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Terms and definitions

Formal learning takes place in the education and training system, in universities, and leads to a certification or a vocational qualification, which can be obtained also through an apprenticeship.

Non-formal learning is an intentionally chosen learning that takes place outside the formal education and training system. It takes place in any organisation with educational and training purposes, also in voluntary bodies, national civil service organizations, organisations of the private social sector or enterprises.

Informal learning refers to activities carried out in every-day life, at work, at home and in leisure time, even without an intentional choice.
[Council of Europe, available at: https://www.coe.int/en/web/lang-migrants/formal-non-formal-and-informal-learning].

Widening countries: Widening actions under the Spreading Excellence and Widening Participation part of Horizon 2020 address the causes of low participation by fully exploiting the potential of Europe's talent pool. The Member States eligible for Widening support in H2020 are Bulgaria, Croatia, Cyprus, Czechia, Estonia, Hungary, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia and Slovenia. The Associated Countries currently eligible for Widening support are (subject to valid association agreements of third countries with Horizon 2020): Albania, Armenia, Bosnia and Herzegovina, Faroe Islands, The Republic of North Macedonia, Georgia, Moldova, Montenegro, Serbia, Tunisia, Turkey and Ukraine. https://ec.europa.eu/programmes/horizon2020/en/h2020-section/spreading-excellence-and-widening-participation.

R&D intensity for a country is defined as the total R&D expenditure as a percentage of gross domestic product (GDP). ec.europa.eu/eurostat.
EU-15 countries (EU Member States before 1 May 2004) and EU-13 countries (EU Members after 2004).

List of abbreviations

CoE – Center of Expertise;

Country codes: EU - AT (Austria), BE (Belgium), BG (Bulgaria), CY (Cyprus), CZ (Czechia), DE (Germany), DK (Denmark), EE (Estonia), EL (Greece), ES (Spain), FI (Finland), FR (France), HR (Croatia), HU (Hungary), IE (Ireland), IT (Italy), LT (Lithuania), LU (Luxembourg), LV (Latvia), MT (Malta), NL (the Netherlands), PL (Poland), PT (Portugal), RO (Romania), SE (Sweden), SI (Slovenia), SK (Slovakia); other - NO (Norway), IN (India), TK (Turkey), AM (Armenia), GE (Georgia), RS (Serbia), UK (United Kingdom);

EEA – European Education Area;

EJP RD ExCom – EJPRD Executive Committee;

EJPRD – European Joint Programme on Rare Diseases;

EJPRD GA – EJPRD General Assembly;

EJPRD PB – EJPRD Policy Board;

ERA – European Research Area;

ERC – European Research Council;

ERN – European Reference Network;

ERN AP – ERN Affiliated Partner;

ERN FM – ERN Full Member;

EU – European Union;

FP7 –7th Framework Programme, EU's research funding programme between 2007 and 2013;

JTC – Joint Transnational Call;

MOOC - Massive Open Online Course;

MS – Member State;

PAO – patient advocacy organization;

PLWRD – people living with rare diseases;

R & I – research and innovation;

RD – rare disease;

RD NP/NS – rare disease national plans or strategies;

UEMS - European Union of Medical Specialties.

1. Executive Summary

Many current issues in RD field may be, at least in part, rectified through the enhancement of an educated, competent, ready to act RD research community. Available data unequivocally shows insufficiency of rare disease (RD) education and training, a general lack of knowledge and awareness about RD, and a huge lack of knowledge and awareness about available RD research resources and data management aspects among the mutistakeholder RD research community. RD (research) education and training ecosystem is highly complex. It involves many "learners", "teachers" and providers, and multiple forms of teaching and learning, including formal, non-formal and informal education. The needs of learners are vastly different across the education and training continuum and follows a principle of educational pyramid. Many RD education and training resources have been recently developed by the main RD organizations, ERNs, professional organizations and other stakeholders.
However, many challenges remain. The major identified challenges include:

- Concept of rarity
- Novelty
- Rapid development and expansion of RD field
- Heterogeneity of RD and multistakeholder community
- Lack of role of professional organizations
- Lack of awareness about existing educational resources
- Unequal competitive conditions as compared to more common diseases
- A higher reliance on international networking and collaboration
- Increasing complexity of ELSI
- Data management and regulatory issues
- Geographic inequities.

Other factors may present both challenges and opportunities for RD research education and training: interconnections with innovative fields; the role of RD patients and PAOs; digital transformation of teaching and learning; professionalism, social accountability, cultural safety and responsiveness.

In the overall RD research education and training ecosystem, EJPRD acts as a major contributor, direct provider and collaborator in education and training activities. EJPRD ensure ecosystem building and advisory role for policy/decision making. EJPRD research education and training programme is exceptional in several ways, including its comprehensiveness across many axes (including career stage, multistakeholder community needs, R & I pipeline), inclusiveness (through special provisions for underserved groups and underrepresented countries), trainings of allied professionals and development of transversal skills, incorporation into the overall RD research ecosystem, means for sharing of good practices in trainings. Some of the impacts of EJPRD education and training programme are already visible: participants from widening countries are very active users of EJPRD education and training activities; special EJPRD provisions to increase participation from widening countries not only empower local communities with knowledge and skills in RD research, but also augment their experience to provide RD research education and training. Active participation of widening countries in EJPRD RD research education and training activities may be one of the factors to increase participation in networking (EJPRD Networking scheme) and JTC activities; longer perspective is required to investigate these impacts. Through education and training activities, directed at both patients and researchers, EJPRD provides a strong basis for patient-centredness in RD research. It may be one of the factors (together with improved regulations for PAO participation in JTCs) for a significant growth in PAO participation in EJPRD JTCs. RD education and training activities complement ERN educational

and training programme, may empower ERN community with RD research knowledge and skills and foster its incorporation into the overall RD research ecosystem. As many face-to-face training activities had to be postponed due to COVID-19 pandemics, currently it is too early to investigate the impacts. Although data on national RD research education and training activities are very limited, some insights about insufficiency of these activities may be drawn from both literature data and surveys. The major responsibility of MS would be provision of basic RD and RD research education (provided mostly in universities and university hospitals), while major European and international efforts are required to provide highly specialized RD research education and training. Another promising option is a concept of "training of trainers" that is provided internationally and ensure standardization, high quality and up-to-dateness of trainings, that are further spread to national networks and adapted to local needs.

During the recent years, intensity of RD research education and training activities have substantially grown due to the comprehensive EJPRD education and training programme and actions of other related stakeholders (as ERNs). It is highly important to maintain the momentum and to further enhance and fill the identified gaps in RD research education and training. It will require actions at three levels: (1) level of organisations, (2) national level, and (3) European and global level. Actions will be most successful if they address the situation at multiple levels. The main recommendations for further progress include:

- **Coherence of RD research education and training activities based on a common strategy across Europe and globally**. Community of RD research learners, teachers and education providers is complex and involves multiple layers across the educational pyramid. EJPRD and many recent initiatives, including ERNs, UEMS and Association of Medical Schools in Europe, work towards strategies and standards of RD education and training. It is highly important to align all these strategies and to ensure that RD multistakeholder community members complement and jointly enhance efforts and available resources for the most optimal results and coherence across Europe and beyond.
- **Better alignment of national and transnational RD research education and training activities to fulfil the needs across RD research educational pyramid**. The major responsibility of MS would be provision of basic RD and RD research education (provided mostly in universities and university hospitals), while major European and international efforts are required to provide highly-specialized RD research education and training. Another promising option is a concept of "training of trainers" that is provided internationally and ensure standardization, high quality and up-to-datetrainings, that are further spread to national networks and adapted to local needs.
- **Awareness-raising and education based on existing resources** to diminish underusage due to non-awareness as compared to underusage due to non-availability. Although many valuable resources have been developed recently, surveys of end-users have shown a staggering lack of awareness about these resources and possibilities. Efforts should be strengthened at all levels (organizations, national, European/global) to increase awareness and usage of available resources (e.g., fostering RD research trainings for project applicants, requirements for standardization and practices in RD research, national or organizational fellowships for trainings, etc.).
- **Incorporation of RD research education and training into the overall RD research ecosystem to ensure up-to-date, empowering education and training and timely response to arising needs**. Incorporation of education and training activities into the overall RD research ecosystem is of the utmost importance for several reasons: it ensures high quality and standardization; as RD research field is rapidly evolving and has multiple connections with other innovative fields, it ensures up-to-dateness, identification of future trends and strategic directions; it is a way to ensure effective and timely response to arising needs of end-users. EJPRD provides the means for such incorporation that otherwise would be impossible.

• **Continuing efforts to diminish inequities and to foster inclusiveness in RD research through special provisions for underserved groups and underrepresented countries**. Education and training provide powerful means to empower underserved and underrepresented for the growth of RD research community. As an international programme, EJPRD provided highly effective means for increased inclusion (targeted at patient representatives, underrepresented countries and ERNs) that would be otherwise entirely or almost impossible (i.e., these means are usually not included into existing RD education and training activities).

• **Commitment for a long-term strategy for the RD research workforce development**. Workforce development in such highly-specialized and complex fields as RD research takes considerable time, especially for experts, principal investigators and thought leaders. National, European and International authorities and organizations should commit themselves for a long-term strategy of RD research education and training and foresee directions and investments for decades.

2. Background and objectives

2.1. Background

Already during the preparation of the EJPRD programme, it was identified that education and training on rare disease research is insufficient, fragmented and geographically unequal across Europe. However, deeper situation analysis was never done worldwide. Although according to the primary 5-year EJPRD plan the overall objective of WP18 was to ensure that capacity building activities within Pillar 3 address the developing education and training needs in RD research of key stakeholders (including clinicians, researchers, patient representatives, but also paramedical sector), across different EU countries, with adaptation of EJPRD capacity building activities accordingly, and only one Deliverable (D18.1. Final report on evaluation and adaptation of training programmes according to EJP RD progress of work, specific needs of EU13 countries and ERN developing needs, M60) was foreseen, following discussions in EJPRD ExCom and EJPRD PB meetings [EJPRD D1.4], an inclusion of Additional Deliverables (AD39 and AD40) into WP18 was proposed. The rationale for the development of AD39 and AD40 stems from the need for "global" measures to evaluate the overall impacts of RD research education and training (under EJPRD and beyond) that is indispensable for decision-making process on further activities (incl. the foreseen RD Partnership), required by funders, MS, and EC.

The motto of ERA is 'Mobilising knowledge for a better and more sustainable future' and education is a crucial part of the "knowledge square" that encompasses education, research, innovation and service to society [Council conclusions 2021]. Education and training is no less indispensable in RD research, as it may enhance:

- Researcher's capabilities to generate meaningful scientific ideas and hypotheses to solve unmet needs in RD;
- Researcher's capabilities to perform high-quality research according to the existing standards and guidelines;
- Researcher's / multistakeholder community's capabilities to rationally use available resources for RD research;
- Researcher's competitiveness in the global market of RD research;
- Collaboration and networking for RD research;
- Patient- and society-centeredness of RD research;
- Translation of research outcomes into clinical practice;
- Diminishing inequalities and enhancing participation of underrepresented countries and underserved groups in RD research.

Indeed, many current issues in RD field may be, at least in part, rectified through the enhancement of educated, competent, ready to act RD research community, including many unmet needs of RD patients and families, under-usage of available resources and limited translation of research outcomes into clinical practice, insufficient quality of research and lack of adherence to existing standards and guidances, fragmentation and inequalities in RD research. Moreover, RD research goes under the realm of and is impacted by the global trends in R & I, including:

- Interdisciplinary, intersectoral collaboration;
- Big data-based research;
- Standardization and good practices for high quality in research;
- Open and transparent research;
- Societal and practical value of research;
- Strict ethics and-legal regulations for privacy-preservation and safety.

Hence, the need to take into account these global trends.

The EJPRD education and training programme on RD research is the first program of its kind and comprehensiveness in Europe and beyond, offering a revolutionary approach to the integration of education and training into the entire RD research ecosystem. The first two years of EJP RD set the stage for deeper analysis:

- An extensive and coherent programme of education and trainings was established with both improvement of existing and creation of novel education and training activities.
- Special provisions to increase accessibility for some underserved groups (ERNs, patients) and underrepresented countries ("widening", EU-13 countries) were implemented.
- Progression of activities in Pillar 1, 2 and 4 point to further identification of educational needs.
- The means to collect extensive information (feedbacks, discussions, proposals, reflections) from multistakeholder RD research community were used thanks to the established RD research ecosystem under EJPRD.

All these resources were eventually used for the evaluation of EJPRD RD research education and training programme. Besides, as the EJPRD actively operates in the overall landscape of RD education and training, external sources of information were addressed and used where relevant and possible (please see the section 2.3 Methodology of the study). The final outcome of the study would be the outlines for a roadmap on RD research education and training, but also some data for continuous monitoring and improvement of RD research education in EJPRD, for national and European authorities to base their decisions on investments and development of educational programmes, and for various stakeholders to set their priorities and to develop RD research education/trainings to fill the gaps.

2.2.Objectives of the study

The main objectives of this study were:

- To evaluate the state-of-the-art of RD research education and training and the place of EJPRD in this general landscape;
- To evaluate RD research education and training programmes in the EJPRD across several axes: the whole R & I pipeline from basic research to preclinical, clinical and translational research; career stages from students to junior and senior investigators; RD research topics; multistakeholder community; patient-centeredness; geographical coverage (covered also in EJPRD AD40).

- To assess the impact of EJPRD's special provisions to increase accessibility of RD research education and training to some underserved groups and underrepresented countries.
- To define the needs and gaps, challenges and opportunities for the further improvement of RD research education and training
- To define recommendations and to disseminate the outcomes of the study to all relevant stakeholders.

2.3.Limitations to the study

From the very outset of the study (and form the set-up of EJPRD education and training programme), several limitations were identified (table 1).

The first limitation stems from the fact that comparable studies were not performed to date.There is a huge lack of available published data on RD research education and training, including both scientific and "grey" literature. Although some strategies for medical education on rare cancers were recently developed by the Joint Action on Rare Cancers [Joint Action Rare Cancers] and a Multidisciplinary Joint Committee on Rare and Undiagnosed Diseases was established in the European Union of Medical Specialties (UEMS) and developed competency training requirements and syllabuses for rare and undiagnosed diseases [European Training Requirements for the Competency of Rare and Undiagnosed Diseases, 2020] and rare adult solid cancers [European Training Requirements for the Competency of Rare Adult Solid Cancers, 2020], there are no any comparable strategies for RD research education and training. Therefore, evaluation of all available literature resources according to the broad list of keywords was performed to meet the objectives of the study. Moreover, direct and indirect indicators were obtained through the extensive evaluation (quantitative and qualitative) of EJPRD education and training programme and EJPRD documentation and qualitative insights were collected from extensive discussions and feedbacks within both EJPRD and external related meetings as a means to capture trends and patterns in RD research education and training (Table 2).

The second limitation is associated with the limited capacities to evaluate long-term Impacts of RD research education and training. The most useful and meaningful assessment of education and training activities is inevitably based on the long-term impact measures, as it takes time for a researcher to improve his/her performance based on acquired competencies and skills (e.g., to develop a successful career, write a successful research proposal, implement a project, etc.). Consequently, education and training strategies must be based on a long-term perspective. However, due to the limited timeframe of the project (5 years) and the novelty of the EJPRD education and training programme, only short-term impact measures could be collected (e.g., numbers and composition of the trainees). Where possible, the trends of direct and indirect short-term indicators were evaluated.

Finally, the boundaries between RD **research** education and training vs. general or clinical RD education and training are frequently blurred. Indeed, any student or junior investigator, clinician involved in the collection of data and samples for RD research and multistakeholder RD research community member needs some basic knowledge on RD. As every RD patient may become a precious resource for RD research (in terms of diagnosis, data and samples), clinical practice and research in RD is often inseparable and medical education on RD increasingly include research aspects [Bertier 2018]. Clinicians and other multistakeholder RD community members are responsible for the translation of RD research outcomes into clinical practice. Finally, RD patients and families are at the core of both healthcare and research and demand for patient-centeredness across the continuum. Therefore, data on general or clinical RD education and training were included were relevant.

Table 1. The main limitations of the study.

Identified limitation	Explanation and the means for rectification
Lack of published data or any other resources for the evaluation of the general RD research education and training.	Evaluation of available literature resources (90 references in total). Extensive evaluation (quantitative and qualitative indicators) of EJPRD education and training programme and other related activities as a means to get trends. Qualitative investigation drawn from extensive discussions and feedbacks collected within both EJPRD and external related activities as a means to capture trends and patterns in RD research education and training (the full list available in ANNEX I. EJPRD documents used for the study).
Focus on short-term (vs. long-term) impacts	Any meaningful evaluation of education is mostly based on long-term impacts, (e.g., impacts on researcher's career, capacities and performance) and require long-term, even decades-long perspective that is not possible within the timeframe of EJPRD. Where possible, hypotheses and recommendations based on the short-term indicators and their trends were presented, and a recommendation to evaluate the long-term impacts in future (presumably RD Partnership) activities was incorporated.
Definition of "RD research education and training" vs. more general "RD education and training"	In many cases, it was not possible to draw a clear line between the two categories of education and training; although general education and training on RD goes beyond the scopes of EJPRD (and is mostly taken by other stakeholders as universities and ERNs), EJPRD provides some general training (esp. in WP16) and data on it is included into this study where relevant.

2.4. Methodology of the study

Several methodologies have been used to reach the objectives of the study, including literature survey, quantitative and qualitative investigation of EJPRD documentation (deliverables, feedback forms of trainings, meeting presentations, etc.), qualitative investigation of feedbacks, discussions, proposals, reflections from multiple meetings (including EJPRD and other relevant stakeholders).

2.4.1. Literature survey

A targeted approach to survey was applied: at first, by using various combinations of keywords "rare disease", "education", "training", "information needs", "teaching", "knowledge", "awareness", "patient empowerment", "policies", "strategies", European Reference Networks", "research infrastructures", "professional organizations", PubMed database was searched (http://www.ncbi.nlm.nih.gov/pubmed). The searches were restricted to English language and publications in peer-reviewed journals, encompassing a period up to December 2021. Cascade searches included references of identified publications. Next, grey literature survey was performed (including legal EU and national documents) by using the same set of keywords. The preliminary list of publications and legal documents included > 300 pieces, while the final reference list used for this study includes 90 references.

2.4.2. Quantitative and qualitative investigation of EJPRD documentation

The whole list of EJPRD documentation available through a dedicated MsTeams platform was reviewed. The final list of 28 internal EJPRD documents (including deliverables, additional deliverables, feedback forms of trainings, meeting presentations, etc.) was included into the further quantitative and qualitative investigations (ANNEX I. EJPRD documents used for the study).

2.4.3. Qualitative investigation of feedbacks, discussions, proposals, reflections from EJPRD and related external meetings

Extensive notes and recordings were collected during the period January 2019 – December 2021 from multiple EJPRD and related external meetings. Recordings of all meetings are available through a dedicated EJPRD MsTeams platform. The main list of EJPRD meetings for collection of feedbacks, discussions, proposals, reflections is presented in table 2 and includes general feedbacks and more in-depth discussions.

Table 2. A list of the main meetings to collect feedbacks, discussions, proposals, reflections on RD research education and training.

General feedbacks and discussions were collected from: EJP RD annual Executive Committee meetings (3rd of July 2019; 7th of July 2020; 6th of July 2021); EJP RD Policy Board meetings (4th of July 2019; 8th of July 2020; 12th of January 2021); EJP RD General Assembly meetings (16 – 19th of September 2019; 14th – 18th of September 2020; 14 -16th of September 2021); Workshop "Rare disease perspectives in Central - Eastern Europe" (16th of September 2019); Joint Transnational Call 2020 Kick-off meeting for funded projects (April 14th 2021); EJPRD Midterm evaluation (16-19 April, 2021); EJP RD Strategy Meeting „Alignment of national rare diseases strategies with EJP RD" (8th July, 2021).	
More in depth discussions (feedbacks and decisions) were collected from:	
The meeting	**The main feedbacks and decisions**
Workshop "Rare disease perspectives in Central - Eastern Europe" (16th of September 2019)	challenges that are specific to EU-13 countries; participation and performance of researchers from EU-13 countries in the international RD research, the role of education and training to increase capacities and participation.
EJP RD General Assembly, dedicated Pillar 3 sessions (18 – 19th of September 2019; 14th of September 2020)	decisions on continuous improvement scheme for Pillar 3 trainings; decisions on proposed adaptations for improvement; identifying and sharing Good Training Practices; development of a Toolkit for EJPRD trainings; dissemination and awareness raising for EJPRD training activities; sustainability issues; contingency plans due to COVID-19 pandemics.
EJP RD Policy Board and Governing Board meeting; a session Annual Work Plan Year 3, presentation of WP18 Identification of new education	Train the trainers concept, opportunities and challenges for scaling-up of EJPRD-developed trainings into national systems (e.g., limited resources, language issues, dissemination channels); impacts of EJPRD trainings: the need to measure and improve/adapt accordingly, short-term vs. long-term impacts; importance of trainings for

& training needs/gaps (8th of July 2020)	standardization and quality of research and proposals for excellence spreading (e.g., active promotion of trainings for EJPRD JTC applicants, inclusion of standards into evaluation of proposals to foster learning, etc.).
EJP RD Policy Board meeting, dedicated session "Back to basics – education & empowerment" (12th Jan, 2021)	the need to evaluate EJPRD capacity building and empowerment programme across many axes (incl. R & I pipeline from basic research to translation; career stages from student to Principal Investigator; multistakeholder community; under-served groups and underrepresented countries; patient-centeredness); alignment with EU research and educational policies (ERA, EEA, Digital transformation); alignment with national educational policies.
General Assembly and Consortium Meeting 2021, dedicated session "Sharing training needs and possible solutions for implementation in Pillar 3 (P3 and P1/2/4)" (15th of September 2021)	research needs arising from the development of work and activities in the EJP across all pillars; a list of potential solutions to address these newly identified training needs; prioritization of activities to be implemented in WP18 vs. implementation in other WP vs. adaptation of existing trainings.

3. Results

3.1. State-of-the-art of RD research education and training and the place of EJPRD in this general landscape

3.1.1. Level of rare disease knowledge and awareness among the multistakeholder RD research community

Although data is limited, several published studies to date have investigated RD knowledge and awareness among the multistakeholder community of RD research, mostly current and future healthcare providers. The studies unequivocally show that future and current workforce lacks even the basic knowledge and awareness of RD (Table 3). In several studies, an objective evaluation of knowledge on RD among physicians (general practitioners and specialists), pharmacists, nurses and students of various specialties was performed by asking questions about RD definition, epidemiology, examples of RD and informational resources for RD [Walkowiak 2020; Miteva 2011; Mijiritsky 2021; Kuhne 2020; Krajjnovic 2013; Walkowiak 2019; Ramalle-Gómara 2015; Jonas 2017; Domaradzki 2019; Domaradzki 2021; Medic 2015]. Generally, the knowledge on RD was insufficient with correct answer rates for various questions from 2% (question about prevalence of RD) to 91% (question about genetic origin of RD). The vast majority of general practitioners (GPs) and students self-rated poorly their knowledge on RD, while self-ratings of pediatricians and specialists were higher [Walkowiak 2020; Ramalle-Gómara 2020; Vandeborne 2019; Li 2021; Zurynski 2017; Kuhne 2020; Walkowiak 2019; Domaradzki 2019; Domaradzki 2021; Medic 2015]. Importantly, in some studies physicians claimed very rare encounters with PLWRD in their practice that may not be compatible with the real RD prevalence rates, hence, it is likely that RD remained unrecognized by responders [Miteva 2011; Li 2021]. According to Australian study, each full time equivalent GP in that country cares for 66 to 86 RD patients in his/her care [Elliott 2015]. Awareness of where to find information about RD (e.g., Orphanet) is generally poor among GPs

and students and better among pediatricians and specialists. Moreover, a significant proportion of dentists in a study from Germany (10%) and students (up to 24% of nursing students) in a study from Poland claim that they do not need or do not search for information about RD [Kuhne 2020; Walkowiak 2019], although general willingness to broaden knowledge on RD is very high. [Pillar 2 Annual Retreat, 22-24 May 2019, presentation]

Educational and informational sources of knowledge about RD have also been investigated in a number of studies. About half of all physicians reported university courses and specialty training as an important source of RD knowledge, although usefulness and completeness may be limited (academic training not useful or insufficient for 7% - 17% of specialists and 80% of GPs) [Vandeborne 2019]. Nursing and physiotherapy students may receive even lower university education on RD when compared to medical students [Domaradzki 2021]. Interestingly, despite a general willingness to broaden knowledge on RD diseases and claims about insufficient academic RD education, respondents were reluctant for inclusion of mandatory RD university courses (expressed need for such course: 29% of GPs, 44% of pediatricians, 39% to 44% of specialists, 85% of nurses, 46% to 88% of students [Walkowiak 2019; Vandeborne 2019; Domaradzki 2019]; this may be due to a combination of both lack of awareness of the magnitude of burden of RD [Navarrete-Opazo 2021] and the perception of already overwhelmed curricula. As expected, continuous medical education, scientific literature and conferences are considerably more important as a source of information on RD for practicing physicians and nurses; many of them completed their studies a number of years ago, when RD educational concepts where not sufficiently developed. However, perhaps unexpectedly, the Internet was mentioned as an important source of information about RD by a considerably higher number of practicing professionals as compared to students; presumably, professionals are forced to search for information about RD when they encounter suspected or confirmed RD cases in their practice [Zurynski 2017; Walkowiak 2019; Domaradzki 2021].

Table 3. Surveys of RD research multistakeholder community about awareness and knowledge on rare diseases.

	Objective evaluation of knowledge on RD	**Self-rated knowledge of RD**	**Self-rated readiness to provide care to RD patients**	**Encountered RD patients in practice**	**Experienced difficulties in caring RD patients**	**Educational/ informational sources of knowledge on RD**	**Awareness where to find information about RD**	**Awareness where to refer RD patients for specialized services**	**Awareness about patient organizations**	**Willingness to broaden knowledge on RD/ expressed need to include mandatory course on RD into university studies**	**RD seen as a societal and bioethical issue**
Walkowiak D, 2020; medical doctors (N 165), PL	Correct answer rates from 15.8% to 53.9%	Insufficient and very poor 94.6%	Rather not and definitely not 93.4%	In practice 75,2%, in family 11,5%	Not evaluated	Mandatory courses at university 46.1%, elective courses at university 13.8%, literature 38.9%, conferences 21.6%, Internet 31.7%.	Not evaluated	Not evaluated	Not evaluated	Yes 83%/ 76,3%.	RD constitute a serious public health issue: 83,1%.
Ramalle-Gómara 2020, GP N 132/ specialists N 37, ES	Not evaluated	Likert scale 1 to 5: GP 1.72/ specialists 2.29.	Likert scale 1 to 5: qualified to coordinate care GP 1.82/ specialists 2.4.	Not evaluated	Achieve diagnosis: GP 67,4/% specialists 62,2%; lack of CPG: GP 59,1%/ specialists 70,3%; information about where to refer: GP 66,7%/ specialists 62,2%; lack of access to diagnostic tests: GP 33,3%/ specialists 32,4%.	University courses 27%, specialty training: GP 18.9%/ specialists 51.4%; CME courses: GP 40.9%/ specialists 45.9%. Medical training on RD is adequate, Likert scale 1 to 5: GP 1,72/	Likert scale 1 to 5: know patient organizations GP 1.58/ specialists 2.26. specialists 2.29.	Likert scale 1 to 5: GP 1.53/ specialists 2.47.	Yes: GP 55,6%/ specialists 62,2%. Likert scale 1 to 5: GP 1.58/ specialists 2.26.	Not evaluated	Not evaluated
Vandeborne 2019, physician, GP N 114/ PED N 95/ specialists 75, BE	Not evaluated	Poor and insufficient: GP 86%/ PED 45%/	Not evaluated	At least once: GP 52%. Multiple times: PED 72%/	Not evaluated	Usefulness of academic training to diagnose RD; not useful or insufficiently useful GP 80%/ PED 41%/ specialists 7-17%.	Yes: GP 27%/ PED 85%/ specialists 75-89% (Orphanet)	Not evaluated	Not evaluated	Yes GP 84%/ PED 95%/ specialists 95%.; expressed need to include RD courses into	Not evaluated

		specialists 16%		specialists 94-100%.						university studies: GP 29%/ PED 44%, specialists 39-44%.	
Miteva 2011, physicians N 1002, BG	Correct answer rates from 2,3% to 19,8%	Not evaluated	Not evaluated	During the last year: 4,2%	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Li 2021, physicians N 224, CN; N.B. response rate only 12,4%	Not evaluated	Insufficient and poor 94,7%	Not evaluated	Overall 53,6%, more than 3 times 19,9%	Not evaluated	Education and training for RD sufficient 27,1%	Not evaluated	Not evaluated	Not evaluated	87,8%	Support RD legislation 96,8%
Zurynski 2017, pediatricians 242, AU	Not evaluated	Not evaluated	Not 28%	Overall 93%, during the last 6 months 74%	Overall 98%; diagnostic delays 65%, lack of available treatments 40%, clinical guidelines 36%, uncertainty where to refer for peer support 35%	University courses 40%, specialty training 50%; consultation with colleagues 92%; Internet 91%; textbooks 49%, mobile phone or tablet applications 30%.	Yes 62%	Yes 64%	Not evaluated	Not evaluated	Not evaluated
Baqué 2019, rare skin diseases GP N 96, FR	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Overall: 95%. Achieve diagnosis 88.5%, provide care coordination 76%; lack of knowledge 95%, insufficient time to search for information 72.6%.	Not evaluated	Not evaluated	Know CoE 35.8%	Not evaluated	Not evaluated	Not evaluated
Mijiritsky 2021, 309 dentists, IL	Correct answer rates 10% to 57.1%	Not evaluated	Not evaluated	Yes 70,1% – 95,2%	Not evaluated	Medical and specialty training 39.4 - 77.3%, literature 50.2–69.7%, colleagues 47.6–75.8%.	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated

Kuhne 2020, odontology specialists N 267, DE	Correct answer rates 7.4% to 85.7%, significant differences among university/non-university educated dentists.	No or little 50% - 77,7%	Not evaluated	Yes 69% - 85,7%	Not evaluated	No education at university or specialty training 21.4%	Do not know 21.6%, do not need info 10.1%	Not evaluated	Not evaluated	Yes 98,9%	Not evaluated
Mancuso 2020, neurologists with special interest in RD N 104, IT; N.B. only 4% response rate	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Yes 82%; aware of coordinated care in the Region 80%	Yes 73%	Not evaluated	Rare neurological diseases are an important disease group: 96%; national health system insufficiently supports rare neurological diseases costs: 25,7%
Krajjnovic 2013, pharmacists N 139, RS	Correct answer rates 33% to 48,2% (2 questions)	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Yes 51,8%	Not evaluated	Not evaluated	Not evaluated	Support RD legislation 91,4%; lack of accessibility to Orphan drugs as a problem 64%
Walkowiak 2019, nursing students N 113, nurses 142, PL	Correct answer rates for nursing students 3.5% to 59.3%/	Insufficient and very poor: nursing students	Rather not and not: nursing students	Not evaluated	Not evaluated	Mandatory courses at university 10.6%/17.4%, elective courses at university 8%/6.5%, literature 13.3%/21.9%,	Yes (Orphanet) nursing students 0,9%/ nurses 18,1%	Not evaluated	Not evaluated	Yes nursing students 83.2%/ nurses 91%; expressed need for mandatory	RD constitute a serious public health issue: nursing

	nurses 8.4% to 67.1%	94.7%/ nurses 97.4%	84%/ nurses 77.4%			conferences 6.2%/14.8%, Internet 54.9%/79.4%, I do not search 23.9%/1.3%				educational courses: nurses 85% students 75%.	students 85%/ nurses 92,9%
Ramalle-Gómara 2015, students of various specialties (nursing, medical, non-health) N 234, ES	Correct answer rates from 7.5 to 78.3	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Although 72.6% considered that the majority of the budget should be used to treat common diseases, the total mean score for questions about willingness to assign resources to RD ranged from 3.3 to 4.6 on a Likert scale from 1 to 5.
Jonas 2017, students N 270, PL	Correct answer rates 14% to 73.7%	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Domaradzki 2019, students N 346, PL	Correct answer rates 9.5% to 90.5%	Insufficient and very poor 95.4%	No 92.2%	Not evaluated	Not evaluated	Mandatory courses at university 51.7%, elective courses at university 22%, literature 10.7%, conferences 10.1%,	Yes (Orphanet) 19,4%	Not evaluated	Not evaluated	Yes 75.1%, but expressed need for mandatory university	RD constitute a serious public health problem: 78%, the need for

						Internet 59.8%, I do not search 11.8%				courses only 54,3%	RD legislation: 64,6% – 74,4%
Domaradzki 2021, students (nursing/ physiotherapy / medical) N 113/ 173/ 368. N.B. data partially overlaps with Domaradzki 2019.	Correct answer rates 3,5% to 89,6%	Insufficient and very poor: 94,7%/ 94,8%/ 95,1%	Rather or definitely not: 84%/ 83,8%/ 91,9%	Not evaluated	Not evaluated	Mandatory courses at university 10,6%/ 32,4%/ 51,1%, elective courses at university 8%/ 11,6%/ 22,3%, literature 13.3%/ 9,3%/ 19,6%, conferences 6.2%/ 5,8%/ 9,8%, Internet 54.9%/ 53,2%/ 58,7%, I do not search 23.9%/ 17,3%/ 11,4	Yes: 22,1%/ 54,7%/ 39,7%	Not evaluated	Not evaluated	Yes 83,2%/ 85%/ 73,9% Expressed need for mandatory university course: 76,1%/ 87,9%/ 45,6%	RD constitute a serious public health issue: 85%/ 89%/ 77,2%
Medic 2015, students N 592, RS	Correct answer rates 8.2 to 83.05	Likert scale 1 to 10: 3 to 4.	Not evaluated	Not evaluated	Not evaluated	Mandatory courses at university 63.14%, elective courses at university 11.4%, Internet 39.4%	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Quality of RD care (Likert scale 1 to 10): 2,2 to 2,4; importance of RD in society 5,9 – 5,9

Several studies of knowledge base in certain RD groups presented similar results [Mancuso 2020; Mijiritsky 2021; Kuhne 2020; Hariyan 2020; Ramadurai 2019; Requena-Fernández 2020] (Table 3). A study performed by the European Reference Network on rare endocrine diseases, Endo-ERN, investigated knowledge base on rare endocrine diseases [Iotova 2021]. The largest knowledge gaps were reported for GPs (71%), followed by students and medical specialist trainees (61% each), and specialists (51%). Out of 146 respondents across 19 EU Member States, only 45% had a structured RD educational plan, and only 36% reported a specific training program for GPs. There was an almost unanimous desire for a more harmonized approach towards education and training through the common e-learning platform of professional organizations (European Society of Pediatric Endocrinology and European Society of Endocrinology) and the Endo-ERN.

Several studies investigated knowledge base in rare cancers. In a study performed by the Joint Action Rare Cancers and UEMS, 104 respondents of all European nations were questioned about education and training in rare cancers, including undergraduate and postgraduate training [Joint Action Rare Cancers 2017]. Only a small proportion of respondents had received specially dedicated undergraduate teaching (19%) or targeted teaching materials (26%) for rare cancers. Knowledge and awareness on rare cancers of a training personnel in the institution or country was frequently rated as poor (accordingly, in 20% and 30% of cases). Similarly, ratings of knowledge and awareness of rare cancers among the new MD graduates were generally low (poor knowledge: 43% of respondents). Additionally, more than half of the participants do not feel that GPs are aware and well informed on rare cancers (56%), while ratings of pediatricians (not aware 21%) and specialists (11%) were more favourable. There was a general agreement that European training in rare cancers is fragmented (77% of respondents agree) and there is a need for pan-European harmonization of training (90% of respondents agree).

Two surveys have been performed by EJPRD Pillar 2 in collaboration with other Pillars, to investigate the needs of ERNs (in 2019) and researchers (in 2020) [EJPRD D10.1; EJPRD D10.2] in RD research and several parts of these surveys are informative for this study.

ERN survey (294 respondents) showed deficiencies in data management, standardization and FAIRification, and sharing: although ERN members collect vast sets of RD patients' data, the most common method for storage of data is having files or databases at host institutions' servers and/or personal computers. A very small percentage of respondents (< 5%) used the listed tools or resources for data deposition, sharing and analyses, such as RD-Connect GPAP, EGA, ArrayExpress, PRIDE or Metabolights. The two major hurdles that limit data sharing are legal jurisdiction and complexity of use of resources. Only approximately 34% of ERN HCP respondents indicated the use of ontologies or standards to annotate data. 132 of 294 (45%) respondents feel they do not sufficiently understand what FAIR research data means; there is a dramatic lack of use and even awareness of most existing European research infrastructures, data management and analysis resources (as ECRIN, EATRIS, BBMRI-ERIC, ELIXIR, RD-Connect, ERDRI, RADICO, hPSCReg); most of the resources were known by < 10% of respondents, frequently only several per-cents.

A survey on research activities and capabilities was also performed by MetabERN, an ERN on inherited metabolic diseases [Heard 2019]. Answers were received from 106 respondents, covering 52 ERN Full Members across 16 countries, the survey was performed in December 2017/January 2018. Almost all respondents were active in research and had published at least one article in an ISI-referenced journal during the last 3 years. These publications associated international collaborators (> 40%) and/or collaborators from other national institutions (> 50%). Strikingly, a large majority of the respondents did not know about the existence the international research infrastructures supported by the European Scientific Forum on Research Infrastructures (BBMRI, EATRIS, ECRIN, ELIXIR, OPENSCREEN, EUROBIO-IMAGING, INFRAFRONTIER, ISBE and MIRRI), and even when they know them, they very rarely collaborated with them. In contrast, responding teams are aware of the existence of patient registries, even beyond their

specific field of interest. Teams were also asked whether they are aware of the existence of international (scientific) organizations including EURORDIS, ISNS (the International Society for Neonatal Screening), SSIEM (the Society for the Study of Inborn Errors of Metabolism), SIMD (the Society for Inherited Metabolic Diseases), ERNDIM (the European Research Network for the Diagnosis of Inherited disorders of the Metabolism), and IRDIRC (the International Rare Disease Research Consortium). All these organizations are known by most of the responding centers, and many of them actively participate [Heard 2019].

EJPRD survey of researchers (most of them (83%) were principle investigators, involved in basic research (70%)) was performed in 2020. Over half of the researcher respondents said they generate or use – mics data (55%), and a higher percentage, as compared to ERN respondents, collect multi-omics datasets originating from the same samples (27%). A very small percentage of respondents (< 5%) used the listed tools or resources for data deposition, sharing and analysis, such as RD Connect, GPAP, EGA, ArrayExpress, PRIDE or Metabolights. In terms of general research data storage, the most common method is having files or databases at host institutions' servers and/or personal computers. Only 21% of respondents deposit and/or share -omics data in open or controlled access resources. The rest of the respondents either indicated no sharing (38%) or did not answer the question. Only approximately 35% of researchers indicated use of ontologies or standards to annotate data (compared to 32% who said no and 33% who did not answer the question). Like the ERNs, 45% of the researcher respondents feel that they do not sufficiently understand what FAIR research data means. No resources available for FAIR effort was the most cited reason as a barrier to FAIR (70% of those who were interested but faced barriers). Only 10-20 % of respondents indicated the listed rare diseases resources on registries, biobanks / biological materials, mouse models, bioinformatics and translational/clinical research support as of importance for research. Strikingly, 40 - 55% of respondents replied they did not know about these resources and 30-40% did not reply to the questions. [EJPRD D10.2].

Conclusions:

- There is a general lack of knowledge and awareness about RD among the multistakeholder RD research community.
- There is a huge lack of knowledge and awareness about available RD research resources and data management aspects among the mutistakeholder RD research community.
- The training needs of various stakeholders in the RD research community are diverse.

3.1.2. The principle of the pyramid in the RD research education and training

RD research education and training ecosystem is comprised of "learners" and "teachers", and these categories may overlap (i.e., educators and experienced investigators also need education and training, although their needs are different). Several categories of institutions/ organizations provide teaching in RD research. The main groups of "learners"/"teachers" and providers of RD research education are listed in table 4.

Table 4. The "learners"/ "teachers" and providers of RD research education and training.

"Learners" and "teachers" in RD research education and training	**Teachers or "providers" of RD research education and training**
• Experienced, principal investigators; • Lecturers and educators; • Researchers: PhDs, postdocs; • Clinicians, multistakeholder community members (e.g., research nurses, lab technicians, bioinformaticians, data managers, etc.); • Patients, families, RD advocates; • Students (medical, nursing, natural science and other); • Primary care (general practitioners, community nurses).	• Universities; • Teaching hospitals; • Research institutions; • ERNs; • Research infrastructures; • Patient organizations; • Professional/ scientific organizations; • Non-governmental organizations; • RD research ecosystem *per se*.

This education and training continuum involves multiple forms of teaching and learning, including formal, informal and non-formal education, vocational training and development of skills through lectures, seminars, bed side teaching, journal clubs, e-learning, webinars, fellowships, computer assisted, self-instruction modules, problem-based learning, team-based learning, simulation, etc. Many providers of RD research education and training, listed in the table 4, are outside of the formal education and training system and provide non-formal learning, mostly for the continuous development of the workforce. Informal learning for the acquisition of knowledge on cutting-edge innovations and trends, know-how and skills development (e.g., transversal skills for leadership and coordination of multilingual, multistakeholder communities), is especially important for experienced, principal investigators, but also other "learners" in the ecosystem.

The needs of learners are vastly different across the education and training continuum and follows a principle of a pyramid (Figure 1). Most of the healthcare workforce (as primary care) and students of various specialties are at the basis of this pyramid; they must be equipped with the basic, general knowledge about RD (like general concepts, "red flags" to recognize RD, principles of diagnostics and treatment). Experienced, principal investigators and highly-specialized experts are situated at the very top of the pyramid; their education and training takes much more time and efforts, includes not only formal, but also informal and non-formal training, and they are not only "learners", but also generators of expertise and knowledge and "teachers". Middle layers of the pyramid involve the whole multistakeholder community with highly variable needs according to the specialty and scopes of work, like clinicians - specialists, research nurses, multidisciplinary team members, bioinformaticians, laboratory technicians, biostatisticians, biobank and data managers, etc. Importantly, PLWRD and their advocacy organizations should be included at all stages of the pyramid: they need knowledge and skills for the empowerment, active and meaningful participation in RD research, and advocacy and leadership skills to engage and partner with multistakeholder RD research community, policy makers and regulatory agencies. As PLWRD are experts of their own disease, they could be consulted and engaged into the creation and alignment of educational contents to unmet needs, provision of peer-to-peer education [Bolz-Johnson 2021; Depping 2021; Farhat 2020].

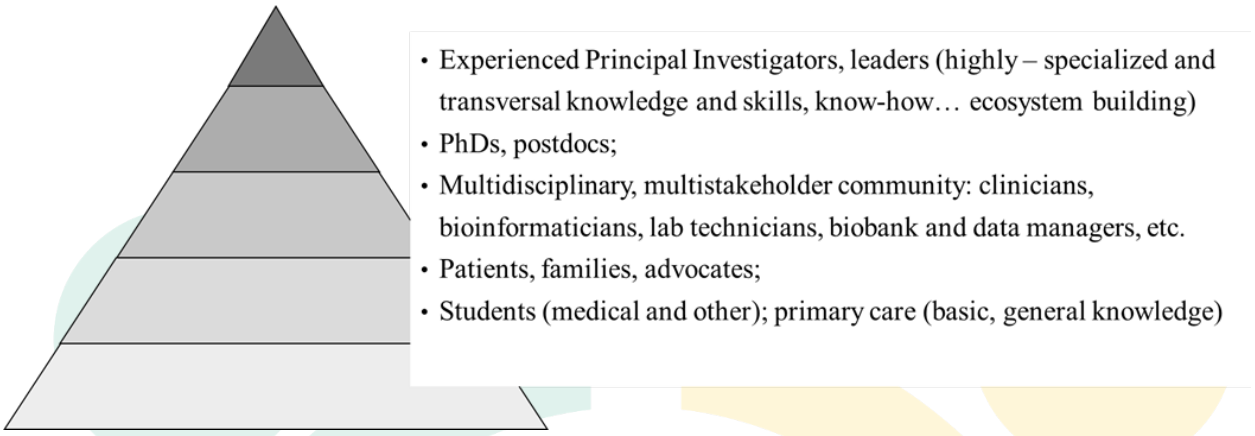


Figure 1. Principle of pyramid in rare disease education and training.

Universities, nursing and medical schools should be the main providers of basic and general knowledge on RD; besides, as many universities have a dual role of both teaching and research, universities may be involved in RD education and training along the whole R & I pipeline from basic research to translational research. Teaching hospitals implement clinical and specialty education and training for clinicians, some of them are involved in clinical research. Professional organizations define educational standards for their specialty, provide continuous education and other resources for professional development (e.g., on-line training modules, conferences and educational events), and have a special role in filling the knowledge gaps of current workforce. Recently, a Multidisciplinary Joint Committee on Rare and Undiagnosed Diseases was established in the European Union of Medical Specialties (UEMS) and developed competency training requirements and syllabuses for rare and undiagnosed diseases [European Training Requirements for the Competency of Rare and Undiagnosed Diseases 2020] and rare adult solid cancers [European Training Requirements for the Competency of Rare Adult Solid Cancers 2020]. These resources may aid in the harmonization of medical training requirements across Europe and beyond and may serve as a base for RD and rare cancers clinical education in the national educational systems.

Highly-specialized knowledge and skills of RD experts are often acquired in the Centers of Expertise (CoE) or Comprehensive Cancer Centers [Ray-Coquard 2017] and research institutions. In 2017, more than 900 of CoE joined their forces and created 24 European Reference Networks (ERNs) across the main RD and rare cancers domains. Currently ERNs include more than 1600 CoE as ERN Full Members or ERN Affiliated Partners (Figure 15) and, through EU-wide leveraging of existing educational and training resources, generation of knowledge and development of novel educational and training means, provide powerful resources of highly-specialized RD knowledge and expertise [Sanges 2020; Alfaro 2021; Blay 2021]. Some of them have already started to provide residency training in RD [Dourado 2022]. Additionally, through the involvement of patient organizations and European patient advocacy groups (ePAGs), ERNs play an important role in the development and provision of educational resources for patient empowerment [Bolz-Johnson 2019; Talarico 2020; Farhat 2020]. ERNs organize their educational strategy via the ERN Knowledge Generation working group formed by ERN coordinators and representatives of the ERN Board of Member States [ERN Board of Member States], aimed at the development of common approaches to promote and sustain courses, masterclasses, post-doctoral programs and mobility programs for pre- and postdoctoral fellows on RDs. All these activities constitute the ERN Academy, a virtual platform which will collect all the educational modules generated by the ERNs.

Education on RD research is also provided by research institutions and research infrastructures, like European Research Infrastructure for biobanking BBMRI-ERIC [BBMRI-ERIC] or European Research

Infrastructure for life sciences ELIXIR [ELIXIR]. Patient organizations play an indispensable role in the education, empowerment and capacity building of PLWRD, families and advocates. Through its extensive patients‘ and mixed audiences-targeted (including both patient representatives and other multistakeholder community members as clinicians and researchers) training programmes, the largest alliance of currently 974 RD patient organizations EURORDIS equips trainees with crucial leadership, advocacy and partnership-building skills for a meaningful inclusion of RD patient representatives into all RD-related activities since 2008 [EURORDIS Open Academy]. Finally, important educational resources are also provided by some non-governmental organizations as Medics4RareDiseases that leverages on the social accountability and involvement of medical students and young professionals to foster RD education [Medics4RareDiseases].

The non-exhaustive list of current resources of RD research education and training is provided in table 5.

Table 5. Non-exhaustive list of RD research education and training resources.

Type of resources	**Knowledge, education and training resources**	**Description**
Knowledge bases, the main organizations for rare diseases	Orphanet; https://www.orpha.net/consor/cgi-bin/index.php	The portal for rare diseases and orphan drugs.
	OMIM*; https://www.omim.org/	An Online Catalog of Human Genes and Genetic Disorders.
	EURORDIS; https://www.eurordis.org/	Alliance of patient organisations representing 984 rare disease patient organisations in 74 countries.
	NORD; https://rarediseases.org/	Umbrella of more than 300 patient organizations. Information about Orphan medicines in the EU.
	European Medicines Agency. Orphan designation: overview; https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview	
	IRDiRC; https://irdirc.org/	International Rare Diseases Research Consortium that promotes international collaboration and advance RD research worldwide.
	GeneReviews; https://www.ncbi.nlm.nih.gov/books/NBK1116/	Information on inherited conditions in a standardized journal-style format, covering diagnosis, management, and genetic counseling.
European Reference Networks	Information and links: https://www.orpha.net/consor/cgi-bin/Clinics_ERN.php?lng=EN; https://ec.europa.eu/health/ern_en ERN on rare bone diseases: ERN BOND; https://ernbond.eu/ ERN for rare and/or complex craniofacial anomalies and ear, nose and throat (ENT) disorders: ERN CRANIO; https://ern-cranio.eu/ ERN on rare endocrine disorders: Endo-ERN; https://endo-ern.eu/ ERN on rare and complex epilepsies: EpiCARE; https://epi-care.eu/ ERN on rare kidney diseases: ERKNet; https://www.erknet.org/ ERN on rare neurological diseases: ERN-RND; https://www.ern-rnd.eu/ ERN on rare and congenital anomalies: ERNICA; https://ern-ernica.eu/ ERN on rare respiratory diseases: ERN-LUNG; https://ern-lung.eu/ ERN on rare and undiagnosed skin disorders: ERN-Skin; https://ern-skin.eu/ ERN on rare adult solid tumours: EURACAN; https://euracan.eu/	

	ERN on rare hematological disorders: EuroBloodNet; http://www.eurobloodnet.eu/index/ ERN on rare neuromuscular diseases: EURO-NMD; https://ern-euro-nmd.eu/ ERN on rare eye diseases: ERN-EYE; https://www.ern-eye.eu/ ERN on genetic tumour risk syndromes: GENTURIS; https://www.genturis.eu/l=eng/Home.html ERN on rare urogenital disorders: eUROGEN; https://eurogen-ern.eu/ ERN on rare and complex diseases of the heart: ERN GUARD-Heart; https://guardheart.ern-net.eu/ ERN on rare congenital malformations and rare intellectual disability: ERN ITHACA; https://ern-ithaca.eu/ ERN on inherited metabolic diseases: MetabERN; https://metab.ern-net.eu/ ERN on pediatric cancer: ERN PaedCan; https://paedcan.ern-net.eu/ ERN on rare hepatological diseases: ERN RARE-LIVER; https://rare-liver.eu/ ERN on rare connective tissue and musculosceletal disorders: ERN ReCONNET; https://reconnet.ern-net.eu/ ERN on rare immunodeficiency, autoinflammatory and autoimmune diseases: ERN RITA; https://ern-rita.org/ ERN on transplantation in children: ERN TransplantChild; https://www.transplantchild.eu/ ERN on rare multisystemic vascular diseases: VASCERN; https://vascern.eu/	
Professional organizations**	European Union of Medical Specialties (UEMS): Multidisciplinary Committee on Rare and Undiagnosed Diseases (MJC RUD); https://uems-genetics.org/links.html	Develops competency training requirements and syllabuses for rare and undiagnosed diseases and rare cancers, organizes European examinations.
	Society for the Study of Inborn Errors of Metabolism (SSIEM); https://www.ssiem.org/training	Organize SSIEM Academy courses on inherited metabolic diseases.
	Rare Cancers Europe; https://www.rarecancerseurope.org/events	Training courses for patient advocates in rare cancers, developed together with ESMO and ESO.
	European Society of Human Genetics (ESHG)*; https://www.eshg.org/index.php?id=education	Provides courses and various educational resources for human genetics.
	International Society of Pediatric Oncology (SIOP); https://casehippo.com/spa/courses/catalog/siop/home	SIOP Knowledge Centre provides educational resources on pediatric cancers.
	European Society for Pediatric Nephrology (ESPN)*; https://www.espn-online.org/espn-ipna-erknet-educational-best-clinical-practice-webinars/#	Provides webinars and other educational resources on rare pediatric kidney diseases (in collaboration with ERN ERKNet).
	European Society of Endocrinology* https://www.ese-hormones.org/about-us/committees/rare-disease-committee/ and European Society of Pediatric Endocrinology* https://www.eurospe.org/education/	Provides some education and awareness raising on rare endocrine diseases (in collaboration with Endo-ERN).
	International League Against Epilepsies*; https://www.ilae.org/education	Provides some e-learning modules on rare epilepsies.
	European Academy of Neurology*; https://www.ean.org/learn/joint-webinars	Provides educational programme (developed in collaboration with ERN-RND and ERN-EuroNMD).
	European Respiratory Society*; https://www.ers-education.org/collections/educational-material-on-rare-diseases/	Provides some educational e-learning materials for rare respiratory diseases (developed in collaboration with ERN-LUNG).

	European Society of Medical Oncology* (ESMO)	Provides some educational resources on rare cancers (in collaboration with EURACAN).
	European Hematology association; https://ehaweb.org/education/	Provides some educational resources on rare hematological diseases (in collaboration with EuroBloodNet).
	European Association for the Study of the Liver*; https://easlcampus.eu/ern-on-demand	Provides webinars on rare liver diseases (in collaboration with ERN RARE-LIVER).
Education and training resources**	ESHG Genetic Educational Materials and Sources*; https://www.eurogems.org/index.html	A compendium of genetic information and resources.
	European School of Oncology*; https://www.eso.net/	Organization for education and training in cancer.
	EURORDIS Open Academy; https://openacademy.eurordis.org/	Capacity-building programmes for patient advocates and mixed audiences.
	BBMRI.QM Academy*; https://www.bbmri-eric.eu/services/e-learning/	E-learning resources on biobanking.
	Elixir Training Platform*; https://elixir-europe.org/platforms/training	Education and training resources on life sciences.
	EATRIS Transmed Academy - course on translational medicine*; https://eatris.eu/services/education/*	e-learning platform which hosts online courses as well as recordings of webinar series.
	European Patients' Academy Webinars*; https://www.eupati.eu/category/webinar/	12 webinars from EUPATI, for patients and advocates
	European Patients' Academy Expert Training Course*; https://www.eupati.eu/eupati-training-course/	Online course in medicines research and development. Not solely focused on rare diseases.
	Integrated DEsign and AnaLysis of clinical trials in small population group (IDeAl) resources; https://www.ideal.rwth-aachen.de/?page_id=1732	Webinar Series on Integrated DEsign and AnaLysis of small population group trials
	Research Data Management online courses*; https://vidensportal.deic.dk/en/RDMELearn	eLearning course about the importance of good research data management (RDM)
	Patient-Centered Outcomes Research Institute (PCORI) Training: A Program for Rare Disease Patient Advocates; https://www.pcori.org/research-results/2015/pcor-training-program-rare-disease-patient-advocates	Tools and templates on the subject of "patient and research"
	Findacure's e-learning resources on rare diseases; https://portal.findacure.org.uk/	The portal is aimed at rare disease advocates, patient groups and charities, it shares 'how to' and best practice on a range of topics – from building the team to running patient registries – to encourage efficient and sustainable growth of patient groups.

	FutureLearn courses on genomics*: The Genomics Era: the Future of Genetics in Medicine https://www.futurelearn.com/courses/the-genomics-era; • Whole Genome Sequencing: Decoding the Language of Life and Health; https://www.futurelearn.com/courses/whole-genome-sequencing; • Genomic Technologies in Clinical Diagnostics: Next Generation Sequencing; https://www.futurelearn.com/courses/next-generation-sequencing; • Genomic Technologies in Clinical Diagnostics: Molecular Techniques; https://www.futurelearn.com/courses/molecular-techniques;	Courses on genomic technologies, whole genome sequencing,
	Genetics education for primary care resources from the Gen-Equip project* https://www.primarycaregenetics.org/?page_id=109&lang=en.	Genetics education for continuing medical or professional education in genetics (general practitioners, primary care pediatricians, midwives, and primary care nurses).
	Medics4RareDiseases (M4RD) video library; https://www.m4rd.org/video-library/.	e-learning for medical students and doctors about the fundamentals of rare diseases.
	Program on rare diseases "Excellence In pediatrics"; https://www.ineip.org/p2p_education_program_on_rare_diseases_excellence_in_pediatrics.	Peer-to-Peer Education Program on Rare Diseases including Live Lectures, Enduring Online Content & Community-Based Education.
	Recordati rare diseases; https://www.rrd-foundation.org/en/courses	Courses and webinars on clinical trials and rare diseases (mostly inherited metabolic diseases).
	Aarhus University, Rare Diseases in Translational and Personalized Medicine; https://kursuskatalog.au.dk/en/course/105020/Rare-Diseases-in-Translational-and-Personalized-Medicine.	MsC course on rare diseases, translational and personalized medicine.
	Wellcome Advanced Courses and Scientific Conferences – Genomics of Rare Disease; https://genetics.org.uk/events/wellcome-advanced-courses-and-scientific-conferences-genomics-of-rare-disease/.	Courses on rare diseases, genomics, undiagnosed diseases.
	Queen's University Belfast; https://www.qub.ac.uk/sites/RareDisease/Events/.	Courses, seminars and webinars on rare diseases.

*Resources that are not specific for rare diseases but include important aspects of rare diseases.
**Some of these resources may have limited duration or accessibility.

Conclusions:

- RD (research) education and training ecosystem is highly complex: it involves many „learners", „teachers" and providers, and multiple forms of teaching and learning, including formal, non-formal and informal education.
- The needs of learners are vastly different across the education and training continuum and follows a principle of a pyramid.
- Many RD education and training resources have been recently developed by the main RD organizations, ERNs, professional organizations and other stakeholders.

3.1.3. Challenges and opportunities for RD research education and training

Although the need for RD education and training is evident from both public health (unmet needs of PLWRD and families) and learners' perspective (objective and self-reported insufficiency of RD knowledge and even awareness), there is a general lack of attention to developing and delivering targeted and coordinated RD education. In recent years, many novel activities and players (as ERNs and a dedicated Multidisciplinary Committee in the UEMS) have appeared and will presumably play a significant role, however, currently there is a lack of a coherent strategy for RD (research) education and training across Europe and in the MS. These deficiencies may be attributed to multiple factors.

- **Rarity everywhere and the paradox of rarity**. Although for individual rare diseases there is a rarity of patients, experts, researchers, specimen, data and resources, collectively PLWRD comprise a significant part of our societies: at any given time, patients with RD comprise 3.5 to 5.9% of a population, excluding rare cancers, intoxications, and infectious diseases [Nguengang Wakap 2020]. Although social and economic burden of rare diseases is substantial [EveryDayLife Foundation; A Rare Barometer survey 2018], for many decades RD were, and in many cases still are, neglected in healthcare systems; due to the lack of specific RD codification, the RD burden is systematically underestimated contributing to the relative invisibility of its public health impact [Rath 2012]. For rare cancers, better codification opportunities and consequently more data on burden are available [Gatta 2019]. Together with a paradox of rarity (i.e., RD and rare cancers are individually rare, but collectively common), it may create a perceived lack of interest towards RD; indeed, both professionals and students usually severely underestimate probabilities of encountering RD in their practice [Sarrafpour 2021]. Due to the similar reasons of perceived rarity, rare diseases are also neglected in the curricula and teaching programs of universities and medical schools. For example, less than 3% of the websites of European medical schools in the World Directory of Medical schools (398 medical schools in the EU and UK, https://www.wdoms.org/, accessed in December 2020) mention rare diseases in their curricula and teaching programmes. A frequent complaint of both educators and students are overwhelmed curricula; although the digital transformation has changed the role of universities from memorization of facts to location of requisite information for synthesis, analysis and decision-making, the sheer amount and dispersion of novel data and information in medicine is immense and RD field is no exception with more than 6000 nosological entities currently known.
- **Novelty, rapid development and expansion of RD field**. RD as a field has novel dynamics; in Europe, RD have been defined and prioritized as a public health issue only two decades ago [EC Regulation 2000] and many current professionals and educators have completed their medical education long before; they may be uncomfortable with and unprepared for RD education. Over

several recent years, major novel players - ERNs – have appeared in the landscape of RD. Currently, ERNs encompass over 1600 CoE in rare and complex diseases and in many cases are based in the large and acknowledged academic hospitals, where highly-specialized healthcare, research and medical education are centralized (Table 8) [Tumiene 2021]. ERN Board of Member States is currently working on the development of ERN Strategy on Education and Training on Rare and Complex Diseases. European research infrastructures and professional organizations are also increasingly engaged into RD education and training activities (Table 5). Recently, a Multidisciplinary Joint Committee on Rare and Undiagnosed Diseases was established in the UEMS. After a workshop "Rare Disease Education in Europe: time for a change", RD were included as one of the strategic directions in the Association of Medical Schools in Europe. Together with EJPRD, national and EU authorities, all these players still have to define their place in the overall RD research education and training landscape and contribution to the common strategy in RD research education and training.

- **Heterogeneity of RD and multistakeholder community**. More than 6000 RD that are currently known may affect any organ or body system at any age, and in most cases RD are multisystem, consequently, healthcare professionals of any specialty will see PLWRD in their practice and RD education is important to everybody in care systems. Along the R & I pipeline from basic to preclinical, clinical and translational research, there is a host of RD research-relevant areas like molecular biology, biochemistry, genetics, genomic/-omic testing technologies, biostatistics, bioinformatics, biobanking, clinical trials, data and ELSI management, etc. (see Table 7, Keywords as an example) that require special knowledge, skills and know-how. Moreover, although these areas in many cases overlap with the overall field of health sciences, many specificities of RD demand for specific knowledge and skills (e.g., undiagnosed diseases, greater reliance on -omic technologies, complicated issues of data management and biobanking due to the rarity and international dimension of collaboration, innovative therapies, methodologies for small population clinical trials, etc.) [Boycott 2019; Hechtelt Jonker 2020; Day 2018; Hilgers 2018; Philippakis 2015; Southall 2019; Graham 2014]. All these factors result in a huge diversity of a multidisciplinary and multistakeholder RD research community, a large educational load of highly-specialized knowledge and skill, and demand for an ecosystem-approach to foster productive collaborations.
- **Role of professional organizations**. Professional organizations play an important role in definition of educational standards and provision of continuous education to their communities of specialists [Reincke 2021; Demmer 2014; Sechi 2019; Dittrich 2016]. Due to the aforementioned heterogeneity and novelty of the field, there is no single professional organization dedicated to RD as a whole. Although some professional organizations are devoted to a specific RD area (e.g., Society for the Study of Inborn Errors of Metabolism (SSIEM) or International Society of Pediatric Oncology (SIOP), Table 5) and all their educational activities are for RD, there is a huge diversity in resources that other professional organizations in subspecialties devote to RD (from 100% in childhood cancers to 0,X% in other professional and scientific organizations).
- **Awareness about existing educational resources**. EJPRD surveys, literature analysis and feedbacks from national authorities, all unequivocally show a limited awareness about existing RD research and educational resources. Although many on-line, face-to-face or blended learning resources for RD education and training have been developed in recent years (Table 5), awareness about these resources is still low. It results in a significant under-usage due to non-awareness as compared to non-availability, with subsequent consequences of wastage and diminished quality of research.

- **Unequal competitive conditions as compared to more common diseases**. RD researchers have unequal competitive conditions as compared to researchers who investigate more common diseases [Reinecke 2011]. For example, lower competitiveness of RD project proposals results from the fact that "relevance of funding" and "research impact" are incomparable when we compare common diseases (e.g., diabetes, millions of patients who may eventually benefit) and an individual RD (dozens or several hundreds of patients who may eventually benefit). The same applies to the research outcomes (e.g., rating of publications; common diseases have common readers with higher citation indexes and impact factors). These factors may deter researchers from seeking career in RD research and, consequently, training [Reinecke 2011]. Moreover, there is a higher reliance of RD research on international collaboration (see below) [Julkowska 2017; Shash 2013; Dawkins 2018], where competitiveness may be even higher and additional requirements for knowledge, skills and networking capabilities arise. An important challenge in medical education on RD and rare cancers, that makes it essentially different from common diseases, is the lack of reinforcement of information for the vast majority of HWF (any given RD is a rare occasion in clinical practice, therefore, clinicians do not reinforce their knowledge after its acquisition) [Joint Action Rare Cancers, 2017]. Therefore, complementary educational strategies and goals should be applied to professionals across the education and training continuum from generalist to specialist and expert, and the most specialized, expert-level knowledge is usually available only in highly-specialized institutions as Centers of Expertise.
- **A higher reliance on international networking and collaboration**. In RD, almost every patient, specimen and data piece may become a precious resource for knowledge generation and research and sufficient cohorts of patients and sets of specimen and data are only collected through concerted actions of many stakeholders and strong, vast international collaboration [Austin 2018; Julkowska 2017; Boycott 2019 (b); Boycott 2017; Monaco 2022; Philippakis 2015; Krischer 2014]. RD experts and researchers are equally rare. Although, according to the Orphanet database for research projects, national funding comprises a higher proportion of the whole portfolio for RD research funding as compared to international funding [Julkowska 2017], a survey performed in EJPRD WP2 and RD-Action data show that only several countries have national programs dedicated to RD research [RD-ACTION; EJPRD Del2.3 Third Analysis of national state of play and alignment process with EJP RD]. Other countries, especially small MS or those with a more limited expertise in RD, mostly rely on transnational research in RD, and even those MS that have national RD research programmes do also participate in the international RD research programmes. Requirement for international collaboration puts an additional educational load onto RD researchers, including the need for extended professional networking, skills to establish and maintain international, multicultural research teams, know-how on the management of multiple European and national bioethical and legal regulations (e.g., for data sharing and management), last but not least – linguistic capacities to communicate, to list just several additional competencies [Hartman 2019; Graham 2014; Reinecke 2011; Somanadhan 2020].
- **Increasing complexity of ELSI, data management and regulatory issues**. This challenge is not specific to RD research, but is a global trend and challenge for the research environment that demands for additional knowledge, skills and know-how.
- **Geographic inequities**. Although RD more or less equally affect people of any ethnic background or nationality, opportunities for researchers to perform research and for patients to engage into clinical research and share their data for the sake of science are not equal across Europe and globally. These inequities eventually result in diminished career opportunities and lower motivation

to gain knowledge and education in RD research. There are many reasons for these inequities, including:

(i) General investments into R & I (national and European)

The European Research Area (ERA) is 'a unified research area open to the world based on the internal market, in which researchers, scientific knowledge, and technology circulate freely and through which the Union and its Member States strengthen their scientific and technological bases, their competitiveness and their capacity to collectively address grand challenges', European Commission (2012). At the start of their integration into the ERA, most of the EU-13 countries faced numerous challenges related to the legacy of the previous governance systems and were characterized by a lack of focus on research and innovation. However, after almost 20 years of participation, as a group the EU-13 countries has lower research and development expenditure and lower innovation performance. The R&D expenditure (Eurostat, 2019) as a percentage of GDP is higher in the EU15 (2.2 %) than in the EU13 (1.1 %). HU (1.35 %), CZ (1.79 %) and SI (1.86 %) approach the average level of the EU28. Levels of R&D spending in IE (1.05 %), EL (1.13 %), ES (1.2 %) and PT (1.33 %) are comparable to those in most EU13 MSs. None of the EU-13 countries are likely to achieve the target of investing 3% of GDP in research and development by 2020 as stipulated in the Europe 2020 strategy. The difference in the percentage of research personnel is also significant: 0.8 % in the EU13 versus 1.4 % in the EU15. According to European innovation scoreboard, among the EU13, only EE is classified as a strong innovator. Ten EU13 MSs are classified as moderate innovators, while RO and BG are labelled modest innovators. No EU13 countries are identified as innovation leaders. Total expenditure on educational institutions as a percentage of GDP is also considerably lower in EU-13 countries; among all OECD countries rated in 2020, no one EU-13 country reached or exceeded and OECD average (Figure 2). Importantly, even though they have similar transformation backgrounds, the EU-13 are socioeconomically a very heterogeneous group of countries with variable performance and progress over time.

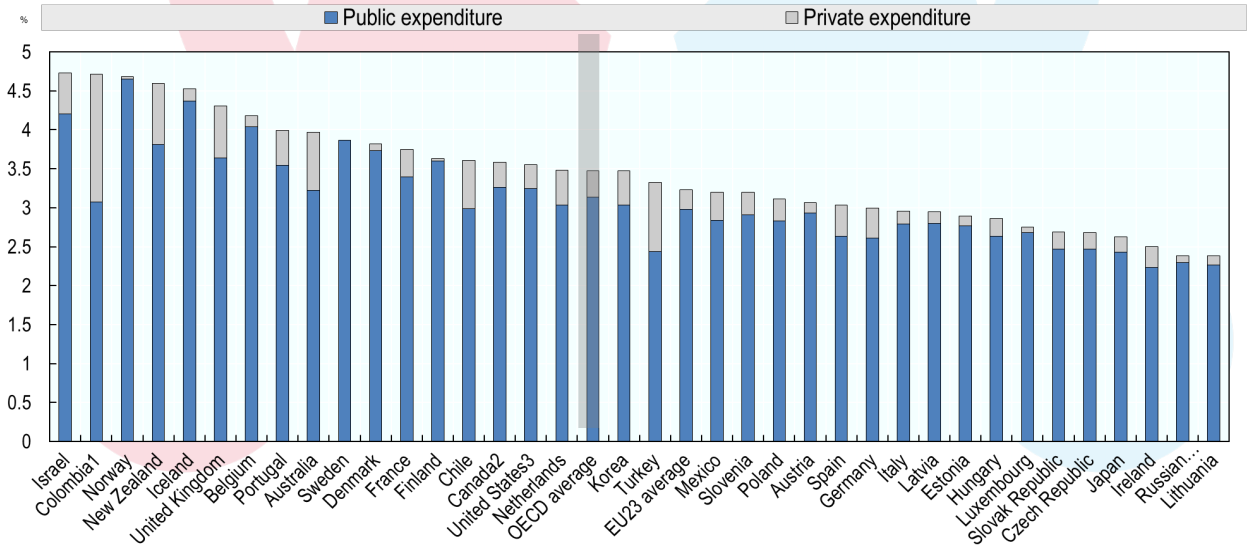


Figure 2. Total expenditure on educational institutions as a percentage of GDP, by source of funds (2017). From: Education at a Glance 2020: OECD Indicators - © OECD 2020

Participation and performance of researchers in the EU research programmes are considerably lower for EU-13 as a group. In FP6, FP7 and Horizon 2020 participation is geographically concentrated. The percentage share of the EU-13 is low and it is declining rather than increasing, from 10.1% in FP6 and

10.3% in FP7 to 8.5% in Horizon 2020. Financial contributions are a key issue in understanding EU-13 participation. Throughout the FPs, EU-15 countries have always been the largest recipients of the EU support [Julkowska 2017; European Parliament, 2018]. In financial terms, the EU-13 obtained 3.7% from FP7 while the EU-15 obtained the remaining 96.3%. The share of funding allocated to the EU13 remains relatively low, reaching 4.4 % in Horizon2020 [European Parliamentary Research Service 2020]. The average financial contribution per EU-13 participation was lower than that of EU-15 participations regardless of funding scheme or the role in project consortia (coordinator versus project member): in FP7, the average EC contribution per EU-13 participation was about half as high as the contribution per EU-15 participation (137k euros vs. 261k euros). In Horizon 2020, the EU-13 has made marginal progress in that the average contribution yields 55% of an average EU-15 contribution 193k euros for an EU-13 beneficiary vs. 351k euros for EU-15 beneficiary) [European Parliament, 2018; European Parliamentary Research Service 2020]. The FPs are based on quality and excellence, which implies that an even geographical distribution of funds based on the principle of 'juste retour' cannot be applied. [European Parliament, 2018]. However, cohesion and global increase of EU's global competitiveness will allow better use of the whole potential and benefits to the EU as a whole.

(i) General lack of excellence and quality of the proposals.

By using fields normalised citation score (FNCS), an analysis of the average citation impact of scientific output per MS in Web of Sciences data extracted from the InCites dataset (period 2014-2016) has been performed by the European Parliamentary Research Service (Figure 3) [European Parliamentary Research Service 2020]. The EU13 MSs generally produced fewer scientific publications per 1 000 inhabitants than the EU15 (2.3 and 4.9 respectively) and have an average FNCS that is almost 30 % lower. However, some EU13 MSs (namely, CY, EE, MT, SI and HU) achieve an average FNCS as high as or near to the level of the EU15.

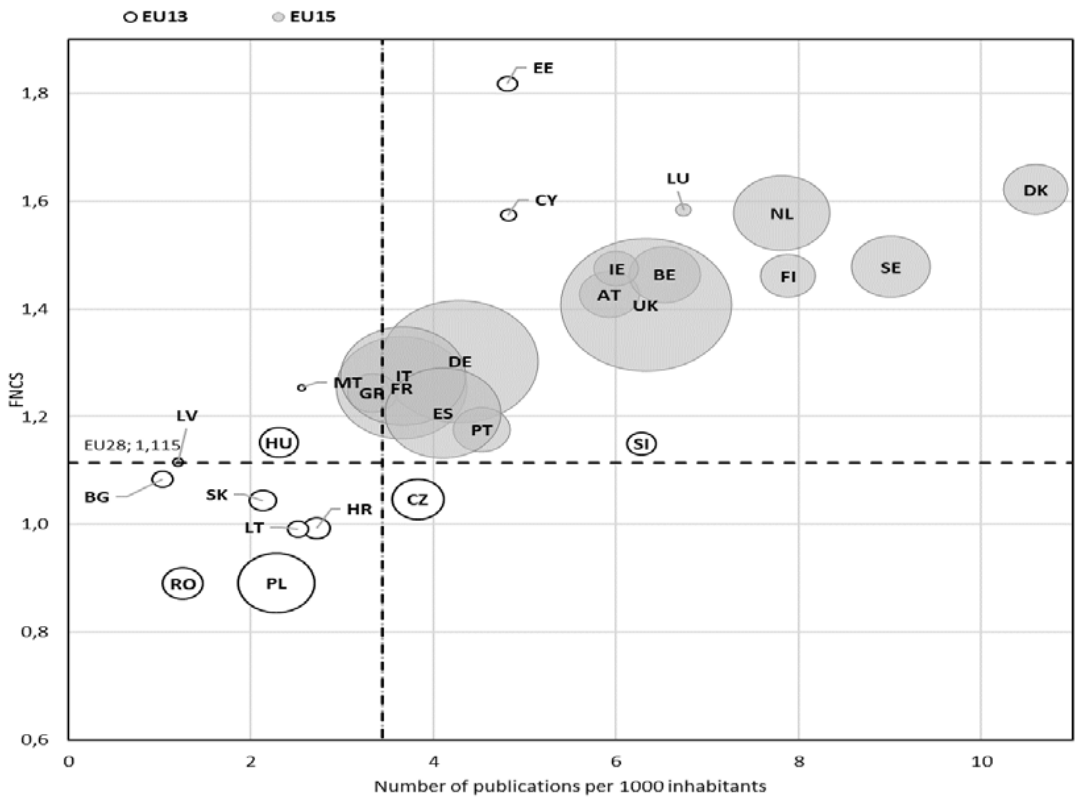


Figure 3. Field-normalised citation scores and number of publications in EU28 MSs, 2014-2016. From: European Parliamentary Research Service. Panel for the Future of Science and Technology. Exploring the performance gap in EU Framework Programmes between EU13 and EU15 Member States. 2020.

Universities from EU-13 also lack excellence: The two university rankings CWTS Leiden ranking and the Times Higher Education world university ranking did not include any universities from the EU13 MSs amongst the top 200 universities. On the contrary, there were 90 universities from EU MSs included in the top 200 in the CWTS Leiden ranking and 85 in the Times Higher Education world university ranking [https://www.leidenranking.com/; https://www.timeshighereducation.com/world-university-rankings/2022/world-ranking#!/page/0/length/25/sort_by/rank/sort_order/asc/cols/stats; European Parliamentary Research Service 2020].

EU13 organizations may be just as active in the FP as EU15 organizations, however they generally participate in proposals of lower quality, resulting in lower success rates. In FP7, submitted proposals involving EU13 organizations scored lower than those involving EU15 organizations and the success rates were 21,8% and 17.8% for EU-13 and EU-15 organizations, respectively [European Parliamentary Research Service 2020]. Low success rate of project proposals may further discourage research teams from preparing and submitting new project proposals [European Parliament, 2018].

(i) Brain drain and lower application activity.

On average, the EU-13 (without CY and MT) has about 245 researchers per 100,000 inhabitants compared to an average of 560 in the EU-15 [Rauch 2012]. The salary 'gap' (which is related to the 'brain-drain' problem) is visible throughout the economy and also affects researchers. Limited human resources may result in a lower application activity: on average, EU-13 Member States have lower levels of participation in proposal submission than the EU-15 Member States. In FP7, there were 334 participations in proposal submissions for every thousand FTE researchers in the EU-15 as against 299 for the EU-13 [European Parliament, 2018].

(ii) Different priorities.

The EU-13 exhibit pronounced differences in size, levels of economic development, general research and innovation efforts, levels of research and development expenditure, areas of scientific excellence, degrees of internationalization, mobility and interaction of human resources, as well as institutions responsible for policy-making in science and information services [European Parliament, 2018]. Moreover, apart from the common challenges due to the recent COVID-19 pandemic and its effects on health and health systems' resilience, EU-13 countries still have much more higher burdens of some non-communicable chronic diseases that may also direct national priorities in health research [European Union 2021].

(iii) Lack of expertise in RD.

Some EU-13 countries may lack expertise in RD. At least in part an expertise in RD may be reflected by the participation rates in ERNs. There are two categories of membership in the ERNs: ERN FM are obliged to conform to the strict quality criteria and take the full responsibilities for ERN's development and performance. MS that do not have sufficient expertise and excellence in RD may designate ERN affiliated partners (ERN AP). ERN AP do not have an obligation to reach certain thresholds of compliance to the criteria, but they should execute activities related to the ERN with which they seek to affiliate (that is formalized through the bilateral agreements). In this way, regulations for the ERNs ensure both excellence of ERN FM and equal accessibility to ERNs across the EU. After the first call for ERN Full Members in 2017, the percentage of ERN FM in EU-13 MS was 11.3% (1,76 ERN FM/mln. of inhabitants in EU-13 vs. 2,14 ERN FM/mln. inhabitants in EU-15) with highly unequal participation rates among EU-13 countries (from 0 to 4,5 ERN FM/mln. inhabitants). Out of 191 current ERN AP, 122 (64% of all ERN AP) are based in the EU-13 MS. After the second call for ERN Full Members in 2021, there is a slight increase in the ERN FM from EU-13 countries: 199 of 1464 (14%) of all ERN FM are based in the EU-13 MS.

Besides, among the 37 European hospitals with the largest number of ERN Full Members there are only 3 from EU-13 countries. Nevertheless, several hospitals in EU-13 are also very active in EU-13 countries: among 14 hospitals with > 10 Full Members and Affiliated Partners, there are 8 hospitals from EU-13 countries (Table 8). Therefore, although the overall participation of EU-13 countries in the ERNs is lower as compared to EU-15 countries, some EU-13 MS are highly active in the ERNs and rapidly gaining expertise in RD.

Some indicators for a comparison of RD research environment are presented in Table 6. Eighteen RD National Plans or Strategies were investigated (available in English or Lithuanian); only 2 of 7 were signed by a national authority responsible for Science or a Government in EU-13 MS, while 9 of 10 available NP/NS were signed by such authorities in EU-15 countries. National RD research programmes (investigated in the RD-ACTION Country profiles) were also much more frequent in EU-15 MS: 7 of 16 available country profiles in EU-15 (44%) vs. 2 of 13 country profiles in EU-13 (15%) mention national RD research programmes [RD-ACTION]. Finally, international collaboration was rated according to the participation in E-RARE 1-3 and EJPRD Joint Transnational Calls; 8 of 13 (62%) of EU-13 MS participate/participated in at least one of these programmes, vs. 14 of 17 EU-15 and EEA countries (82%).

Table 6. Comparison RD research environment in the EU-15 vs. EU-13 MS.

EU-13	**Formal inclusion of research into NP/NS***	**Participation in E-Rare and EJPRD (JTCs)**	**National RD research program****	**EU-15**	**Formal inclusion of research into NP/NS***	**Participation in E-Rare and EJPRD (JTCs)**	**National RD research program****
BG	(-)	(-)	-	AT	+	E-RARE 1-3; EJPRD	-
CY	N/A	(-)	-	BE	+	E-RARE 2-3; EJPRD	-
CZ	-	EJPRD	-	CH	N/A	E-RARE-3; EJPRD	N/A
EE	N/A	EJPRD	-	DE	+	E-RARE 1-3; EJPRD	+
HR	N/A	(-)	-	DK	N/A	(-)	-
HU	+	E-RARE 2-3; EJPRD	+	ES	+	E-RARE 1-3; EJPRD	+
LT	-	EJPRD	-	FI	+	EJPRD	-
LV	N/A	E-RARE 3	-	FR	+	E-RARE 1-3; EJPRD	+
MT	N/A	(-)	-	EL	N/A	E-RARE 2-3	-
PL	+	E-RARE 2-3; EJPRD	-	IE	+	EJPRD	+
RO	-	E-RARE 3	-	IT	+	E-RARE 1-3; EJPRD	-
SI	-	(-)	+	LU	N/A	EJPRD	+
SK	-	EJPRD	-	NL	+	E-RARE 1-3; EJPRD	-
	2/7 (29%)	**8/13 (62%)**	**2/13 (15%)**	NO	N/A	(-)	-
				PT	N/A	E-RARE 1-3; EJPRD	+
				SE	N/A	EJPRD	-
				UK	-	(-)	+
					9/10 (90%)	**14/17 (82%)**	**7/16 (44%)**

N/A - Data not available or not applicable.
*Formal inclusion of research in RD NP/NS was formally rated according to the signature of a National Plan or Strategy for RD, i.e., signature by the Ministry of Health only vs. signature by several Ministries/Government.
** Data on national programmes for RD research were collected from RD-ACTION country profiles, available at http://www.rd-action.eu/rare-disease-policies-in-europe/.

(iv) Lack of collaborative professional networks

Participation in the European FPs depends at least as much on an organization's network as on the quality of its research capacity. Many EU-13 teams have limited networks and few links to foreign organizations and researchers. Moreover, existing networks may constitute barriers to entry. These networks tend to be dominated by research performing organizations from the large countries. It is sometimes argued that this constitutes a kind of 'closed shop', which newcomers can find difficult to enter. By using metrics for social network analysis, European Parliament group investigated numbers of different types of organizations in EU-13 vs. EU-15 countries: Isolates have no connections to other organizations, Brokers are organizations that connect different parts of the network, and Hubs are brokers with many connections. The number of organizations that have been identified as hubs in the FP7 and Horizon 2020 collaboration networks in EU-13 MS was 29 vs. 407 in EU-15. The FP network is dominated by EU-15 organizations, in particular by a small group (the so-called TOP15 organizations) that form the 'core' of the network [European Parliament, 2018]. A similar situation could have arisen in the ERNs, however, the aforementioned regulations for the inclusion of ERN AP (these centers are designated by the national authorities and ERNs are obliged to incorporate them) significantly increased accessibility of ERNs and equity across the EU. Lack of collaborative networks may also, at least in part, explain the lack of awareness about existing resources and opportunities that is sometimes mentioned as barrier for participation.

(v) Factors related to specific funding schemes of the EU FP and the measures to increase participation.

The FPs consist of different instruments and activities: some of them are more targeted at scientific excellence and innovation (e.g., ERC, CP), while in others existing knowledge is used for specific purposes (e.g., CSA). Generally, EU13 participate relatively more in areas of the FPs where existing knowledge is used for specific purposes (e.g., participation rates in CSA were 14% in FP7 and 18% in Horizon2020), and relatively less in funding schemes aimed at excellence and innovation (e.g., participation rates in ERC were 2% in both FP7 and Horizon2020, in MSCA - 5% in both FP7 and Horizon2020, in CP - 7% in both FP7 and Horizon2020).

Aforementioned factors – lack of available national funding and infrastructures, lack of expertise and professional networks may result in a lack of scientific excellence and low success rates. Low success rates result in demotivation for further participation and eventually start a vicious circle of low success and participation – low scientific outputs and excellence – low success and participation, etc. In a new programme Spreading Excellence and Widening Participation was introduced under Horizon 2020, geared towards those MS with relatively lower performance in research and innovation [European Parliament, 2018]. Some of the Widening principles and measures to increase participation of Widening countries were also implemented in the EJPRD (see section 3.1.4.3. Geographical coverage of RD research trainings and measures to increase participation of underrepresented countries for the overview).

A survey and interviews to identify the factors behind lower participation of EU-13 countries in the EU FPs were performed by the European Parliament Working Group [European Parliament 2018]. According to the responses from 82 EU-13 participants of FP7 and/or Horizon2020 projects, the most important structural barriers to the participation were: low success rate of project proposals; limited in-house internal skills in drafting proposals or managing projects; the wage and remuneration gaps; inadequate evaluation system with a low emphasis on internationalization; limited in-house internal skills on drafting proposals or project management; easier access to national resources for funding R&D projects; long time from submitting proposal to contract; inability to get co-funding for FP7/H2020 projects; and bureaucratic application and reporting procedures. Interviews with 21 research policy experts from EU-13 MS revealed that the participation of EU-13 countries was generally perceived inadequate by all of them. Several issues repeatedly mentioned as the key barriers to participation in FP7/H2020 included low success rate of project

proposals; rules of remuneration introduced in H2020 programme; importance of support infrastructure that provides professional services for preparation of project proposals; lack of research collaboration networks; lack of critical mass in R&I that decreases the possibility of participating in large H2020 projects; lack of synergies between national and FP funding, lack of ambitions and strategic management of universities and public research institutions.

Many of these challenges have also been reflected in a survey of national authorities performed by the EJPRD WP2. Ten EU-13 MS responded to the survey in 2020. The main perceived obstacles and barriers for the development, improvement and translation of RD research results were "Funding" (indicated by 89%); "Difficulties in accessing to national resources for funding of research and development of RD projects" (56% respondents); "Lack of options for exploitation of research results at national level" (40%); whereas "Language" and "Other" were pointed out by 11% of the responding countries. Regarding the participation in EU/International projects in the RD field, 78% of the countries indicated "Limited links to potential partners" as the most important estimated obstacle and barrier. The other critical aspects included "Lack of information on funding opportunities" (56 %) "Bureaucratic application on reporting procedures" (50%), "Limited skills on drafting proposals" (44%), "Irrelevance of programme topics and goals to own research agenda" (25%), "Quality of support provided by national contact points" (22%) [EJPRD D2.3].

A survey of ERN members performed by WP17 in collaboration with Pillar 2 also investigated opportunities and barriers for the participation of partners from underrepresented countries that may be addressed through education and training. The main opportunities identified were networking and sharing of expertise within and among the ERNs and standardization of RD research practices for the improvement of RD research. The main barriers included were funding issues and unequal access to resources, heterogeneity among the ERN teams, lack of time for education and training and language issues were also mentioned [EJPRD D17.1].

The following factors may present both challenges and opportunities for RD research education and training:

- **Interconnections with innovative fields**. RD are intrinsically associated with many current innovative fields: up to 80% of RD are genetic and many breakthroughs in genetics, genomics and multiomics, genomic technologies were fueled by investigations of RD. RD were the first where personalized medicine was applied, and many current innovative therapies and those still under investigation (as gene and cell therapies or genome curation therapies) are being developed for RD. That puts an extensive educational load of "cutting edge" knowledge and the need for vast collaborations with innovative fields.
- **The role of RD patients and PAOs**. This role has always been exceptional in RD field, as PLWRD and caregivers are frequently exceptionally knowledgeable: many of them know more about their disease than the professionals whom they meet on their care journey [Bolz-Johnson 2019]. PLWRD and caregivers have high needs for information and skills in self-management, coping, communication and advocacy [Farhat 2020]. Hence, there is a need to develop patient empowerment and educational programmes [Talarico 2020; Farhat 2020]. Collaboration with patient organizations may play a highly important role in the fulfillment of patients'informational and educational needs and the establishment of partnerships among patients and professionals, while one of the most effective ways to ensure partnerships may be through the integrated learning of mixed audiences (patient representatives and professionals together). EURORDIS Open Academy trained over 600 RD patients and patient advocates since 2008, empowering them with knowledge and skills to take part in patient engagement roles side-by-side with all stakeholders and to advocate for rare diseases on a European and national level [EURORDIS Open Academy;

Chisolm 2014]. Besides, as the experts of their own disease, PLWRD may provide valuable information on unmet needs and fill the gaps of missing information [Bolz-Johnson 2019].

- **Digital transformation of teaching and learning**. Digital transformation affects healthcare, education and research. In RD, it is critical to overcome geographical barriers for RD data, samples and patients' cohorts, and empowerment of PLWRD, and interconnect RD expertise and knowledge. During recent years, many valuable on-line RD educational and informational resources have been developed by ERNs, EJPRD, EURORDIS, European Society of Human Genetics (ESHG), European School of Oncology (ESO), Medics4RareDiseases and other stakeholders (Table 5). The importance of these resources cannot be underestimated: high quality on-line information for both researchers, professionals and PLWRD is a high unmet need [Litzkendorf 2020]. While the recent COVID-19 pandemic has induced major disruptions in healthcare, research and educational systems, advances in digital technologies provided crucial means to overcome at least some of the challenges and may provide an enduring basis for long-term changes [Djermester 2021; Lucey 2020; Wang 2021]. Notably, the major drivers for a constructive digital transformation are not only the hardware or software, but the so-called humanware [Nazeha 2020]; hence, there is a high need to equip workforce with the crucial digital skills and to evaluate further potential of digital RD education and training under both normal and emergency conditions.
- **Professionalism, social accountability, cultural safety and responsiveness**. The recent movement towards socially accountable professionalism [Frenk 2010] and value-based care [Fantini 2019] enforces the focus on socially vulnerable groups such as PLWRD. Both current and future HWF generally acknowledge RD as a significant public health issue that requires some special measures (Table 5) [Walkowiak 2020; Li 2021; Mancuso 2020; Krajinovic 2013; Walkowiak 2019; Ramalle-Gómara 2015; Domaradzki 2021, Medic 2015; Desser 2013].

Conclusions:

- Although the need for RD education and training is evident from both public health and learners' perspective, there are multiple challenges, including: concept of rarity; novelty, rapid development and expansion of RD field; heterogeneity of RD and multistakeholder community; lacke of role of professional organizations; lack of awareness about existing educational resources; unequal competitive conditions as compared to more common diseases; a higher reliance on international networking and collaboration; increasing complexity of ELSI, data management and regulatory issues, and geographic inequities.
- Other factors may present both challenges and opportunities for RD research education and training: interconnections with innovative fields; the role of RD patients and PAOs; digital transformation of teaching and learning; professionalism, social accountability, cultural safety and responsiveness.

3.1.4. The role of EJPRD in the overall landscape of RD research education and training

3.1.4.1. General overview of EJPRD education and training activities

Education and training programme on RD research, developed in Pillar 3 of EJPRD, is the first program of its kind and completeness in Europe and beyond, offering a revolutionary approach to the integration of education and training into the entire RD research ecosystem that is developed under the EJPRD.

Importantly, many other educational activities, especially those attributed to informal, vocational training and development of transversal skills are ongoing in other EJPRD Pillars and activities. In many cases, these educational activities were developed *ad hoc*, as a response to the (immediate) identified needs of RD research community (e.g., a series of webinars on RD research resources, developed by Pillar 2 after a survey of ERNs and researchers on RD resource awareness, or a "Short guide on patient partnerships in rare disease research projects", developed by Pillar 1 in collaboration with Pillar 3, to increase patient-centeredness of JTC project proposals). Besides, informal learning is obtained through many EJPRD meetings (including EJPRD General Assemblies, Pillar 2 Annual retreats, and RE(ACT) Congress).

Table 7. Overview of the main EJPRD RD research education and training activities (Pillar 3 and other Pillars).

Activity	Targeted stakeholders	Keywords	Collaborations	Countries of training provision*	Development
P3 WP 14.1: Training on the Orphanet nomenclature and RD ontologies for RD research. Training for Trainers; National courses.	Orphanet National Teams	Ontologies, RD codification, data management	Orphanet	Training for trainers: on-line (FR) National trainings: NO, FI, IT, PL, ES, CH	Foreseen in the 5-year plan of EJPRD, adapted according to the feedbacks for continuous improvement
P3 WP 14.2: Standards and quality of genetics/genomics data in laboratory and clinical research practice F2F courses.	Laboratory scientists, clinical geneticists, medical specialists, policy makers and assessors for laboratory accreditation, patient representatives with a basic knowledge of biology or medicine.	Genetic diagnostics, genomic technologies, quality assurance and management of laboratories, data analysis and management	EuroGeneTest, ESHG, UDNI, International Conference for Rare Diseases and Orphan Drugs (ICORD)	IT, DE, BE, TK, PL	
P3 WP 14.3 Training on strategies to foster solutions of undiagnosed rare disease cases F2F courses.	Clinicians, medical specialists, rare disease patient representatives, multistakeholder community	Undiagnosed diseases, multi-omics, functional analyses, diagnostic pathways, networking and matchmaking	ISS, Solve-RD, UDNI	IT (5)	
P3 WP 14.4: Training for biobanks and researchers/clinicians on sample data management F2F courses.	Clinicians, data managers, biobanking specialists, rare disease patient representatives	Biobanking, management of data and samples, quality assurance, ontologies, ethical, legal and social issues (ELSI), stem cells	BBMRI, EASI-Genomics, ERNs (ERICA)	TK, DE, PL, AT, NL, ES, IT (2), LT	
P3 WP 14.5: Training on rare disease registries and FAIRification of data at the source F2F courses.	Clinicians, medical specialists, registry curators, database managers, rare disease patients' representatives, multistakeholder community	RD registries, data FAIRification, ontologies, data management	ISS	IT (5)	
P3 WP15.1 - ExPRESS Expert Patients and Researchers EURORDIS Summer School Pre-training and e-learning courses; F2F courses	Patient advocates, researchers	Clinical trials, Orphan drugs, regulatory and ethicolegal issues, patient engagement, pharmacovigilance, European Medicines Agency, Health Technology Assessment	EURORDIS, Solve-RD	ES (5)	

P3 WP15.2 – Training for patient advocates on scientific innovation and translational research - EURORDIS Winter School Pre-training and e-learning courses; F2F courses	Patient advocates	Translational research, genetics, bioinformatics, ERNs, RD diagnostics, undiagnosed diseases, gene/advanced therapies, genome editing, patient engagement	EURORDIS	FR (5)	
P3 WP15.3 – Training for patient advocates on leadership and communication skills Pre-training and e-learning courses; F2F courses	Patient advocates	Leadership, self-awareness, conflict resolution strategies, authority, negotiation, networking, communication	EURORDIS	IT, TK, PL, ES	
P3 WP 15.4: Educational materials and activities for paediatric patients e-learning; F2F courses	Pediatric patient advocates	Rare diseases, patient engagement, clinical research, ethicolegal issues, informed consent/assent form, patient wellbeing, Rare Disease Day	EURORDIS, TEDDY	Not decided	
P3 WP16 MOOC#1 - "Diagnosing Rare Diseases: from the Clinic to Research and back" On-line academic course.	Students, multistakeholder community (researchers, clinicians, patients and patients' representatives)	General concepts about RD and genetic diagnostics, genomic technologies, care pathways, patient-centeredness, undiagnosed diseases, genetic consultation, genetic research	ERNs	N/A	
P3 WP16 MOOC#2 - Innovative personalized therapies On-line academic course.	Students, multistakeholder community (researchers, clinicians, patients and patients' representatives)	Rare disease treatment, innovative therapies, gene & cell therapy, regenerative medicine, genome editing, personalized medicine	ERNs	N/A	
P3 WP16 MOOC#3 - Translational Research On-line academic course.	Students, multistakeholder community (researchers, clinicians, patients and patients' representatives)	Translational research, preclinical and clinical research, disease models, biomarkers, clinical trials, regulatory issues, ethicolegal aspects, postmarketing	ERNs	N/A	
P3 WP16 MOOC#4 Rare Disease Clinical Trials innovative methodologies On-line academic course.	Students, multistakeholder community (researchers, clinicians, patients and patients' representatives)	Small population clinical trials, clinical trial designs, statistical analysis	ERNs	N/A	

P3 WP17 Research training workshops	Clinicians, multistakeholder community	N/A	ERNs	N/A	
P3 WP17 Fellowships for research mobility secondments	Young clinicians, multistakeholder community	N/A	ERNs	N/A	
P4 WP20.5: Educational program to disseminate advanced statistical trial methodology	Clinicians, ERNs, researchers, biostatisticians, multistakeholder community	Small population clinical trials, clinical trial designs, statistical analysis, drug repurposing		N/A	Developed ad hoc due to identified need; awareness-raising/educational activity
P1 WP6 Webinars for JTC Call participants	JTC call applicants: researchers, patient representatives, multistakeholder community	Ethicolegal regulations, tips for writing a successful applicant, patient-centeredness in RD research		N/A	Developed ad hoc due to identified need; awareness-raising/educational (how to write a successful proposal) activity
P2 WP10 Series of webinars on RD research resources	Users of EJPRD Virtual Platform; multistakeholder community				Developed ad hoc due to identified need; awareness-raising/educational resource on RD research infrastructures and resources
P2 WP10 FAIRification stewards	ERN clinicians, ERN registry staff	Data management and FAIRification, RD registries		N/A	Mentoring acitivity
P4 WP19.1 Real-time mentoring and technical support for translational research projects	JTC project beneficiaries	Translational research, Intellectual property, ELSI regulations	EATRIS	N/A	Mentoring activity

*During the COVID pandemics, the face-to-face courses were adapted to the on-line format.
Note: shaded – RD research education and training activities in other EJPRD Pillars (Pillar1, 2 or 4).

In the overall pyramid of RD research education and training, EJPRD activities are mostly incorporated into the highest levels of the pyramid, although some activities are relevant for the basic and general education and training as well (Figure 4). Overall, the programme serves the needs of RD research community across different career stages from students to junior investigators and experienced, principal investigators (Table 7). While the overall programme to a variable extent addresses the needs of the whole or the vast majority of the RD research multistakeholder community, individual trainings are targeted at various groups of stakeholders. Finally, the programme incorporates a vast range of RD research topics (Table 7, Keywords) along the whole R & I pipeline from basic to preclinical, clinical and translational research. The vast majority of EJPRD educational activities are non-specific for a certain RD or RD group, hence, the programme incorporates all RD nosologies.

Figure 4. RD research education and training in EJPRD across the levels of the educational pyramid.

Note: these WP and Pillars are mostly, but not exceptionally involved into RD research education and training activities along the educational pyramid and there is some overlap.

EJPRD plays several roles in the overall ecosystem of RD research education and training:

- **Education and training providers** – direct provision of education/training and mobility funds.
- **Contributors**, esp. for education/ training at the base of the pyramid.
- **Collaborators** - EJPRD is engaged into collaborations with multiple education/ training providers, like EURORDIS, ESHG, EuroGeneTest, Orphanet; these collaborations may have a high significance for sustainability of trainings.
- **Ecosystem building** – RD research ecosystem developed under EJPRD provides the main means for informal learning and development of transversal skills, identification of trends and patterns for strategic directions in the future.
- **Advisors for policy/decision-making** – especially through EJPRD Policy Board and National Mirror Groups, with an impact on national and European policies on RD education/ training.

3.1.4.2. Exceptional features of the EJPRD RD research education and training programme

RD research education and training programme, developed in EJPRD is exceptional according to several aspects:

- **Comprehensiveness**. By addressing the needs of the whole RD research community across many axes (career stage, multistakeholder community, R & I pipeline), EJPRD RD research education and training programme is the most comprehensive to date.

- **Special provisions for underserved groups; ERNs**: a special support is given to ERNs as a novel stakeholder in the RD research community.
- **Special provisions for underrepresented countries**: special provisions to increase participation from widening countries were implemented.
- **Patient-centeredness**: patient-centeredness of the programme is ensured through the incorporation of extensive educational programme for the empowerment of patients and their advocates, inclusion of patient representatives in almost all educational activities as full participants, fellowships for patient representatives, and engagement of a patient representative as Pillar 3 co-leader and a member of EJPRD Operating group to ensure that all aspects of patient-centeredness are taken into account.
- **Trainings for allied professionals, vocational and skills training**: EJPRD provides many trainings for allied professionals (e.g., laboratory and biobanking specialists, data managers, biostatisticians, bioinformaticians). These professionals are quite often left behind in other educational programmes, as it was also stressed in a recent White paper of the European Strategy Forum on Research Infrastructures [European Strategy Forum on Research Infrastructures 2020].
- **Incorporation into the overall RD research ecosystem**: incorporation of the education and training programme into the overall RD research ecosystem provides many opportunities for informal learning and development of transversal skills and the means for identification of trends and patterns for strategic directions in the future. Multiple bilateral and multilateral connections are established among all four EJPRD Pillars, and extend to the entire RD research education and training ecosystem. Due to this ecosystem environment, EJPRD as a whole was able to respond in an extremely efficient and rapid way to some of the identified educational needs of RD research community (e.g., development of a series of webinars on RD research resources in Pillar 3 as a response to identified lack of awareness, informational/ educational webinars to JTC applicants, educational programme on the methodologies of small population clinical trials in WP20, adaptation of MOOCs to the identified needs of the stakeholders in WP16, etc.; Table 5).
- **Sharing of good practices in trainings**. Continuous monitoring of activities and interactions among Pillar 3 community of educators results in the identification and sharing of good practices for the development, management and continuous improvement of education and training activities. Examples of such collaboration include sharing of templates and methodologies for feedback evaluation, development of "train the trainer" concept, tips on the adjustment of trainings to the local needs of participants (e.g., in WP14.1 and WP14.4), sharing of pedagogical methods (e.g., bring-your-own-data or BYOD, problem-based learning), etc.

3.1.4.3. Geographical coverage of RD research trainings and measures to increase participation of underrepresented countries

EJPRD research education and training programme is aiming to equip researchers with appropriate knowledge, skills, know-how and networking opportunities. Education and training activities are especially important for widening countries to diminish inequities in research performance and to achieve a coherence among MS. Therefore, several **specific measures for widening participation** were implemented in the EJPRD RD research education and training programme:

- **Rotation of courses**. Traditionally, the majority of RD research education and training activities were based in several developed (e.g. EU-15) countries as compared to widening countries (see table 5) due to several factors, including:
- (i) establishment of education providers, e.g., European research infrastructures, international professional or patient organizations, ERN Coordinators, etc.
- (ii) available expertise in RD;
- (iii) available infrastructures or facilities for trainings.

Although the participants of international trainings usually come from various countries, possibilities to participate in such events for the participants from widening countries are frequently limited due to several factors, including:
(i) differences in financial capacities to cover registration fees and travel expenses;
(ii) differences in career opportunities, i.e., in application of training results;
(iii) differences in professional networks (e.g., lack of awareness about existing training activities was mentioned by several respondents from EU-13 countries, surveyed in WP2 [EJPRD D2.23]);
(iv) language issues.
Indeed, only 10 out of 300 participants (3%) of RE(ACT) 2021 Congress came from widening countries [EJPRD D5.3]. The rotation of courses, where possible, was included into the Pillar 3 programme and resulted in the expansion of participation from widening countries in training provision: 22% (8 out of 36) of all Pillar 3 courses in WP14 and WP15 have been or will be provided in widening countries (note: due to COVID pandemics, courses were adapted to an on-line format in 2020 and 2021, but local course organizers remained the same) (Figure 5). In some of these courses (e.g., WP14.4 “Organizing & maximizing rare disease biological sample data in biobanks” in Vilnius) the majority of the course participants came from EU-13 countries. Therefore, course rotation not only empowers local communities with knowledge and skills in RD research, but also increases the experience of local communities to provide RD research education and training.

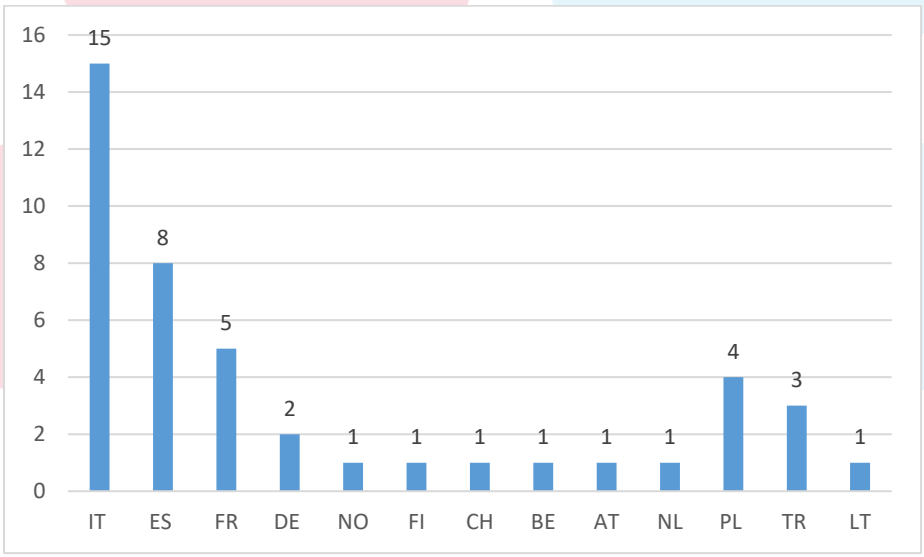


Figure 5. Course rotation in EJPRD WP14 and WP15.

- **Fellowships to participants coming from widening countries.** In all WP14 courses, 2 -3 fellowships to cover travel expenses were allocated to participants coming from widening countries. These fellowships have been used on all occasions.
- **No registration fees, on-line free-of-charge courses**. Although these measures were applied to all training participants, they could also have an impact on participation rates from widening countries due to the aforementioned factors.
- **Adaptation of trainings to the local needs of participants**. In many Pillar 3 trainings, adaptation of trainings to the local needs was fostered: e.g., the training programme on data management in biobanking in WP14.4 incorporates 80% of core programme to ensure standardization and 20% of adjustable contents up to the needs of the participants. As these courses rotate, courses in some widening countries (LT and TR) were more targeted at the beginner level, while those in IT, DE, NL were more targeted to advanced researchers. In WP14.1, Trainings for trainers ensured standardization and quality of teaching on ontologies and ORDO, while national trainings are adapted to the local needs (and are provided in local languages were required). In this way, international committees of training programmes supervise the overall quality and standardization of trainings, while local committees take care about adjustments to the local needs.

Overall, there was a significant participation in the Pillar 3 training activities from widening countries. For example, participants from widening countries comprised from 12 to 50% of all course participants in WP14 trainings in 2019 (Figure 6) [EJPRD D14.1; EJPRD D14.3; EJPRD D14.5; EJPRD D14.7; EJPRD D14.9]. In WP15 trainings, widening countries comprised from 18% in WP15.3 Training for patient advocates on leadership and communication skills to 33% in WP15.1 ExPRESS EURORDIS Summer School [EJPRD D15.1; EJPRD D15.3; EJPRD D15.5] Similar trends were also observed in WP17 education and training activities directed at ERNs. Five out of 25 (20%) fellows in WP17 Fellowships for research mobility secondments came from widening countries (LT, LT, RO, HU, TR). Meanwhile, participation in training provision (i.e., WP17 Research training workshops) was lower: among 20 beneficiaries in 2020 and 2021, only 2 (10%) came from the widening countries (LV and PL).

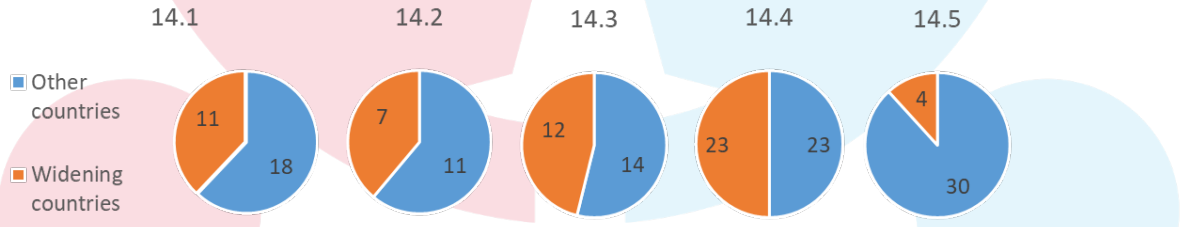


Figure 6. EJPRD WP14 trainings in 2019 (WP14.1 – Training for trainers session, 2020): participation (number of participants) according to the country of origin.

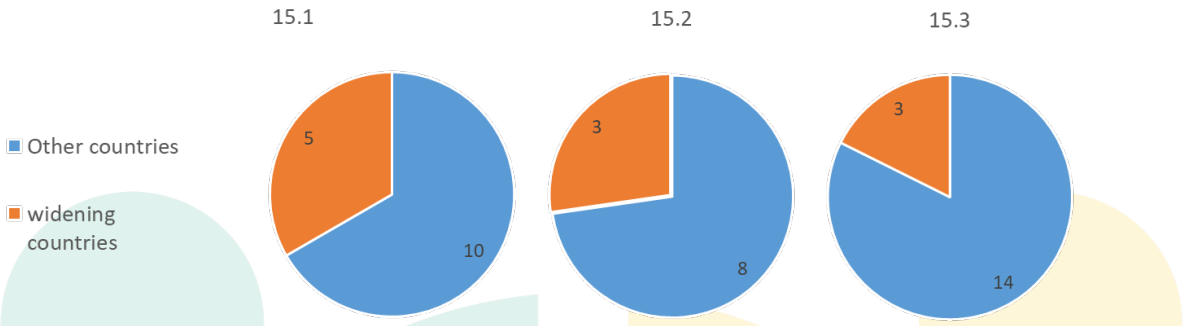
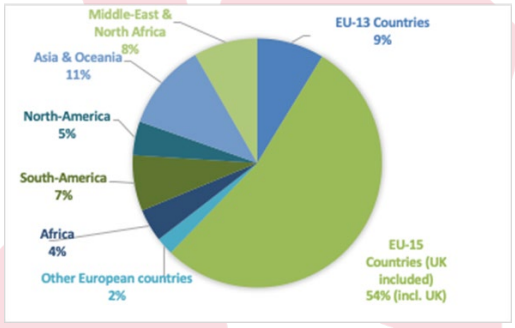
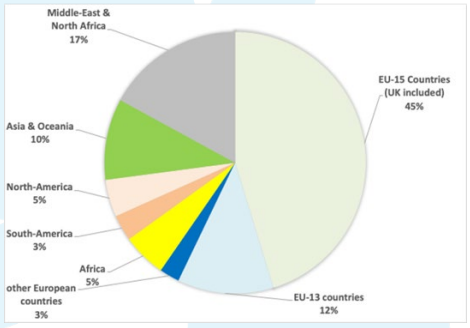


Figure 7. EJPRD WP15 trainings in 2019. Participation (number of countries) according to the participants' country of origin.

In 2021, the first two runs of the WP16 on-line academic course MOOC 1 "Diagnosing Rare Diseases: from the Clinic to Research and back" have been completed. This on-line course was attended by a large audience from all over the world (Figure 8): 1797 learners registered for the first MOOC 1 run (2021 January – July); 1249 (70%) of them visited at least 1 step, 256 (14%) of learners completed 50% of the course, 192 (11%) of learners completed at least 90% of the course. More than half of the participants came from the EU-15 countries (the most active were participants from FR, UK, IT, IN), participants from EU-13 countries comprised 9% of all participants. For the second run of MOOC 1, 1194 participants were registered, 716 (60%) of them visited at least 1 step, 128 (11%) of learners completed 50% of the course, 91 (8%) of learners completed at least 90% of the course. Forty five per cents of learners came from EU-15 countries, 12% - from EU-13 Member States. The course was especially actively attended by learners from FR, UK and LT, also IT and IN.



a) geographical distribution of learners for MOOC#1 run 1 (2021 October - December)



b) geographical distribution of learners for MOOC#1 run 1 (2021 January – July)

Figure 8. Geographical distribution of learners for EJPRD WP16 on-line academic course - MOOC#1.

In conclusion, participants from widening countries are very active users of EJPRD education and training activities. Currently, stakeholders from the widening countries are more frequently "learners" than "teachers" in the RD research education and training activities, however, their competencies to provide RD research education and training may presumably grow in the future with current trends and specific provisions for inclusion and coherence. Moreover, a considerable growth in RD research competencies may be foreseen.

Ideally, participants with enhanced capacities in RD research will become active applicants for project proposals. EJPRD supports various research activities, including those targeted at networking

and establishment of collaborative partnerships (WP9, Networking scheme, "COST-like" activities) and competitive calls for transnational research projects, mostly targeted at scientific excellence (WP6, JTCs, activities, similar to FP7 and H2020 Collaborative projects). In this study, we investigated participation rates according to the country of origin in the EJPRD Networking schemes and JTC calls. In the first five rounds of the Networking scheme, funded applicants from widening countries comprised 31 of 151 applicants (21%) (Figure 9). Of the first 6 funded networking events, only one consortium did not involve beneficiaries from widening countries (5 of 6, 83%). As a comparison, in the COST Action network 82% connections involve EU-15 countries and 40% involve EU-13 countries [Eparvier 2021]. Interestingly, success rate of applicants from widening countries in EJPRD Networking scheme was lower as compared to other countries: the rate of applicants from widening countries in submitted applications was 24% (67 applicants of 281, 12 countries of 29 (41%)), while the rate among funded applicants diminished to 21% [EJPRD D9.9]. Lower success rates of applicants from widening countries were observed across all FP7 and H2020 activities previously [European Parliament 2018]. Applicants from 10 widening countries (out of 26 in total, 38% of countries) received funding for networking. None of beneficiaries from widening countries was a principal investigator for a Networking event.

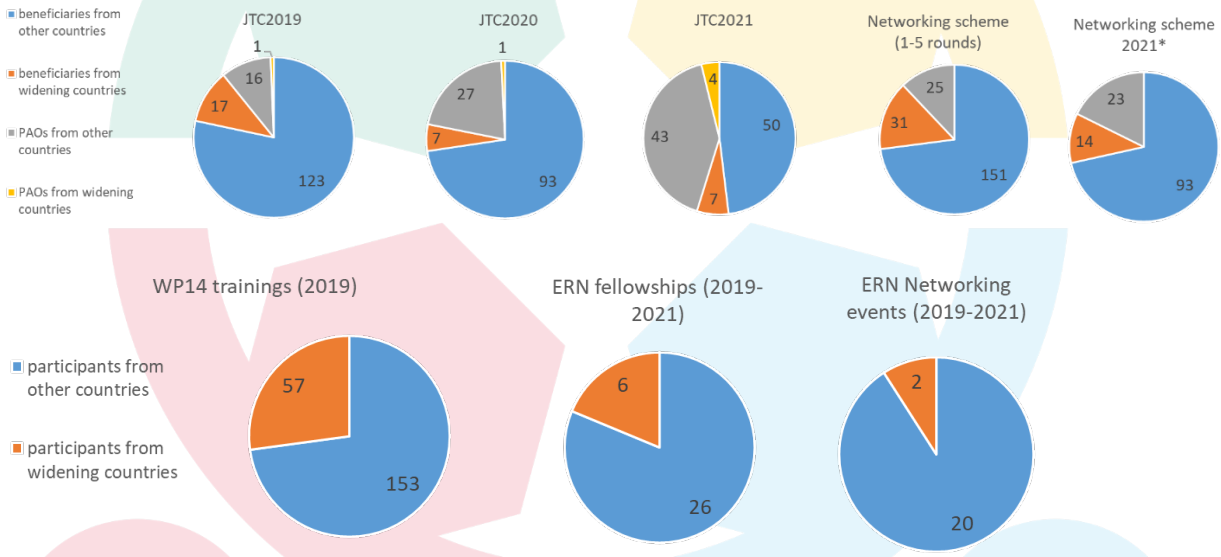


Figure 9. Participation rates according to the country of origin in the EJPRD trainings, Networking scheme and JTCs. Note: * the last round of Networking scheme for 2021 not included.

In the three EJPRD Joint Transnational Calls (2019-2021), beneficiaries from widening countries comprised from 7 to 12% (10% on average, 37 of 389) of all beneficiaries (Figure 10). For comparison, EU-13 participations comprised 8% of total participations in FP7 and 9% in Horizon 2020. However, EU-13 participations in funding schemes aimed at excellence and innovation were considerably lower (e.g., participation rates in European Research Council (ERC) projects were 2% in both FP7 and Horizon2020, in Marie Skłodowska-Curie Actions (MSCA) - 5% in both FP7 and Horizon2020, in Collaborative Projects - 7% in both FP7 and Horizon2020) [European Parliament 2018].

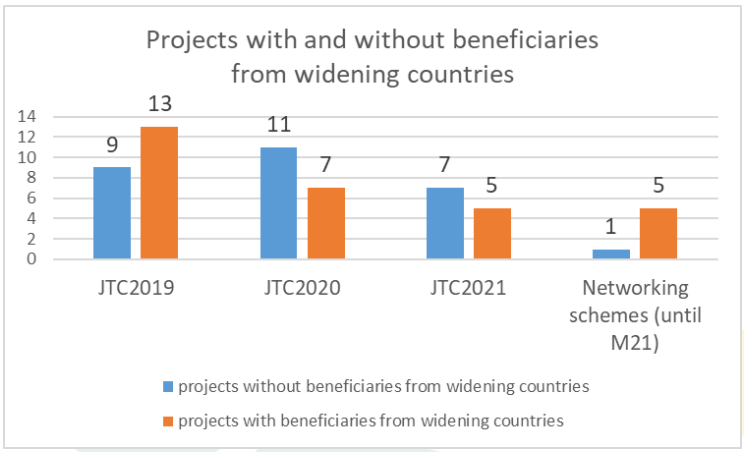


Figure 10. Numbers of EJPRD JTC projects with and without beneficiaries from widening countries.

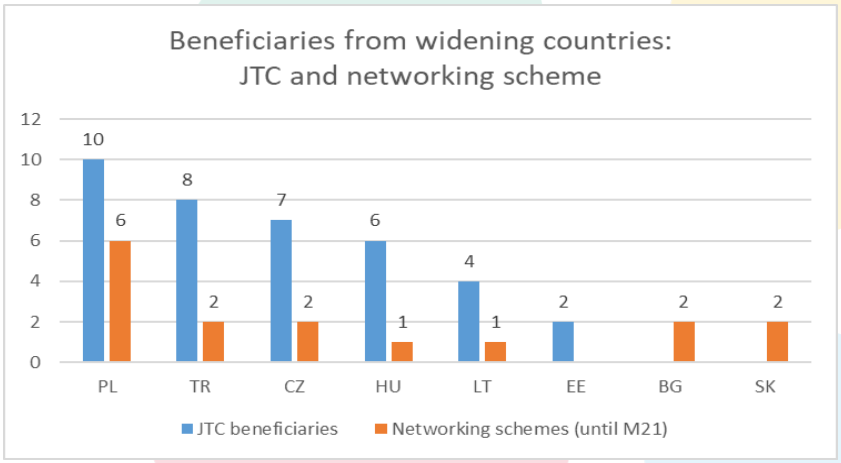
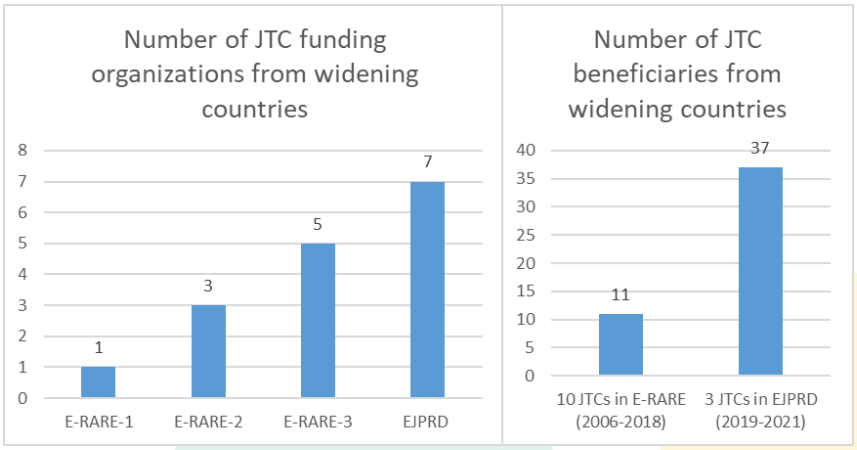


Figure 11. Beneficiaries from widening countries in EJPRD JTCs and Networking scheme.

As compared to previous E-RARE JTCs, there was a significant growth in participation of researchers from widening countries: in the previous 10 JTCs in E-RARE-1, E-RARE-2 and E-RARE-3, there were 11 beneficiaries from widening countries in 8 projects. Already during the first three EJPRD JTC calls there were 37 beneficiaries from widening countries (Figure 12). The most active widening countries in both Networking scheme and JTCs were PL, TK, CZ, HU and LT (Figure 11). Importantly, TK participate in E-Rare JTCs from E-RARE-1 (since 2006), PL and HU – from E-RARE-2 (since 2010), hence, their participation success at least in part may be attributed to the established research partnerships over the years [Julkowska 2017]. None of beneficiaries from widening country was a Coordinator of a project.

In 2015, Widening principles to increase participation from underrepresented countries were included into E-RARE-3 in 2015 (and subsequently in EJPRD since 2019). In EJPRD JTCs, (i) consortia may involve up to 8 partners instead of max. 6, if beneficiaries from the Widening countries or Early Stage Investigators are included; (ii) beneficiaries from widening countries may join the consortia in the second stage of applications. Over the years, there is a substantial growth in the participation of funding organizations from widening countries in JTCs, from 1 funding organization in E-RARE-1 (TK) to 7 funding organizations (CZ, HU, EE, LT, PL, SK, TK) in EJPRD (Figure 12). JTC consortia in all three EJPRD calls actively involved partners from widening countries (Figure 10): on average, 47% of EJPRD JTC consortia involved at least one partner from widening countries (from 39% in JTC2020 to 59% in

JTC2019). For comparison, 41% of all FP7 or H2020 Collaboration projects involved at least one partner from EU-13 countries [European Parliament 2018].



a) b)

Figure 12. Numbers of JTC funding organizations (a) and JTC beneficiaries (b) in E-RARE and EJPRD JTCs.

The average financial contribution per beneficiary in JTC2019 comprised 168k euros for a participant from widening countries and 245k euros for a beneficiary from other countries (i.e., the average of widening countries was 30% lower than the average of other countries), while the average financial contribution per beneficiary in JTC2020 was 145k euros for the beneficiary from widening countries vs. 248k euros for the beneficiary from other countries (i.e., the average of widening countries was 41% lower than the average of other countries). For comparison, in FP7, the average financial contribution per EU-13 participation was about half as high as the contribution per EU-15 participation (137k euros vs. 261k euros, 52% lower). In Horizon 2020, the financial contributions were 193k euros for an EU-13 beneficiary vs. 351k euros for EU-15 beneficiary (55% lower) [European Parliament, 2018; European Parliamentary Research Service 2020]. Overall, beneficiaries from widening countries received 8,7% of funding in JTC2019 and 4,1% of funding in JTC2020. For comparison, the EU-13 obtained 3.7% of financial contribution from all FP7 programmes and 4.4 % from all Horizon2020 programmes [European Parliamentary Research Service 2020]. Widening principles may result in a win-win situation for all consortium participants through the increased participation of beneficiaries from widening countries and increased financial contribution for the whole consortium. Indeed, the average sum of the total requested funding was 1503k euros in JTC2019 projects that involve partners from widening countries vs. 1234k euros in projects that do not involve participants from widening countries (18% lower), and 1405k euros in projects that involve participants from widening countries vs. 1296k euros in projects that do not involve (8% lower) in JTC2020 projects.

Although there was no possibility to evaluate directly, it is possible that enhancement of capacities through training and increased networking possibilities through training and networking scheme activities, were participants from widening countries were highly active, may play a role in their participation rates in EJPRD JTCs.

3.1.4.4. The role of RD education and training for patient-centeredness in RD research

Patient-centeredness in research is impossible without direct inclusion of patients [Young 2019]. Three annual WP15 courses for patient representatives, advocates or mixed audiences of patients and researchers comprise approximately one third of all EJPRD Pillar 3 programme of face-to-face courses

and empower participants with a vast set of knowledge on clinical trials, translational research and many RD research-related knowledge, and leadership/ advocacy/ communication skills. WP15.2 EURORDIS Summer School ExPRESS (Expert Patients and Researchers) provides joint training of patients and researchers. In 2020, a Short Guide on Patient Partnerships in Rare Disease Research Projects have been prepared in collaboration with WP6 [EJPRD AD25]. This educational resource is aimed to guide JTC applicants and other researchers in the establishment of meaningful and productive research collaborations.

According to the EJPRD JTC regulations, PAO may be included into EJPRD JTCs as either beneficiaries or associated partners. Over the three EJPRD JTC calls, there was a considerable growth of participation of PAOs in the JTCs: from 17 of 157 (%) beneficiaries in JTC2019 to 28 of 128 (22%) in JTC2020 and to 47 of 104 (45%) in JTC2021; 92 patient organizations have been included into EJPRD JTCs over the three years (Figure 13). Financial contributions allocated to PAO were also growing from 0.9% of all financial contributions allocated to JTC beneficiaries in JTC2019 to 2% of all financial contributions allocated in JTC2020.

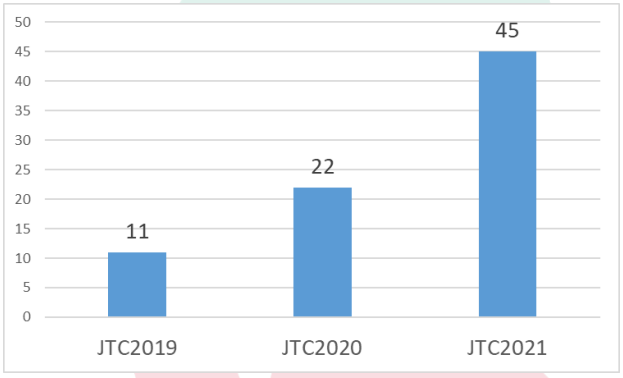


Figure 13. Participation of patient organizations in EJPRD JTCs (2019-2021).

There was low (although increasing) participation rate of patient advocacy organizations from widening countries (from 4 to 8,5% of all PAOs receiving funding): in JTC2019 and JTC2020, only one PAO in each call have been included as beneficiaries (from CZ and PL), while in JTC2021, 4 PAOs from HU (2), LT and PL have been included. Possible factors for lower participation of PAOs from widening countries in EJPRD activities may be similar to those, that are noted by ePAGs in ERNs (importantly, very low number of ePAGs in ERNs come from EU-13 countries) and include (i) lack of funding; (ii) lack of capacities to participate, including language issues; (iii) lack of awareness about existing opportunities. Besides, in many EU-13 countries patient organizations and national alliances have been founded only recently or are still not created, while in the EU-15 countries they already accumulated a considerable experience (Figure 14). Presumably, participation of PAOs from EU-13 countries will increase with increasing experience and awareness.

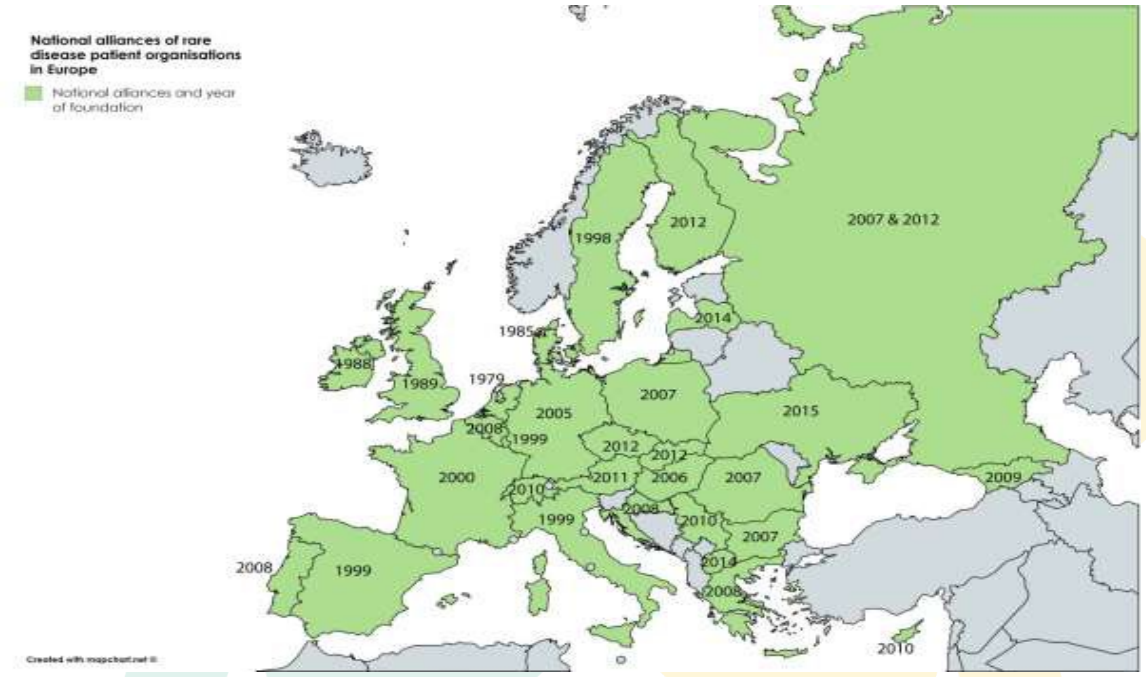


Figure 14. National alliances of PAOs and their year of foundation. From: RD-ACTION. Overview Report on the State of the Art of Rare Disease Activities in Europe. RD-ACTION WP6 Output, 2018.

3.1.4.5. ERN-targeted RD research education and training in EJPRD

Currently, there are more than 1600 ERN Full Members and Affiliated Partners across all EU countries and Norway (Figure 15). Many of these centers are based in the acknowledged academic hospitals and/or are affiliated to universities that have a strong track record in RD research (Table 8). All ERNs carry out many educational activities (Table 5). ERNs organize their educational strategy via the ERN Knowledge Generation working group formed by ERN coordinators and representatives of the ERN Board of Member States [https://ec.europa.eu/health/ern/board_member_states_en], aimed at the development of common approaches to promote and sustain courses, masterclasses, post-doctoral programs and mobility programs for pre- and postdoctoral fellows on RDs. All these activities constitute the ERN Academy, a virtual platform which will collect all the educational modules generated by the ERNs. The aim of the EJPRD education and training programme is to complement ERN educational and training programme with RD research training, to empower ERN community with RD research knowledge and skills and to foster its incorporation into the overall RD research ecosystem.

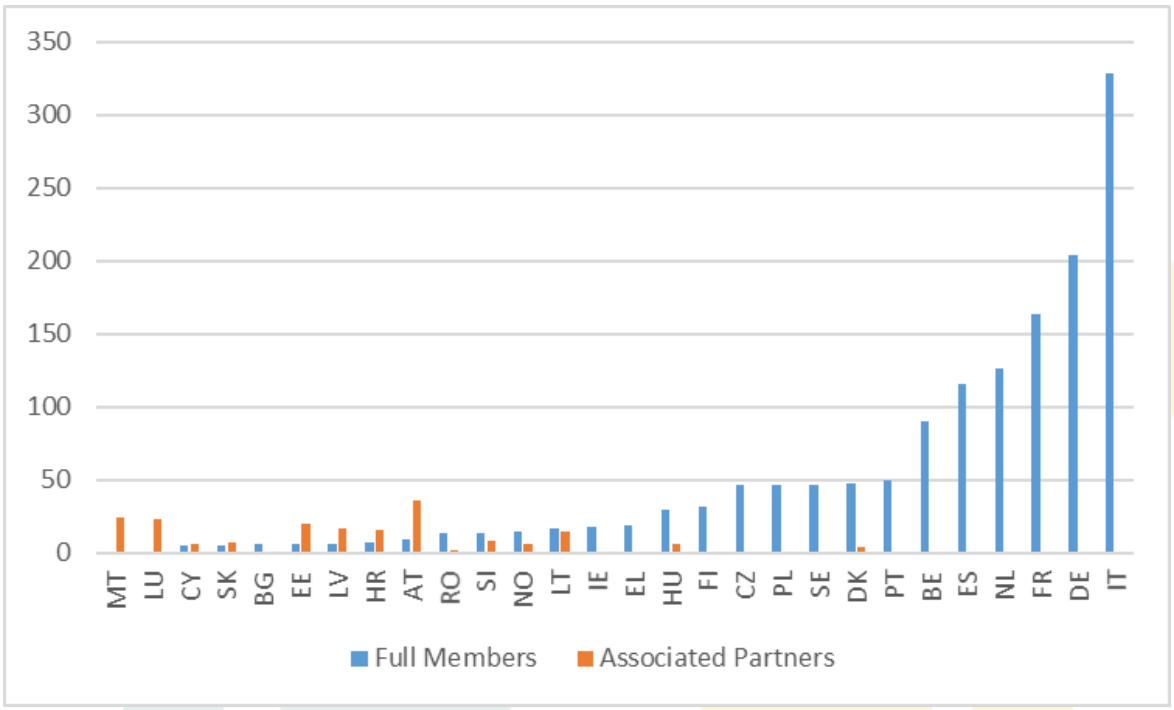


Figure 15. Number of ERN Full Members and Associated Partners in the EU countries and Norway.

Table 8. Hospitals with the largest number of ERN Full Members and Affiliated Partners.

Hospitals with the largest number of ERN Full Members (> 10 Full Members)	NL: Erasmus MC: University Medical Center Rotterdam – 24; FI: Helsinki University Hospital – 21; IT: AO di Padova – 21; DK: Rigshospitalet - 20; IT: IRCCS Ospedale Pediatrico Bambino Gesù, Roma – 20; BE: UZ Gent – 20; SE: Karolinska University Hospital – 20; BE: UZ Leuven – 19; ES: Hospital de Sant Joan de Déu – 19; DK: Aarhus University Hospital – 18; ES: Hospital Universitari Vall d´ Hebron – 18; NL: Radboud University Medical Center Nijmegen – 18; NL: University Medical Center Utrecht – 18; IT: Fondazione Policlinico Universitario A. Gemelli – Roma – 16; BE: Cliniques universitaires Saint-Luc – 15; **CZ: University Hospital Motol – 15;** DE: Charité Universitätsmedizin Berlin – 15; FR: APHP, Hôpital Necker Enfants Malades – 15; IT: Fondazione IRCCS CA'Granda Ospedale Maggiore Policlinico – 15; NL: Academic Medical Centre of Amsterdam – 15; NL: University Medical Centre Groningen – 15; NL: Leiden University Medical Center – 14; SE: Sahlgrenska University Hospital – 14; BE: Antwerp University Hospital – 13; DE: Universitätsklinikum Hamburg-Eppendorf – 13; NO: Oslo University Hospital - 13;

	LT: Vilnius University Hospital Santaros Klinikos - 12; DE: Universitätsklinikum Freiburg – 11; FI: Hospital District of Helsinki and Uusimaa – 11; IT: AOU Senese – 11; IT: IRCCS Istituto Giannina Gaslini, Genova – 11; **SI: University Medical Center Ljubljana - 11;** ES: Hospital Clinic de Barcelona – 10; ES: Hospital Universitario La Paz – 10; IT: AOU Federico II di Napoli – 10; IT: AOU Meyer di Firenze – 10; PT: Centro Hospitalar Universitario do Porto – 10.
Hospitals with the largest number of ERN Full Members and Affiliated Partners (> 10 FM and AP)*	LU: Centre Hospitalier du Luxembourg – 24 (1); **MT: Mater Dei Hospital – 24 (0);** DK: Rigshospitalet - 22 (20); **EE: Tartu University Hopital - 21 (5);** DK: Aarhus University Hospital – 20 (18); **SI: University Medical Center Ljubljana - 19 (11);** **LT: Vilnius University Hospital Santaros Klinikos - 18 (12);** **HU: Semmelweis University - 16 (10);** NO: Oslo University Hospital - 16 (13); AT: Medical University of Vienna/ Vienna General Hospital - 14 (2); **HR: University Hospital Center Zagreb - 14 (6);** **LV: Children`s Clinical University Hospital, Riga - 14 (5);** **LT: Hospital of Lithuanian University of Health Sciences Kauno Klinikos - 13 (5);** AT: Medical University Innsbruck – 12 (2).

Note: **in bold** – hospitals from EU-13 countries.
*Number of hosted ERN Full Members is provided in parentheses.

In 2019, a survey on ERN preferences, needs and resources in training was performed in WP17, in collaboration with Pillar 2 [EJPRD D17.1]. Only 51 of 291 (17.5%) respondents indicated that there is a specific research skills and support training available in their countries, whereas 60% indicated that there is a need for training stays of research fellows and almost 40% answered that there is a need to promote active engagement of ERNs with the RD research ecosystem. There was a strong interest in the development of highly-specialized technical skills, acquiring methodologies, hence the strong preference for in-person trainings. ERNs are less oriented at basic education in RD research. Both junior and senior ERN investigators require trainings, the other multistakeholder group members include laboratory scientists, PhD students, IT staff and research nurses. EJPRD education and training resources may also increase capacities of ERN community to partner with PAO in RD research: according to the survey, currently engagement of patients into ERN research is mostly restricted to invitations to the conferences and awareness-raising activities, although more than 35% of respondents indicated t, hat they include patients into the research boards. Involvement of patients' perspective into RD research was identified as an opportunity by ERN respondents, however, many barriers were also mentioned, including difficulties of traveling, lack of experience, leadership skills, psychological and language issues.

EJPRD trainings actively targeted and involved participants from ERNs: e.g., in WP14.5 course on undiagnosed diseases, prioritization in the selection of participants was also given to participants from ERNs and among the selected participants there were representatives from 12 ERNs [EJPRD D14.5].

The WP14.5 course on RD Registries and FAIRification of data at the source was developed and provided in close collaboration with task partners from Endo-ERN, BOND ERN and MetabERN and among the selected participants there were representatives from 12 ERNs [EJPRD D14.9]. Due to COVID19 pandemics many in person education and training activities in WP17 had to be postponed, therefore it is too early to assess their impacts at the current stage.

3.1.4.6. National alignment of RD education and training

Although data on national RD research education and training activities are very limited, some insights about insufficiency of these activities may be drawn from both literature data (see studies in Table 3, performed in PL, ES, BE, BG, FR, DE and IT) and surveys. In the studies described in Table 3, basic knowledge and awareness of RD was mostly investigated among clinicians, students and nurses. However, a survey of ERN members shows that education and training on highly-specialized RD knowledge and skills are also highly limited: only 51 of 291 (17.5%) respondents indicated that there is a specific research skills and support training available in their countries [EJPRD D17.1]. Moreover, the vast majority of identified educational activities (Table 5) are based in the EU-15 countries, therefore, RD research education and training may be even more insufficient in the EU-13 countries.

In 2019, a survey of national authorities (27 countries, including 20 EU MS, 10 of them - EU-13 countries) was mostly based on RD NP/NS analyses. 78% of interrogated national authorities (from AM, BG, HR, CZ, FR, GE, DE, IE, IT, LT, LU, PL, PT, RO, RS, ES, TK, UK) answered "yes" to the question "Does the NP/NS for RD promote and/or support training activities?" Topics of supported trainings include empowerment of patients, registries, data management, standard and quality of genetics/genomics data in clinical practice and laboratories. However, after analyzing available RD NP/NS (18 RD NP/NS, available in either English, Polish or Lithuanian, BG, CZ, HU, LT, PL, RO, SI, SK, AT, BE, DE, ES, FI, FR, IE, IT, NL, UK), it seems that support is mostly non-financial, through the endorsement of universities and university / teaching hospitals. Another conclusion (collected from EJPRD D2.3 and an EJPRD Strategy Meeting "Alignment of national rare diseases strategies with EJP RD" in 2021) was that the outspread of the Covid-19 pandemic channeled the resources and efforts of the countries to face the emergency situation over the last two years.

Although responsibilities for the basic RD and RD research education have to be taken at the national level (mostly universities and university hospitals), major European and international efforts are required to provide highly-specialized RD research education and training (e.g., international professional organizations, ERNs, RD knowledge bases in Table 5). Indeed, all Scientific Committees and Faculties in EJPRD face-to-face and on-line courses are comprised of international membership, because RD research expertise is scattered across countries.

Conclusions:

- In the overall RD research education and training ecosystem, EJPRD acts as a major contributor, direct provider and collaborator in education and training activities and ensure ecosystem building and advisory role for policy/ decision making. EJPRD RD research education and training programme is exceptional in several ways, including its comprehensiveness across many axes (including career stage, multistakeholder community needs, R & I pipeline), inclusiveness (through special provisions for underserved groups and underrepresented countries), trainings of allied professionals and development of transversal skills, incorporation into the overall RD research ecosystem, means for sharing of good practices in trainings.
- Participants from widening countries are very active users of EJPRD education and training activities; special EJPRD provisions to increase participation from widening countries not only

empower local communities with knowledge and skills in RD research, but also augment their experience to provide RD research education and training. Active participation of widening countries in EJPRD RD research education and training activities may be one of the factors to increase participation in networking (EJPRD Networking scheme) and JTC activities; longer perspective is required to investigate these impacts.

- Through education and training activities, directed at both patients and reserachers, EJPRD provides a strong basis for patient-centredeness in RD research. It may be one of the factors (together with improved regulations for PAO participation in JTCs) for a significant growth in PAO participation in EJPRD JTCs.
- RD education and training activities complement ERN educational and training programme, may empower ERN community with RD research knowledge and skills and foster its incorporation into the overall RD research ecosystem. As many face-to-face training activities had to be postponed due to COVID-19 pandemics, currently it is too early to investigate the impacts.
- Although data on national RD research education and training activities are very limited, some insights about insufficiency of these activities may be drawn from both literature data and surveys. The major responsibility of MS would be provision of basic RD and RD research education (provided mostly in universities and university hospitals), while major European and international efforts are required to provide highly-specialized RD research education and training. Another promising option is a concept of "training of trainers" that is provided internationally and ensure standardization, high quality and up-to-dateness of trainings, that are further spread to national networks and adapted to local needs.

4. Conclusions and recommendations

Many current issues in RD field may be, at least in part, rectified through the enhancement of an educated, competent, ready to act RD research community. During the recent years, the intensity of RD research education and training activities have substantially grown due to the comprehensive EJPRD education and training programme and actions of other related stakeholders (as ERNs). It is highly important to keep the momentum going and to further enhance and fill the identified gaps in RD research education and training. It will require actions at three levels: (1) level of organisations, (2) national level, and (3) European and global level. Actions will be most successful if they address the situation at multiple levels.

- **Coherence of RD research education and training activities based on a common strategy across Europe and globally**. Community of RD research learners, teachers and education providers is complex and involves multiple layers across the educational pyramid. EJPRD and many recent initiatives, including ERNs, UEMS and Association of Medical Schools in Europe, work towards strategies and standards of RD education and training. It is highly important to align all these strategies and to ensure that RD multistakeholder community members complement and jointly enhance efforts and available resources for the most optimal results and coherence across Europe and beyond.
- **Better alignment of national and transnational RD research education and training activities to fulfil the needs across RD research educational pyramid**. The major responsibility of MS would be provision of basic RD and RD research education (provided mostly in universities and university hospitals), while major European and international efforts are required to provide highly-specialized RD research education and training. Another

promising option is a concept of "training of trainers" that is provided internationally and ensure standardization, high quality and up-to-dateness of trainings, that are further spread to national networks and adapted to local needs.

- **Awareness-raising and education based on existing resources** to diminish underusage due to non-awareness as compared to underusage due to non-availability. Although many valuable resources have been developed recently, surveys of end-users have shown a staggering lack of awareness about these resources and possibilities. Efforts should be strengthened at all levels (organizations, national, European/global) to increase awareness and usage of available resources (e.g., fostering RD research trainings for project applicants, requirements for standardization and practices in RD research, national or organizational fellowships for trainings, etc.).
- **Incorporation of RD research education and training into the overall RD research ecosystem to ensure up-to-date, empowering education and training and timely response to arising needs**. Incorporation of education and training activities into the overall RD research ecosystem is of the utmost importance for several reasons: 1) It ensures high quality and standardization; as RD research field is rapidly evolving and has multiple connections with other innovative fields.
  2) It ensures up-to-dateness, identification of future trends and strategic directions.
  3) It is a way to ensure effective and timely response to arising needs of end-users. Herein, EJPRD provides the means for such incorporation that otherwise would be impossible.
- **Continuing efforts to diminish inequities and to foster inclusiveness in RD research through special provisions for underserved groups and underrepresented countries**. Education and training provide powerful means to empower underserved and underrepresented groups and communities. As an EU programme, EJPRD provides highly effective means for increased inclusion (targeted at patient representatives, underrepresented countries and ERNs) that would be otherwise entirely or almost impossible (i.e., these means are usually not included into existing RD education and training activities).
- **Commitment for a long-term strategy for the RD research workforce development**. Workforce development in such highly-specialized and complex fields as RD research takes considerable time. National, European and International authorities and organizations should commit themselves for a long-term strategy of RD research education and training and foresee directions and investments for decades.

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6. Annex. EJPRD documents used for the study

EJPRD D1.4 Second report from the face-to-face ExCom and Policy Board meeting.
EJPRD D1.5 Third report from the face-to-face ExCom and Policy Board meeting.
EJPRD D1.10 Third Summary Progress Report and Annual Work Plan.
EJPRD D1.13 First Technical and Financial Report.
EJPRD D1.14 Second Technical and Financial Report.
EJPRD D2.23 Third Analysis of national state of play and alignment process with EJP RD.
EJPRD D5.3 First RE(ACT) [and IRDiRC Conference 2021] Congress report.
EJPRD D6.9 First Joint selection list of the projects to be funded JTC2019-2022 (Confidential).
EJPRD D6.10 Second Joint selection list of the projects to be funded in JTC2020 (Confidential).
EJPRD D7.3 List of funded networks in the Networking Support Scheme due at Month 21
EJPRD D9.9 First Report on the assessment of results of a 1st, 2nd and 3rd set of funded Networking events and a final general report on all funded Networking events (Confidential).
EJPRD D10.1 First Annual strategic report and Action plan for Pillar 2, including: Systematic surveys reports, QMS of Pillar 2 description, GDPR compliance report and sustainability planning reporting.
EJPRD D10.2 Second Annual strategic report and Action plan for Pillar 2, including: Systematic surveys reports, QMS of Pillar 2 description, GDPR compliance report and sustainability planning reporting.
EJPRD D10.3 Third Annual strategic report and Action plan for Pillar 2, including: Systematic surveys reports, QMS of Pillar 2 description, GDPR compliance report and sustainability planning reporting.
EJPRD D14.1 First Report of Orphanet nomenclature training for trainers and national trainings.
EJPRD D14.3 First Report on Course on interpretation of genetic variants and quality standards.
EJPRD D14.5 First Report on International course on undiagnosed diseases.
EJPRD D14.7 First Report on Sample data management training workshops.
EJPRD D14.9 First Report on International course on RD Registries and FAIRification of data at the source.
EJPRD D15.1 First Report on ExPRESS.
EJPRD D15.3 First Report on training of patient representatives on scientific innovation and translational research in RD.
EJPRD D15.5 First Report on EURORDIS's Leadership Programme.
EJPRD D15.7 Training plan for paediatric patients in the EJP.
EJPRD D16.1 Draft Content of the Online Academic Course.
EJPRD D16.2 Content of the first five online modules.
EJPRD D17.1 Results of survey on preferences, needs and resources from the ERNs ecosystem.
EJPRD AD25. Report on workshops for patient engagement in research.
EJPRD AD28. Technical platform developed and ready for online academic course deployment.