y10:** Time to diagnose decreases
	GO2	New therapies approved for rare diseases	ERDERA publications, surveys; clinicaltrial.gov, EudraCT, FDA & UK(MHRA) reports and Databases, Orphanet | Number of new therapies where ERDERA resources (Human expertise, developed tools, etc.) are/have been involved, as reported by the ERDERA partners and connected initiatives | Number (new therapies approved for rare diseases)	**Responsible:** ERDERA monitoring task leaders & reporting system. **Assessment frequency:** >7Y (Y10).	**Baseline**: number of existing RD therapies (as in Orphanet 2023). **Target: Y10:** at least 5% of new therapies approved by EMA developed with the support of ERDERA
	GO2	Clinical Trial Readiness	Same as above GO2 indicator | Number of Clinical Trial Applications (CTAs) where	**Responsible:** Task leaders (CRN and RD funding workstreams)	**Baseline:** 0. **Target: Y3:** 5. **Y7:** 10

			ERDERA resources (Human expertise, developed tools, etc.) are/have been involved, as reported by the ERDERA partners and connected initiatives | Number of approved CTAs	and contact-person of the connected initiative (listed in the SRIA annex1). **Assessment frequency:** Y3 and Y7.	
	GO3	Policy changes related to RD burden	NMGs Annual investigations (national plans/ surveys, Reports) | Policy changes refer to modifications made to existing rules, guidelines, or procedures by governments or organizations aiming to improve the assessment and understanding of the impact and challenges posed by Rare Diseases on individuals and society. They involve adjusting methodologies, data collection processes, or criteria to accurately measure and quantify the burden of Rare Diseases, ultimately leading to informed policy decisions and resource allocation. Initiatives are specific actions contributing ultimately to policy changes. The measurement of these will consider only those impacted by ERDERA activities | Number of policy changes or initiatives at local, national, and international levels aimed at addressing the impact of rare diseases on patients, families, and society.	**Responsible:** To be collected annually by the National Mirror Groups. **Assessment frequency:** Y3 and Y7.	**Baseline:** 0. **Target: Y3:** TDB. **Y7:** TBD.
	GO3	Funding for research on the impact of rare diseases in patients, families, and society	ERDERA Funding workstream and In-house research financial & administrative data (managed by the ERDERA call application portal that is part of the monitoring system) | ERDERA funding dedicated to research activities on the impact of RD on patients, families and society | Million €	**Responsible:** ERDERA monitoring task leaders & reporting system in coordination with the RD Funding workstream and In-house research . **Assessment frequency:** Y4 and Y7/Y10.	**Baseline:** Historic data from EJP RD (11.5M€). **Target: Y4:** TDB. **Y7:** increased by 50%. **Y10:** TBD

Specific objectives* (linked to outcome/result indicators)	SO1	Projects outputs translated into innovative RD (research) models/solutions	ERDERA Monitoring and reporting system/ Total number of RD research projects supported by the Partnership (or a previous co-fund on Rare Diseases) resulting in new Clinical Studies, guidelines and patent applications/ Number	**Responsible:** ERDERA monitoring task leaders. **Assessment frequency:** Yearly from year 3.	**Baseline:** 0. **Target: Y3:** 10. **Y4:** 15. **Y5:** 20. **Y6:** 25. **Y7:** 30.
	SO1	Public-private collaborations	Coordination and Management workflow & monitoring and reporting system | Collaborations between academia and for profit and/or non-profit organisations to develop and implement medical and holistic interventions for RD (MoUs/ Letters of intents/Agreements/Pilots) | Number of new collaborations	Responsible: ERDERA Coordination team. Assessment frequency: Y3, Y5 and Y7.	**Baseline:** Historic data from EJP RD (4 collaborations). **Target:** Y3: 5. **Y5:** 10. **Y7:** 18.
	SO2	Access to data sources	ERDERA Data Hub & monitoring | Number of healthcare and research data sources that are onboarded and made available for scientific and regulatory evaluation and healthcare delivery | Number	**Responsible:** Data services Hub. **Assessment frequency:** Every 2 years.	**Baseline:** 20 (resources already onboarded on the EJP RD Virtual Platform). Target: **Y2:** 25. **Y4:** 30. **Y6:** 40.
	SO2	Use of data sources	ERDERA Data Hub & monitoring system | increase of access to research data sources through the Virtual Platform | %	Responsible: Data services Hub Work Packages leaders. Assessment frequency: Yearly.	**Baseline:** Number of VP Access at the end of EJP RD. **Target: Y0:** +5% **Y1:** +5%. **Y2-Y5:** +10% every year . **Y6-Y7:** +5% every year
	SO3	Capacity building of RD patients	Training activity surveys & monitoring system | Number of patients empowered, within the Partnership, through capacity-building and training activities related to research | Number patients participated at training activities per year	**Responsible:** Workstream Education and Training leaders & PPIE. **Assessment frequency:** Yearly.	**Baseline:** Historic data from EJP RD : 350 per year. **Target:** Y1-Y7: 2500-3000 every year
	SO3	Patients involved in RD funded projects	Funding workstream reports; Project reports; & monitoring system | Percentage of funded research projects that involve patient organisations as co-designers. | Percentage	**Responsible:** RD funding Workstreams leaders & PPIE. **Assessment frequency:** Yearly.	Baseline: Historic data from EJP RD: 60%. **Target: Y1:** 70%. **Y2:** 75. **Y3:** 80%. **Y4:** 85%. **Y5:** 90%. **Y6:** 95%. **Y7:** 100%

	SO4	Transdisciplinary training programmes as part of the RD research educational pipeline	Data & Reports from Workstreams Education and Training & Inter(National) Capacity Alignment workstream & monitoring system | Number of transdisciplinary research training programs developed and implemented at the European level | Number	**Responsible:** Workstream Education and Training leaders. **Assessment frequency:** Year 3, 5 and 7.	**Baseline:** 15 transdisciplinary programmes in EJP RD. **Target: Y3:** 60. **Y5:** 120. **Y7:** 180
	SO4	Alignment of capacity and skills at national / local level	Data & Reports from Workstreams Education and Training & Inter(National) Capacity Alignment workstream & monitoring system | Number of national/local training and education programs aligned with ERDERA (at least 1 training per Country; 37 Countries) | Percentage	Responsible: Education and Training & Inter(National) Capacity Alignment leaders. Assessment frequency: Y3, 5 and 7.	**Baseline:** 0. **Target: Y3:** 4%. **Y5:** 50%. **Y7:** 100%
	SO5	National RD research and Innovation Integration	Coordination and Management workflow & monitoring system / Number of countries with national RD research strategies aligned with EU and international collaborations supported by the Partnership | Percentage	**Responsible:** Coordination team & International Alignment Workstream leaders & NMGs. **Assessment frequency:** Y3, 5 and 7.	**Baseline:** 0. **Target: Y3:** 10. **Y5:** 30. **Y7:** 50.
	SO5	ERDERA RD research and Innovation synergy with other programs	Coordination and Management workflow & monitoring system | Number of complementarities and synergies established with other relevant programmes and initiatives | Number	**Responsible:** Coordination team & International Alignment Workstream leaders. **Assessment frequency:** Y2, 4 and 6.	**Baseline:** 0. **Target: Y2:** 2. **Y4:** 5. **Y6:** 7.
Operational objectives* (linked to output indicators)	OO1	Progress towards (financial and in-kind) contributions from partners other than the Union	Funding workstream reports & monitoring system / Percentage of contributions achieved out of total commitments made by the partners other than the European Commission at the beginning of the partnership/ Million € i.e., committed vs. actual	**Responsible:** Funding workstream WP and task leaders & coordination team. **Assessment frequency:** yearly .	**Baseline:** in kind and in cash commitment to ERDERA: 167M€ of in cash and 37M€ of in kind. Target: **Y10:** At least initial commitment achieved
	OO1	JTC funding spending for research	Funding workstream reports & monitoring system | Amount of funding provided to researchers through JTCs | Million €	**Responsible:** Funding workstream WP and task leaders. **Assessment frequency:** yearly.	**Baseline:** 26,5 M€ committed for the 1st year of ERDERA. **Target: Y7 :** 76,8 M€

	OO2	Integrated Data Service's infrastructure	ERDERA Data-Hub, monitoring system & coordination and Management workflow / Services provided by the integrated data infrastructure/ Number	**Responsible:** Data Service Hubs WP and task leaders, and Coordination team. Assessment frequency: yearly.	**Baseline:** 0. **Target: Y1:** 30. **Y2:** 50. **Y3:** 70. **Y4:** 90. **Y5:** 110. **Y6:** 130. **Y7:** 150.
	OO2	Integrated Expertise Service's infrastructure	ERDERA Data-Hub, monitoring system & coordination and Management workflow | Services provided (i.e., ELSI, IPR, regulatory, methodology, etc.) by the integrated expertise infrastructure | Number	**Responsible:** Expertise & Data Service Hubs WP & Task leaders, and Coordination team. Assessment frequency: yearly.	**Baseline:** 0. **Target: Y1:** 20. **Y2:** 25. **Y3:** 30. **Y4:** 35. **Y5:** 40. **Y6:** 45. **Y7:** 50.
	OO3	NMGs created/ functioning	International Capacity Alignment workstream (WPs) reports & ERDERA monitoring system | Total number of NMG operational | Number	**Responsible:** International Capacity Alignment WP and Task Leaders. **Assessment frequency:** Y1 and Y2.	**Baseline:** 4. **Target: Y1:** 14. **Y2:** 31.
	OO3	Interactions/projects with non-EU entities	International Capacity Alignment workstream (WPs) reports & ERDERA monitoring system | Total number of interactions (e.g., good practices, harmonisation)/ projects with International legal entities | Number	**Responsible:** International Capacity Alignment WP and Task Leaders. **Assessment frequency:** yearly.	**Baseline:** 0. **Target: Y1:** 1. **Y2:** 2. **Y3:** 3. **Y4:** 4. **Y5:** 5. **Y6:** 6. **Y7:** 7.
	OO4	Capacity building	Data & Reports from Workstreams Education and Training & ERDERA monitoring system | Number of researchers/stakeholders having benefited from upskilling activities (through training, mobility, and access to infrastructures) | Number	**Responsible:** ERDERA monitoring task leaders in coordination with training leaders & contributors. **Assessment frequency:** yearly.	**Baseline:** Historic data from EJP RD : 2500-3000 per year. **Target: Y1:** 4640. **Y2:** 6285. **Y3:** 8150. **Y4:** 8760. **Y5:** 9360. **Y6:** 9960. **Y7:** 10570.
	OO4	Funding invested into capacity building activities	ERDERA monitoring system & coordination and Management workflow, ERDERA periodic reports | Total Funding committed for training, mobility, and access to infrastructures | Million €	Responsible: ERDERA Coordination team & ERDERA monitoring task leaders. Assessment frequency: yearly.	**Baseline:** Historic data from EJP RD : 6.5M€ (overall budget for Training & education activities). **Target:** Y1-Y7: commitment every year of 1.2M.
	OO5	Expansion to new stakeholders	ERDERA monitoring system & coordination and Management workflow | Number of new stakeholder (by category) involved with	**Responsible:** ERDERA Coordination team & ERDERA monitoring task leaders. **Assessment frequency:** yearly	**Baseline:** 94 beneficiaries in EJP RD, and 152 beneficiaries + 19 associated partners in

			ERDERA after launch | Number by category of stakeholders		ERDERA. **Target: Y1:** +10. **Y2:** +5. **Y3:** +3. **Y4-7:** +1 every year.

7. SRIA Annexes

7.1.1. Annex 1 - European Partnerships, EU Missions, EU Programmes, Projects and Organisations of potential relevance

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
ERA4Health *[EU Partnership _ Health Cluster]*	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 Investigator Initiated Clinical Studies on various health interventions addressing important public health needs.	• The model for establishment and financing of multi-national clinical trials. • Possible joint funding activities on transversal topics
Innovative Health Initiative (IHI) *[EU Partnership _ Health Cluster]*	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 ERDERA, synergies will be sought with them too.	• Joint activity on Accelerator Hub • Alignment with IHI projects related to RD or relevant platforms (e.g., clinical trials, use of data, regulatory aspects)

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
Personalised Medicine *[EU Partnership _ Health Cluster]*	To align national research strategies, promote excellence, reinforce the competitiveness of European players in Personalised Medicine and enhance the collaboration with non-EU countries.	• Data infrastructure • Possible joint calls • Personalised treatment approaches
Transforming Health and Care Systems (THCS) *[EU Partnership _ Health Cluster]*	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).	• Innovative solutions and their integration in healthcare systems • Models for research to healthcare pathway
Artificial Intelligence, data and robotics *[EU Partnership _ Digital, Industry and Space Cluster Cluster]*	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.	• Optimisation of data use through AI technologies (e.g., diagnostics)
High Performance Computing *[EU Partnership _ Digital, Industry and Space Cluster Cluster]*	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 RD data infrastructures

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
Innovative SMEs *[EU Partnership _ Other Partnerships (across other themes)]*	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.	• Joint funding models • Public-private collaboration (Proof of Concepts for RDs) • Optimisation of support for innovative SMEs in the space of RDs
European Institute of Innovation & Technology Health (EIT Health) *[EU Partnership _ Other Partnerships (across other themes)]*	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.	• Joint training activities • Accelerator hub
European Open Science Cloud (EOSC) *[EU Partnership _ Other Partnerships (across other themes)]*	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).	• Optimisation and integration of RD data infrastructure • Expansion of data sources for the benefit of RDs
EU Mission: Cancer	New initiative rooted in Horizon Europe's research and innovation programme to improve the lives of more than 3 million people by 2030 through prevention, cures, and for those affected by cancer and their families, to live longer and better with 4 key objectives: understand cancer and its risk factors; Prevent what is preventable; Optimise diagnostics and treatments; Support the quality of life of people.	• Innovative and holistic research to healthcare pathway models • Possible joint activities (including funding) fostering rare cancers

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
Digital Europe Programme *[EU Programme]*	A new EU funding programme focused on bringing digital technology to businesses, citizens and public administrations.	• Digital tools for the benefit of RD community (diagnosis, RWE, PCOMs, etc.)
European Innovation Council – (EIC) *[EU Programme]*	It aims to identify and support breakthrough technologies and game changing innovations to create new markets and scale up internationally.	• Accelerator hub
EU4Health *[EU Programme]*	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 ERDERA for example: • 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.	• Maximized alignment of funding and activities supporting healthcare (especially ERNs)

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
European Regional Development Fund (ERDF) *[EU Programme]*	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.	• Use of structural funds to support research funding and Clinical Research Network (including facilities/ infrastructure)
European Social Fund Plus (ESF+) *[EU Programme]*	The main EU instrument for investing in people and supporting the implementation of the European Pillar of Social Rights. With a budget of almost EUR 99.3 billion for the period 2021-2027, the ESF+ will continue to provide an important contribution to the EU's employment, social, education and skills policies, including structural reforms in these areas.	• Use of structural funds to support research funding and Clinical Research Network (including facilities/ infrastructure)
Horizon Europe *[EU Programme]*	The EU's key funding programme for research and innovation with a budget of €95.5 billion. The programme facilitates collaboration and strengthens the impact of research and innovation in developing, supporting and implementing EU policies while tackling global challenges. It supports creating and better dispersing of excellent knowledge and technologies.	• RD knowledge hub (sharing of competences and outputs generated by HE funded projects) • Complementary funding
InvestEU *[EU Programme]*	It will provide the EU with crucial long-term funding by leveraging substantial private and public funds in support of a sustainable recovery. It will also help mobilise private investments for the EU's policy priorities, such as the European Green Deal and the digital transition. The programme consists of three components: the InvestEU Fund, the InvestEU Advisory Hub, and the InvestEU Portal. The InvestEU Fund will be implemented through financial partners who will invest in projects using the EU budget guarantee of €26.2 billion. The entire budgetary guarantee will back the investment projects of the implementing partners, increase their risk-bearing capacity and thus mobilise at least €372 billion in additional investment.	• RD knowledge hub (sharing of competences and outputs generated by HE funded projects) • Complementary funding • Accelerator hub

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
Accelerating research & development for advanced therapies (ARDAT) (IMI project, 2020-2025) *[Project or Organisation]*	IMI project which aims at delivering the knowledge, tools and standards needed to speed up the development of Advanced Therapy Medicinal Products (ATMPs).	• Outputs to be integrated into the CRN research strategies
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) *[Project or Organisation]*	Large collaborative European network that aims to facilitate the development of new drugs and other therapies for the entire paediatric population. It is builds capacity for the implementation of multinational paediatric clinical trials whilst ensuring the needs of babies, children, young people and their families are met. It is committed to meeting the needs of paediatric patients thanks to a novel collaboration between the **academic and the private sectors.** **c4c** endeavours to provide a sustainable, integrated platform for the efficient and swift delivery of high-quality clinical trials in children and young people across all conditions and phases of the **drug development process**.	• Contribution to CRN

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
The Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP®) *[Project or Organisation]*	An FDA-funded initiative that provides a centralized and standardized infrastructure to support and accelerate rare disease characterization, with the goal of accelerating therapy development across rare diseases. RDCA-DAP promotes the sharing of existing patient-level data and encourages the standardization of new data collection. By integrating such data in a regulatory-grade format suitable for analytics, RDCA-DAP accelerates the understanding of disease progression (including sources of variability to optimize the characterization of subpopulations), clinical outcome measures and biomarkers, and facilitates the development of mathematical models of disease and innovative clinical trial designs.	• Alignment/contribution to RD data infrastructure
Data Analysis and Real World Interrogation Network (DARWIN EU) *[Project or Organisation]*	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	• Optimisation of RD data infrastructure, especially generation and use of RWE
European Genomic Data Infrastructure *[Project or Organisation]*	The **Genomic Data Infrastructure (GDI)** project is enabling access to genomic and related phenotypic and clinical data across Europe. It is doing this by establishing a federated, sustainable and secure infrastructure to access the data. It builds on the outputs of the Beyond 1 Million Genomes (B1MG) project and is realising the ambition of the 1+Million Genomes (1+MG) initiative.	• Alignment/integration with RD data infrastructure • Re-use of genomic data for diagnosis

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
European Health Data & Evidence Network (EHDEN) *[Project or Organisation]*	IMI project that aims to build a large-scale federated network of data sources standardised to a Common Data Model.	• Optimisation of RD data infrastructure
• **European Health Data Space (EHDS)** • ***[Project or Organisation]***	• 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.	• Alignment and integration of RD data infrastructure as part of the EHDS
• **European Platform on Rare Disease Registration (EU RD Platform)** • ***[Project or Organisation]***	• 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 European Reference Networks, researchers, patients, and policy makers in the common effort to improve diagnosis and treatment for patients living with a rare disease.	• Alignment/ integration with RD data infrastructure • Optimisation of the ERN registries
• **ERICA (Coordination and Support Action under Horizon Europe, 2021-2025)** • ***[Project or Organisation]***	• Builds on the strength of the individual ERNs and create a platform that integrates all ERNs research and innovation capacity.	• Strategic alignment to optimise ERNs research activities

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
GenoMed4ALL *[Project or Organisation]*	The European initiative to transform the response to Haematological Diseases by seizing the power of Artificial Intelligence, pooling genomic/ '-omics' health data through a secure and trustworthy Federated Learning platform. This stakeholder-driven and self-governed initiative aims to support implementation of the FAIR data principles via Global and Open FAIR implementation networks.	• Strategic alignment with RD data infrastructure • Support of FAIR services
Global Alliance for Genomics and Health (GA4GH) *[Project or Organisation]*	The Global Alliance for Genomics and Health fosters common technical standards, seeking to enable responsible genomic data sharing within a human rights framework.	• Two-way alignment for data standards
Gaia-X *[Project or Organisation]*	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.	• Optimisation of the whole European Rare Diseases Research Alliance structural models and processes
Orphanet Data for rare Diseases (OD4RD) – Direct Grant *[Project or Organisation]*	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	• Alignment/integration with CRN activities
Patient Focused Medicine Development (PFMD) *[Project or Organisation]*	Not-for-profit collaborative initiative benefiting patients and health stakeholders by designing a patient-centred health care system with patients and all stakeholders.	• Contribution to CRN activities

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
Rare Disease Moonshot *[Project or Organisation]*	A coalition of public and private partners joining forces to accelerate scientific discovery and drug development in rare and paediatric diseases for which currently there is no therapeutic option. By fostering greater collaboration and improving the sharing of data and knowledge, they aim to accelerate clinical development of new solutions for adults and children living with rare conditions by developing novel clinical trials designs, enhancing data infrastructures and trial networks and defining processes adapted to very small populations.	• Strategic alignment • Public-private partnerships
Screen4care: Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies (IMI project, 2021-2026) *[Project or Organisation]*	IMI project that aims at shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies	• Integration of outputs into the diagnostic pathway models of CRN
Together4RD *[Project or Organisation]*	A multi-stakeholder alliance supporting ERNs to collaborate with stakeholders, particularly with the pharmaceutical industry, to pursue opportunities that will address unmet medical needs of people living with rare diseases, in areas such as basic to translational research, clinical trials for rare & ultra-rare conditions, testing and accelerating innovative approaches to diagnosis, development and implementation of data/evidence generation initiatives.	• Strategic alignment for public-private collaboration with ERNs

Initiative [Type of initiative]	**Objectives**	**Pre-identified synergies (non-exhaustive)**
Towards the European Health Data Space - Joint Action (TEHDAS JA) *[Project or Organisation]*	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	• Use of outputs to improve RD data (use and reuse) models
X-eHealth *[Project or Organisation]*	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.	• Alignment with CRN activities

7.1.2. SRIA list of abbreviations

AI	Artificial Intelligence	JA	Joint Action
c4c	connect 4 children	JRC	Joint Research Centre
CRN	Clinical Research Network	JTC	Joint Transnational Call
EC	European Commission	MSCA	Marie Sklodowska-Curie Action
EHDS	European Health Data Space	NMG	National Mirror Group
EIC	European Innovation Council	OO	Operational Objective
EIT	European Institute of Innovation & Technology	PCOM	Patient Centred Outcome Measure
EJP RD	European Joint Programme on Rare Diseases	PENREP	Patient Engagement in biomedical Research Project
EOSC	European Open Science Cloud	PLWRD	Patient Living With a Rare Disease
EOSC	European Open Science Cloud	PROM	Patient Reported Outcome Measure
ePAG	European Patient Advocacy Group	PSIP	Partnership Specific Impact Pathway
ERDERA	European Rare Diseases Research Alliance	R&D	Research and Development
ERDF	European Regional Development Fund	R&I	Research & Innovation
ERICA	European Rare Disease Research Coordination and Support Action	RD	Rare Diseases
ERN	European Reference Network	RWE	Real-World Evidence
ESF+	European Social Fund Plus	SDG	Sustainable Development Goal
EU	European Union	SME	Small and Medium Enterprise
FAIR	Findable Accessible Interoperable Reusable	SO	Specific Objective
GO	General Objective	SRIA	Strategic Research and Innovation Agenda
HTA	Health Technology Assessment	THCS	Transforming Health and Care System
IHI	Innovative Health Initiative	UN	United Nations
IMI	Innovative Medicines Initiatives	US	United States
IRDiRC	International Rare Diseases Research Consortium		