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Pillar 2 Annual Strategic Report

The problem: Expertise, data and resources important for rare diseases research remain fragmented and scattered

The Rare Disease (RD) challenge has been identified both at the European and international level for years, as a challenge that could not be overcome without a specific coordination effort of currently scattered and fragmented initiatives. The European Council Recommendation of June 8, 2009[1] specifically emphasized the coordination of the Community; national and regional programmes for RD research should be improved. In 2011, the international community started working together towards better research for rare diseases globally, through the International Rare Disease Research Consortium (IRDiRC) that has defined, in 2017, three major goals for the rare disease community[2]:

- **Goal 1**: **All patients** coming to medical attention with a suspected rare disease **will be diagnosed within one year** if their disorder is known in the medical literature; **all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline**.
- **Goal 2**: **1000 new therapies** for rare diseases will be approved, the majority of which will focus on diseases without approved options.
- **Goal 3**: **Methodologies** will be developed **to assess the impact of diagnoses and therapies** on rare disease patients.

In its 2017 report "Rare Diseases - a major unmet medical need"[3] the European Commission pinpoints five key policy recommendations:

- Support integration and networking among EU research, patient and healthcare organisations;
- Adapt implementation of regulatory requirements, especially for clinical trials in rare diseases;
- Develop legally and ethically robust agreements for collecting and exchanging health and genetic data;
- Support health technology assessment, standards and evidence-base for guiding public health policy;
- Collaborate globally through the International Rare Diseases Research Consortium (IRDiRC) to accelerate research on improving the lives of patients with rare diseases.

[1] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ%3AC%3A2009%3A151%3A0007%3A0010%3AEN%3APDF

[2] Austin, C. P., Cutillo, C. M., Lau, L. P., Jonker, A. H., Rath, A. , Julkowska, D. , Thomson, D. , Terry, S. F., Montleau, B. , Ardigò, D. , Hivert, V. , Boycott, K. M., Baynam, G. , Kaufmann, P. , Taruscio, D. , Lochmüller, H. , Suematsu, M. , Incerti, C. , Draghia-Akli, R. , Norstedt, I. , Wang, L. , Dawkins, H. J. and , (2018), Future of Rare Diseases Research 2017–2027: An IRDiRC Perspective. Clinical And Translational Science, 11: 21-27. doi:10.1111/cts.12500

[3] https://ec.europa.eu/info/sites/info/files/rarediseases_p4p-report_2017.pdf

These recommendations, together with identified challenges are the main driving force of the EJP RD, in which Pillar 2 specifically addresses the coordination of access to resources and data relevant for rare disease research.

Altogether, rare diseases represent a non-negligible proportion of the population: around 6% of people worldwide suffer from a rare disease. However, the >6,000 rare diseases are clinically heterogeneous, difficult to diagnose because of intrinsic complexity and also because of lack of knowledge and recognition in the medical community, and difficult to treat because a small population for each single disease makes it hard to develop therapies. **The common problem of rare diseases lies in their rarity.** Rarity requires the community to pool patients, data and expertise, and share common tools, integrated in an efficient way: registries, biobanks, knowledge bases, clinical, genomic and multi-omics data, samples, animal and cell models, as well as support resources to conduct basic, translational and clinical research.

Despite the significant resources already in place (knowledge bases, databases, registries and infrastructures), the fragmentation and duplication of effort and resources in relation to data, information or samples persist, making efficient and timely use of these resources in RD research challenging.

Background: Building Pillar 2

In the past 20 years, the European Commission has supported not only key actions to produce data necessary to improve identification and knowledge on RD under the form of large multinational scientific projects but also strategic and coordination initiatives to provide recommendations on specific areas to support and guide Member States' policies on RD. Some are European rare-disease-specific endeavors: RD-Connect, Orphanet, EURORDIS, European Reference Networks (ERNs), the JRC's European Rare Disease Platform, as well as the support provided to IRDiRC since its creation. Others are more generic, notwithstanding relevant, resources for RD research, biomedical and life sciences European Research Infrastructures such as BBMRI, ELIXIR, EU-Openscreen, EATRIS, or Infrafrontier and ECRIN, which were developed in the past years through collaborative efforts of Member States. Finally, rare disease research can take full advantage of cutting-edge data-focused initiatives in current European policy, including the European Open Science Cloud (EOSC), which aims to accelerate and support the current transition to more effective Open Science and Open Innovation, making FAIR data come to reality.

During the preparation phase of the EJP RD, rare disease specific resources, as well as generic resources relevant for rare diseases already in place were identified and brought together to form a working group designing the future Pillar 2 (for a comprehensive state of the art of these resources, see Deliverable 10.5).
Pillar 2 was designed to mainly contribute with one of the major objectives of the EJP RD: to improve the integration, the efficacy, the production and the social impact of research on RD through the development, demonstration and promotion of Europe-

wide and even world-wide sharing of research and clinical data, materials, processes, knowledge and know-how. More precisely, Pillar 2 has been set to create an innovative coordinated access to data and services for transformative RD research aiming at **rationalizing, optimizing and increasing potential of existing resources and services**, and to address the gaps on data essential to enable multidisciplinary, holistic approaches for rare disease diagnostics and therapeutics by fostering creation of complete disease pathways.

Pillar 2 will create a sustainable and interoperable ecosystem of resources (the EJP RD Virtual Platform, or "VP" in short), coupled to robust standards, tools and procedures that will infuse FAIR principles into advanced and secure forms of data discovery, linkage and sharing. It will allow flexible, real-time access to data (under suitably controlled conditions), with supporting tools and services that serve the ultimate goal of increasing the efficiency and efficacy of RD research. Driven by concrete use-cases and needs arising from the RD clinical and research community, not least ERNs, it will provide the means to harmonise and standardise the way RD relevant data, samples, tools and other relevant resources are made findable, accessible, interoperable and re-usable, and the means to query the progressively increasing number of resources and repositories connected to the EJP RD virtual platform through a central facility.

Pillar 2 strategy is to establish a stronger and broader collaboration between the RD community and European Research Infrastructures and global consortia. This will have major mutual benefit and impact. On the one hand, RD research, supported by patient representatives and ERNs, presents an exemplar challenge and opportunity for research infrastructures to create common solutions and stimulate collaboration. On the other hand, progress in RD research depends on the strongest possible infrastructure to address its needs towards efficient information retrieval and analysis across its distributed data resources. The increased capacity of infrastructures and their seamless integration with the RD community will ultimately translate to higher innovation potential and benefit for patients.

To that point, Pillar 2 partners decided to develop three parallel and complementary axes of work, all three governed by consistent quality, regulations and compliance with agreed standards requirements, and driven by research and clinical user community, ensuring that the Virtual Platform is built for and adopted by this community. The axes are:

- **Centralized metadata repository** describing pre-existing **resources** (including catalogues, data repositories, tools and infrastructures) with RD-specific semantic standards and metadata that conforms to an ontological, machine-readable model that also encompasses consent and data use conditions. This is expected to make resources Findable, and their Accessibility conditions to be known. Furthermore, it will provide guidance and services to produce, store and share phenotype-genotype data for researchers, as well as standards for data processing, generation and deposition of multi-omics data, relevant for RD. This axis of work will have the double benefit to make all relevant resources (RD-specific or not) findable and queryable through a single entry point, so optimizing their use by researchers, and to increase normalisation and standardisation of resources'

metadata as well as their progressive adaptation to the rare diseases community needs;

- Federated ecosystem of FAIR-at-the-source resources, in order to enable data discovery, sharing and analysis down to the **record** level. This axis of work organizes partnering with target resources to make them FAIR compliant, as well as the required interdisciplinary collaboration between RD experts and data experts. Beyond achieving FAIRification of resources in the VP, Pillar 2 will offer to the RD community at large the means and support, including training, to enlarge the scope of the federated ecosystem, by building a sustainable FAIRification service.
- Extension of the virtual platform with workflows that allow holistic research based on rare disease data and biological knowledge, by **filling gaps** in data on disease modifiers such as nutrition and metabolism, aspects of lifestyle and exposure to toxicants with the final aim to improve the understanding of the aetiology and progression or rare diseases and to support the discovery of biomarkers and the identification of druggable pathways and targets. This axis of work requires exploitation of previously performed explorative studies and the conduction of proof of principle studies specific for RD. It will be based on important collaboration between European Research Networks and top-level research teams excelling in data mining and interpretation.

The final product of Pillar 2, namely the VP, will therefore allow to centrally query a myriad of heterogeneous resources, as well as build a federated discoverability, query and analysis facility by promoting the progressive FAIRification of data sources, including multi-omics rare disease pathways created by Pillar 2 itself. A graphic representation of this final ecosystem is given in Figure 1

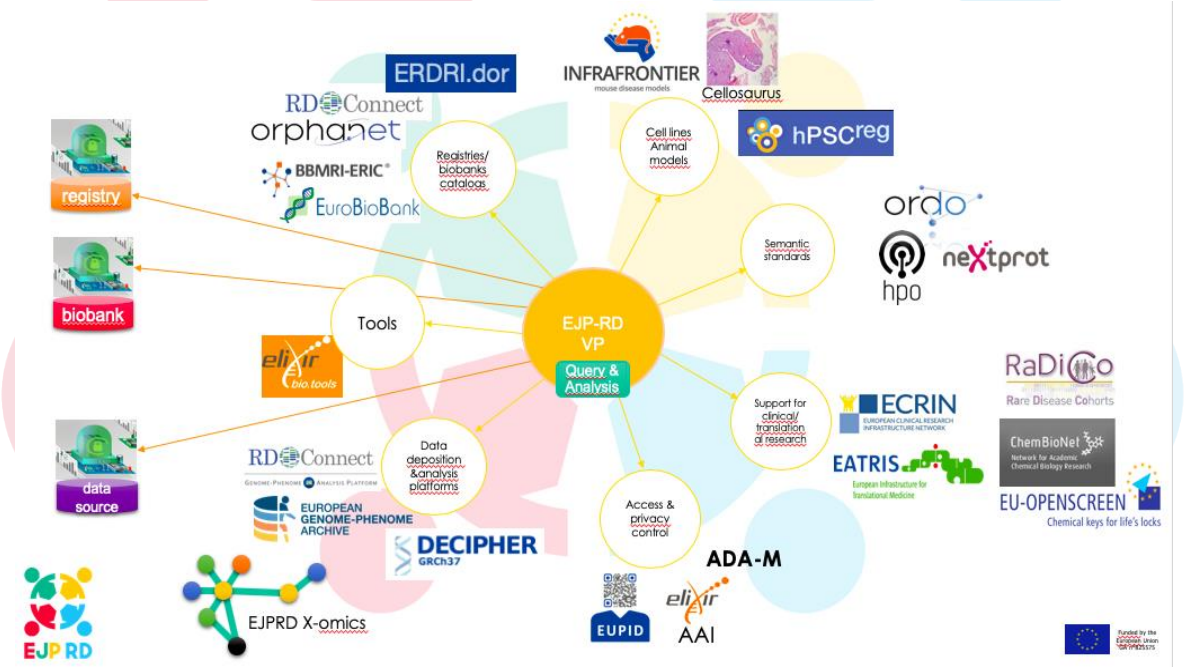


Figure 1. Schematic representation of the Pillar 2 Virtual Platform and the Pillar 2 resources network.

Methods

Pillar 2 structure

Pillar 2 work was organized in 4 Work Packages (WPs) as represented in Figure 2.

WP10 : **User-driven strategic planning and transversal activities for Pillar 2 data ecosystem, which** provides the critical 'coordination and navigation' role for the Virtual Platform, where users (especially ERNs) will participate as key leaders and decision makers, and ensures that the work in Pillar 2 (WP11, WP12 and WP13) is synergised and optimised.

WP11: **Common virtual platform for discoverable data and resources for RD research, of** which the main aim is to tackle fragmentation of data repositories, catalogues, resources and tools, by: (i) building a comprehensive, FAIR-compliant virtual platform extensively describing resources with their metadata (including registries, biobanks, research infrastructures, genome-phenome repositories, methods, standards, etc.) allowing for these resources to be findable online via a central access point and (ii) providing researchers the means to deposit, share and analyse phenotypic, genomic and multi-omics data in a harmonised, standardised manner, building-on and scaling-up existing resources, which will be findable through the virtual platform (VP) as well.

WP12: **Enabling sustainable FAIRness and federation at the record level for RD data, patients and samples,** which will develop and apply procedures, standards, and tools, with the RD community to achieve FAIRness at the record level. This will enable clinical and biological researchers to discover useful and usable data with high-specificity across resources, assess access restrictions for specific data quickly (e.g. consent, data usage licenses), and develop powerful analysis across multiple resources without delay caused by data incompatibilities.

WP13: **Enabling multidisciplinary, holistic approaches for rare disease diagnostics and therapeutics**, which objectives are directed at filling the gaps that currently make it hard to perform multi-omics analysis on rare diseases. The aim of multi-omics analysis is ultimately to find better diagnostics (for instance, process biological based panels) and to develop better therapies.

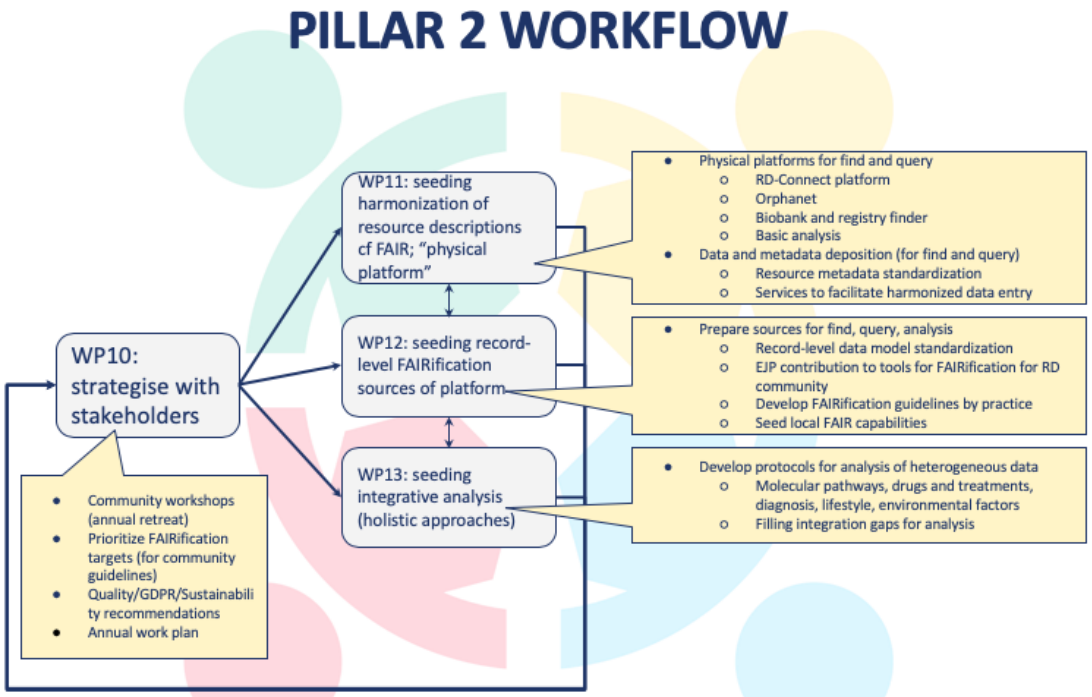


Figure 2. Pillar 2 Work Packages and Workflow.

Pillar 2 strategy

The Pillar 2 strategy is based on continuously developing and testing the VP against real-life use cases, by bringing research questions and establishing, together with Pillar 2 partners, sustainable mechanisms for ensuring a virtuous cycle between care and research. This will be made possible by giving the European Reference Networks a leading role in driving the way the VP is built, with the ultimate aim to accelerate the take up of research results in clinical practice for the benefit of patients. ERNs will ensure the usability and usefulness of the VP by collaborating with Pillar 2 partners, not only during the Annual retreat making strategic decisions, but continuously by contributing to surveys and working groups as needed.

Pillar 2 VP builders are data and computing experts, whereas ERNs host the clinical expertise in rare diseases. Pillar 2 strategy revolves around establishing virtuous cycles of functioning towards enhanced research, ERNs and Pillar 2 data and computational experts learning from each other and allowing to progressively develop the VP from a Minimum Valuable Product (MVP) based on a few simple use cases to a complete rare disease data ecosystem. This strategy supposes to revise the strategic plan annually, in dedicated "retreats" in which ERNs representatives and Pillar 2 VP builders come together to decide on the major strategic directions for the project. Tasks and subtasks progression are further monitored in monthly follow up distant meetings.

For the first year of the project, and before the first annual retreat, a workplan has been adopted based on the EJP RD preparatory phase. Basically, it can be summarized in some major orientations:

- Start building on the low hanging fruits: well-structured already existing catalogues of resources, some of them dedicated to rare diseases; already existing genomics-phenomics data deposition platforms; collating already existing relevant standards, tools and FAIRification methods, creating rare disease pathways from ready-to-use data.
- Perform a survey to assess ERNs' research needs to further guide the prioritization of future steps.
- Organise the work of Year 1 in two phases: a pre-annual retreat preparatory phase, setting the ground for teams in each task and subtask to start working together, and in particular, increasing each other's knowledge and awareness of resources in place; the annual retreat; starting the building phase based on strategic decisions taken during the retreat. These three phases are represented in Figure 3.

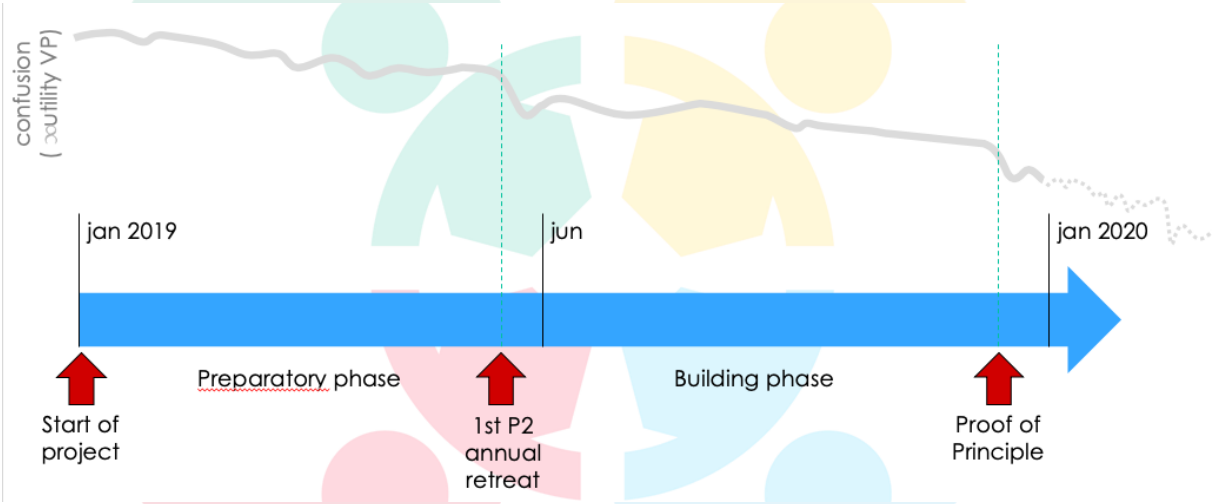


Figure 3. Pillar 2 first year progression: the year of de-confusion.

Strategic plan

Below, the main strategic orientations decided during the first annual retreat are summarized. The actions planned, following these strategic axes, are detailed in the EJP RD Second Annual Work Plan.

Increasing efficiency towards building the Virtual Platform

According to the first draft of the VP architecture elaborated during the preparatory phase in year 1, most of the Pillar 2 activities will be performed by cross-task teams with distinctive Work Foci (WF) intended to develop VP technical components and other transversal pieces of work. Since the different components of the VP should be consistently developed towards making resources, records and data findable and queryable through a single-entry point, organizing the work by work foci will allow related tasks to be conducted together in a more efficient and coherent way. WFs do not replace tasks and subtasks as per the Description of Work (DoW) in the Grant Agreement (GA), but make them work together towards a common objective therefore optimizing the use of resources. A mapping exercise between tasks and subtasks and WFs was performed, and a RACI (Responsible, Accountable, Consulted, Informed) table has been prepared for each partner perfectly identifies his/her area of work. Tasks and subtasks not fitting a specific WF are conducted as expected as per the GA's DoW.

WF teams (WFTs) will work according to the Agile methodology involving both Pillar 2 partners and ERNs designated representatives for each of them. This will allow for cycles of development and testing. Further delineation of WFs will be done as the project evolves in a flexible way. Experiences from field-testing based on use cases will ensure that Pillar 2 developments fit the needs of users and have the expected impact on accelerating research.

Operations at the WP and task levels, including transversal issues such as quality (establishing principles/approaches), governance (focused on GDPR) and sustainability by design, will be monitored using project management tools provided by the coordination (Microsoft Teams).

The following WFs have been prioritized in year 2, with WFTs having started to work in the second half of year 1:

- **Use cases WF**: setting up research questions by committed stakeholders, including ERN partners that will drive the development of VP components based on real-world needs;
- **Overall architecture WF**: global overviewing the VP components and connections between them;
- **FAIRification WF**: allowing data sources to become progressively FAIR, pertaining to incorporating technical services from Pillar 2 and collaboration with local data stewards, focusing on ERN registries and selected OMICS data resources;
- **Distributed and federated consent control WF**: defining where and how consent control is done based on the state-of-the-art and fitting it into the overall architecture of the VP. Defining other legal bases and definitions of roles (controller vs. processor in GDPR) for entities contributing or interfacing to the VP;

- **Authentication Authorisation Infrastructure WF**: providing Authentication and Authorization Infrastructure (AAI) to be used by other components of the VP. Building on ELIXIR AAI, BBMRI-ERIC AAI and the upcoming LifeScience AAI;
- **Personal data linkage service WF**: identify datasets which belong to the same person (Privacy-Preserving Record Linkage);
- **Query builder WF:** Developing a federated discoverability and query facility for the VP;
- **Metadata model and alignment service WF**: computable ontology-based model of interoperable data descriptors using semantic standards;
- **Interoperability for registries WF**: mapping expertise and standards between GA4GH, ERNs, and EJP RD partners, with an initial focus on suggestions and guidelines for ERN registries;
- **Resources for sharing experimental data and materials WF:** Improving, adapting, scaling-up and documenting resources for data and material deposition, access and sharing;
- **Resources for experimental data and analysis interpretation WF:** prioritising novel user-friendly and cloud analysis functionalities;
- **Biological networks analysis methods WF:** collecting and curating conceptual rare disease pathways, collecting and analysing rare disease multi-omics data, creation of networks using prior knowledge in the form of pathways and other database information and experimental data
- **Adverse outcome pathways WF:** Extending rare disease molecular networks with drug targeting and toxicants initiating adverse effects

Supporting ERNs to make their current and future registries interoperable and compatible with the EJP RD VP according to FAIR principles

Registries have been already identified as a priory area of work in year 1, and a proof-of-principle has been designed, making registries present in catalogues findable and queryable in the first version of the virtual platform, and making simple use cases addressed by federated queries at the record level. To achieve this, prioritization based on the low hanging fruits has been decided, meaning the five already funded registries, and with those previously working on FAIRification.

The fact that a new call for ERN registries has been launched by the European Commission provides a challenge and an opportunity to ERNs and Pillar 2 partners to work together, aligning our respective effort towards a consistent RD data ecosystem.

A specific WF on interoperability for registries has been launched to tackle this priority decided during the first annual retreat. It will provide the framework for registries interoperability and promote the continuous dialog in order to streamline the common work.

FAIRification plans are therefore prioritized towards making all ERN registries FAIR, by designing a three-parties process for collaboration, involving:

- An ERN registry steward
- An EJP RD interoperability steward
- A registry software provider

This process, together with the overall interoperability consideration for ERNs' registries, has been provided in a document submitted to the dedicated ERNs' research working group. Specific budget for this activity has been allocated.

Involving basic researchers in future strategic plans

The year 1 survey was intended to capture the needs from ERNs as they are drivers for Pillar 2 developments. During the first annual retreat, it was decided to enlarge the consultation to basic researchers in the next year, in order to have a more comprehensive view of the RD research environment and capture use cases from projects funded through EJP RD Pillar 1 and from partner research institutes.

Therefore, during the first five months of year 2, a second community-wide survey will be conducted to capture the needs of the RD research community in relation to access to services, tools and data, focused on technical, scientific and strategic requirements, and how the outputs of Pillar 2 should address these needs. This will follow the same design and implementation process as was successfully used in the year 1 survey, but this time focus more on RD researchers rather than solely ERNs. It will leverage our connections with EJP RD funded scientists (Pillar 1, projects funded previously under E-Rare ERA-Net) and EJP RD partners such as INSERM (FR), IMAGINE (FR) and CIBER (ES) as well as through Pillar 3 training activities. All reports and ideas generated by this effort will be explicitly discussed with the Steering Group and the Task 10.1 leaders to help with Pillar 2 refinement.

Revising and updating the VP architecture based on agreed standards

A first version of the overall EJP RD VP architecture has been drafted in year 1, forming the basis for the future WFs developing its components. Indeed, following the annual retreat, the first version of the road map for the first proof-of-principle platform was drafted, the software development multi-party team relationships were organised into the WFTs as an operational framework for joint software development which will be

accelerated into year 2 based on an agreed collaboration and project management infrastructure. A continuous assessment of VP compliance to GDPR and quality standards is prioritized, working hand in hand with dedicated tasks in Pillar 2. A report on unified FAIR data standards based on the current state of the art and in line with the current focus of the project will be delivered.

Prioritising resources to further populate the Virtual Platform

During the first year of work, catalogues of registries, biobanks and tools were prioritized (Orphanet, BBMRI, RD-Connect Biobank and Registry Finder, JRC's ERDRI and ELIXIR bio.tools) to develop a comprehensive suite of catalogues using standardized fine-grained metadata and utilizing existing recommended ontologies and semantic standards (i.e. Orphanet rare disease ontology (ORDO), Human Phenotype Ontology (HPO) and HOOM, the ontological module making ORDO and HPO be usable together). This work will be extended to other resources having been prioritized by the ERNs during the 1st annual retreat: the RD-Connect GPAP and infrastructures for clinical and translational research (ECRIN and EATRIS). In fact, the results of the first survey carried out in year 1 showed that the main research needs expressed by ERNs were related to clinical and translational research as well as to -omics databases, as shown in Figure 4. The prioritized work will ultimately allow registries, biobanks, data repositories, and tools to be findable by queries in terms of disease, genes, phenotypes, sample types (for case identification), and other data elements for tools, services and documents mapping.

In year 2, metadata for each of the above-mentioned resources will be included in the VP. Metadata will be co-defined by catalogs' and identified resources holders, and the ontological model of these metadata built will be expanded to allow querying the VP by exploiting the semantic relationships in the application ontology. This centralized metadata system is being made FAIR compliant from the start.

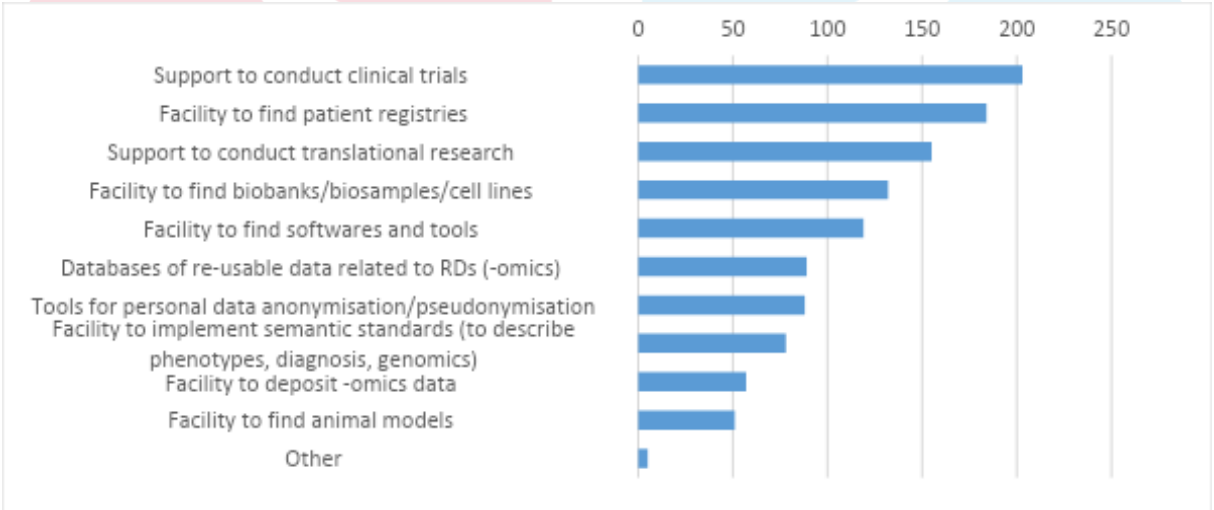


Figure 4. Main ERNs' needs to conduct research.

Improving data deposition and analysis facilities

Two Working Foci (WF) were established in 2019 for experimental data and materials deposition, sharing and analysis. The WF on "resources for sharing experimental data and materials" will prioritise actions to improve, adapt, scale-up and document participating Task 11.3 resources for data and material deposition, access and sharing. This will be done by mapping the ERNs' needs with available functionalities and promoting the usage of such resources. A EUPID pilot will be scaled-up and more resources will be enabled to connect to the common AAI. As planned in the Task 11.4 2019 AWP, a WF on "resources for experimental data analysis and interpretation" was established to prioritise novel user-friendly and cloud-based analysis functionalities according to the ERN needs. In 2020, newly funded projects from the EJP RD JTC 2019 call will be contacted to understand their needs and the most relevant ones will be selected as pilot projects. Some of the novel developments that might be prioritised include CNV analysis, RNA-Seq integration, availability of QC metrics in the GPAP and connection to Mendelian API.

Enhancing and expanding RD pathways creation and analysis

Based on the work performed in year 1, and the results of ERNs consultations about the readiness of multi-omics data to be used, two WFs have been formed:

- **Biological networks analysis methods WF:** collecting and curating conceptual rare disease pathways, collecting and analysing rare disease multi omics data, creation of networks using prior knowledge in the form of pathways and other database information and experimental data
- **Adverse outcome pathways WF:** Extending rare disease molecular networks with drug targeting and toxicants initiating adverse effects

These WFs will allow for close collaboration with tasks 11.3 and 11.4 (data deposition and analysis platforms) as well as with 12.3 (FAIRification).

The following work has been prioritised for year 2:

- Continue adding rare disease pathways and teaching ERNs how to make and curate pathways
- Low-level integration of mapping tools for rare disease variants to genes and rare disease variants to protein function into BridgeDb and GPAP and plan for full integration.
- First FAIR representations of pathway and -omics datasets available in the NDEX registry

- Implementation of toxicology data from different resources (drug, nutrition/lifestyle, AOPs)
- Implementation of pathway and network analysis approaches around concrete use cases (data from ERNs)

The work will be guided by the already adopted "network-pathway-network" approach: because the work will start with literature, database and expert evaluations of things that play a role in rare disease related processes and their interaction, the collection of network nodes and their relations, the edges, will be performed first and then used to draw conceptual pathways that can be easily understood and curated further. Then these pathways will be used for omics enrichment analysis, where they are employed as part of a much larger set of available biological pathways. That enrichment analysis will lead to selection of a subset of pathways, which will be loaded in a network environment and combined. In year 2, further to the gene-to-variant and variant-to-protein function pathways, networks will be extended with drug targeting and toxicants initiating adverse effects.

Use cases will be selected to address concrete research questions focusing on disease mechanisms, disease modifiers and druggable pathways defined together with the use case owners, and subsequently driven through analysis plans based on the workflows designed. Close collaboration with ERNs, as data owners, will be prioritized, and resulting publications are expected.

ERN Survey report

Problem/Background

The key goal of Pillar 2 is to create a virtual platform (VP) where rare diseases research data and resources are discoverable and available for research.

To have a first understanding of the needs of the RD research community so that the design of the VP is fit-to-purpose, a survey was necessary to capture the current practice of research data generation, analysis, deposition and storage. The focus of Pillar 2 VP is to cater to the research community, and in this context, ERNs were prioritised as the key stakeholder in research in RD. In the kick-off of EJP RD, at M4, the survey was specifically designed to understand their current use of resources for research and significance/importance of different types of data, research infrastructure, as a way to prioritise and formulate a strategy for VP development.

At the kick-off of EJP RD, 8 work packages across the project had planned survey activities towards ERNs within the first six months of the project as a way to initiate activities. We quickly realised that different work packages needed to align on the survey efforts to avoid fatigue in ERN response rate. A cross-Pillar "Survey Task Force" was created ad hoc to align on the common task and it was agreed that only one survey covering different subjects was to be created, rather than sending multiple surveys to ERNs. The WPs involved were WP11, 12, 13, 15, 16, 17, 19 and 20, coming from Pillars 2, 3 and 4.

Methods

The Survey Task Force discussion was coordinated by Franz Schaefer (ERKNet). The creation and analyses of the cross-pillar survey was carried out by Mary Wang (FTELE).

For the cross-pillar survey, each WP provided questions that were validated among partners and WP leaders. These questions were then pooled together to create a homogenous, comprehensive "ERN Survey". As the questions came from different sources, the styles were uniformed, cleaned of duplications, reordered and categories to aid reading and comprehension of to be responders (Figure 1).

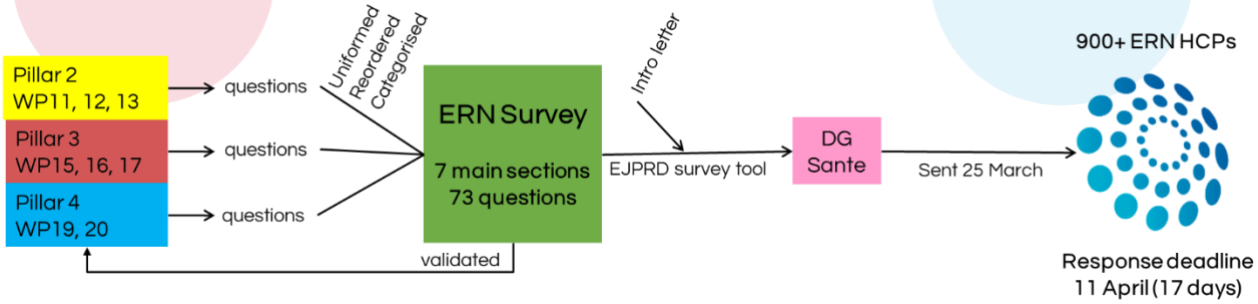


Figure 1: The creation of the cross-WP ERN Survey and its distribution.

The pooling and cleaning resulted in a survey with 73 questions divided into 7 main sections (the complete question list is attached in Annex I):

1. About the ERN
2. Data generation and storage
3. Data annotation and FAIRification
4. Use of existing resources and infrastructure for research data
5. Resources for translational and clinical research
6. Clinical trial study designs and methodologies
7. Training needs (including patient involvement)

Corresponding WP leaders validated the pre-final question list before the creation of the electronic survey via the EJP RD dedicated platform. The survey was sent out by DG Santé to the 900+ ERN healthcare providers (HCPs) on 25 March 2019 with an introductory letter drafted by the ERNs coordinator Franz Schaefer. The ERN HCPs were given 17 days to respond to the survey (deadline 19 April). For the purpose of this Deliverable, only results related to Pillar 2 are reported here below.

Results

Survey response rate and coverage

A total of 294 completed responses were received, which corresponded to a response rate of 31%. In terms of coverage, responses came from 22 out of 26 European countries with ERNs (4 missing countries were Croatia, Cyprus, Luxembourg and Norway). All the 24 ERNs submitted at least one response to the survey. ERN HCPs located in Eastern European countries were particularly responsive. The breakdown of responses by ERN or by country is detailed in Annex II. The majority of the respondents (74.4%) were willing to be recontacted by EJP RD partners for a better understanding of their research needs.

The responding ERN HCPs confirmed their activities in performing basic, translational and clinical research, or combinations of different types of research. Almost all ERN HCPs perform clinical research (97.6%).

Data generation and storage

ERN HCPs collect and use multiple types of data including patient information, natural history data, biological samples, electronic medical records, phenotypes and medical images. Interestingly, -omics data are used and generated by 48% of respondents. Out of these, genomics data are the most common type of data generated/used, followed by transcriptomics, epigenomics, proteomics and metabolomics. Within the genomics data, the most common data are gene panels and exomes. Less than 20% of respondents indicate that they have different types of –omics data origination from the same sample from multi-omics studies.

On the collection or use of data related to environmental factors, 26.9% indicated yes compared to 55.4% who indicated no. The most commonly cited environmental factors information includes physical activities, smoking habits, alcohol consumption, occupation, diets and lifestyles.

In terms of research data storage, the most common method 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. A significant proportion of respondents (44%) do not deposit or share data in open or controlled access resources. The two major hurdles that limit data sharing are legal jurisdiction and complexity of use of resources.

Data annotation and FAIRification

Only approximately 34% of ERN HCP respondents indicated the use of ontologies or standards to annotate data. Out of these respondents, ICD-10, OMIM, ORDO and HPO are the most used ontologies. Often, multiple ontologies are used to annotate data.

Strikingly, 45% of the 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 (28%).

Use of existing resources and infrastructure for research data

ERN HCPs responded that support to conduct clinical trials, translational research, facilities to find registries, biobanks/biological samples, tools and –omics databases was important for their research.

However, the ERNs often are not aware or not familiar with existing research infrastructures (ECRIN, EATRIS, BBMRI-ERIC, ELIXIR) and tools (RD-Connect, ERDRI, RADICO, hPSCReg).

Dissemination and validation

The survey results were presented to ERN representatives and Pillar 2 partners at the 2019 Pillar 2 annual retreat. The results of the survey were discussed at the meeting. The ERN survey confirmed the goal and development of the EJP RD VR to ease findability of resources and tools as important to support RD research. Discussions during the annual retreat with ERN representatives indicated that a greater emphasis on dissemination of existing resources and concepts should accompany the ongoing VR development. The barriers on data deposition and sharing should be lowered and removed as a part of Pillar 2 strategy.

Copies of the presentation slides and raw results were disseminated to Pillar 2 partners. In summary:

- Feedback received from 30% of ERN units
- Wide variation of research interest across ERNs: ERN-specific response rates <10% to 60% of units
- Strong focus on clinical research: diagnostics, biomarkers, therapeutics
- Bulk of available -omics data is genomic.
- Little use of transcriptomics, proteomics and metabolomics to date
- Less than 10% of -omics data is stored or shared in public databases
- Dramatic lack of use or awareness of most existing European research infrastructures, resources, and the data FAIRification concept
- General interest in data sharing but limited funding and time are major barriers for implementation

Next steps

Discussions during the annual retreat also indicated that not all ERN HCPs have a focus on research, as the original design of ERNs is based on healthcare. ERNs are aware of counterpart RD researchers outside of current ERN networks. It was agreed that the Year 2 (2020) Survey should also target a wider RD research community beyond ERNs.

Second steps on re-contacting and engaging of interested ERN HCPs are being defined as a part of the Work Foci for Use Cases. The results from the survey will be re-examined to capture scenarios and use cases for technical requirements.

Annex I

List of questions in the 2019 Survey for the ERNs

About ERN	ERN1. Your specialized unit is a member of the following ERN:
	ERN2. Your institution is located in the following country:
	ERN3. You are involved in which type of research - [Basic research, including genetic research]
	ERN4. The main purpose of your current research is: [to develop disease models]
	ERN5. Are you willing to be contacted by EJPRD partners for a detailed analysis of your research needs
	If yes, please leave your email here:
A	A1. Which of the following data types do you collect or use- (tick all that apply)
	A2. Do you generate or use –omics data in your work-
	A2.1 Genomics or other DNA level genetic variation data:
	A2.2 Transcriptomics
	A2.3 Proteomics
	A2.4 Metabolomics
	A2.5 Epigenomics
	A3. Do you have different types of –omics data that originate from the same sample, from multi-omic studies-
	A4. Do you collect or use data related to environmental factors (e.g. nutrients, lifestyles, pollutants)-
	If yes, please list
	A5. Do you have any data on diseases/risk factors/drugs/metabolic/signaling pathways that could be added into an existing pathway or structured into a new one- Tick those apply.
	A5. Do you have any data on diseases/risk factors/drugs/metabolic/signaling pathways that could be added into an existing pathway or structured into a new one - comment
	A6. What best describes your current research data storage method-
	A7.1 Do you use any of the following resources as your primary data deposition mechanism-
	A7.2 Do you use any of the following resources as your primary data sharing mechanism-
	A7.3 Do you use any of the following resources as your primary data analysis mechanism-

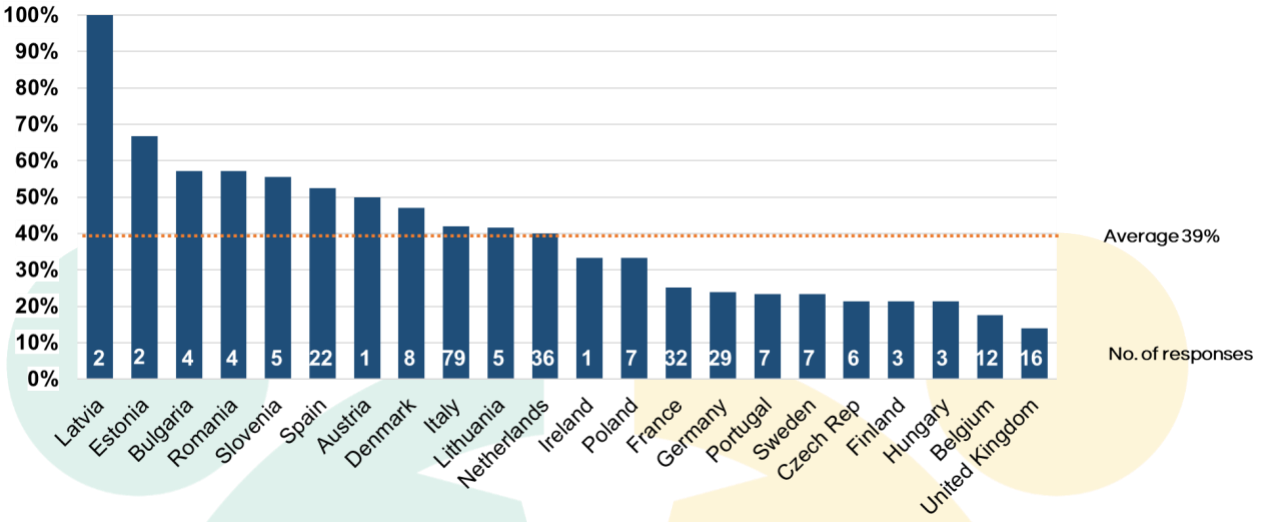
	A8. Do you usually deposit and/or share your -omics data in open or controlled access resources-
	A9. What are the issues that are more limiting for you to deposit / share your data in such open or controlled access resources- (tick all that apply)
B	B1. Do you use ontologies or standards to annotate your data-
	If yes, which of these ontologies or standards do you use-
	B2. Please describe your interest in making your research data FAIR*-
	What could raise your interest-
	What are these barriers-
	In what stage is your FAIRification process-
	What type of data does your FAIRification involve-
C	C1. Which of these services are of utmost importance for your research-
	C2. Which of these research infrastructure resources are of utmost importance for your research-
	C3. Which of these databases and catalogues are of utmost importance for your research-
	C4. Which of these data management and analysis resources are of utmost importance for your research-
	C5. Any other resources that you need and use that were not listed in the previous questions-
D	D1. What should be offered by the translational research self-help toolbox-
	D2. Which of the translational research 'self-help' tools detailed below do you already have access to-
	D3. Which of the translational research tools detailed below would you be willing to share via a EJP-RD translational research 'self-help' toolbox-
	D4. What are the top 3 points of problems you have with conducting clinical trials in your rare disease area- [1]
	D5. What are the top 3 points of action you have with conducting clinical trials in your disease area- [1]
	D6. Regarding in the setup of a clinical trial, what of the following areas are more relevant to your ERN-
E	E1. In which phase do you usually conduct trials-
	E2. Which type of study endpoints do you usually have-
	E3. Which type of data for the primary outcome criterion do you assess usually during your trial-
	E4. Which study design do you usually have in your trial-
	E5. Do you usually use randomization to allocate patients to the study groups-

	E6. Do you or would you like to conduct multi-center studies-
	E7. Do you combine or would you like to combine single-arm trials or multi-arm trials in a meta-analysis to gather more information-
	E8. Do you or would you like to test multiple hypotheses in one clinical trial to reduce the number of conducted clinical trials-
	E9. Which type of studies are of most interest for you and (in your opinion) would fit your domain of pathologies-
	E10. Do you or would you like to use the following methods-
	E11. Do you or would you like to include information from sources external to the data obtained during the trial into your trial design-
F	F1. Is there a specific research skills and support training practice currently available in your country or at your local level that might be of interest and transferable to other ERN healthcare providers-
	F2. What, in your view, are the most important research support needs to help ERN researchers achieve the goals of the EJP-RD goals (max 3):
	F3. What, in your view, are the most important research skills training domains that need to be addressed to help ERN HCPs raise the level of their research- Please pick your top 3!
	F4. Which of the following types of training measures would address these domains most efficiently for your group (choose top 3)-
	Physical visits: What would be the main target group for this format in your group- [(Principal) investigators, either clinical or non-clinical researchers]
	Physical visits: What would be the main expertise level of users of this format:
	Training Workshops/Seminars: What would be the main target group for this format in your group- [(Principal) investigators, either clinical or non-clinical researchers]
	Training workshops/seminars: What would be the main expertise level of users of this format:
	Webinars: What would be the main target group for this format in your group- [(Principal) investigators, either clinical or non-clinical researchers]
	Webinars: What would be the main expertise level of users of this format:
	e-Learning: What would be the main target group for this format in your group-
	e-Learning: What would be the main expertise level of users of this format:
	Blended Learning: What would be the main target group for this format in your group- [(Principal) investigators, either clinical or non-clinical researchers]
	Blended Learning: What would be the main expertise level of users of this format:
	Blended Learning: What would be the most efficient size of training workshops-
	F5. In addition to more general training and support needs mentioned above: does your group have any disease group-specific:

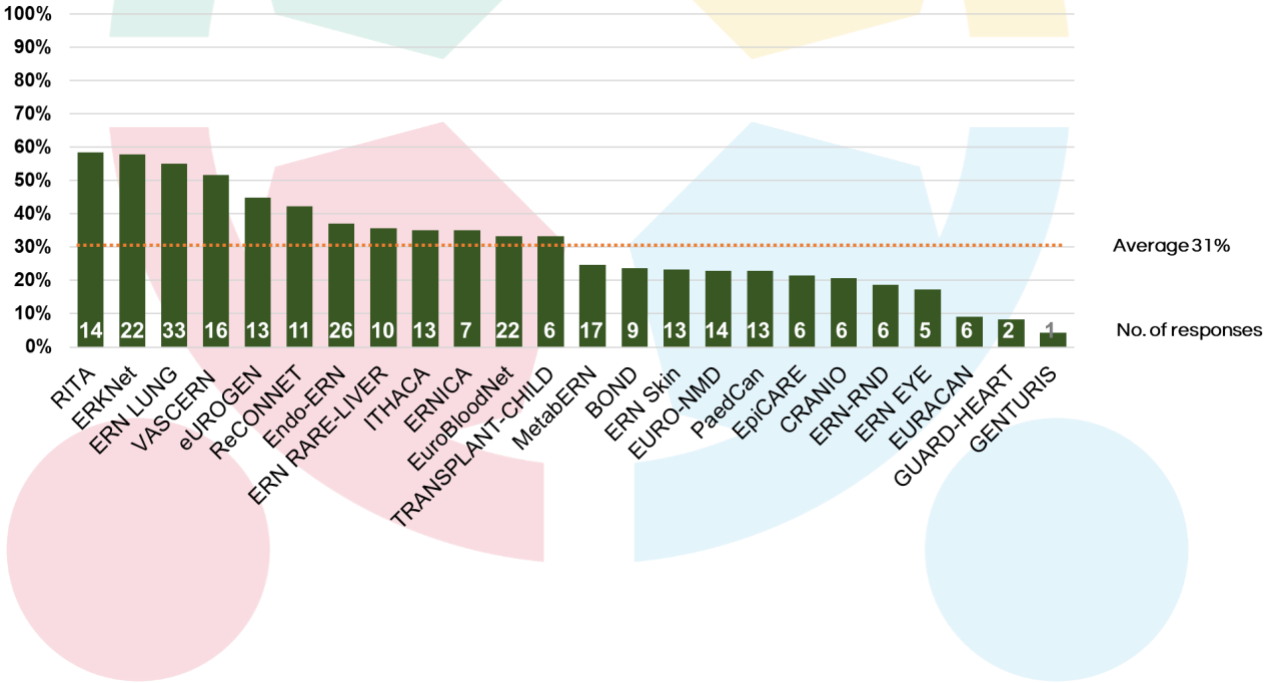
	training needs- research support needs-
	F6. In what way(s) are patients/patient representatives currently involved as members in your research practice-
	F7. What opportunities and barriers do you see to promote patient involvement in the near future- Major opportunities: Please describe briefly (max 2) Major barriers: Please describe briefly (max 2) Please elaborate on how opportunities could be strengthened and barriers overcome:
	F8. What, in your view, are the most important opportunity and barrier to equal access to research for countries less or not yet represented in your ERN that can be addressed by research training measures- Major opportunity: Major barrier:
	F9. Do you think that any form of research skills training and/or research support could help to create this opportunity and overcome this barrier- Please briefly clarify why & how.

Annex II

Responses of ERN HCPs by country, normalised to number of HCPs present in each country.



Responses by ERN, normalised to the number of HCP in each ERN.



Requirements for GDPR Implementation in Pillar 2

The General Data Protection Regulation (GDPR) has become the main regulatory framework for general-purpose data protection on the European level in 2016, with national implementations following. The GDPR is, however, not the only regulation: specific domains have their own additional regulatory frameworks, such as clinical trials.

These recommendations follow FAIR[4] and FAIR-Health[5] principles in order to maximize the value of the data for research purposes. These are initial requirements that will be further elaborated upon into more technically detailed measures during the course of development of the EJP RD Virtual Platform (VP).

Definition of roles and data

- For each legal entity involved in processing of the data subject to data protection, their role MUST be defined (data controller, data processor).
- For each data made accessible via the VP of EJP RD, it MUST be clear which legal entity is data controller and it MUST be specified what is the legal basis for processing the data. Definition of the data controller and contact information for that data controller must be kept as a part of metadata accompanying the data.
- Data controllers MUST inform data subjects about the extent of the processing of personal data and how data subjects can execute their rights.
- Data controllers MUST collect and archive provenance information about the data collection process.
- The EJP RD VP SHALL provide a registry of those data sources that are part of the VP and monitor compliance with the requirements.

Processing personal data

- Privacy enhancing technologies SHOULD be used when processing personal data to protect privacy of data subjects (unless there is justification why it cannot be used). Selection of privacy enhancing technologies MUST be assessed to balance ration between acceptable residual risk and maximizing utility and reliability of the data. Documentation of that assessment process MUST be kept.
- Recipients of the data MUST be informed about any consequences of application of the privacy enhancing technologies that might impact meaningfulness, reliability or reproducibility of the anticipated research.

[4] Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, Blomberg N, Boiten JW, da Silva Santos LB, Bourne PE, Bouwman J. The FAIR Guiding Principles for scientific data management and stewardship. Scientific data. 2016;3.

[5] Holub P, Kohlmayer F, Prasser F, Mayrhofer MT, Schlünder I, Martin GM, Casati S, Koumakis L, Wutte A, Kozera Ł, Strapagiel D. Enhancing reuse of data and biological material in medical research: From FAIR to FAIR-health. Biopreservation and biobanking. 2018 Apr 1;16(2):97-105.

- When data is released for a particular purpose, extent of the data MUST be minimized to the set necessary to achieve that purpose.

Execution of data subject rights

- Provenance information MUST be kept about data releases for research purposes. This is necessary to allow effective implementation of data subject rights.
- For each data set, a contact point MUST be defined to allow data subjects to execute their rights.

An overview of processes related to data is available in a guideline[6], including when exemption for research applies based on GDPR Art 89.

Anonymization and processing anonymous data

Anonymization is a process of rendering data non-personal and hence the resulting data being outside of protection domain. Anonymization is, however, an inherently imperfect process balancing between utility of the resulting data and residual risk of re-identification[7,8]. For this reason, the following requirements and recommendations should be taken into consideration by the VP of EJP RD:

- The anonymization process concerns processing of personal data and as such the controller MUST have a documented legal basis for anonymization.
- When possible, anonymized data should be avoided for medical research because of hard to assess impact of anonymization on data quality.
- When aggregating data sets, the anonymization shall be implemented after aggregation in order to minimize harm done to the data[9], unless there is some other restriction preventing aggregation of non-anonymized data (e.g., missing legal basis for aggregation).
- Anonymized data shall be regarded as having non-zero risk of re-identification and, therefore, the recipient of the data must agree with not attempting to re-identify persons from the anonymized data set. This also applies transitively to any further data recipients that receive the data from the first recipient.

Compliance of infrastructure

The infrastructure operators for the VP are advised to adopt relevant certifications such as FitSM[10], ISO 27001, possibly combined with ISO 27017 and ISO 27018, or at least build

[6] Page 104 of Radim Polčák, Leoš Ševčík, Michal Koščík, Jakub Klodwig, Petr Holub. Metodika aplikace GDPR na výzkumná data v prostředí vysokých škol v ČR. Zenodo; 2018. doi:10.5281/zenodo.2533865.

[7] Section 1.1 of Dwork, C and Roth, A. The algorithmic foundations of differential privacy. Theoretical Computer Science 2013;9:211– 407.

[8] Fredrikson, M., Lantz, E., Jha, S., Lin, S., Page, D., & Ristenpart, T. (2014). Privacy in Pharmacogenetics: An End-to-End Case Study of Personalized Warfarin Dosing. Proceedings of the USENIX Security Symposium. UNIX Security Symposium, 2014, 17–32. Retrieved from http://www.biostat.wisc.edu/page/WarfarinUsenix2014.pdf

[9] PR-5 rule of FAIR-Health: Holub P, Kohlmayer F, Prasser F, Mayrhofer MT, Schlünder I, Martin GM, Casati S, Koumakis L, Wutte A, Kozera Ł, Strapagiel D. Enhancing reuse of data and biological material in medical research: From FAIR to FAIR-health. Biopreservation and biobanking. 2018 Apr 1;16(2):97-105.

[10] https://fitsm.itemo.org/

the infrastructure according to the requirements for those certifications. This is in order to help demonstrating their compliance when operating the infrastructure for processing personal data.

Quality oversight report

Problem

Part of the work of the EJP RD is to develop a VP bringing together a number of software tools in a coordinated, integrated pipeline. These tools are likely to vary considerably, and we will need a flexible solution to be able to rank and understand the quality of the tools for the users of the VP.

Background

A core part of EJP RD is to assemble a suite of tools and services, relevant to the understanding of rare diseases and associated data analysis into a virtual platform. A user of the VP will need to be assured of the inherent quality of any service that they choose to use. This is a complex issue to assess, the services are likely to be inherently different, be at varying stages of their life cycle, be well funded or not so well funded and so on. The broad goal for Task 10.4 (Quality oversight) is to provide some degree of quality assurance for the virtual platform and the associated services. In this first reporting period, we have started to explore this challenge, with the aim to produce a draft set of service assessment criteria in 2020.

Methods

The criteria list has been drawn up through consultation with developers and users, and from a number of other sources:

- ELIXIR Core Data Resources / Recommended Interoperability Resource - independently reviewed lists of tools.
- Open Ebench - analytics, uptime, available via Bio.Tools
- See also Software Evaluation.

These criteria are intended to be indicators of a high quality, production-ready tool. Not all tools will meet every indicator, some criteria indicate tool maturity rather than a primary user need:

- Policy (Clear documentation available to users)
- Review (Tool has been used successfully in a number of real-world situations)
- Functionality (Accurate, Reliable, Ease of Use)
- Support (an indication of the level of support available)

Achievements

The main achievement to date has been an initial set of service assessment criteria, categorised by type and summarised in the table below.

Table 1. Draft set of Service quality criteria grouped by category.

Criteria	Notes
Policy	
Access agreements	Terms of Use available and clear
Open Source	Recognised repository egGitHub, GitBucket, SourceForge
GDPR compliance	Probably under ToU / Access Agreement. "Complies with all National and international requirements."
FAIR	Support for Open Science (Need to be clear what 'FAIR' means for different tools. Eg. apply recommendations from ELIXIR Implementation Study on FAIRification.)
Oversight	Have established a Scientific Advisory Board or similar body
Cost	Ideally free, or by use rather than by annual subscription (allow occasional use)
Reviewed	
By peers	Publication Citations Standalone (F1000)
By users	A clear user community who have adopted this tool. Seen as default / norm (i.e. accepted to the point of not being cited) Examples of tool in use
Independently	Eg. ELIXIR CDR / EDD / RIR

Functionality	
Reliably accurate with reproducible results	Use robust components: • API (ease of accessibility) • Recognised standards (eg. GA4GH) • Identifiers (Ontology terms) • Metadata • Benchmark data available (Independant)
Technical performance	Availability (average % uptime/month over last year) Response time
Secure Access	eg. AAI
Installation	Either local: • Useful when internet connection is limited • Standard architecture (agnostic) • Documentation or other support for installation Or web-based: • Avoids downloading quantities of data • Incorporated into pipeline or virtual platform Containerised
Intuitive Interface	Adjustable parameters, functions, settings, Default settings and advanced mode (fine tuning) Simple inputs, detailed outputs.
Command line	Modifiable to particular, non-standard requirements
Scalable / automatable	Can be incorporated into a pipeline / workflow (either pre-existing or purpose built) Interoperability
Standard file formats	Both input and output. (Conversions increase time and risk of errors) Flexible (able to accept data as is, avoid retrofit to make readable)
Clear processing	Track progress (Avoid 'black box') Intermediate results are checkable Errors, Warnings and Log Files
Support	

Expertise	University / Institute / Company (a group not an individual) Commercial software => dedicated customer support Others (eg. community or others outside the host, consultants)
Ongoing development	Release cycle Permanent archive of releases, eg zenodo.org, figshare.com
Bug report / fix, new features requests.	Point of contact Dedicated support desk
Maintenance	SOP or similar plan
Training materials available	Consultant, User documentation, Release documentation versions Webinar
Included in registry?	Findable (eg. Bio.tools, Markup)

Next Steps

A next step will be to refine the list of criteria in discussion with a selected number of tool developers (eg. those tools identified in the ELIXIR Rare Disease Service Bundle, as being drawn up in collaboration with WP13). This will include further discussions with BBMRI and other partners in WP10.4 to identify gaps and improvements.

These criteria will be used as the basis for a webform and the form will be tested with a number of key tools and fed back before taking more widely. The aim is to have a working, tested version of the form to demonstrate at the WP2 retreat (May 2020).

Contribution from Sustainability report

Problem

Many of the outputs of the EJP RD, including Pillar 2's, will have value when the project ends. Each of these outputs will require explicit thoughts on how they will be sustained after the project. Sustainability in a public health program is important for four main reasons: (1) sustained programs can maintain their effects for a long time, (2) there is often a latency period between the beginning of program-related activities and their effects on population health, (3) absence of sustainability can lead to an investment loss for the organisations and people involved, and (4) discontinuation of program-related activities may bring disillusion to participants and make subsequent community mobilisation difficult[11]. In order to give a long-term perspective to actions contributing to visibility, registration, surveillance, and knowledge dissemination of RD, there is a need to use legal and funding tools[12].

Background

Without a proper sustainability plan, any services or other resources that are created in a project may no longer be systematically developed and maintained after the project. In that case, they will be losing their value, and potentially have to be redeveloped in new projects. To prevent such a thing from happening to the EJP RD VP and its services, financing models to sustain and scale up the development and use of the VP are being studied. Program implementation and sustainability should not be distinct and successive phases but should be concomitant processes in order to take into account the recursive or reflexive character of sustainability and learning or of the continuous adjustments that shape the sustainability process[1].

Methods

In order to design sustainability options, the Work Package (WP) 10 is working in close collaboration with sustainability experts from the transversal WP3 to explore needs, opportunities and methods for sustaining and scaling up each WP component. Two approaches are used to support the work on sustainability:

Education: It is important that the developers of resources to be sustained are made aware of the fact that their design choices can influence the sustainability. Therefore, every developer in Pillar 2 is made aware of sustainability aspects, and the WP10 also makes sure that sustainability is explicitly on the agenda.

[11] Pluye, P., Potvin, L., & Denis, J.-L. (2004). Making public health programs last: conceptualizing sustainability. Evaluation and Program Planning, 27(2), 121–133. http://doi.org/10.1016/j.evalprogplan.2004.01.001.

[12] Montserrat Moliner, A., & Waligóra, J. (2013). The European Union policy in the field of rare diseases. Public Health Genomics, 16(6), 268–277. http://doi.org/10.1159/000355930.

Planning: Sustainability plans will be created for all resources that are deemed valuable in the project.

Achievements so far

Most of the current work on sustainability is done in the transversal WP3 dedicated to sustainability. In WP3, a handbook has been written explaining the different aspects of sustainability. This handbook will soon be distributed to all WP leaders in the EJP RD. Also, with support from WP3, a primer on sustainability has been given to all participants at the Pillar 2 annual retreat in May 2019.

To bootstrap the creation of sustainability plans, WP3 has created a survey that will collect information about resources that will need to be planned to be made sustainable. The questions of the survey have been crafted, the survey itself will now be created and tested in a small circle before being distributed over the whole project.

Next steps

Starting in October 2019, we will organize separate meetings of the partners involved in Task 10.5 (Sustainability and scaling up) in order to make sure that the products of Pillar 2 (a) will be suitable for sustaining and (b) will get realistic sustainability plans. Collaboration with WP3 will continue as started.