EURORDIS
RARE DISEASES EUROPE

TOOLKIT TO SUPPORT INTEGRATION OF EUROPEAN REFERENCE NETWORKS AND NATIONAL HEALTHCARE SYSTEMS

MAY 2022

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Introduction

European Reference Networks (ERNs) are networks of healthcare professionals working in the field of rare, low prevalence and complex diseases across Europe. The ERNs have been established in order to pool the scarce and scattered medical expertise on rare and complex diseases throughout the European Union (EU) with the objective to provide timely, accurate diagnosis and treatment for patients affected by a rare or complex disease, wherever they live in the EU. The ultimate goal is to provide equal access to specialised care, leaving no rare disease patient behind.

ERNs have a clear governance structure for knowledge sharing and care coordination across the EU, but to benefit the 30 million people living with a rare disease in Europe, they must establish the operating mechanisms that will govern their interaction with national health systems. **The integration of the ERNs into national health systems refers to the set of policies, rules and procedures required to anchor the ERN system to the national level so that all patients with a rare disease or complex condition across Europe can benefit from this model** [1], [2]**.**

Following the second call for members of existing ERNs in 2019, there is now greater coverage; all EU Member States and Norway participate in the Networks through their Centres of Expertise. However, the new ERN system needs to be connected to the national healthcare infrastructures for rare and complex diseases.

Each Member State has a distinct healthcare system and varying rare disease population needs. Careful consideration and reflection at national level is therefore needed to align the new ERN system with the national healthcare systems to complement the existing systems and align policies, legislations and care pathways.

The integration of ERNs into the national systems is an ambitious and complex process with major technical and budgetary implications, which require at the very least:

1. Member States to define clear referral pathways, access policies, organisational processes and infrastructure (referral management) to link their national healthcare systems with the ERNs;
2. Adjustments in the rare disease National Plans and legal reforms to address the technical capacities and legal arrangements required to anchor this new structure in each national health system;
3. Organisation of national networks with agreed shared care arrangements between the different levels of care, namely the local healthcare services, national Centres of Expertise and the ERN system that should be integrated as a new layer;
4. ERNs to implement their integration strategies for Affiliated Partners and explore innovative strategies to cooperate with other Centres of Expertise and national networks;
5. Adequate infrastructure and organisational arrangements to adopt and disseminate the knowledge assets curated and generated by the ERNs l - reaching out to national and regional and local levels.

In October 2017, the ERN Board of Member States (BoMS) established a Working Group on Integration of the ERNs, composed of Member States representatives, ERN Coordinators and European Commission representatives.

The Working Group on Integration of the ERNs issued a statement [1] on 25 June 2019 that encourages Member States to facilitate the integration of ERNs into their healthcare systems by:

- **Assessing and adapting or updating as needed the national policy and/or legal framework** to ensure the smooth integration of the ERNs into the national healthcare systems of the Member States, including, for example, national rare diseases plans/strategies and national cancer plans;

- **Creating appropriate (clear and well-defined) patient pathways** in order to improve the care and management of patients with rare or complex diseases. This should be accomplished by building on existing pathways, where possible, and linking them to the ERNs where they have not previously been linked. Member States that have no defined pathways for rare or complex disease patients are encouraged to build these along current best practices and in accordance with the disease-specific pathways being developed by the ERNs;

- **Developing clear systems for referral to ERNs** to be used by the healthcare providers. Referral procedures shall be transparent, seamless and effective. The referral is relatively easier when a Member State has one or more healthcare providers that are Members or Affiliated Partners of an ERN. It is also important for Member States to identify the link between any healthcare providers that provide care for patients with rare or complex diseases and healthcare providers that are the Members or Affiliated Partners of an ERN. Rules on cooperation at national level are needed in case of multiple Members or Affiliated Partners;

- **Developing a clear strategy for communicating and disseminating information about ERNs** to all levels of healthcare providers in their territory and facilitating access for healthcare professionals to the knowledge generated by the ERNs (clinical guidelines, training materials, etc.);

- **Reflecting on the means to best support (administrative, financial, organisational, informational, etc.) Coordinators, ERN Members and Affiliated Partners** to ensure patients will have access to the best available expertise. Strengthening the coordination role of national authorities shall be pursued.

The Annex to this statement [2] includes a list of potential actions under each of these 5 areas to guide Member States on their planning, and provides a view of the breadth and scope of the activities that each country will need to undertake. The integration process will require time and resources, and will need to be accomplished in parallel to the expansion and consolidation of the Networks over the next 5 years.

The European Commission will launch a Joint Action in 2022 [3] to support Member States over the next 3 years in this area. Activities will include exchanges of best practices and concrete proposals and guidelines for better integration of ERNs in the national healthcare systems, including well-defined patient pathways, referral procedures, development of national networks on rare diseases (including support for capacity building in the Member States, national rare disease plans, establishing the national networks and their integration with the ERNs) and guidelines for developing national teleconsultation tools interoperable with the ERN Clinical Patient Management System (CPMS).

The anticipated results developed through the Joint Action are the exchange of best practices and concrete proposals, guidelines, models and recommendations for better integration of ERNs into the national healthcare systems, including well-defined patient pathways, referral procedures, development of national networks on rare disease and guidelines for the development of national teleconsultation tools interoperable with the ERN CPMS. A mechanism should be developed by the Joint Action to monitor the progress and implementation of these proposals, guidelines, models and recommendations.

If the ERN system is to reach its full potential and benefit the 30 million people living with a rare disease, progress on national fronts in the coming years is as critical as the consolidation of the Networks. Therefore, Member States, in collaboration with the national rare disease community, need to establish the **legal instruments, operational processes and structures** to support an effective integration of the ERNs into their national health systems. This toolkit provides an overview of the relevant areas of intervention and proposes tools and processes to define concrete actions in each of them.

Structure of the Toolkit

This toolkit is organised around **5 blocks of action at national level**. For each area, the document collects the processes, tools, templates and best-practice examples to support the rare disease patient community engagement in the journey towards integrating ERNs into each national health system. These resources will need to be adapted to the local context through a structured dialogue with the rare disease community at national level, including national and regional health authorities, clinical leads, researchers, hospital managers, scientific societies, etc.

Objectives

The primary aim of this first edition of the ERN Integration Toolkit is to help the patient community engage with clinical teams, hospital managers and national/regional health authorities to take action towards integrating the ERNs into their national health systems.

The Toolkit gathers a selection of existing methodologies, tools, templates and best practices that can be used to support implementation of the recommendations outlined in the BoMs statement on integration of ERNs [1]. The best practice examples have been developed based on a series of webinars on integration of ERNs organised by EURORDIS in 2021, during which ERN Board of Member State leads, ERN Coordinators and experts from the rare disease community were invited to present their best practices to the patient community. It is envisaged that this series of webinars will continue in 2022 and beyond, to support the exchange of best practices in different areas.

This edition advances a first collection of tools and best practices, which is by no means exhaustive. In the context of the future Joint Action on Integration of ERNs, the Member States, in partnership with the rare disease community at national and European level, will expand and lead on the sharing of best practices and develop recommendations, models and guidance to support the integration of ERNs into the national health systems. Future editions of this Toolkit could be developed under the Joint Action as part of a resource centre for health authorities, hospitals, ERN Members and Patient Organisations to advance integration. As such, the Toolkit may continue to be enriched over the next 3 years as a live reference document.

Roles and Responsibilities in the integration process

Patients, Patient Organisations and their representatives will need to collaborate with the Centres of Expertise that are members of the Networks and with national and regional health authorities to raise awareness of the ERNs in their countries, build a bridge between the local clinical teams and the Networks and define how the Networks can best complement the national healthcare systems to address their needs. Patient groups have a critical role within their respective Member States to highlight the needs of their communities in discussions on service development and how care can be optimally organised locally to meet their needs.

Centres of Expertise/ERN Members play a "boundary role" between the ERNs and their national healthcare systems, specifically to coordinate and connect with other hospitals within their country through formal and informal networks. Expert teams need to draw on the ERN knowledge assets (innovations, emerging best practices, clinical practice guidelines, etc.) to implement them locally in their clinics and share them with other hospitals and health professionals in their own country.

Hospital Managers have an essential role to re-organise care processes, successfully implement service improvements and redesign clinical templates and protocols based on new knowledge and insights from the Networks. They also have an important role in supporting their expert teams to be active in the Networks and to lead the development of national networking, to ensure that information and knowledge assets are disseminated and referral systems are functioning, creating a two-way communication and collaboration between national Centres of Expertise and other hospitals in the country.

Health Authorities need to define and implement the mechanisms and organisational changes necessary to integrate the ERN system at national level to support the organisation of healthcare for rare and complex conditions. Notably, the footprint of a mature ERN system will revolve around ERN members that are formally recognised within their national healthcare systems as Centres of Expertise through a national process for identification, assessment and designation.

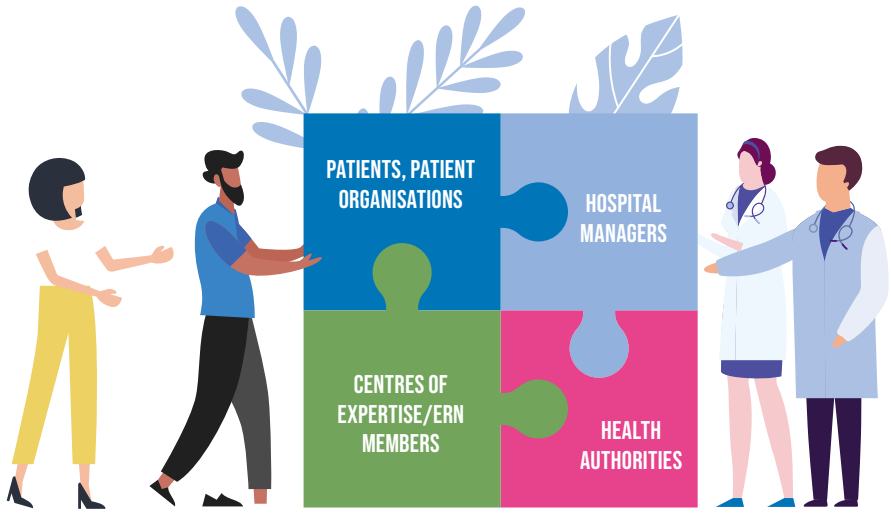
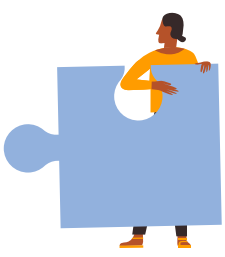


Table 1 – Summary of roles and responsibilities of key stakeholder groups in the ERNs and at a national level to support connecting national healthcare systems into the Networks

STAKEHOLDER GROUP	ROLE AT EUROPEAN / NETWORK LEVEL	ROLE AT NATIONAL LEVEL
Patient Community	• Represent and champion the interests of the wider patient community in the ERNs • Bridge between the ERNs and the European and national rare disease patient communities • Contribute to the strategic development of the ERNs	• Highlight the needs of patient communities in their care journey • Bridge between the ERNs and the national rare disease community • Raise awareness of ERNs • Sharing of information • Participate in national clinical networks
Centres of Expertise/ERN Members	• Lead the strategic development of the ERNs (Coordinators and clinical leads) • Participate in their ERN to develop collaborative activities (clinical practice guidelines and other decision support tools; provide expert advice on CPMS; research, etc.)	• Implement ERN knowledge assets in their clinics • Share and disseminate ERN knowledge assets at national level • Referral of patients to ERNs • Take a national coordination role (new function) for certain ERN Members/Centres of Expertise • Raise awareness of ERNs • Drive national clinical networks
Hospital managers	• Support experts to contribute to the ERN collaborative activities • Contribute to the strategic development of the ERNs	• Re-organise care processes, successfully implement service improvements and redesign clinical templates / protocols based on new knowledge and insights from the Networks. • Participate in national clinical networks
Health authorities	• Lead the strategic development of the ERNs • Endorsement of healthcare providers in the ERN application process • Provide support to healthcare providers/ERN members and Affiliated Partners	• Define the model of care for rare diseases and design/re-design care pathways, leveraging the ERN knowledge assets • Organisation of referral pathways to ERNs • Define formal process for the assessment and adoption of ERN clinical practice guidelines • Raise awareness of ERNs • Support the establishment of national clinical networks



APPROACHES, TOOLS AND BEST PRACTICES TO FACILITATE THE INTEGRATION OF THE ERNS

1. NATIONAL RARE DISEASE PLANS, STRATEGIES, LEGISLATION AND DESIGNATION OF CENTRES OF EXPERTISE

The Council Recommendation[4] and the Commission Communication on rare diseases [5] positioned the national Rare Disease Plans and Strategies as the central vehicle to drive change at a national level to address the challenges faced by citizens and healthcare systems faced with the public health needs of rare diseases. The EUROPLAN - European Project for Rare Diseases National Plans Development (2008 - 2011) supported community action by 27 Member States and 3 non-EU European Countries to facilitate the development and implementation of National Plans or Strategies. EUROPLAN recommendations were developed to steer a common approach between Member States, while allowing for adaption to different needs and health system structures. This approach included recommendations in 7 areas: Plans or Strategies in the Field of Rare Diseases (1); Adequate Definition, Codification and Inventorying of Rare Diseases (2); Research on rare Diseases (3); Centres of Expertise and European Reference Networks for Rare Diseases (4); Gathering the Expertise on rare Diseases at European Level (5); Empowerment of Patient Organisations (6), and; Sustainability (7).

Today, 24 EU MS (plus Norway and the UK) have adopted a national plan or strategy for rare diseases, compared to only 4 in 2008, and the focus has shifted somewhat from 'adopting' the plans to implementing them and evaluating the success of these first (and in some cases second) national plans. France has already produced a second and third plan for rare diseases. Some Rare Disease National Plans have dedicated funding whereas others lack a specific budget allocation.

Among other things, the Rare Disease Plans and Strategies support the readiness of national healthcare systems to select and designate Centres of Expertise and connect these centres under national clinical networks. These national networks and recognised Centres of Expertise would prepare the foundation for the development of the European Reference Networks in 2016.

Rare diseases are gaining momentum as a global policy priority, with the United Nations unanimously approving a new UN Resolution on addressing the challenges of persons living with a rare disease and their families [6] that encourages UN Member States to review their progress in tackling the challenges of people living with a rare disease and their families, and renew efforts, both politically and operationally, to strengthen their healthcare systems to meet the needs of the rare disease community. The Resolution specifically calls upon Member States to adopt *national strategies, action plans and legislation* to contribute to the well-being of persons living with a rare disease and their families. The UN Resolution should stir a reflection process in each EU Member State on their existing rare disease plans and strategies; this reflection should explore how the new ERN system can be embedded as an integral and complementary part of the national system.

The ERN Board of Member States in 2019 adopted a Statement on Integration of ERNs into national health systems [1] that calls for:

1. National Plans, Strategies and legislation to be assessed and adapted or updated as needed now that the ERNs are operational and coordinate national actions to integrate the ERNs into the national healthcare systems; and;
2. Establish clearly, and if necessary, legally, defined procedures for the identification and designation of national Centres of Expertise, and for their endorsement to apply and join an ERN and/or designation as Affiliated Partners to the ERNs.

1.1 National rare disease plans / strategies and legal framework for ERN integration

National Rare Disease Plans and Strategies, as well as the relevant legislation, should be updated where necessary to align and embed the new ERN system as an integral part of the national healthcare system, to strengthen the existing competencies.

APPROACH AND PROCESSES

1. Workshops on Integration of ERNs

Health authorities and other key stakeholders in each Member State may build on the EUROPLAN conferences approach to organise a series of national workshops to discuss together the health needs for their rare disease population as well as the needs of their respective healthcare systems. These workshops should be designed to reflect on how each country can best benefit from the ERNs' expertise and knowledge, the services they provide through the virtual expert panels, and how best to utilise the ERN knowledge assets (such as clinical guidelines, medical education and training and clinical pathways) to enhance their healthcare system capacities. For example, Member States that do not have a population size sufficient to provide expertise on specific rare diseases can consider using the ERNs to provide diagnostic review, clinical assessment and surveillance for these rare diseases. To accommodate and access this resource, they will need to develop national care pathways and referral routes from tertiary hospitals to the healthcare providers belonging to selected ERNs.

The virtual or face-to-face national workshop or series of workshops could be structured around the 5 key areas outlined in the Board of Member States' Statement on Integration as guiding recommendations, including **i. Review of Rare Disease Plans, Strategies and Legislation; ii. Mapping of Care Pathways; iii. Defining Referral Pathways and National Networking; iv. Adoption of ERN Knowledge Assets and v. Member State support.**

It will be key to carefully reflect upon the areas to address in such workshops to maximise their impact. The objective should not be to tackle all 5 areas simultaneously if the policy environment is not yet mature enough, but rather to select key themes for the workshops, depending on the national context (existing debates at national level, processes and/or changes related to rare disease policy, strategic priorities of the MoH and other key stakeholders, shared needs, etc.).

Another option would be to dedicate the workshop to creating a shared Roadmap for which the different stakeholders would agree on a timeline to address each of the areas, including funding and resources needed. A series of topical workshops could then follow to monitor the evolution of this Roadmap.

The Joint Action on integration of ERNs into national health systems will possibly provide additional assistance to support the organisation and facilitation of these national multi-stakeholder workshops.

2. Engagement of national policy-making bodies with ERN Coordinators and healthcare providers/ ERN members

Engagement can be organised via the inclusion of ERN Coordinators, representatives from ERN Members and Affiliated Partners into policy-making bodies (e.g. those agencies responsible for the adoption of national rare disease plans/ implementation/ monitoring). Alternatively, Member States could elect softer options to include their expertise into the policy-making process, such as organising regular consultations to capture feedback, holding ad-hoc meetings with ERN representatives, conducting surveys, etc.

3. Updating relevant legislation and procedures

Responsible authorities and organisations should review and update their legal framework and procedures as needed to:

- Identify, designate and monitor Centres of Expertise (see the next section for further details);
- Organise care pathways, including interregional collaboration in care pathways;
- Develop national clinical networks;
- Organise and manage referral systems, including the interoperability with CPMS, patients' data management and follow-up;
- Adopt or implement ERN knowledge assets, such as clinical practice guidelines, clinical decision support tools, care pathways and medical education on rare diseases.

Furthermore, the Ministries of Health or delegated authorities responsible for the appraisal of clinical guidelines should review the methodology used by the ERNs to develop clinical guidelines and clinical support decision tools, in order to assess their robustness, independence and quality. Once the ERN methodologies are considered acceptable, the responsible authorities can consider the status of ERN developed guidelines and other clinical decision support tools either as approved or fast-tracked for adoption.

TOOLS AND TEMPLATES

Best Practice National Workshop on Integration – Denmark (see agenda)
Best Practice National Workshop on Integration – Belgium (see agenda)
Best Practice National Workshop on Integration – Italy (see agenda)
Rare Disease Plans and Strategies in European Countries

BEST PRACTICE EXAMPLES

1. National workshops on Integration

In Denmark, the rare disease National Alliance Sjaeldne Diagnoser (Rare Diseases Denmark) organised 2 face-to-face workshops on the topic of ERNs. The workshops allowed Danish expert teams, who were members of an ERN, to connect with other centres and teams throughout Denmark to discuss ways to coordinate care locally under a national network, provide a referral system to the ERNs and a route for dissemination and communication of ERN knowledge assets.

The workshop attracted 40 experts and patient leaders to discuss how to make ERNs operable in the Danish context, including representatives from the Ministry of Health, hospital managers and clinical leads either belonging to or interested in joining ERNs as members or Affiliated Partners.

The rare disease National Plan was used as a starting point to organise the reflection on the needs of the Danish health system and how the new ERN system could best be aligned to complement the national health system capacities to diagnose, manage and treat rare diseases.

More details: Best Practice National Workshop on Integration – Denmark

In Belgium, the rare disease National Alliance RaDiOrg (Rare Diseases Belgium) organised a roundtable in 2019 around the theme "designation of expert centres", as this was one of the highest priority areas under the National Rare Disease Plan that had not been addressed. Although the legislation was in place, the health authorities, healthcare professionals, hospital managers and patients needed to develop a better understanding of how to take action to implement the legal mandate.

The rare disease National Alliance understood this need and took the initiative of bringing key stakeholder groups together to discuss the topic with external experts invited to present alternatives and evidence and stimulate the discussions.

RaDiOrg's event mobilised political support and stirred policy action to improve the organisation of healthcare for rare diseases, presenting alternatives and potential methodologies to move forward on a very specific and critical matter, namely the identification and designation of rare disease expert centres.

More details: Best Practice National Workshop on Integration – Belgium

In Italy, a multi-stakeholder task force comprised of Italian ePAG advocates, Italian ERN Coordinators (ERN ReCONNET, MetabERN, ERN BOND), the rare disease National Alliance (UNIAMO FIMR Onlus) and representatives from the Istituto Superiore di Sanitá, organised a series of online events in 2020-2021 to explore ways to advance the integration of the Networks into the Italian healthcare system while addressing patients' needs.

After a first general conference on the topic of integration of ERNs, a series of 5 workshops were organised to discuss concrete actions to facilitate the integration of ERNs in the Italian national health system, focusing on the needs of the Italian rare disease community. The workshops addressed 5 main topics: patient involvement, care pathways, education and training, clinical trials, and research and guidelines. A final online event, organised to discuss the points raised during the workshops, provided an important opportunity for rare disease stakeholders to network and obtain a deeper understanding of the ERNs.

The equitable role of the patient representatives in organising the initial and final conferences and the subsequent workshops serve to illustrate how patients and clinicians should partner and collaborate. Building the workshops around the theme "What could ERNs do to serve the patient community needs?" provided healthcare providers with a compass for their work within the ERNs and a better understanding of how they could better address patients' needs.

More details: Best Practice National Workshop on Integration – Italy

1.2 National Accreditation and Designation of Centres of Expertise

The 2009 Council Recommendation [4] encouraged EU Member States to identify "appropriate Centres of Expertise throughout their national territory by the end of 2013 and consider supporting their creation". The call for Member States to designate Centres of Expertise was endorsed by the European Union Committee of Experts for Rare Diseases (EUCERD), which saw the nationally accredited or designated Centres of Expertise as the key components of the future ERNs. Under this organisation, the Centres of Expertise would be the expert structures for the management and care of rare disease patients in a defined catchment area, preferably at national level, or international level if necessary (EUCERD Quality of Centres of Expertise Recommendations 2 and 45 [7]).

Centres of Expertise have been designated nationally in Austria, France, Netherlands, Romania, Spain, Sweden and the UK. Other countries (Denmark, Germany) are in the process of designating centres as rare disease centres. Some countries have decided to use the endorsement process of their Centres of Expertise to participate in the ERNs as an alternative, soft accreditation process.

Irrespective of whether Member States conduct a formal or a softer accreditation process to designate Centres of Expertise, the selected centres should have the same legal recognition and role in their national healthcare system and be visible to the patient community. Member States should continue to identify and designate Centres of Expertise, with recognition from their legal systems, to provide care for the rare disease patient community and to connect with the ERNs.

APPROACH AND PROCESSES

Accreditation schemes may be construed by clinicians or hospital managers as a 'hurdle' to cross at a single point in time; an administrative burden with little value to their day-to-day work. However, evidence shows that healthcare accreditation processes can become 'continuous quality improvement schemes' which over time, year by year, drive quality healthcare improvements by increasing the threshold for centres that want to maintain national accreditation. Developing a national accreditation scheme as a system of continuous evaluation is essential to making any designation sustainable and reliable in the long run.

While national accreditation requirements vary between Member States, there are some core characteristics common across all systems, including oversight by an application process, an advisory board, technical assessment and an evidence base.

1. Accreditation Models

Every assessment or accreditation model has its strengths and its weaknesses, and it is likely that the best approach would comprise a combination of 'multiple models'. The European Commission, for example, used the following model to assess ERNs candidate centres to triangulate the information being assessed.

1. self-assessment by applicants to be peer reviewed by the Network;
2. documentation review by an independent assessment body, and;
3. on-site visit to obtain evidence to validate the self-assessment and documentation review information.

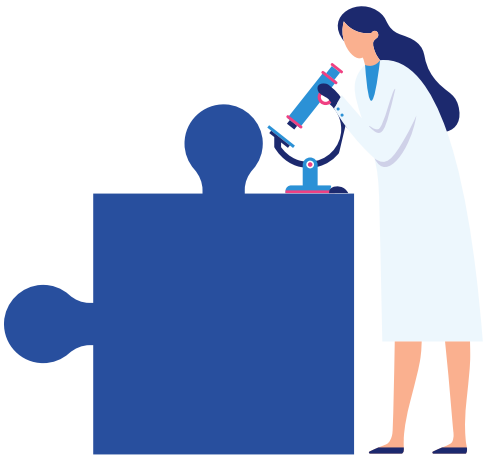
Table 2 – Summary of the strengths and weaknesses of the different models for assessment and accreditation

				ABILITY TO ASSESS...		
METHODS	SOURCES	LOCATION	EFFORT/ INTENSITY	STRUCTURE	PROCESS	OUTCOME
Re-use of datasets collected for other purposes	National/regional/local health information system	Remote	+	+	+	+
	Service-specific information system	Remote	++	++	++	++
Service Based evaluations	Visit	Local	++	+++	+++	+
	Staff Interviews	Local	+++	+	+++	++
	Patient Interviews	Local	+++	+	+++	++
Questionnaires	Service Survey	Remote	+	++	++	+
	Staff	Remote	+	++	++	+
	Patient	Remote	+	+	+++	++
Case Review	Medical Record Review	Local	+++	+	+++	+++
	2nd Opinion	Remote	++	+	+	+++

In the framework of a service contract with the European Commission, a literature review was conducted in 2015 of the different assessment and accreditation models and their evidence base for accreditation, in tandem with a mapping exercise of national accreditation, designation and licensing processes.

The literature review on the different models showed that:

1. A multi-domain assessment programme will optimise its efficacy and the use of an organised structured validated framework will enhance the assessment.
2. Patient involvement in the process of assessment, both designing the instruments and submitting views, improves the relevance to patient care and improves accuracy of differentiation of services according to their quality.
3. An effective assessment programme must involve multiple methods of assessment with a minimum consisting of re-use of datasets, service-based evaluations and questionnaires (see table 2 above).
4. Patient experience of service quality should be assessed irrespective of methods used.



The 'Mapping Exercise of EU MS National Accreditation Systems' provides a summary of each EU MS accreditation system. There are two different models which Member States use for designation of expert teams as Centres of Expertise:

1. Rare Disease model for diagnosis, e.g. centres for paediatric genetics , and/or for treatment, e.g. centres for Epidermolysis Bullosa, Haemophilia, Neurofibromatosis Type 1 and 2, Bladder Exstrophy Sarcoma, Cystic Fibrosis, Primary Ciliary Dyskinesia
2. Highly specialised healthcare intervention or surgery model e.g. centres for Extracorporeal Membrane Oxygenation, Heart and Lung transplantation, Proton-beam Therapy, High-cost Drugs

2. Governance and Oversight

The governance of national accreditation or designation systems **takes time and resources.** Countries typically have a national team that coordinates the process and an independent advisory group to provide advice and make decisions, e.g. prioritisation and application approval.

All Member States with a formal designation process have a national team and advisory board overseeing the process. Their capacity to process the volume of applications is the 'rate-limiting' factor impacting the number of Centres of Expertise that are designated each year.

Most advisory groups have representation from their regions or municipalities, as is the case for Spain and Sweden, as well as clinical leads from professional societies and patient representatives to provide transparency and good governance. Patient involvement and patient opinion is always included, and is considered part of the national application process, e.g. Netherlands, UK, Sweden, etc.

3. Models for the delivery of highly specialised healthcare

European countries currently have different arrangements in place to organise the delivery of care for highly complex and rare diseases:

1. mandating specific centres to provide care for all affected individuals in a given country (France, Sweden, UK);
2. designating national centres without imposing a mandate for local services to refer (Spain);
3. market-led healthcare systems with no centralisation, patient choice (Germany).

The centralisation of care for complex, rare or ultra-rare diseases operates according to the rationale that having the same limited number of experts examine and treat the total caseload of people with a rare or ultra-rare disease allows these experts to increase their knowledge and experience, thereby improving the clinical outcomes of patients [8], [9]. As patients receive the appropriate care and treatment under this scheme, inappropriate high-cost tests and treatments are reduced, along with patient co-morbidities; consequently healthcare expenditures are also reduced.

The key factor for identifying a centre or clinical team as a national expert is typically based on the volume of caseloads or surgeries/interventions, e.g. a minimum of 50 surgeries for bone sarcoma in one year (UK criteria); a minimum of 5 positive new diagnoses for primary ciliary dyskinesia in one year (ERN-LUNG criteria), etc. Specific criteria are not solely focused on competency/level of expertise, caseload volume or number of interventions, but can also include i. facilities and equipment, ii. composition of the multidisciplinary team iii. volume of scientific publications.

4. Types of financing arrangements for highly specialised healthcare

Contracting and payment models are very important aspects of national accreditation. Highly specialised interventions and healthcare services for rare diseases are more time intensive in terms of diagnostics and care, and must draw on a highly competent workforce and supra-specialist teams. Funding is therefore higher than that of standard care for high-cost, highly specialised services [10].

Every payment system creates a set of behaviours, which can incentivise either good or poor performance, and each system typically creates both positive and negative incentives. Different contracting models should balance the incentives created and exposure to risk to create the optimal conditions for individual services, as each highly specialised service and rare/ultra-rare disease has different needs. For example, block contracts, cost and volume and payment by results (pay for activity) all have merits, but a payment by results contract is typically not suitable for a healthcare service that serves an ultra-rare disease patient population where the activity levels can vary from 10 patients in one year to just 2 patients in another. The budgetary stability that a block contract provides enables the hospitals to maintain their clinical teams, build their clinical competencies, safeguard patient access and maximise clinical outcomes.

TOOLS AND TEMPLATES

Quality Criteria, Application Forms, plus other documents for designation as a specialist centre (Spain)
Highly Specialised Healthcare (Sweden)
Core Mission for Competence & Reference Centres (France)
ERN Operational Criteria and Application form and self-assessment tools

BEST PRACTICE EXAMPLES

1. Assessment models

Health Standards Organization (HSO) is an independent, non-governmental, not-for-profit organisation working across 38 countries. It co-creates internationally recognised evidence-based standards, assessment programmes, and quality improvement solutions for health and social service providers around the world. HSO standards are developed by technical committees that include topic experts, providers, policy makers and patient/family representatives.

Assessment Programmes are used by assessment and regulatory bodies, governments, associations and institutions to evaluate organisation and/or system performance against a defined set of standards based on quality assurance and quality improvement principles. Assessment programmes are founded on a person-centred philosophy to transform health care, using the collective experiences, learnings and insights of people with lived experience, clinicians, and administrators. Health and Social Services are continuously assessed throughout an accreditation cycle with self-assessments, attestation and peer assessments that can be conducted by virtual or on-site assessment.

More details: Best Practice Assessment – Health Standards Organization

2. Designation models of rare disease Centres of Expertise

In Denmark, it is the treatment stage of the pathway that is commissioned and delivered by the hospital specialty departments. Centres that specialise in diagnosis, for example, are designated as rare disease diagnostic centres and not as treatment centres.

In Germany, the National Action Alliance for People with Rare Diseases (NAMSE) has coordinated the national activities aimed at improving care for people with rare diseases since 2010, specifically to develop a National Action Plan for Rare Diseases. Under NAMSE, teaching hospitals in each of the Federated States have submitted self-assessment reports and applications to be recognised as Rare Disease Centres (for diagnosis). Rare disease activities in these centres are duly coded to allow for enhanced reimbursement for the more complex services provided to the rare disease patient population.

3. Designation models of centres for highly specialised healthcare interventions or surgery

In Spain, the central government works together with the 17 autonomous communities under a Central Designation Committee (DC) to provide oversight for the national designation process. The DC decides which clinical or disease areas are a priority for new applications and proposes the designation criteria with the support of an expert group. While health professionals are formally involved in every step, patient associations are consulted but are not formally part of the DC.

Experts, appointed by the regions and by scientific societies, draft the designation criteria for each area of specialisation. These are identified according to the needs for specialised expertise in diagnosis and treatment, based on volume of activity, epidemiological data, demography, and geographic coverage, etc.

The designation of national Centres of Expertise is organised as follows:

- an application is endorsed by the autonomous community. Candidate reference centres must have at least 3 years' experience in the work area and the coordination of activities prior to the application submission
- a self-assessment process
- extensive documentation of resources, protocols and coding schemes for patient related information, all available in a digitalised format
- an on-site survey that includes an analysis of randomly selected patient records.

Selection criteria for national commissioning is organised under three key areas: the needs of the population, the current provision of care relative to this needs area and the added value of centralisation. Centres can submit applications for national accreditation for procedures/therapeutic interventions or for conditions that require highly specialised care and technology to ensure equity, professional expertise and experience and improvement of care.

In Sweden, the delivery of highly specialised healthcare services (surgery, diagnosis, medical treatments and rehabilitation) is centralised in 5 hospitals. Patient groups and experts define new medical areas and criteria for national licensing. Decisions on accreditation are based upon the capacity to meet pre-defined quality criteria, equity of access and geographical coverage. The accreditation system in Sweden has progressively developed and now includes regular and ongoing reporting of referrals, equity and outcomes measures, which provide a framework for continuous quality improvement.

Sweden also grants a budget to each of the major hospitals (Gothenburg, Uppsala, Stockholm, etc.) to serve as 'rare disease centres' and commission care for their rare disease patient population. Each hospital receives additional funding for case management and for referring parents and patients to the right clinical expert team.

More details: Best Practice Accreditation of Highly Specialised healthcare Services – Sweden

In the UK, the system of national commissioning is an extremely successful approach to facilitating the designation of Centres of Expertise, which has been led by the government and departs from the bottom-up identification of available expertise through an annual application process. Commissioning of highly specialised healthcare services can either be based on a population size of 1M people to achieve economies of scale at regional level for rare diseases or may be at national level, for ultra-rare diseases, e.g. those with a total national caseload of 250 patients or less per centre.

The National Specialised Commissioning Team (NSCT) has an annual application development process for groups of clinicians collaborating from different hospitals across the UK to submit an application for national commissioning/ funding. The NSCT has contracts with the majority of the major hospitals to provide highly specialised services. For example, services are commissioned from four hospitals for neurofibromatosis type 2 (NF2) and from two hospitals for complex NF1. The NSCT has Public Health Advisors who engage with hospital experts and manage the initial interest to develop an application for national funding. The number of applications developed in a given year is successfully managed through this scheme.

The NSCT has an advisory committee composed of actors from the different Royal Societies and Patient Organisations. The Advisory Group for National Specialised Services (AGNSS) reviews the list of potential applications and decides upon the priority services for development each year. The clinical leads work together to develop an application for each agreed priority service, which is supported and submitted by commissioners. Each application includes a needs assessment, societal impact assessment, costing, patient organisations/representatives opinion, service model, multi-disciplinary team and evidence-base for services/interventions. Once approved by the AGNSS, the NSCT develops a 'service specification' for each national service, which is then formalised in a contract with the selected Centre of Expertise.

- List of highly specialised services (national services) U.K
- List of service specifications in the UK - this is really good information!
- Example: Epidermolysis bullosa service (All Ages) – National Service Specification

2. CARE PATHWAYS

The European Pathway Association defines care pathways as a "methodology for the mutual decision making and organization of care for a well-defined group of patients during a well-defined period".[11]

Care pathways are structured care processes that translate guidelines and evidence into local frameworks and are organised stepwise from diagnosis to treatment, detailing the multidisciplinary plan of care for a specific population. In addition to the clinical workflow, care pathways also operationalise the administrative workflow that staff should follow to assist a patient.

Care pathways are also referred to as *clinical pathways*, *integrated care pathways*, *protocol-based care*, *critical pathways*, *care paths*, *case management plans or care maps*.

The table below shows the differences between care pathways and the clinical practice guidelines that support clinical decisions at different stages of a care pathway.

Table 3 - Summary of differences between care pathways and clinical practice guidelines

CARE PATHWAY	CLINICAL PRACTICE GUIDELINES
• Supports mutual decision taking for complex interventions • Organises care for a well-defined group of patients for a well-defined period • Varying level of granularity; can be multi-faceted (multi-professional)	• Statements to support clinical decisions at a point of the patient pathway • Based on systematically evaluated evidence • For a specific clinical circumstance, procedure or episode of care

A care pathway document maps the sequence, timing and expected outcomes of care for patients who share a similar diagnosis or are undergoing a similar procedure. Care pathways standardise care to ensure that all patients are provided with the same timely, cost-effective high-quality care.

A care pathway yields an explicit statement of the goals and key elements of care based on evidence, best practices and patient expectations. The care processes are carefully coordinated by sequencing the activities and roles of the multidisciplinary care team, patients and their relatives.

Establishing care pathways has a number of advantages and benefits, which include:

- Promoting patient focused care, facilitating communication among the team members and with patients and families
- Allowing patients to participate in care planning and provide feedback on whether outcomes have been achieved
- Facilitating collaboration within the multidisciplinary team in the continuum of care
- Identifying tests and investigations to be ordered and completed
- Documentation is by exception, which reduces duplication within the clinical record
- Facilitating the introduction of care and treatment practices based on best available evidence, which can be adapted to local conditions
- Reducing costs and maximising the use of resources, for example, minimising unnecessary tests or procedures.
- Documenting, monitoring and evaluating clinical practice variations and outcomes
- Providing a guide for the care of patients with particular conditions
- Providing a legal record for the care provided
- Facilitating the collection of clinical indicator data

Ultimately, care pathways strengthen interprofessional collaboration and contribute to the enhancement of quality of care across the continuum by improving risk-adjusted patient outcomes, promoting patient safety, increasing patient satisfaction, and optimising the use of resources [12], [13]

APPROACH AND PROCESSES

The first step in developing a care pathway is to select the clinical condition or rare disease and identify the target patient population. It is critical to obtain a commitment to ongoing support from clinicians and management as well as patient representatives.

The subsequent steps to develop a care pathway include:

1. Form a multidisciplinary group with key stakeholders (including patients)
2. Determine the type and scope of the pathway (e.g. service, clinical or integrated care pathway)
3. Identify specific processes and procedures
4. Review the evidence base and collect local clinical data
5. Map the care pathway and draft the pathway documents
6. Write the clinical protocols for each process or procedure
7. Review of the draft pathway by key stakeholders; achieve consensus on pathway document
8. Provide information and education for staff who will pilot the care pathway
9. Pilot the care pathway
10. Evaluate the efficacy and effectiveness of the care pathway, make any adjustments to pathway based on results of evaluation
11. Provide information and education for **all** staff who will use the care pathway
12. Establish ongoing review processes with ongoing monitoring of the care pathway metric specifications

TOOLS AND TEMPLATES

The European Pathway Association offers teaching and research to help organisations on the development of care pathways
Integrated Care Pathways: A guide to good practice, Wales NHS, 2005
A toolkit for developing a Clinical Pathway, Queensland Government, 2005
Clinical Excellence Queensland's repository of clinical pathways
Children's Hospital of Philadelphia, Clinical Pathways Library
Children's Hospital Colorado's A to Z of clinical pathways

BEST PRACTICE EXAMPLES

Care Pathways – Ireland. The Republic of Ireland has a population of 5 million, of whom an estimated 300,000 people live with a rare disease. Affected individuals have reported experiencing delays in diagnosis and a fragmented care journey, which can be more challenging than in larger Member States, due to the capacity of the healthcare system. Therefore, integrated diagnostics, care pathways and cooperation with other countries for highly specialised healthcare, under the ERNs, is critical to help build the capacity of the system. The Department of Health's initiative for healthcare reform in Ireland (Slaintecare Reform Programme), promotes the development of a universal single-tier health and social care system through which everyone has equal access to services based on need and delivery of care as close to home as possible.

In the context of this initiative, the rare disease patient community has highlighted the development of care pathways as a priority area to address three leading unmet needs: i. better care co-ordination between health care professionals, ii. improved access to specialists, and iii. enhanced treatment opportunities.

In response to this demand, the Irish National Rare Diseases Office developed and piloted a cooperative methodology to develop integrated diagnostic and care pathways in the Irish healthcare system, as there exists no single recommended best practice methodology for the development of care pathways for rare diseases in the health system.

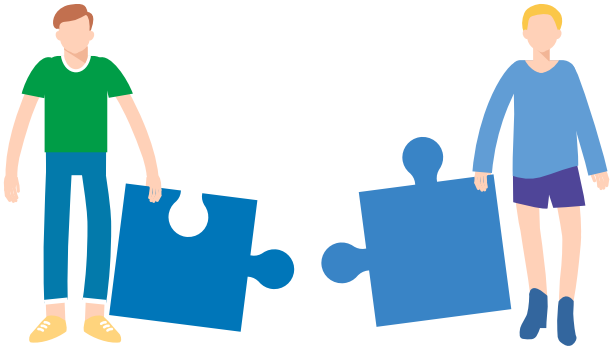
More details: Best Practice Care Pathways – Ireland

Care pathways – ReCONNET. The ERN ReCONNET developed the RarERN PATH methodology as a "reference model" pathway for organising care for rare and complex diseases. The model can be adapted to different hospitals or healthcare systems.

RarERN PATH addresses the challenges clinicians face translating existing evidence and recommendations from clinical practice guidelines into local services and local care due to variations in healthcare services, structures and policies between hospitals and countries.

The methodology proposes a specific monitoring process that can be used in real-time to revise the reference pathways on an ongoing basis, enabling the integration of learning in the clinic setting and providing direct feedback for treating clinicians.

More details: Best Practice Care Pathways – ERN ReCONNET



3. REFERRAL PATHWAYS AND NATIONAL NETWORKING

Each national healthcare system must defined and organise referral systems (including pathways, processes and infrastructure) to ensure that people living with a rare disease can access the expertise in national Centres of Expertise as well as the ERNs. The referral pathways should connect tertiary hospitals and national centres of expertise to ensure that local expertise and capacities are first accessed before generating a referral to the ERNs [14] Therefore, each Member State should develop **referral pathways** in conjunction with the establishment of **national networks** where possible.

3.1 Referral pathways

A referral pathway is a simple method to facilitate appropriate referrals, usually developed by the service that refers the patient. Referral pathways are typically clinician to clinician documents. When a referral generates some form of payment, usually the referral pathway must be approved or recognised by the body that funds the subsequent care, although referral pathway documents should not be used to limit or ration care.

Ideally, referral pathways should facilitate access to highly specialised healthcare, breaking down barriers by connecting the care chain from the local health systems to the ERNs [14].

There is currently a significant lack of rare disease referral pathways and supporting public and professional information mapped out at both Network and national levels. The BoMS statement on integration [1], recommends the development of referral pathways with accompanying information and guidance for local communities, but this ambition remains largely unfulfilled. The collaboration between ERNs and the national health systems needs to be clarified at a local level with clearly defined rules for management of patient care between local services and the Networks, including follow-up for patients whose case or treatment has been reviewed by the ERN.

Referral management to the ERNs is a critical function that should be available in all Member States. National Coordination Hubs have the specific mandate to serve as referral management centres for the Networks. However, to date only four Member States have designated hospitals as National Coordination Hubs – *Mater Dei Hospital (Malta), Centre Hospitalier du Luxembourg (Luxembourg), Semmelweis University (Hungary) and Clinical Institute for Genomic Medicine (Slovenia).*

In each Member State, the National Contact Points for cross-border healthcare play an important role in supporting patients' access to cross-border healthcare. These services should have the specific responsibility of advising on the procedures for accessing the ERNs as part of the referral process and pathway.

The role of the ERN full Members and National Associate Centres is focused on sharing expertise and conducting networking activities (e.g. guideline development, research, etc.) and these centres may not have the capacity to also act as an ERN referral management centre in their respective countries. There is therefore a pressing need for each Member State to determine how the referral pathway to an ERN should be managed. In the interim, some ERNs have identified one healthcare provider per country to act as a National Coordinator, working in partnership with the local patient community to build relationships with the national professional societies and the national research leads.

APPROACH AND PROCESSES

Referral pathways are usually developed by those healthcare professionals who may make a referral. This process typically takes the form of iterative development, and it is not uncommon for the service that receives the referral (especially highly specialised services) to be unaware of the working processes of the services of the referring clinicians; without this knowledge, and the involvement of specialists, the resulting referral pathways are often not operational and of no benefit to the specialist service, referrer, or patient.

The **referral pathway document** usually contains the following items:

1. a brief description of the receiving service
2. the eligibility criteria for referral, or reasons for referral
3. eligibility criteria for making a referral: self-referral (very unusual), general practitioner (e.g. for families with an identified first-degree relative with the condition); specialists (e.g. a geneticist)
4. the referral process (the form(s) to use, contact information)
5. essential information to include in the referral (without which the referral will not be considered) and additional useful information to include.

Often referral pathway documents will also contain information such as a schematic of the referral pathway or information on what will happen after the referral is made.

TOOLS AND TEMPLATES

Examples of disease-specific referrals pathways:
Rare Mitochondrial Disorders referral pathways, Oxford University Hospitals. NHS Foundation Trust
Epilepsy surgery service referrals, Oxford University Hospitals. NHS Foundation Trust
Clinical Genetic referral pathway, Manchester Centre for Genomic Medicine
Ehlers-Danlos syndrome service referrals, London Northwest University Healthcare. NHS Trust

BEST PRACTICE EXAMPLES

Referral pathways – Denmark. Referral pathways establish the rules and processes in a health system to transfer a patient from one level of care to another, from primary care to secondary care and from secondary to tertiary care. Eventually an additional level will be added with the onward referral to an ERN for rare disease specialist advice. The referral pathway for rare diseases in Denmark starts with a GP referral to an acute or university hospital. GPs and acute hospitals can refer patients to university hospitals that have been granted a permit to accept referrals. Today referrals to ERNs are made on an informal basis. To facilitate these referrals, the Danish Health Authority has published the list of Danish ERN members, as well as the contact details for each expert centre, to allow Danish patients and healthcare professionals to easily locate a contact point for each ERN.

In the context of the next evaluation of the rare disease National Plan, a 'generic referral pathway for people living with a rare disease', will be developed that will probably include ERNs. Likewise, further communication actions are being planned to raise awareness among the population and the healthcare professionals of the ERNs and the referral pathway.Danish expert centres now participate in all 24 ERNs. Referral pathways via these expert centres to the ERNs will need to be formally articulated through a national network of expert centres in order for the referral to be directed first to the local expert team, before onward referral into the ERNs is signed off. The robust level of cooperation between expert centres in the university hospitals, acute hospitals and the national tertiary hospital in Denmark will facilitate the organisation of the Danish referral pathway to the ERNs.
More details: Best Practice Referral Pathways – Denmark

3.2 National Networking

The recent UN Resolution on addressing the challenges of persons living with a rare disease and their families encourages UN Member States to strengthen efforts to address rare diseases, specifically to foster the **creation of networks of experts** and multidisciplinary specialised expert hubs for rare diseases and to **strengthen international collaboration and sharing of data** [6].

As countries look to organise healthcare for people living with a rare disease and complex conditions, the organisation of highly specialised healthcare for rare and complex diseases and highly specialised interventions has developed across the EU and globally, specifically by formally designating Centres of Expertise and connecting these centres under national clinical networks. While there is growing political readiness to establish rare disease centres and networks, the approach being adopted varies significantly between countries.

The core functions of national networks are designed to foster collaboration between centres that are recognised as experts for the same clinical areas, to provide:

1. Case discussion and bi-directional referral systems;
2. Standardised care through training, guidelines and pathways;
3. Access to treatment by drug assessment, approval and delivery;
1. Sharing of outcomes and experiences to identify emerging best practices and innovations;
2. Clinical research.

Centres of Expertise in some European countries and regions, such as France, UK and Catalonia, have been organised either under national or regional networks, specifically in France (Filières de santé maladies rares) in the UK (Highly Specialised Healthcare Services and in Spain, at regional level (Catalan Reference Network, XUEC).

APPROACH AND PROCESSES

Member States that have developed a national healthcare network approach for rare diseases build on the selection and accreditation / designation of national Centres of Expertise, either by opening a joint Call for Applications for recognition as national centres of expertise AND forming a national network or service (for specific rare disease areas or highly specialised interventions); OR through the development of national networks, organised after the selection and designation of national Centres of Expertise.

Existing evidence on the value and benefits of clinical Networks has shown that:

1. **collaborative working improves healthcare outcomes** [15]–[17]
2. **learning together is a key component for the success of effective networks** [18]–[26]

It is common for a National Advisory Board to be established, with representatives from the health authorities (payers) as well as national leads representing professional and scientific societies, to complete a prioritisation exercise for the selection of clinical areas to include in the first and second rounds of Centre of Expertise designation (please refer to Section 1.2 on National Accreditation and Designation of Centres of Expertise) and National/Regional Clinical Networks.

Countries interested in creating National Clinical Networks for rare diseases, may revisit the work of the European Joint Action for Rare Diseases (EJA) on how to cluster diseases or form thematic groupings. The partners of this Joint Action (Orphanet, Newcastle University (UK), and EURORDIS) completed a mapping exercise on the different models for grouping rare diseases, to inform the structure of the ERNs. The partners reviewed five existing models for organising networks and considered their respective value and benefits [27].

Based on a review of the five existing models: (i) Classical Medical Ontology; (ii) Les Filières de Santé Maladies Rares, France; (iii) Orphanet Classifications; (iv) EURORDIS Proposal for the grouping of ERNs and (v) UK Research Collaboration in Rare Diseases, NIH, the study concluded that rare diseases can be organised following three different approaches:

- Clinical area or grouping
- Clinical intervention
- Shared molecular aetiology

The mapping exercise suggested that a molecular aetiology approach would be beneficial in a research context, but too restrictive to encompass all rare diseases as it would imply focussing purely on clinical interventions.

On the other hand, the 'Filières de Santé Maladies Rares' follows a bespoke structure, which goes from disease specific networks (e.g. cystic fibrosis) to broad groupings of rare diseases (e.g. rare autoimmune and auto-inflammatory diseases). The partners concluded that this approach was specifically designed based on the structure and organisation of the French healthcare system.

The conclusions from this exercise determined that networks should be organised based on the specific needs of each respective healthcare system, but should also be aligned with the clinical groupings of the ERNs, with the caveat that Networks should be multi-disciplinary, not single professional networks. In addition, there should be collaboration between the Networks as one infrastructure, thereby ensuring that the holistic needs of multi-system rare diseases are addressed.

TOOLS AND TEMPLATES

French National Plans for Rare Diseases (in English)
Filières de Santé des Maladies Rares, France
Video of the Filières de Santé, France (in English)
Catalan Reference Networks (XUEC), Catalonia, Spain
England Rare Diseases Action Plan, 2022

BEST PRACTICE EXAMPLES

National Clinical Networks for rare diseases – France. The French health system has established 23 national rare disease healthcare networks, the 'filières de santé des maladies rares', which cluster rare diseases into groups of related diseases, and whose role is to lead and coordinate the care and management of rare diseases. Each of the *filières* or sectors connects rare disease Reference Centres and Competence Centres, as well as diagnostic laboratories and platforms, scientific societies, health and social care structures, basic, clinical and translational research teams and patient organisations of people living with a rare disease. These networks have progressively developed over a decade, consolidating their structures and maturing. They are now a central actor for the delivery of rare disease policy action. Driven by the networks, the organisation of genomic testing, research activities, medical and social structures and patient groups has gained a central position that is recognised and extensively used by the Ministry of Health to implement rare disease policies. Funding allocated for the Reference Centres and Competence Centres to participate in the initiatives set out in the French Rare Disease National Plan has been key to connecting the networks to the French health system. The French health system allocates funding to support the French ERN coordinators as well as the participation of French clinicians in the ERN virtual expert panels.

More details: Best Practice Rare Disease National Clinical Networks – France

Regional Clinical Network for rare diseases – Catalonia, Spain. The Catalan government developed a rare disease plan to ensure equity of access for the rare disease patient population. The government adopted an 'Instruction' (12/2014) to establish the development and implementation of a model of care for rare diseases in Catalonia and the organisation of networks of Units of Clinical Expertise (UEC) for rare diseases (malalties minoritàries or minority diseases). The Catalan Reference Networks are composed of clinical expert centres in minority diseases - the *Xarxes d'Unitats d'Expertesa Clínica en Malalties Minoritàries* (XUEC) - established to support collaboration and knowledge sharing. The Catalan Reference Networks coordinate with the health and social care services closest to the home of the affected person, in order to provide a more personalised and efficient service. The XUEC Networks have been developed to align with the ERNs and are organised under thematic groupings.

More details: Best Practice Rare Disease Regional Clinical Networks – Catalonia, Spain

National Clinical Networks for rare diseases – Switzerland. The Swiss Confederation comprises 26 'cantons', each with its own regional government and health budget. Although a founding member of the European Free Trade Association, Switzerland is not a member of the EU, European Economic Area or Eurozone. The country has a population of approximately 8.5 million people.

The Swiss national rare disease policy was adopted in 2015 and contemplates the following activities:

1. Designation of rare disease Centres and Reference Centres (RC) and the codification and registration of rare diseases
2. Access to treatment and diagnosis; and revision and update of the list of rare diseases for which treatments are reimbursed
3. Platform for information focussing on psycho-social needs
4. Research activities connecting Switzerland to international research programmes; and educational activities to raise awareness among medical students and early-career physicians
5. Alignment and connection to the ERNs, managed by the Federal Office for Public Health.

In 2017, the Rare Disease National Coordination Office (Kosek) was established to coordinate rare disease policy in Switzerland, comprised of representatives from university and non-university hospitals, patient groups, ministries (from the 26 cantons) and scientific and research bodies.

One of the main goals of Kosek is to develop a national network for rare diseases aligned with the ERN model, to facilitate interaction and collaboration with the ERNs. As the leader of this effort, Kosek is responsible for designating expert centres. The national networks will consist of two types of members: the Rare Disease Centres, which are the entry point for undiagnosed patients; and the treatment centres, which are identified as Reference Centres for specific groups of rare diseases. Following diagnosis, patients in Switzerland are referred to the appropriate Reference Centre for care and treatment.

More details: Best Practice Rare Disease National Clinical Networks – Switzerland

4. ADOPTION OF ERNS KNOWLEDGE ASSETS

Communicating and disseminating information about the ERNs to the public and to medical and patient communities is critical to enhancing the national healthcare systems' competencies to treat rare diseases locally by enabling expertise to travel, not the patient. However, effective communication relies on the coordination of national action from national authorities, scientific societies, hospitals and patient groups. This is why the development of a strategy to coordinate national communication and dissemination is a recommended action included in the Board of Members Statement on Integration of ERNs into national health systems.[1].

APPROACH AND PROCESSES

The strategy for enabling the adoption of ERN knowledge assets should aim to achieve four key objectives, specifically:

1. support communication and coordination between the different stakeholders;
2. increase public awareness of ERNs;
3. facilitate healthcare professionals' access to the knowledge curated or generated by the ERNs;
4. promote medical education and training.

1. Supporting communication and coordination between key stakeholders

A central action to kick-start a communication and dissemination strategy is the engagement of the different stakeholders involved in the provision of care for rare and complex diseases. This can be undertaken either through the organisation of national workshops to synchronise the efforts by key stakeholders and determine the actions that specifically address the needs of the health care system and/or by establishing a national advisory group of lead representatives from among ERN members and hospital managers, national health authorities and the rare disease patient community. At a minimum, the organisation of a workshop on the integration of ERNs into the national health system (please refer to Section 1.1 on National rare disease plans/strategies and legal framework), would provide an opportunity to map the needs of patients, hospitals and the health system, and to agree upon priority areas and the responsible leads to take forward actions.

Creating a space to discuss the country's healthcare needs specific to rare diseases and highly specialised healthcare is the first step for each Member State to define the role and function of the ERNs in their own country and to answer the following question: *how can ERNs support and complement your healthcare system for the rare disease patient community; for expert teams; for primary care services; for hospital services, and for regional and national health authorities?* It would also be helpful to identify the actions needed nationally to formalise the role of ERNs, e.g. incorporating ERN HCP members in advisory boards or strategy groups; amending appropriate legislation; defining the referral criteria and the pathways to access care, etc.

2. Increase public awareness on ERNs

Public awareness of the existence of the ERNs and the scope of the services available nationally will enable local populations to access care through either a national Centre of Expertise or a referral to specialist advice under an ERN.

Information should be readily accessible, patient-friendly, and should include i. patient rights, ii. The referral pathway to access ERN advice, iii. The national Centres of Expertise that are participating in the Networks, iv. factsheets on the Networks and their services.

ERNs should become the "go-to" trusted source of information on rare diseases and related healthcare for patients, family members and the general public. Updating the websites of the Ministry of Health, hospitals and patient groups to provide clear and accessible information is critical and would contribute to both empowering people facing uncertainty because they are living with a rare disease or an undiagnosed condition and to building trust around the quality of the ERN information, clinical tools and training material.

At a minimum, information should be available outlining how each country's expert teams and hospitals are connected to the ERNs; the ERNs structure and work; the services provided at local ERNs centres; how patients and their families can access the ERNs.

Patient representatives involved in the ERNs are playing an important role in sharing ERN information and knowledge assets, such as clinical practice guidelines, clinical decision support tools, clinical pathways and patient information. Patient leads are encouraged to work closely with each other and with the National Alliances and the patient community at national level to coordinate engagement and information dissemination with the rare disease communities and work closely with national authority leads and hospitals.

3. Facilitating access to the knowledge generated by the ERNs

The experts and clinical teams involved in the ERNs contribute to sharing their experience, expertise and knowledge gained from delivering diagnosis, care and treatment for the total patient populations in their respective countries. This experience, knowledge and expertise is also shared with clinical leads from other Member States through the ERNs, thus generating the body of evidence and knowledge for rare diseases, which is captured in ERN knowledge assets such as clinical guidelines, care pathways, training materials, etc.

Access to these knowledge assets at national level requires:

1. **Adoption at national level:** Each Member State should develop a process for reviewing, endorsing and adopting ERN knowledge assets at national level and hospital level. This process should clarify who, when and how the ERNs should submit these clinical tools and information to the responsible national authorities; for example, submitting ERN clinical guidelines to national health assessment agencies.
2. **Targeted communication and dissemination at national level:** ERN clinical tools and information should be disseminated to patients, health professionals and health managers once they have been endorsed by national authorities and should be made available on an online platform, library or repository to these stakeholders and the public. National Coordination Hubs should support communication and dissemination at national level. All Member states should formally establish a National Coordination Hub as the interface between the ERNs and all national stakeholders. Today only four countries have endorsed a hospital to fulfil this role nationally: Mater Dei Hospital (Malta), Centre Hospitalier du Luxembourg (Luxembourg), Semmelweis University (Hungary), and (Clinical Institute for Genomic Medicine (Slovenia).

4. Promoting medical education

Medical training institutions, hospital educational programmes and medical societies should review the ERN training and education materials (online courses, webinar programmes and short-term training placement schemes) and consider how these can be promoted and accessed by medical doctors and clinical teams as part of continuous medical education. Communication and promotion of online seminars and webinars provide an easily accessible way for medical communities to access knowledge and expertise from across the EU.

TOOLS AND TEMPLATES

European Reference Network's websites (x24)

BEST PRACTICE EXAMPLES

Best practice examples are being identified from the ERNs and the Member States and will be presented in a series of webinars in 2022-2023. These best practices will be included in the next edition of this toolkit.

5. SUPPORT BY MEMBER STATES TO ERN COORDINATING CENTRES, FULL MEMBERS AND AFFILIATED PARTNERS

The ERNs are built on solidarity and voluntary cooperation between EU Member States, hospitals and the patient and clinical communities. While the participation of Centres of Expertise in the Networks is through voluntary contribution, the capacity of the clinical teams and their hospitals to participate in the ERNs and facilitate the uptake of ERN knowledge assets at national level does require that these teams are adequately supported.

Centres of Expertise have been endorsed by the Member States and their respective Hospital Directors to apply and participate in the ERNs. This endorsement secured commitment to support the clinical teams to contribute to the Networks and also to be active at national level to ensure that the benefits of participation within the ERNs are realised at the local level, either via their clinics and hospitals or through facilitating the engagement of clinical teams in tertiary hospitals, supporting referrals, and sharing knowledge assets (such as guidelines, medical education, etc.).

Indeed, Member States have committed to directly support their experts and clinical teams to participate in the ERNs through local health resources and budgets, instead of investing in a common, central budget as part of the development of the Directive **on the application of patients' rights in cross-border healthcare**. In turn, Hospital Directors pledged to support their experts and clinical teams to be active in the ERNs, signing a letter of support as part of the application process.

5.1 Support to ERN Coordinating Centres, Full Members and Affiliated Partners

National authorities and hospital managers should reflect on the means to best support ERN Coordinating Centres, ERN Members and Affiliated Partners. Support can be administrative, financial, organisational and informational, and should ensure the sustainability of ERN Members and/or Affiliated Partners and enable experts and clinical teams to have the capacity to participate in the Networks as well as coordinate activities at national level to ensure patients have access to the best available expertise.

It is worth highlighting that from 2017-2021 all hospitals that hosted an ERN Coordinating Centre co-funded 40% of the Networks' operational annual budgets through in-kind contributions, while the Commission grant co-funded 60%. As of 2022, the European Commission grant does not have co-funding requirements.

APPROACH AND PROCESSES

Agreeing upon the resources needed at national level to adequately support the centres could be achieved as follows:

1. Establish a task force on ERN financing with the participation of all relevant parties. This could also be fulfilled by a sub-group of an existing national committee or advisory body on rare diseases
2. Scope, characterise and clearly identify the specific needs of expert teams to enable their efficient participation in the different ERN activities. Typically, ERN Coordinating centres, full members and affiliated partners have different needs, given their different roles in the ERN system. This scoping exercise should be as comprehensive as possible, and not driven by budgetary constraints. Notably, this process should consider ALL activities: the collaborative ERN activities as well as the activities that the centres will perform at national level to support the integration of ERNs.
3. Estimate the costs, including in-kind contributions, such as clinicians' time, per activity.
4. Based on budgetary availability, agree upon an annual budget, the rules pertaining to budget distribution among the different centres and the financial reporting procedures for the centres.

TOOLS AND TEMPLATES

3rd French National Plan for Rare Diseases (2018-22)

BEST PRACTICE EXAMPLES

1. Member State support

In France, the Ministère des Affaires Sociales et de la Santé provides additional financial support to the ERN Coordinating Centres. Each clinical team leading an ERN as a Coordination Team receives €50,000 per year to support leading the Network. The French health system has also allocated funding to support the participation of French clinicians in the ERN virtual panels to deliver expert advice.

2. Hospital Managers support

In the Netherlands, Erasmus Medical Centre, Rotterdam, is funding the project management office to support two of the ERN coordinating teams hosted in this centre.

Additional best practice examples are being identified from Member States and Hospitals and will be presented in a series of webinars in 2022-2023. These best practices will be included in the next edition of this toolkit.

5.2 Tackling waste in Rare Disease Healthcare: Potential Role of ERNs

Participation in an ERN must go beyond the recognition of expert teams and hospitals to be a tool to leverage the redesign of service for the improvement of frontline clinical services to improve health outcomes and address wasteful clinical care. Clinical waste, from a system perspective, refers broadly to unnecessarily expending resources to achieve a given outcome, such as situations in which patients do not receive the appropriate care for reasons that could be avoided.

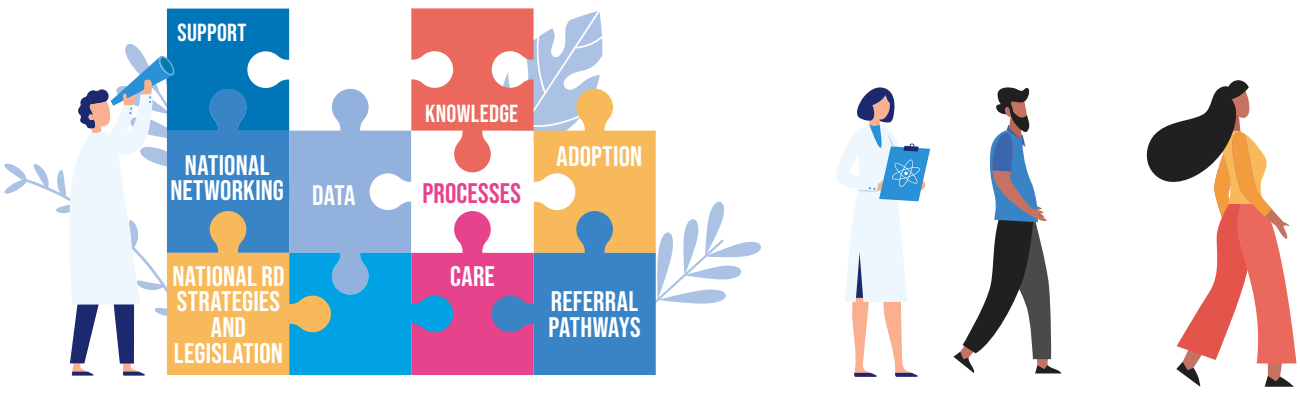
It is important for national health authorities and hospital managers to assess the gains and benefits for their healthcare system and hospitals through participation in the ERNs. These can include increasing the expertise and evidence base of their highly specialised healthcare services, improving clinical templates and clinical pathways and the capacity to outsource specialised advice in areas where, due to the population size and the rarity of disease, it is more cost effective to access clinical advice under the Network.

The mean time to a rare disease diagnosis is 5 years [28] and many rare diseases are only diagnosed after numerous ineffective, high cost and time-intensive work-ups, tests and treatments. The ERNs provide an opportunity for hospitals and healthcare systems to access timely and accurate diagnosis, unlocking access to earlier care and treatment, thereby enabling better outcomes and a better allocation of health resources.

Delays in securing accurate diagnosis and the lack of available treatments can engender extensive waste in rare disease healthcare spending, specifically[1]:

a. **wasteful clinical care** (e.g. preventable adverse events, ineffective or inappropriate care due to lack of specialised knowledge and skills, etc.) and
b. **operational waste** (e.g. inefficient use of expensive infrastructures and human resources due to lack of centralisation, duplicated or redundant healthcare services caused by poorly developed rare disease care pathways, etc.).

A case study should be scoped and evaluated to support the participation of expert teams in an ERN to draw on the ERN's collective knowledge and transfer it back into local services. This knowledge transfer could, for example, lead to a redesign of clinical pathways and clinical templates to build more cost-effective services for rare and complex diseases, thereby reducing operational waste [29].



1 Presented in 2019 at the EURORDIS Leadership School on European Reference Networks by Birute T. (Vilnius University, Faculty of Medicine)

APPROACH AND PROCESSES

Tackling waste in healthcare is a crucial initiative to optimise a cost-effective allocation of limited resources and improve patient health outcomes. LEAN thinking [30] proposes a framework to systematically tackle waste in production or management systems .

The areas of waste are typically considered in 7 areas:

1. **Defects:** errors or defects when performing a task, producing a service or making a product.
2. **Overprocessing:** repeating tasks or activities during the process.
3. **Overproduction:** producing more than necessary.
4. **Movement:** unnecessary or inadequate movement of personnel to execute a task
5. **Transportation:** carrying out or moving materials from one location to a different location where a new task will be performed.
6. **Inventory:** excess of materials or goods which are accumulated in case they are needed.
7. **Delay:** additional waiting time when a process stops more than is usual.

One additional area is often considered in service industries, namely unused talent (underused qualified workers).

Using this framework, we can consider areas where ERNs might play a valuable role in improving health system efficiency and effectiveness.

It is a common experience for patients with a rare disease, not seen by experts, to initially receive an incorrect diagnosis (defects). This leads to repeated investigations (overprocessing), and delays in receiving a correct diagnosis and appropriate treatment and care. Patients are frequently required to travel to multiple hospitals in search of appropriate care (transportation). The possibility for patients to access the correct expert through the ERNs to diagnose and develop an effective treatment plan would impact all of these areas of waste. Administering the appropriate test to obtain an initial accurate diagnosis would prevent defects, delays, overprocessing and transportation related waste.

TOOLS AND TEMPLATES

Quality, service improvement and redesign (QSIR) tools **UK NHS**
Quality, service improvement and redesign (QSIR) tools by type of approach **UK NHS**

BEST PRACTICE EXAMPLES

Best practice examples are being identified from Member States and hospitals and will be presented in a series of webinars in 2022-2023. These best practices will be included in the next edition of this toolkit.

References

[1] ERN Board of Member States, "Statement of the ERN Board of Member States on Integration of the European Reference Networks to the healthcare systems of Member States," 2019.

[2] ERN Board of Member States, ANNEX to the Statement of the ERN Board of Member States on Integration of the European Reference Networks to the healthcare systems of Member States. 2019.

[3] European Commission, ANNEX I to the Commission Implementing Decision of 14.1.2022 on the financing of the Programme for the Union's action in the field of health ('EU4Health Programme') and the adoption of the work programme for 2022. 2022.

[4] European Council, "Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)," 2009.

[5] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. 11.11.2008 COM(2008) 679 final. .

[6] UN General Assembly, "UN Resolution adopted by the General Assembly on 16 December 2021. Addressing the challenges of persons living with a rare disease and their families." 2021.

[7] European Union Committee of Experts on Rare Diseases, "EUCERD RECOMMENDATIONS QUALITY CRITERIA FOR CENTRES OF EXPERTISE FOR RARE DISEASES IN MEMBER STATES EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States 2," 2011.

[8] J. Morche, T. Mathes, and D. Pieper, "Relationship between surgeon volume and outcomes: A systematic review of systematic reviews," Syst. Rev., vol. 5, no. 1, p. 204, Nov. 2016.

[9] C. Hentschker and R. Mennicken, "The Volume–Outcome Relationship Revisited: Practice Indeed Makes Perfect," Health Serv. Res., vol. 53, no. 1, pp. 15–34, Feb. 2018.

[10] R. Sukenik-Halevy, M. D. Ludman, S. Ben-Shachar, and A. Raas-Rothschild, "The time-consuming demands of the practice of medical genetics in the era of advanced genomic testing," Genet. Med., vol. 18, no. 4, pp. 372–377, 2016.

[11] "E-P-A.org – European Pathway Association." [Online]. Available: https://e-p-a.org/. [Accessed: 14-Mar-2022].

[12] A. B. Sweeney, H. S. Flora, E. J. Chaloner, J. Buckland, C. Morrice, and S. G. E. Barker, "Integrated care pathways for vascular surgery: an analysis of the first 18 months.," Postgrad. Med. J., vol. 78, no. 917, pp. 175–177, Mar. 2002.

[13] M. Asmirajanti, A. Y. Syuhaimie Hamid, and T. S. Hariyati, "Clinical care pathway strenghens interprofessional collaboration and quality of health service: a literature review," Enfermería Clínica, vol. 28, pp. 240–244, 2018.

[14] B. Tumiene and H. Graessner, "Rare disease care pathways in the EU: from odysseys and labyrinths towards highways," J. Community Genet., vol. 12, Apr. 2021.

[15] S. B. Clauss et al., "Quality improvement through collaboration: The National Pediatric Quality improvement Collaborative initiative," Current Opinion in Pediatrics, vol. 27, no. 5. Lippincott Williams and Wilkins, pp. 555–562, 01-Jan-2015.

[16] A. Haj-Mirzaian, B. N. Patel, E. K. Fishman, and A. Zaheer, "Value of multidisciplinary collaboration in acute and chronic pancreatitis," Abdominal Radiology, vol. 45, no. 5. Springer, pp. 1458–1467, 01-May-2020.

[17] M. Fung-Kee-Fung et al., "Regional Collaborations as a Tool for Quality Improvements in Surgery," Ann. Surg., vol. 249, no. 4, pp. 565–572, Apr. 2009.

[18] S. McInnes, K. Peters, A. Bonney, and E. Halcomb, "An integrative review of facilitators and barriers influencing collaboration and teamwork between general practitioners and nurses working in general practice," J. Adv. Nurs., vol. 71, no. 9, pp. 1973–1985, Sep. 2015.

[19] A. Bollen, R. Harrison, P. Aslani, and J. C. M. van Haastregt, "Factors influencing interprofessional collaboration between community pharmacists and general practitioners—A systematic review," Health and Social Care in the Community, vol. 27, no. 4. Blackwell Publishing Ltd, pp. e189–e212, 01-Jul-2019.

[20] S. Bookey-Bassett, M. Markle-Reid, C. A. Mckey, and N. Akhtar-Danesh, "Understanding interprofessional collaboration in the context of chronic disease management for older adults living in communities: a concept analysis," J. Adv. Nurs., vol. 73, no. 1, pp. 71–84, Jan. 2017.

[21] M. Karam, I. Brault, T. Van Durme, and J. Macq, "Comparing interprofessional and interorganizational collaboration in healthcare: A systematic review of the qualitative research," International Journal of Nursing Studies, vol. 79. Elsevier Ltd, pp. 70–83, 01-Feb-2018.

[22] H. Trier, J. M. Valderas, M. Wensing, H. M. Martin, and J. Egebart, "Involving patients in patient safety programmes: A scoping review and consensus procedure by the LINNEAUS collaboration on patient safety in primary care," European Journal of General Practice, vol. 21, no. sup1. Taylor and Francis Ltd, pp. 56–61, 14-Aug-2015.

[23] S. Rumping, L. Boendermaker, and D. J. de Ruyter, "Stimulating interdisciplinary collaboration among youth social workers: A scoping review," Health and Social Care in the Community, vol. 27, no. 2. Blackwell Publishing Ltd, pp. 293–305, 01-Mar-2019.

[24] T. Lemetti, M. Stolt, N. Rickard, and R. Suhonen, "Collaboration between hospital and primary care nurses: a literature review.," Int. Nurs. Rev., vol. 62, no. 2, pp. 248–266, Jun. 2015.

[25] H. Laverty and P. Meulien, "The Innovative Medicines Initiative –10 Years of Public-Private Collaboration ," Frontiers in Medicine , vol. 6. 2019.

[26] M. Cooper, Y. Evans, and J. Pybis, "Interagency collaboration in children and young people's mental health: a systematic review of outcomes, facilitating factors and inhibiting factors," Child. Care. Health Dev., vol. 42, no. 3, pp. 325–342, May 2016.

[27] T. Evangelista et al., "The context for the thematic grouping of rare diseases to facilitate the establishment of European Reference Networks," Orphanet J. Rare Dis., vol. 11, no. 1, p. 17, 2016.

[28] N. Black, F. Martineau, and T. Manacorda, "Diagnostic odyssey for rare diseases: exploration of potential indicators," Policy Innov. Res. Unit, p. 72, 2015.

[29] OECD, Tackling Wasteful Spending on Health. OECD.

[30] D. Womack, J., Jones, D. and Roos, The Machine That Changed the World: The Story of Lean Production, Toyota's Secret Weapon in the Global Car Wars That Is Now Revolutionizing World Industry. Free Press, New York, 1990.

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