

## Section 1

# Towards effective, interoperable rare disease registries, in collaboration with the EJP RD

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## Introduction

In this document EJP-RD describes interoperability considerations pertinent to the development and operation of ERN registries. The suggestions herein provided are equally relevant to groups setting up new registries or improving existing registries, and relate to all types of registries (primary resources, aggregation focused, clinical objectives, research objectives, etc.). In all cases, promoting interoperability at the software and the data levels will help make registries more useful and more sustainable. Even high-quality registries can quickly lose their usefulness if they are hard to find, if data access is not possible or access procedures are challenging, and if their data are not optimised for use in combination with other data in other locations. Establishing an RD registry in a manner that will progressively increase its quality and interoperability will typically entail a collaborative effort between **at least three parties**:

- 1) An ERN team** (or combination of teams) to lead, own and manage the registry
- 2) A registry software provider** who implements the software underlying the registry
- 3) Interoperability collaborators** (such as EJP-RD project members, including the JRC who provide the EC's RD Platform which must be collaborated with under the terms of the funding call), to help guide the design/development work of the registry, and simultaneously feedback the registry's needs and experiences to EJP-RD teams. Additionally, there are vital roles for patients in terms of supporting and driving registries (e.g., providing PRO/PROM data, shaping governance policies, political and financial backing), which help with the wider relevance, impact and sustainability of the resource - and so ERNs might want to consider this in their registry plans. This document, however, is focused on the tripartite underpinning, as this is particularly relevant to registry interoperability.

## Background

### *The Rare Disease Patient Registry Concept*

A patient registry is an organised system that uses observational study methods to collect uniform data (medical and other, entered by clinicians and/or patients) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and serves one or more predetermined scientific, clinical, or policy purposes. It is usual to distinguish between population-based registries, which refer to a geographically defined population and aim to register all cases in that population, and non-population-based registries, which are based on clinical centres or other criteria (members of a patient organization, participants registered via an

ERN or other disease-specific registry etc.) where the population coverage may not be comprehensive.

In the spirit of the [Council Recommendation on RD \(2009\)](#) and on the [EUCERD recommendations on patient registration \(2013\)](#), the European Commission has decided to support ERNs in setting up patient registries. Previously five registries were financed through the Annual Work Plan 2016 of the Health Programme: ERKReg (ERKNet), ERN-LUNG registry, EuRRECa (Endo-ERN), PARTNER (PaedCan) and U-IMD (MetabERN). These five projects were initiated in April 2018 and are running for three years (i.e., to 2021).

A new funding call from the Annual Work Plan 2019 of the EU Health Programme has now been launched to finance registries in the frame of the 19 ERNs.

### **Registry Funding Call:**

<https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/pj-01-2019/freeTextSearchKeyword=registries;typeCodes=1;statusCodes=31094503,31094501;programCode=3HP;programDivisionCode=null;focusAreaCode=null;crossCuttingPriorityCode=null;callCode=Default;sortQuery=openingDate;orderBy=asc;onlyTenders=false;topicListKey=topicSearchTablePageState>

Deadline: 10 September 17:00 (Brussels time)

This Call requires that funded registries employ the 'JRC standards and tools', as established by the European Rare Disease Platform (<https://eu-rd-platform.jrc.ec.europa.eu/>). Specifically, this entails registering with the platform's European Rare Disease Registry Infrastructure (ERDRI) to be made searchable and findable, and adopting standards furnished by the platform such as the JRC Common Data Elements (CDE) and the EUPID approach to ID encryption.

## **Developing a registry in collaboration with the EJP-RD**

EJP-RD is a major European rare disease initiative that links directly with international infrastructure initiatives and places interoperability at the core of its mission. As such, collaborating with EJP RD in establishing an RD registry will enhance the utility of the resulting resource, and yet require only a minimum extra degree of effort (a few persons-months).

EJP-RD has designed a process for collaboration, and this is elaborated in **Section 2**.

In general, the approach entails linking:

- 1) an '**ERN registry steward**' (responsible for managing the registry);
- 2) the **registry software provider** who implements the software underlying the registry; and
- 3) one or more '**EJP-RD interoperability stewards**' (who offer guidance regarding standards and technologies that will help make registries increasingly FAIR, and help

spread the lessons learned by these interactions).

Typically, the ERN registry steward would be the person(s) undertaking data management tasks within an ERN. He or she is asked to take on an extra responsibility towards the interoperability of the registry, and interact with the EJP-RD interoperability steward(s) who are drawn from and represent EJP-RD partners, including the JCR for EU RD Platform support. EJP-RD interoperability steward(s) will work from within the EJP-RD 'Pillar 2' towards application of EJP-RD technologies and expertise to meet the specific needs of the registry. EJP-RD will offer the expertise of the team it has set up to help with different aspects of registry interoperability as these needs emerge and evolve. Together with the registry software provider, these three parties can deliver an interoperable registry. Marginal extra effort can be provided by domain experts, such as a medical doctor who might co-lead the registry.

## General Interoperability Considerations

### Why interoperability?

1. A large, stand-alone, registry for an ERN can be useful, but its utility and durability will increase significantly if it is made **interoperable** with other registries. This entails designing it to comply and harmonise with international standards of quality, structure and content, and access control and information governance/protection, and also adopting common methods and processes for information/patient discoverability, sharing and federation with other registries (for the same or different RDs). Thereby, users can more easily compare, pool and analyse patient datasets, using sufficient numbers of cases for meaningful clinical research and public health purposes.
2. Construction and maintenance of RD registries is challenging, but considerable efficiencies can be gained if different groups work together with registry software providers, especially those who are committed to working on adhering to global interoperability standards. This not only reduces the cost per registry established, but also makes interoperability far easier to achieve.
3. Excellent resources now exist to help teams build their RD patient registries. These include:
  - a) European Platform on Rare Disease Registration (EU RD Platform) developed by the European Commission Joint Research Centre with its European RD Registry Infrastructure (ERDRI) which provides a Central Metadata Repository, the EUPID pseudonymisation tool, standards for data collection and exchange, and training on the use and implementation of the EU RD Platform;
  - b) five ERN registries constructed in recent years and pilots organised by other ERNs, from which lessons and expertise can be gained;
  - c) the EJP-RD program, which can provide relevant standards, tools, collaboration and training.

4. Interoperability enables registries to be connected ('federated') so their data can be used in concert, almost as if they were a single database. **The driving purpose behind this federation should always be explicit.** For example, this could be to interconnect sets of local or ERN specific registries, unification at the national or international levels, integration with hospital electronic health record systems, or interaction (remote or integral) with CPMS.

## How to achieve interoperability?

### 1) Interoperability is not all or nothing

A registry can be constructed to be highly interoperable by design, but it is also possible to start with a basic registry and improve this over time by progressively adding or changing procedures, policies, IT systems, data standards, etc to increasingly align or harmonise with other registries with whom you wish to interact. That said, some core features of a registry would be wise to standardise early on (e.g., the ontologies used, the metadata and data models employed, the identifiers used for patients/samples, etc). It not only costs nothing more to employ such core standardised approaches rather than non-standard options from the start (to facilitate interoperability from the outset), but arguably saves money overall as registry efficiency will be higher and there will be no need to pay for system changes and user retraining later on.

*EJP-RD can help by building your needs into common standards development work, and guiding you on the use of standards*

### 2) Collaboration and synergy are valuable

One certain way for ERNs to make better registries, at a lower unit cost, with more sustainability, would be by ERN teams merging and unifying their efforts. Working closely with expert registry software providers and interoperability experts would certainly be advised, and it would be sensible to commit to organising and joining ERN forums to discuss and agree on many aspects of registry construction and evolution.

*EJP-RD can collaborate on creating a 'hub function' to provide information and expertise on registry interoperability (an EJP-RD mailing list for ERNs to ask questions on this topic has now been set up, at [registryadvice@ejprarediseases.org](mailto:registryadvice@ejprarediseases.org)), and such interactions will also promote alignment with the EJP-RD 'Virtual Platform'*

### 3) Practical aspects of interoperability

To build registries where the platform and the data within it are optimally Findable, Accessible, Interoperable, and Reusable for humans and computers (i.e., FAIR), there are several practical considerations to address.

#### a) Semantic interoperability

This is about how the data in a registry, the registry itself, and consent information are described for humans and computers. It concerns the choices made regarding ontologies, terminologies, definitions, data labels, classifications, nomenclature, and coding systems – and also the mapping between different options for each of these. This also pertains to, as a starting point, the Common Data Elements for registries (CDE – available at EU RD Platform), and the Minimum Dataset recommended by EUCERD.

#### b) Technical interoperability

This is about how the registry data and metadata (information about the data and the registry) are structured and managed in the registry database, and it concerns the implementation choices made regarding the scope and relationships between data elements, the ID systems employed, the input/output formats and file types handled, arrangements for making data and patients findable (discoverability and matching) and accessible (sharing, pooling, cross-site analysis). Methods for identifying, authenticating and authorising users and their permissions also falls under this heading. The standards in this area are rapidly evolving and there are often competing alternatives, and so carefully choices must be made based on exactly what functionality the registry is seeking to achieve.

#### c) Legal and organisational interoperability

This is about data governance and operational policies, and it concerns aspects such as data security and safety, patient privacy, design and capture of consent, rules and objectives for sharing, quality assurance/metrics, and compliance with regulatory requirements.

*With respect to semantic, technical and legal/organisational considerations, EJP-RD can help improve registry interoperability by connecting projects to major international efforts, on aspects such as the use of standards, highlighting tools that you can connect to, defining relationships (mappings) between standards, providing training on interoperability, etc.*

### 4) EJP-RD support for ongoing FAIRification of registries

Resources and expertise have been assembled in EJP-RD, along with structured processes for joint work to grow and improve RD registry 'FAIRness'. EJP-RD investigates, and offers guidance for, ways by which stakeholders can optimise their registry design and management practices. That process is described in **Section 2**. Each registry team can take its own preferred route through the collaboration

process, to ensure that the end result is a FAIRer resource that can interact with other resources and wider community system to the degree the registry needs to in order to achieve the impact it desires.

*EJP-RD can help apply practical steps towards making an ERN registry become FAIRer*

## 5) Basic standards that could be employed now/soon

Depending on the type of registry and its objectives, different standards and different types of interoperability may be more or less important. Some of the most well developed and generally pertinent standards are listed below, for ERNs to consider:

- Minimum information (Common Data Elements (CDE), available at ERDRI) – a core set of data fields that are widely used and hence ensure basic utility of registry data
- International unique global identifier systems for patients (EUPID) - an EJP-RD supported method for encrypting patient IDs, to help protect patient identity whilst still being able to track and connect patient records (available via ERDRI)
- Ontologies (ORDO, HPO, LOINC, ...) - universally adopted sets of coding terms with unambiguous definitions, to ensure data compatibility
- Nomenclature (HGNC, HGVS, SPDI) - consensus ways to name genes, variants, etc, to bring certainty over what genome positions are being referred to
- Metadata logical models and metadata alignment services (ERDRI and EJP-RD Pillar 2) - standard ways to describe a registry (logical models for how data elements are interrelated) and enter it into a registry catalog services so they can be found by potential users
- Digitising consent and use conditions (GA4GH ADA-M & DUO) - a global standard way to structure consent and related information into an unambiguous, computer-readable and exchangeable format
- AAI (Authentication and Authorization Infrastructure; Oauth2 based, as per LifeScience Cloud project) - a technology for managing users and their permissions across systems (e.g., collections of registries) so that an approved user need login only once at any one site and then be recognised by all other sites in network (with each site setting its own permissions for the recognised user)
- Discovery query and response APIs (e.g. GA4GH Beacons, FAIR data access API)-services built into a registry that enables data to be interacted with by other computers (e.g., registries, websites) in order to find (not necessarily share) records of interest
- Types/Levels of patient matchmaking (e.g. IRDiRC/GA4GH MME) - advanced, secure methods that enable similar RD patients to be located, without exposing any actual patient data

*EJP-RD has committed to identify, scale up, and develop such standards to improve the overall RD data interoperability, and to prioritise its work together with ERNs.*

## Section 2

# ERN registry projects in association with the EJP-RD: Organisation and budget considerations

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### Purpose of this document

The purpose of this document is to provide organisational advice towards making a registry more interoperable in association with the EJPRD. The scope of this document is organisation only: interoperability considerations for registries as advised by the EJPRD are described in **Section 1**.

### Background: the EJPRD infrastructure

The aim of the Infrastructure and Virtual Platform that the EJPRD is building is to provide ERNs and the rare disease community means to boost the efficiency of multi-source discovery, query and analysis for rare disease goals. Therefore, EJPRD consortium partners are investigating and developing state-of-the-art IT services, best practices, and standards for registries and their data to become findable, accessible (under well-defined conditions), interoperable, and reusable, for optimally efficient use by humans and computers (FAIR). Collaboration with EJPRD-associated partners emphasizes an ERN's ambition to optimize reuse of their data in multiple scenarios, thereby negating the risk that registries become isolated silos within the global rare disease data landscape.

## Budget considerations

### Organisation of collaboration with the EJPRD

We reiterate the key roles in the proposed three-party organisation as described in the interoperability considerations document for ERN registries<sup>1</sup>:

1. The 'ERN registry steward' (responsible for managing the registry), [budget holder: ERN];
2. The registry software provider who implements the software underlying the registry [budget holder: ERN];
3. The 'EJPRD Interoperability steward(s)' [budget holder: EJPRD].

**In practice**, the three parties form a team that works together by face to face and remote interactions. The stewards collaboratively lead the practical work: preparing plans of action, involving the experts that they need, and creating the interoperability artefacts specific for the registry with the aid of experts (e.g. ontologies, data models, data access software). They make sure that artefacts such as standards and software solutions are identified and subsequently employed, within or associated with a registry system, to make the registry and its data more FAIR. The stewards are supported by their seniors (e.g. a leading medical doctor for party 1, senior IT specialists for party 3). If need be, EJPRD teams and affiliated groups can advise on profiles and candidates for parties 2 and 3.

### EJP-RD support

The EJP-RD will support ERNs engaging in the three-party approach. First, it will **provide the EJP-RD Interoperability steward** who contributes in the role of a guide, or 'catalyst', towards a FAIRer registry. This involves organising collaborations with EJPRD experts and acting as 'translator' in EJP-RD teams. Secondly, the EJP-RD will **facilitate ERN registry stewards** to form an ERN registry steward network, visiting expert groups, and participating in workshops, including those associated with the EJP-RD training pillar. Thirdly, EJPRD teams commit to **treating ERN registry stewards as priority stakeholders** and involving them directly in their work.

### Budgetary advice

The three-party collaboration also involves deploying effort of personnel to fulfil the various roles. For an effective collaboration that the EJP-RD can support, we expect that the effort of an ERN registry steward (party 1) will amount to at least several weeks, but this may be much more as needed subject to the capacities of each party and the goals of the registry. The ERN is the budget holder for the ERN registry steward. Arrangements for party 2, the registry software provider are between the

ERN and the provider and beyond the scope of this document. We advise to make a commitment to implementing [FAIR guiding principles](#) (an IRDiRC recognized resource) a requirement for the software provider. As aforementioned, **the EJP-RD will take responsibility for the EJP-RD interoperability steward role**. While the collaboration with the EJP-RD can be long-lasting, the specific ‘catalyst’ role is more time-limited and expected to amount to several weeks on average depending on the complexity of the registry. The distribution of responsibilities is summarized in the table below.

**Summary table budget holders**

	Budget holder = ERN	Budget holder = EJPRD
<b>ERN registry team</b>	ERN registry steward (party 1) Registry software provider (party 2)	Support for ERN and EJP-RD data steward interactions
<b>EJPRD R&amp;D teams</b>		EJP-RD Interoperability steward (party 3) Interoperability support teams