TOOL 4

The advantages of ERNs as partners for research

Together4RD
RARE DISEASES

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Together4RD Toolkit to foster ERN and Industry Collaborations

Introduction

European Reference Networks (ERNs) are often viewed as structures dedicated first and foremost to care – and indeed, they *do* have significant duties under the heading of 'advancing care' (e.g. supporting virtual case review, generating guidelines, supporting training activities). However, ERNs also have a formal mandate to contribute to research into rare diseases and highly specialised medicine. Although these research goals have perhaps been somewhat overshadowed to-date, this research mandate is clearly there, in the legislative acts on which ERNs are based: Annex I of the Delegated Decision (2014/287/EU)[1] stipulates that one of the horizontal criteria (i.e. criteria which all members of any ERN should fulfil) is as follows:

"(5) To fulfil the requirement set out in point (iv) of Article 12(4)(a) of Directive 2011/24/EU ('make a contribution to research'), the Networks must: (a) identify and fill research gaps; (b) promote collaborative research within the Network; (c) reinforce research and epidemiological surveillance, through setting up of shared registries"

Although some ERNs have embraced research goals from their launch, in one way or another -particularly those which emerged from communities which were already quite research-focused - it is probably fair to say that for most Networks, research *per se* has been less of a priority to-date.[2] The Together4RD Position Statement explains in more details some of the reasons for this.[3]

An important step in enabling ERNs to reach their research potential, particularly when it comes to fostering collaborations with industry, is ensuring that the advantages and potential of ERNs as partners for research are understood and appreciated.

1 https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks/establishing-ern_en

2 https://pubmed.ncbi.nlm.nih.gov/33733400/

3 https://ojrd.biomedcentral.com/articles/10.1186/s13023-023-02853-9 see part 2

ERNs in Numbers

ERNs are arguably the single most important innovations in health and research for rare diseases in Europe, if not globally.

- ☑ There are 24 ERNs, launched in 2017, established across broad rare disease groups such as rare liver diseases, rare eye disease, etc., or are dedicated to areas of highly specialised medicine such as paediatric transplantation
- ☑ ERNs are networks connecting EU/EEA centres of expertise in specialised healthcare fields necessitating a concentration of expertise
- ☑ At present, they bring together 1613 Healthcare Providers/centres/units, nested in 382 separate hospitals across all 27 EU Member States plus Norway
- ☑ The primary focus of ERNs is improving care, and the networks are officially coordinated under the European Commission Directorate General concerned with Health (DG SANTE). However, they have strong research responsibilities and priorities too, offering enormous potential
- ☑ ERNs are designed to be patient-centred, with patients embedded in the governance and in all activities – this is facilitated by the concept of ePAGs (European Patient Advocacy Groups). Today, there are over 300 ePAGs working with ERNs
- ☑ The Clinical Patient Management System (CPMS), a secure digital platform used by the ERNs, has enabled the virtual consultation of more than 4000 complex cases
- ☑ Over 95,000 patients have already been included in the dedicated ERN registries

How are ERNs Well-Placed to Add Value to Rare Disease Research?

A number of fundamental advantages of ERNs for research are highlighted below (NB: these are based upon Part 2 of the aforementioned **Position Statement** from Together4RD, which itself incorporated and expanded upon conclusions from the first EMA and RD-ACTION workshop dedicated to ERN research.[4] These earlier ideas have been supplemented here with additional and updated content.

4 https://endo-ern.eu/wp-content/uploads/2018/12/Conclusions-and-Next-Steps-from-the-workshop-%E2%80%98How-ERNs-can-provide-added-value-in-the-area-of-clinical-research%E2%80%99-1.pdf

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ERNs are permanent infrastructures

For many years, EU projects dedicated to rare disease - funded both through the Framework Programmes and the 1st and 2nd Public Health Programmes, in particular - often made good progress in establishing networks:[5] these were dedicated to a diverse range of rare conditions, sometimes quite specific diseases (such as McArdle Disease; Duchenne Muscular Dystrophy; Wolfram, Alstrom and Bardet-Biedl Syndromes; etc.) and other times focused on broader clusters such as intoxication-type metabolic diseases, rare anaemias, and paediatric cancers. These projects were often called 'pilot networks', once the concept of ERNs was born in the lead-up to the publication of the Cross-Border HealthCare Directive. They built consortia linking expert centres across Europe, and undertook crucial activities like establishing registries, developing guidelines, creating patient support materials, setting-up biobanks, developing educational resources, and much more. A major challenge, however, was finding routes to sustain these networked communities and, in particular, sustain their newly-created infrastructure and tools, after the funding period ended. This was not conducive to such communities developing into research-active networks or communities with which industry might partner. **ERNs, therefore, have a major advantage here, in the sense that they are NOT projects, and are not temporary**. DG SANTE committed to formally evaluating the ERNs and their constituent HealthCare Providers, or HCPs, every 5 years. The process and results of the first evaluation, initiated in late 2022 and concluded in 2023, can be viewed here[6] – in a nutshell though, the first evaluation concluded that "the ERN ecosystem is functioning well, meaning they are delivering on highly specialist work for rare disease patients such as consultations for diagnosis and therapies, the production of clinical guidelines and specialised trainings". All 24 ERNs obtained satisfactory results, meaning none were targeted to be disbanded (88% of their member HCPs also obtained satisfactory results[7]). Presuming the ERNs continue to be evaluated positively in future, they may be viewed as **permanent** structures, making them important stakeholders for partnerships in research of all kinds. These are not groups of experts united by individual projects, whose structures and resources are likely to fall into disuse once the funding period ends.

ERNs sit at the interface of the Research and Clinical Spheres

The Legal Acts upon which ERNs are based mandate that the Networks provide added-value across both the clinical and research domains. This is essential in rare diseases,

5 See **Rare diseases 2008-2016- EU-funded actions paving the way to the European reference networks** (https://op.europa.eu/en/publication-detail/-/publication/fd1f05fc-6def-11e8-9483-01aa75ed71a1)

6 https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks/erns-evaluation_en

7 *Ibid.*

where traditionally that line between care on the one hand and research on the other has, of necessity, been somewhat blurred (when 94-5% of the conditions lack any dedicated treatments, it is necessary for treating clinicians to generate knowledge 'as they go along' and apply lessons learned from any and all emerging research studies, in order to provide the best possible care). All HCPs participating in ERNs as full members should - assuming they fulfil the EC's horizontal criterial for all centres wishing to participate as full members of an ERN – possess clinical expertise in at least some of the conditions underneath the grouping of that ERN, **but should also be research-active**. The proximity of research spaces and the clinic is a major strength of the ERN model, facilitating the generation and translation of knowledge and best practice.

ERNs are designed to ensure comprehensive disease (and specialised procedure) coverage

When applications for the first 24 ERNs were submitted, would-be coordinators were encouraged to establish their Networks based upon a list of suggested Thematic Groupings:[8] this was to ensure that collectively, all rare disease would have a 'home' under at least one ERN. In actuality, many ERNs followed this suggested Groupings schema very closely, and **consequently the vast majority of conditions classed as rare are covered by the 24 Networks created under the first call**, along with several less disease-focused ERNs more dedicated to specialised *procedures* and areas of medicine in which a concentration of expertise is also of paramount importance (e.g. ERN-TransplantChild). (One notable missing area, which was included in the recommended list of ERN groupings back in 2016 but was not eventually included in any application, is rare gynaecological diseases – it is possible that Gyneco-Obstetrics, along with additional specialised procedures as opposed to pathologies per se, will be addressed in a future call for new ERNs). **The fact that ERNs are founded upon this principle of inclusion of all rare diseases is a major benefit and holds real potential for research of the future**.

The word 'potential' is important here. Some ERNs consciously commenced operations by focusing primarily on a subset of conditions under their wider headings. And even where ERNs are very much trying to map resources and knowledge on any and all conditions under that heading, the reality for many networks is that there is usually a 'focal' disease or group of diseases which has attracted a relatively large amount of research attention to-date, and/or is better understood and supported in terms of diagnosis and care. This is sometimes a condition or group of conditions which were the focus of successful proposals under past European Framework Programmes or Health Programme calls, which enabled

8 https://health.ec.europa.eu/publications/rare-disease-european-reference-networks-addendum-eucerd-recommendations-january-2013_en . See also the foundational work upon which the list appearing in the Addenudum to the 2013 Recommendations was based https://link.springer.com/article/10.1186/s13023-016-0398-y

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networking to emerge relatively early. These sorts of conditions are sometimes amongst the more common of the rare diseases (e.g. Duchenne Muscular Dystrophy and Cystic Fibrosis would be good examples) but it must be noted that even these more active areas often still lack truly transformative, let alone curative, treatments. EURORDIS, in its 'Recommendations to Achieve a Mature ERN System in 2030'[9] highlights the need for a stronger focus on the conditions which are currently somewhat out of scope, or not receiving the requisite coverage.

Of course, the fact that neglected conditions which have never seen significant R&D attention are technically included under the combined scope of ERNs does not magically translate into knowledge and research effort. It will take time - and resources - to generate understanding of the less-well-studied rare diseases, and build a basis for research to thrive. But crucially, the expectation is there that each ERN will, in time and via a stepwise approach, come to tangibly support the diagnostics, treatment, care and research for all rare diseases under their heading.[10] Therefore, **the inherently egalitarian nature of the ERN model is, in itself, a strong step in the right direct of casting much-needed light on the many thousands of so-called neglected diseases** which have traditionally lacked any research interest.

ERNs offer unique data generation/linkage and digital health opportunities

ERNs provide unprecedented opportunities to collect high quality, relevant, and interoperable data. The Networks are based upon centres which have demonstrable expertise in particular areas, but the Networking *tools* and platform which connect these well-established centres are being created -or at least delivered- anew. This offers exciting opportunities for the over 1600 member HCPs across Europe to subscribe to best practices around collecting and pooling precious rare disease data which can support the provision of highly specialised care and advance research. The Clinical Patient Management System (CPMS) has already resulted in more harmonised and interoperable data being collected for specialist virtual reviews. But the area of registration holds possibly the greatest potential in terms of advancing research and understanding.

Registries are essential tools for generating knowledge about rare diseases, and -depending on the data they collect – can serve multiple purposes.[11] Notwithstanding the variety in

9 https://download2.eurordis.org/documents/pdf/Our_vision_on_mature_ERNs.pdf (especially p.30 'Disease Coverage of the ERNs')

10 This was a stipulation of the original 2013 EUCERD Recommendations on European Reference Networks for Rare Diseases - https://health.ec.europa.eu/publications/eucerd-recommendations-european-reference-networks-rare-diseases_en . The EURORDIS Recommendations https://download2.eurordis.org/documents/pdf/Our_vision_on_mature_ERNs.pdf (especially p.30 'Disease Coverage of the ERNs') highlight the need for a stronger focus on the conditons which are currently somewhat out of scope, or not receiving the requisite coverage.

11 https://www.frontiersin.org/articles/10.3389/fendo.2022.832063/full ; Hedley, V., Kole, A., Rodwell, C., and Simon, F. (2019) Rare 2030 Knowledge Base Summary on Data Collection and Utilisation for Rare Diseases https://www.rare2030.eu/our-work/ (p. 4-5)

scope of the 24 ERNs, there have been robust attempts to ensure a baseline compatibility and interoperability via a concerted European approach. The best example of the latter is the European Platform on Rare Diseases Registration, initiated in 2013 by the European Commission's Joint Research Centre in collaboration with DG SANTE. An important component of this platform is the ERDRI or European Rare Disease Registry Infrastructure.[12] ERDRI seeks to make data held in rare disease registries searchable and findable. It does this via a suite of tools: the European Directory of Registries (ERDRI.dor); a Central Metadata Repository (ERDRI.mdr); a Pseudonymisation Tool (ERDRI.spider); and a Search broker (ERDRI.sebro).

The creation of a European platform to increase the reuse potential of precious rare disease data was an important step, given the variety of registries which exist (845 globally, according to Orphanet) but also the fact that only 1000 of the known rare conditions are included in at least one of those 845.[13] Into this complicated ecosystem, **the creation of ERN registries -or platforms to link new ERN registries with historical or possibly new disease-specific registries- holds major potential for advancing knowledge and better care, but also naturally for stimulating and advancing research**. Supported by projects like the EJP RD[14], ERICA[15], and now ERDERA[16], attempts are being made to ensure a certain level of interoperability in terms of the data collected in these new ERN registries. For instance, the Common Data Elements issued by the ERDRI were turned into a richer data dictionary under the EJP RD: this is just one example of efforts to make registry data FAIR (Findable, Accessible, Interoperable, and Reusable). Greater value will come with the advance of individual ERNs agreeing and standardising domain-specific datasets.[17] 5 of the ERNs received EC funding to develop their registries early on in the ERN story with the remaining 19 receiving their funds via the 2019 work programme of DG SANTE. Although still relatively young registries, the number of patients enrolled is increasing (and now exceeds over 95000). Different ERNs are approaching their registry set-up/linkage in different ways and increasingly, tools are being created to optimise their potential (see below).

Beyond the registry space, the fact that ERNs connect so many of the leading centres of expertise for rare disease across Europe also offers huge potential to increase the standardisation and reuse potential of electronic health data – rare diseases are a natural beneficiary of the anticipated EU Health Data Space.

12 https://eu-rd-platform.jrc.ec.europa.eu/erdri-description_en
13 https://www.orpha.net/pdfs/orphacom/cahiers/docs/GB/Rare_Disease_Registries.pdf
14 https://www.ejprarediseases.org/
15 https://erica-rd.eu/
16 https://erdera.org/
17 https://pubmed.ncbi.nlm.nih.gov/35594066/

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ERNs are networks centred on patients

Patients sit at the heart of the ERN concept (and indeed, the concept emerged largely from the patient community in Europe). The Addendum to the EUCERD Recommendations stipulated that patients should have a meaningful role in all levels of ERN activity, governance included. To facilitate this, EURORDIS created the concept of an ePAG – a European Patient Advocacy Group[18]- to work with each ERN. Over 300 ePAG advocates have been approved and are working closely with the Network most connected to their particular condition. ERNs have conducted surveys on people living with rare conditions under their Thematic Grouping which is helping to understand patients' needs and realities better than ever before. Just as clinician networks are growing under ERNs, so patient communities across Europe are coalescing around the ERNs, making it easier to engage patients and develop patient partnerships in research and care (though challenges persist).[19] The ePAG advocates address cross-cutting issues together, across ERN boundaries, and their existence constitutes an excellent opportunity for external stakeholders to work with networks that are genuinely patient-centric.

ERNs offer Independent Expertise

Another advantage of the ERNs, for industry, is the fact that these networks -which as above, should be considered permanent, for all intents and purposes- are established independently of any industry influence. Companies often remark that the existence of structures and networks like this, assembled by the communities themselves, can be helpful in avoiding any accusations of bias.

18 https://www.eurordis.org/our-priorities/european-reference-networks/epag/
19 https://www.oaepublish.com/articles/rdodj.2021.001

Important Resources to Showcase the Power of ERNs for Research

Together4RD Webinar

One important resource, to showcase the value and advantages of ERNs as partners for research, is the **webinar** organised jointly by Together4RD and the **European Rare Disease Research Coordination and Support Action consortium (ERICA)** in late 2024

Resources Created by/With the dedicated ERN Research Action, ERICA

The ERICA website is actually an important gateway to ERN resources, especially pertaining to research. This 4-year project was specifically designed to advance ERN research, and has developed resources to improve various aspects of rare disease research (e.g. developing more effective data collection strategies, optimising patient involvement etc.). A few key resources generated by ERICA are linked below.

Title/Summary of ERICA Resource	Link
In terms of understanding the development choices, progress, and potential of the ERN registries, the 1st Monitoring Report on ERN Registry Data Collection (updated in 2024) is a useful resource	https://erica-rd.eu/wp-content/uploads/2024/11/ERICA_D2.5_02_24_NEW.pdf
Informed Consent Form templates were created via the European Joint Programme for RD, EJP-RD, specifically for ERN registries. The templates can be adapted at ERN, national and site level, and include versions for patients and for parents/legally-designated representatives. They have been translated into 26 languages.	https://erica-rd.eu/work-packages/data-collection-integration-and-sharing/generated-documents/
Data Sharing Agreements. In a centralised registry, where all the data collected by a ERN centre is transferred to a centralised server, a Data Sharing Agreement should be signed between the registry and every HCP contributing data. A customisable Data Sharing Agreement template was developed for the ERNs, for this purpose.	https://erica-rd.eu/work-packages/data-collection-integration-and-sharing/generated-documents/
The ERN registries have established Data Access Committees. If such a Committee agrees to grant access to the registry data to an external stakeholder, a data transfer agreement should be signed between the registry and the data requestor. A customisable Data Transfer Agreement template for the ERNs has been developed in the framework of ERICA, for this purpose.	https://erica-rd.eu/work-packages/data-collection-integration-and-sharing/generated-documents/
Patient Reported Outcome Measures are very important in rare diseases. ERICA has developed a PROMs Repository - as the first attempt to identify and centralize Clinical Assessment Outcomes questionnaires of relevance for rare diseases. This Resource has been created through the joint collaboration between Orphanet, Mapi Research Trust/ICON and ERN EuroBloodNet (VHIR, APHP), with the active contribution of ERNs more widely, and ePAGs. The repository should be regarded as 'a centralized and standardized access gate to more in depth information contained in PROQOLID™.'	https://erica-rd.eu/work-packages/patient-centred-research/proms-repository/
ERICA delivered a series of webinars of relevance to clinical trials in rare diseases. Some were developed within ERICA itself, whilst others showcase partnerships with other initiatives such as c4c. Some of these webinars should help external stakeholders to become more familiar with the ERNs.	https://erica-rd.eu/events/webinars/

The status quo of ERN registries

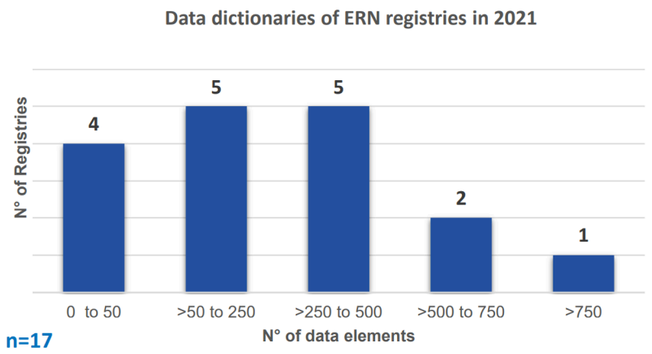
The registries established by the ERNs are perhaps particularly attractive resources for stakeholders who might be considering partnering with the ERNs for a range of research-related activities. The ERICA project generated a report, updated in late 2024, which summarised the status quo of these registries, in terms of the different approaches ERNs have taken to creating these infrastructures, the number of patients registered to-date, the size of their respective data dictionaries, and more. This report is linked in the ERICA resources table above, but is highlighted **here** too.

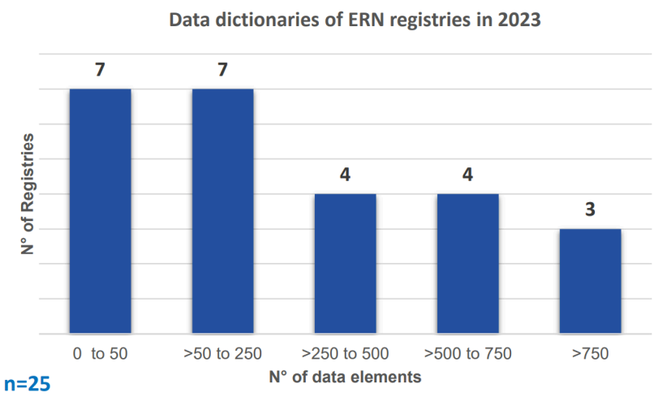
Amongst the highlights of this important report are the following:

- Most ERNs have opted to establish a core patient registry, using a centralised system (20 registries).
- Others have established/integrated multiple registries, or are in the process of doing

so. Therefore, the number of ERN registries (29) actually exceeds the number of networks (24).

- These multiple registries are sometimes embedded within the same infrastructure of the core registry (e.g. as is the case of the subregistries in ERKNet, the ERN for rare renal conditions), or else have been implemented separately, often following different design principles (i.e., centralised vs. federated in VASCERN, the ERN for rare vascular diseases).
- Occasionally, multisystemic diseases are 'shared' under the scope of 2 or more ERNs; therefore, some ERNs have chosen to collaborate in shared patient registry projects. For example, the Core Registry, originally established as part of the European Registries for Rare Endocrine and Conditions (EuRRECa) project, now supports the activities of both EndoERN and ERN BOND. In these cases, collection of shared data elements is supplemented with the inclusion of more specific condition-dependent modules.





[Figure 3] Progression of finalised ERN registries data dictionaries and their sizes, from 2021 (above) to 2023

Figure directly from ERICA Deliverable D2.5

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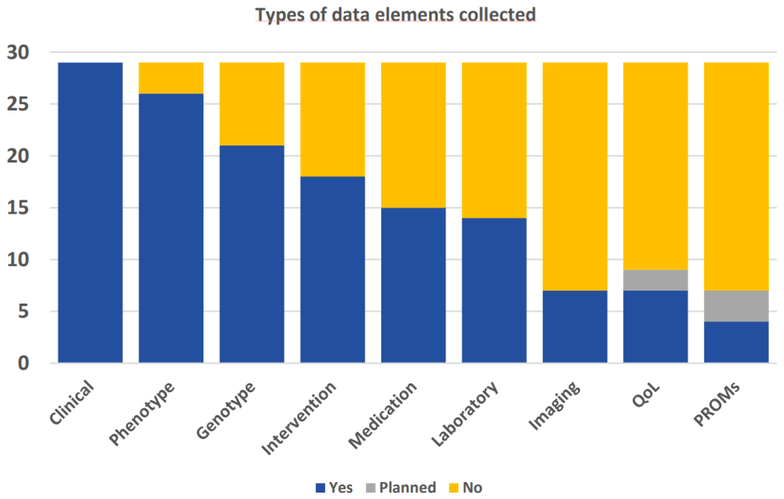
- Most ERN registries use external software solutions, including Molgenis (3), Castor (7), and RedCap (4), as well as other providers (10). Only a minority of ERNs have decided to develop their registries in-house (5).
- ERN registries have been steadily increasing their data dictionaries. Whereas in 2021, 8 registries had data dictionaries with over 250 data elements, in 2023 that figure was 11 (see figure on previous page).
- The type of data items collected by ERN registries is quite broad – whereas all collect clinical data, and almost all collect phenotypic and genotypic data this figure, few collect imaging, QoL or PROMS data at present.



[Figure 4] Data element categories present in ERN patient registries

Figure directly from ERICA Deliverable D2.5

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