EURORDIS
RARE DISEASES EUROPE

RECOMMENDATIONS TO ACHIEVE A MATURE ERN SYSTEM IN 2030

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CONTENTS

FOREWORD

The European Reference Networks promise to *Share, Care and Cure* offers the rare disease community hope that everyone will have the equal access to the best quality of care available; as frontline services draw on the collective knowledge and experience of leading rare disease centres of expertise across the European Union. The Networks should take steps to treat each rare disease equitably. This doesn't mean that they should provide the same services for all rare diseases, but rather that they offer a basket of services that can be provided depending on the specific needs of each rare disease.

The vision and recommendations outlined in this paper have been developed by EURORDIS, representatives from our member organisations and ERN ePAG advocates.

Our vision is for a mature ERN system that leaves no person living with a rare disease in uncertainty regarding their diagnosis, care and treatment.

ERNs promise to share…

Knowledge sharing at scale will only succeed in an inclusive ecosystem, where ERNs coordinate with the national healthcare systems and are fully integrated with local services. **We expect to see real collaboration between the right experts**, supported by effective tools and **we want the ERNs to be the first-stop, go-to place for trusted information on all rare diseases**.

ERNs promise to care…

Member States should ensure that ERNs' services are accessible to any patient at any moment. Patients from any country should get referred to the best European experts to get proper diagnosis and treatment. The signature of care under an ERN, should be care based on the leading knowledge and experience of a multidisciplinary team, empowering patients in their care. **ERNs may contribute to improve our quality of life by providing good standards of care and guidelines, but health authorities, hospital managers and clinicians must ensure that these are implemented at local level** and that people living with a rare disease can access the right care.

ERNs promise to cure…

Our hope is that **ERNs will allow rare disease patients to secure a diagnosis within 6-12 months from coming to medical attention.** At the same time, we expect the ERNs to accelerate the development and uptake of treatment options for rare diseases, as they integrate European-wide clinical research and care settings, supported by registries.

We strongly believe that ERNs are the greatest achievement that the rare disease community as a whole has ever accomplished. We cannot afford to waste the political support gained nor let our hard-won success fail. Progress is being made incrementally, as the Networks are now formed and experimenting with new ways of working. We now need nourish them, if we are to unlock their true potential and accelerate the consolidation of this new structure into our national health systems. The window of opportunity is open to drive transformational change in healthcare services for rare diseases, as healthcare systems across the EU Member States are increasingly more flexible and responsive to adapt and adopt new ways of working. Virtual consultations and networked care can be connected to and be an extension of the national healthcare systems.

The ERNs and their members are well positioned to be the 'engine of change' for transforming our local healthcare systems. They can offer unprecedented access to expertise by countries that lack these resources and will contribute to remove the barriers for people living with a rare disease to access universal health coverage, offering real support to families by speeding up diagnosis and offering affected individuals the best possible treatment options.

Our children, families and community deserve the highest quality care. To achieve this all stakeholders and partners in the ERNs community, need to think bigger. We must think bigger in our ambition and actions, if we are to successfully address some of the most pressing EU public health needs of rare diseases, once and for all. However, the Networks will need to adjust their activities to the level of investment that they receive. This is why the investment in this new system should be proportionate to the size of the Networks' ambitions and must be committed from multiple sources.

Together, we can benefit from our collective strength, competency and energy, to drive change and improve local healthcare services for our communities. United as a community, we are able to share our expertise, improve care and find cures for rare diseases. The weight of the ERNs' promise has united the rare disease community in our fight for the lives and future of the people affected with one of the 6,000 rare diseases. And in turn, delivering on this promise will make us stronger

PAPER OUTLINE

The paper is structured into 4 separate chapters as follows:

PART 1

We begin this paper by providing an overview of the rare disease patient population healthcare needs that should act as a compass for European and national RD policies. Whether a single rare disease affects thousands or only a handful of individuals, they all share similar challenges to get a timely diagnosis, barriers to access highly specialized care and treatment options and a substantial psychosocial burden. The ERNs should contribute to meet the healthcare needs of the rare disease patient population and their success should be measured by how well they perform against those specific needs.

PART 2

Different infrastructures and organisational arrangements are required in each country to address the healthcare needs of its rare disease population in an effective way. In **Part 2 we describe how the different national healthcare models address these needs, with a focus on how to improve the situation regarding the quality of Centres of Expertise (CoEs).** The new paradigm of cross-border networked care initiated by the ERNs is an excellent model to support diagnosis, highly specialized care and research for rare diseases. However, in some countries and for certain conditions, national networks of Centres of Expertise anchored to the ERNs could be more effective at addressing specific needs.

From the beginning, the vision of reference networks for all rare diseases in all Member States of the European Union was extremely ambitious. EURORDIS believes that this vision is still relevant. This comprehensive coverage can and should be achieved as long as the ERNs supplement and bridge the existing gaps in care, knowledge generation, training and research. Therefore, the depth of this coverage per disease will necessarily vary, depending on how well these areas are serviced for each disease by national health systems and international healthcare arrangements. This approach builds on the principles of equity, solidarity and cooperation, and is a preferred option to the alternative, that would entail selecting a limited number of rare diseases and developing a comprehensive catalogue of services and collaborative activities only for a few diseases, thereby increasing existing health inequalities.

PART 3

In Part 3 we analyse the scope and structure of the ERNs. The **geographic coverage of the Networks** has gained traction with the enlargement process that started in 2019 with the inclusion of 247 Affiliated Partners. However, current forms of affiliation are not enough to ensure full geographic coverage and inclusivity. Regarding the **disease coverage**, with the information available today it is difficult to have an accurate picture of the real coverage of all rare diseases. We may consider that the **strategic coverage of the Networks** includes all the conditions under the sub-thematic groups of rare diseases and complex conditions included in the ERN original applications and the ones added later, right before the 2019 call for membership. This would imply that today the strategic coverage, and ambition, of the Networks would cover today almost all rare diseases with a few important gaps related to rare and complex gynecologic-obstetric diseases and conditions and benign tumours.

On the other hand, we may consider that around 1,000 diseases are **operationally covered by the Networks**, meaning that the ERN members have been assessed against the set of specific criteria for those diseases developed by the Networks and are actively developing collaborative activities to improve healthcare and diagnosis for those diseases. Over time, the diseases under the operational coverage of the Networks should match their strategic coverage. Following a stepwise approach, after defining specific criteria for each rare disease, the EC should open consecutive calls for full members followed by the designation of Affiliated Partners to cover gaps.

PART 4

Finally, Part 4 explores the progress of ERNs on four core functions (care, knowledge sharing, training and research) identifying gaps and providing recommendations to have mature ERNs by 2030. When it comes to **care**, the added value of the Networks should not and cannot be measured solely by their performance in providing specialist advice through the Clinical Patient Management System (CMPS). Altogether, the 24 Networks have successfully conducted over 1,000 virtual cases discussions; however, even when considering these cases to be the more complex and rare presentations, these are only catering for the 'tip of the iceberg' needs of a community of 30 million people living with a rare disease in the EU. The CPMS expert panels are clearly an important feature of the new system and provide a much-needed secure platform to deliver networked care, but the Networks, through their members, need now to extend their reach and drive improvements in their respective local health systems. All stakeholders involved in the successful development of ERNs, clinicians, patients and health authorities, will now need to make the 'gear change' from development mode to full deployment mode to implement the networked care model within the national health systems.

Effective **Knowledge sharing** should be one of the cornerstones of the ERNs' success: the Networks should celebrate the variation in clinical practice across their members, through the establishment of a culture and system for quality improvement based on sharing and benchmarking disease specific clinical outcomes and publishing new innovation and emerging best practice.

The ambition (and potential) for the Networks to promote and deliver medical **training** and education activities along the chain of care in all Member States remains yet to be fulfilled. Significant increased support, resources and e-training tools are needed to unlock this potential and support the development of local healthcare systems competencies in rare diseases and complex conditions.

The ambition to embed Clinical **Research** Networks (CRN) into the ERN structure is a realistic goal that can be achieved over the next five years. By 2030 all ERNs could be performing high quality collaborative clinical research that complies with the expected standards required by regulatory and Health Technology Assessment (HTA) bodies provided that (i) they have the support of a centralised research support structure and (ii) there are clear rules that enable ERNs to partner with industry. Clinical Research Networks (CRNs) embedded in the ERNs will allow pursuing a health-systems research approach where clinical settings will regularly inform clinical research activities, such as the design of the studies or the selection of endpoints that are useful for clinicians and relevant for patients. At the same time, they will contribute to accelerate the uptake of therapeutic innovations in real world settings. These CRNs will provide a framework for clinicians, researchers and patient representatives to work together to advance collaborative research on rare diseases by providing support for clinical studies and facilitating study enrolment and data sharing.

INTRODUCTION

Rare diseases[1] qualify as a public health priority; they are disabling and degenerative conditions, most of them with no cure, that affect 30 million people in Europe that very seldom have access to the right expertise and diagnostic infrastructure where they live. This vision paper for the future of the European Reference Networks (ERNs) comes at the time of great changes in how the delivery of care and public health is perceived. The COVID-19 pandemic has shown, if anything, that structured collaboration is key to achieve better health outcomes in complex situations such as those experienced by people living with a rare disease [1].

Whilst the idea of cross-border healthcare cooperation for complex and rare conditions powered by European Reference Networks took a decade to germinate and find its way into the EU legislation, the consolidation of this system is now under a fast moving political and policy environment. The next stage of development of the Networks should harness on this momentum for greater EU cooperation on healthcare. Indeed, the need (and willingness) for more European coordination in health has matured and is behind the European Health Union Commission's proposal. A European Health Union that has been scoped initially with the aim of tackling future health crises together, emergency response and preparedness, but that might evolve to other health domains over time.

The preparation, launch and establishment of the European Reference Networks (ERNs) in 2017 was driven as an EU initiative based on the voluntary collaboration of all Member States with the support of the European Commission. However, the ERN system cannot be understood exclusively on its European cross-border healthcare dimension. For these Networks to deliver on their mission, the time has come for Member States to focus on the national dimension of the Networks and integrate the ERN system within their national health systems. We need a European healthcare system for rare diseases to be present in each EU country, one that complements and enhances the national healthcare systems competencies in rare diseases. A mature ERN system is a network of truly expert

[1] In this paper the term rare diseases includes also rare cancers

centres, connected to local healthcare services, creating together an ecosystem. These centres are the flagships of the ERNs that enhance the capacities of the ecosystem as a whole, strengthening national healthcare systems and offering resources and tools to frontline services.

It is important to understand that the Centres of Expertise remain the pivotal elements of the ERN system. When Member States strengthen their competencies and capacities, the ERNs as a whole increase their critical mass of expertise and knowledge that can be harnessed to create a sea-change in local health systems, increasing their ability to tackle the complex needs of rare diseases. With more than 1,500 expert teams expected to participate in the Networks by 2021, ERNs bring together a significant capacity of human resources, clinical expertise and knowledge, that offers all stakeholders a 'once-in-a-lifetime' opportunity to leverage this scale of commitment and drive forward improvements in healthcare systems capacities and capabilities in the field of rare diseases. Under the shadow of COVID-19, ERNs experience with cross-border healthcare collaboration can lead the way to greater cooperation in health between the EU27. Cross-border virtual healthcare has finally been accepted as a valuable and essential approach, and this push will help to move networked care from the drawing board, into mainstream healthcare services.

As a result of the COVID-19 crisis, we have seen in 20 days changes in the delivery of healthcare that would have taken years to implement under normal circumstances[2]. While, under the pressure to find solutions, some of these measures might have been rushed with little consideration of privacy, ethics and clinical governance aspects, this pandemic has also revealed that, in the face of an unprecedented challenge, healthcare providers have the capacity to adjust at a fast pace. Planning ahead requires all stakeholders to acknowledge their individual responsibility to drive the ERNs to success and, at the same time, commit to work together in a much more agile and coordinated way than what we have seen so far. If we fail to do so, we will have failed the 30 million people living with a rare disease in Europe.

It took the rare disease community over 15 years of policy developments to get to the establishment and launch of the Networks. The vision and conceptual policy framework for the Networks developed during that period is still valid today, but we should review our progress to date and renew our collective commitment to this shared vision and ambition before embarking into the next decade. Staying true to this original vision, this paper aims to contribute to this strategic reflection and to plan for the incremental changes that will take us to a mature ERN system in the next 10 years. Beyond these changes, the Networks will require a mature and enabling environment to evolve from their early stage to a mature and consolidated structure. A mature environment requires (i) governance and engagement mechanisms to ensure that the ERNs are driven by patients' needs (ii) adequate funding from different sources and an accompanying set of policies for the financial governance of the Networks (ii) political leadership and ownership of the ERNs system at national level and (iv) timely and clear identification by national health systems of their specific demand for ERN services to allow the Networks to plan their activities accordingly.

[2] For example, many rare disease care patients experienced remote consultations online or via phone- 1 out of 2 respondents to the EURORDIS RBV Survey on COVID-19 reported that they had experienced this type of care during the months of April and May 2020. . Also hospitals relied on multi-disciplinary and departmental collaboration to find innovative ways to respond to the outbreak to increase their ICU capacities - *Opening the unit and the whole hospital emergency process required the multidisciplinary, multi-level involvement of healthcare providers and hospital managers all working towards a common goal: patient care and hospital safety* [36].

This paper outlines a future vision for the European Reference Networks system that is driven by the rare disease patient population healthcare needs. With this vision and the recommendations set out in each chapter, EURORDIS and the community of people living with a rare disease want to contribute to the current debate on the future of the ERNs and the actions needed to realise their full potential.

OUR VISION OF A MATURE ERN SYSTEM IN 2030

The building blocks that should make up a mature ERN system are outlined in the diagram below:

AREAS OF WORK OF THE ERNs

CARE

- **Health outcomes** are used to facilitate continuous learning and improve quality of care
- **Adoption of clinical governance principles** and pricing and reimbursement model for online specialist advice and online consultations (outpatient clinics)
- **Annual work plan** to develop care pathways, clinical decision support tools (CDSTs) and patient information for each disease under each ERN operational scope driven by a life-long approach to care
- **Referral pathways** published for all diseases under each ERN operational scope

KNOWLEDGE SHARING

- **CDSTs tools** developed for all diseases under each ERN operational scope
- **Systematic collection of outcome measures** for all diseases under each ERN operational scope
- **Annual clinical summit** to present outcomes and best practice
- **Data** is used to identify emerging best practice & new surgical concepts
- **Digital technologies** are used in routine care to implement best practice

RESEARCH

- **Collaborative research** compliant with regulatory & HTA standards
- **Policies** to conduct research & regular revisions of research agenda
- **Patient-centered outcomes** are used on clinical research and patients' advice is used to identify unmet needs
- **Development of testing capacities** in research settings
- **Minimum two natural history studies** developed on average annually by each ERN
- **Regular collaboration with RD research** infrastructures, EMA, EJP, IRDiRC and industry partners

TRAINING

- **Annual training programme** includes a Clinical and a Leadership track delivered via f2f/e-trainings, interactive tools & innovative training approaches
- **ERN clinicians do short-term placements** to develop supra-specialised expertise
- **Formal twinning** of Affiliated Partners and HCP Member to develop their expertise
- **Target trainings** for medical students to identify RD red flag signs earlier

OUR VISION OF A MATURE ERN SYSTEM IN 2030

COMMON SERVICES THAT ERNS NEED IN ORDER TO BE ABLE TO ACHIEVE THEIR OBJECTIVES

- **Clinical decision support tools competence centre** (support on selected functions such as literature review and methodological training)
- **Data management Centre**: architecture; data collection protocols; data curation services, data mgmt. tools, data analytics tools/services and data governance
- **Virtual and e-learning platform**
- **Framework for patient engagement in the ERNs** to fully legitimise and recognise their role in the ERNs
- **Common research support structure** covering 4 domains: clinical research, data management, engagement and dissemination and administrative support
- **Suite of digital tools and services** to support ERNs specific needs, including tools for online consultations, shared decision making, physiotherapy, rehabilitation therapies and different 'channels' for patients to access ERNs.

ERN FUNDING, GOVERNANCE, SCOPE AND STRUCTURE

- Public funding is granted through a 'cost and volume' model. There is also a mechanism to receive funds from other sources (industry, donations, etc.) and a governance mechanism in place for public-private partnerships 1
- Membership is a dynamic process based on a benchmark model that incentivizes HCPs to improve health outcomes and quality of care year-on-year 2
- There is a clear set of rights and obligations for the different types of membership and process for termination to manage 'sleeping' members
- Patients' role is fully recognised in all ERNs and funding is allocated to enable meaningful patient engagement activities
- Specific criteria reviewed regularly and reflects the granularity of prevalence and complexity of each rare disease and complex condition
- Operational disease expansion is completed and the ERNs covers all diseases under its thematic groupings (comprehensive operational coverage) 3
- Clinical units have committed to undertake a set of specific commitments for each of the diseases included in the operational scope of the ERN
- ERN clinical leads and patient representatives work in the permanent inter-ERN working groups for multi-system rare diseases 4
- ERN has integrated health professionals from other disciplines and is running networked multidisciplinary collaborative activities on a regular basis
- ERN members work with their hospital managers and national health authorities to connect with hospitals within their country, extending the ERN locally
- ERN has achieved full geographic coverage through full members, affiliated partners & partnerships with HCPs not endorsed/designated nationally 5
- ERN has formal agreements with global or regional clinical networks and can show tangible achievements from this cooperation 6

OUR VISION OF A MATURE ERN SYSTEM IN 2030

WHAT NEEDS TO BE IN PLACE AT THE NATIONAL LEVEL:

➡ POLITICAL LEADERSHIP AND OWNERSHIP

➡ ACCREDITATION OF CENTRES OF EXPERTISE

➡ INTEGRATION OF ERNS IN ALL MEMBER STATES

- **All MS have a process to identify and designate national centres of expertise**. The criteria used to designate centres of expertise is aligned with the operational criteria to qualify for full membership in the ERNs.

- **All MS have an annual work plan to strengthen their RD centres of expertise competency and capacity** to fulfil the vision lay down in the EUCERD Recommendations on Quality of Centres of Expertise.

- **There is a common guidance regarding endorsement** criteria and process to join the ERNs and all MS conform to it.

- **All MS have implemented their roadmap to integrate the ERNs into their national health system**
  - National policy and/or legal framework updated
  - Clear and well-defined RD national patients' pathways and referrals to centres of expertise and ERNs, easy to navigate for clinicians and patients
  - Clear referral procedures to all ERNs. All Member States have endorsed a HCP as a Coordination Hub to manage referrals
  - Communication strategy to disseminate information about ERNs towards at local level - all levels of healthcare providers
  - National reference networks of rare disease centres of expertise
  - Mechanisms to facilitate access to the knowledge assets generated by the ERNs
  - Assessment and adoption of ERN guidelines and other clinical decision support tools allow uptake at local level
  - Mechanisms in place to support Coordinators, ERN Members and Affiliated Partners (administrative, financial, organisational, informational, etc.)
  - Clear identification by national health systems of their specific demand for ERNs' services

THIS VISION IS BUILT BASED ON THE ASSUMPTIONS THAT IN 2030:

1. The BoMS has adopted a common Conflict of Interest policy to address financial and non-financial conflicts, and a Code of Conduct for all ERNs
2. The EC enables a continuous cycle of peer review and independent assessment of HCPs, to ensure that ERN members maintain their competency
3. The BoMS, ERNs and the EC have specified how to operationalise the disease expansion.
4. Cross-ERN WGs have been formally established for all the diseases that overlap the operational scope of several ERNs, benign tumors and integrated care
5. New rules of affiliation allow the designation of Associated Centres when a country has a full member in a given Network as well as other forms of partnerships
6. The BoMs has developed strategic guidelines on international collaboration and defined the role and remit of an "ERN international partner"

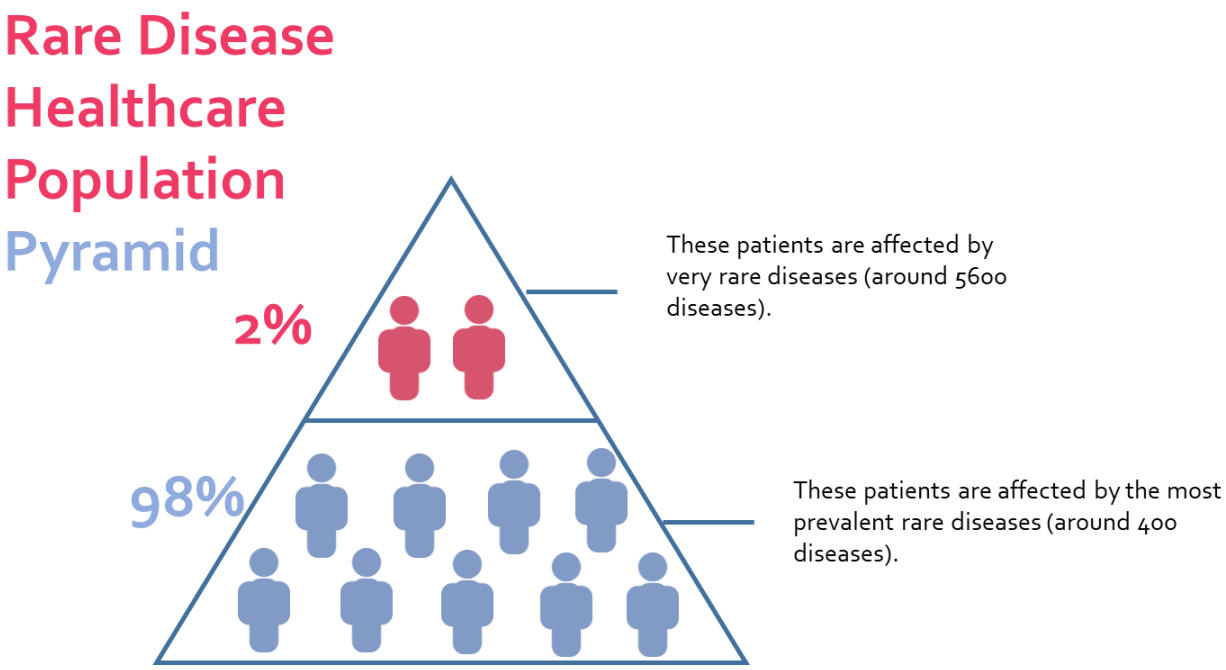
PART 1

RARE DISEASE PATIENT POPULATION HEALTHCARE NEEDS

PART 1. RARE DISEASE PATIENT POPULATION HEALTHCARE NEEDS

There are more than 6,000 rare diseases, 70% of which start in childhood and 72% have a genetic origin. The latest epidemiological estimates on the prevalence and incidence of these rare diseases confirm that they affect over 30 million people in Europe and 300 million worldwide. These new estimates throw a picture of a highly skewed patient population; the vast majority of people living with a rare disease (>98%) are affected by one of the 390 most prevalent diseases (more common than 1 per 100,000), whereas the remaining 2% have an extremely rare condition (prevalence less than 1 per 100,00) [2]. The needs of these extremely rare conditions are of such magnitude, that they require greater cross-border healthcare collaboration to meet them.

FIGURE 1: RARE DISEASE HEALTHCARE POPULATION PYRAMID



Source: Own elaboration. Data from "Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database"[2].

Whether a single rare disease affects thousands or only a handful of individuals, they all share similar challenges: getting a timely diagnosis; barriers to access highly specialized care and treatment options and a high psychosocial burden. The challenges faced by people living with a rare disease and their healthcare needs, briefly summarised in Tables 1 and 2, should serve as a starting point for policy makers at national and EU level, to scope the healthcare services and delivery models to guarantee appropriate and effective healthcare for this population.

TABLE 1: MAIN CHALLENGES FOR PEOPLE LIVING WITH A RARE DISEASE

DIAGNOSIS ODYSSEY

- Accurate and timely diagnosis remains a challenge in many cases due to the heterogeneity in onset and symptoms.
- Misdiagnosis is common and can lead to inappropriate medical interventions (including surgery and psychiatric treatments [3].
- Patients need to see different experts and often have to travel to a different region to obtain the confirmatory diagnosis, and sometimes to a different country [3].
- Long delays in securing an accurate diagnosis, coupled with the uncertainties and challenges of progressive life-threatening morbidities, translate into a significant psychological burden for patients.

BARRIERS TO ACCESS ADEQUATE HEALTHCARE SERVICES

- The majority of rare diseases are multisystem and the average patient requires access to more than nine different medical services [3].
- Lack of referral is often reported as the greatest barrier to accessing essential medical services. The next most significantly reason for lack of access is the unavailability of services, followed by waiting times, distance and personal cost [3].
- Variations and inequities in rare disease care, due in part to a lack of standardised care pathways.

DIFFICULTIES TO ACCESS TREATMENT

- There is no cure for the vast majority of rare diseases and few approved treatments are available.
- When a treatment exist, it is often not available in the country where the patient lives or patients are prevented to access the treatment because of long waiting times [4].

IMPACT ON EVERYDAY LIFE

- For the majority of patients and families, the rare disease has a severe or very severe impact on everyday life (e.g. capacity to carry out daily tasks, motor and sensorial functioning, personal care) [5].
- Often, patients and carers need to reduce or stop professional activity due to their own or their family member's rare disease[5].

The table below summarises some of the key healthcare needs of the rare disease patient population clustered under four areas: (1) diagnostic resources, (2) care delivery, (3) patient awareness and psychosocial support and (4) research and access to treatments.

TABLE 2: RARE DISEASE PATIENT COMMUNITY HEALTHCARE NEEDS

AREA	RARE DISEASE PATIENT COMMUNITY KEY HEALTHCARE NEEDS
1. Diagnostic resources	• **Equitable, timely and affordable access to high-quality diagnostic services** and structures, including to new diagnostic tests across Europe and genetic counseling, to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention. • **Increase efforts to educate primary care physicians** to suspect a rare disease so that they do not become a bottleneck to diagnosis. • **Access to information about sources of expertise** (contact details for experts and services including access mechanisms) • **Sustainable programmes dedicated specifically for undiagnosed diseases to enable rapid and equitable access to diagnosis and social support**[6].
2. Care Delivery	• **Equitable, timely and affordable access** to evidence-based highly specialised multidisciplinary care. • **Simple and standardised care pathways**, including care transition processes from childhood to adulthood and later geriatric and palliative care and adequate support to navigate national and cross-border healthcare pathways. • **Integrated long-term care delivered through the coordination of care between health, social, education and community services** where different specialists and the affected individual share an integrated care pathway and new experts are incorporated at different stages to address age-related and new emerging care needs.
3. Patient community, information and psychosocial support	• **Greater access to validated information** about the condition, peer support groups, affordable psychological support and education to help patients and families cope, understand and case manage their condition [5]. • **Joint social and health strategies to address the specific challenges linked to being diagnosed at an earlier age as well as to increased survival rates and ageing with a rare disease** such as family planning, long-term complications of medication, increased co-morbidities, greater support for independent living, loneliness, sense of isolation, disempowerment, loss of independence, etc.[7] • **Easy access to information about social rights and benefits** to guide patients and families about the benefits they are entitled to.
4. Research and access to treatments	• **Timely, equitable and affordable access to therapies and medical devices** following regulatory approval. • **Clinical research and innovation embedded in highly specialized clinical practice** to facilitate translation of new therapies, new approaches such as repurposing, innovative care models and emerging best practice into innovations in routine clinical practice. • **Routine and systematic collection of outcome measures** that are relevant for patients used in clinical trials and other types of research.

These unique set of healthcare needs, the small number of patients in each country and scarcity of knowledge and expertise makes this area a "unique domain of very high added value of action at EU level" as duly recognised by the Council Recommendation back in 2009 [8]. How to best address these needs should be the compass that guides national and European policy action in this domain, and also be the measure for its success. Likewise, the ERNs should contribute to meet the healthcare needs of the rare disease patient population and their success should be measured by how well they perform against those specific needs.

Following this logic, the ERNs assessment, monitoring, evaluation and quality framework (AMEQUIS) should focus on how the Networks have improved the quality of life and life expectancy of the 30 million people living with a rare disease.

Along these common healthcare needs, each rare disease has its own unique specificities. Thus, even if general challenges are similar, some needs are very specific. Striking the right balance between common and specific needs is probably the greatest challenge to successfully tackle rare diseases. To have a significant impact, the collaborative activities undertaken by the ERNs for each disease will need to be necessarily supplemented by action at national and international level. This is why the **integration of the ERNs into national health systems and international collaboration are key to the success of this new system**. At the same time, the Networks will need to adjust their activities to the needs of each disease, clinicians and patient representatives will need to agree on what is the best use of the ERN for their diseases.

RECOMMENDATION

To be effective and useful in assessing the impact of the Networks over time, the ERNs evaluation framework should be mapped against the relevant population needs that the Networks aim to address. Our understanding of these needs is primarily based on surveys that were conducted more than 10 years ago (EurordisCare2 and EurordisCare3), the European Commission should fund a methodologically robust needs assessment study to capture the current needs and expectations of the rare disease population.

Target deadline: 2021

PART 2

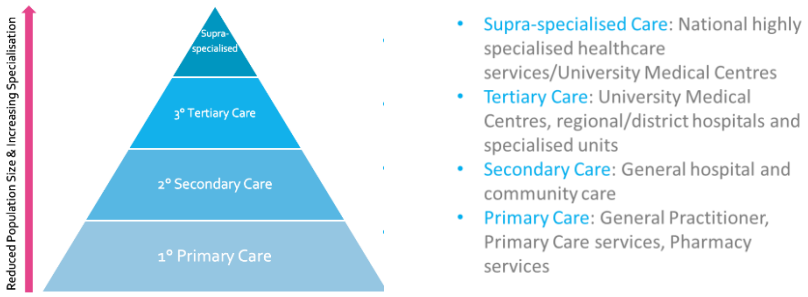
HEALTHCARE SYSTEMS ARRANGEMENTS TO MEET RARE DISEASE POPULATION CARE NEEDS

PART 2. HEALTHCARE SYSTEMS ARRANGEMENTS TO MEET RARE DISEASE POPULATION CARE NEEDS

Introduction

Healthcare systems face specific challenges to organise and deliver care for rare diseases, due to their unique characteristics that also make them a common public health need across all EU countries. The principle that healthcare should be organised as close as possible to the local patient population to meet their needs, as long as the catchment area covers a critical mass of people, is widely recognized. This is why the organisation of healthcare, as well as health budgets, are normally devolved to municipalities, regions or federated states (Sweden, Spain, Italy, Germany, Belgium and Austria). Conversely, the organisation of care for rare diseases requires interregional or national catchment populations, sometimes of over 1M people for extremely rare diseases, to reach sufficient numbers of affected individuals.

FIGURE 2: MODEL OF HEALTHCARE FROM PRIMARY CARE THROUGH TO SUPRA-SPECIALISED SERVICES



Source: own elaboration

Evidence shows that healthcare outcomes improve with increasing experience of the clinicians. Typically, 70 to 110 procedures are needed per year to get to a level of experience where the problems are commonest and the rate of improvement slows down only when some variant is encountered [9], [10]. At the same time, high-volume clinical teams or high-volume hospitals have a higher rate of adherence to evidence based guidelines that leads to improvements in the services capabilities, which translates into better outcomes for patients. As rare disease patient populations are normally small and scattered across large geographical areas, hospitals can struggle to ensure highly specialised healthcare services that are both financially and clinically sustainable. However, national policies on centralisation of care (and budgets) for rare diseases to regional centres and for highly specialised healthcare for extremely rare diseases to national centres vary between EU Member States, depending on the size of the country and the structure of their health system. Despite volume being a driving factor for quality, centralisation of care for rare diseases and the designation of centres of expertise bundled with mandated referrals is a politically sensitive topic in some EU Member States with highly decentralized health systems

TABLE 3: CHALLENGES FACED BY HEALTH SYSTEMS, HOSPITALS AND EXPERT CENTRES TO DELIVER HIGHLY SPECIALISED HEALTHCARE

MISMATCH BETWEEN RD PATIENT POPULATION PROFILE AND HEALTH SYSTEMS ORGANISATIONAL AND TERRITORIAL ARRANGEMENTS	- Small patient population scattered across large geographical areas implies that each hospital catchment area in a single country will cover a very small number of patients. - Lack of centralisation of care due to devolved competencies in the planning and provision of health services (politically sensitive). - No national designation and no mandated referral pathways to expert centres. - Shrinking referral criteria and commissioning policies (cuts in scope and depth of publicly funded health services).
MAINTAINING SAFETY AND SERVICE CAPACITY	- Low caseload is a challenge to maintain clinical competency and delivering safe interventions. - Single expert services with holding lifetime of experience leads to poor service sustainability
HIGHLY POLITICAL AREA OF HEALTHCARE	- Highly political area of healthcare with high media scrutiny. - Lack of effective treatments and therapies to cure. - Excessive out-of-pocket expenses and long-time waiting lists are barriers to access therapies and healthcare.
INADEQUATE FUNDING ARRANGEMENTS & INCREASED INVESTMENT	- Increasing fixed costs and high investment required for new technologies. - Unsuitable contract models and tariff prices to reimburse the costs of complex and highly specialised care services, which are normally significantly higher than other more common interventions Negative impact on short-medium term service stability. - Competitive healthcare market stretched with too few patients / smaller regional catchment areas. - Fragmented budgets hampering effective care coordination across different levels of care

Vision

The 2009 Council Recommendation on an action in the field of rare diseases [8] ignited EU action in the development of national and European initiatives to organise healthcare for rare diseases, specifically around the identification of expertise and designation of centres. The Council encouraged Member States to identify "**appropriate Centres of Expertise throughout their national territory by the end of 2013 and consider supporting their creation**". Building the EU capabilities in rare diseases was therefore predicated first on Member States that were call to organise their expertise and capacity within their own healthcare system.

Drawing on the 2009 Council Recommendation, early in the preparatory phase of developing European Reference Networks, various initiatives supported EU countries to establish and designate national Centres of Expertise under their National Rare Disease Plans or Strategies (EUCERD Joint Action, 2012-15; EUROPLAN Conferences, 2008-11; 2012-15). In 2011, the EUCERD adopted its Recommendations on the Quality of Centres of Expertise to support Member States in their "reflections or policy developments concerning national plans and strategies for rare diseases when addressing the issue of organisation of healthcare pathways at national and European level" [11]. These Recommendations provide specific guidance for countries to designate their Centres of Expertise and seek to ensure quality rare disease care across the EU.

The EUCERD envisioned nationally designated Centres of Expertise (CoE) as the key components of the future ERNs. Under this vision, Centres of Expertise would be expert structures for the management and care of RD patients in a defined catchment area, preferably national, or at international level if necessary (EUCERD Q. CoE Rec. 2 & 45 [11]).

The EUCERD Recommendations envisaged a step-wise rollout to designate Centres of Expertise that, when connected under an ERN, would expand the 'footprint' of service coverage and strengthen EU rare disease capabilities. The national rare disease healthcare structure in each country, with CoE as their pivotal element, would be guided by the following principles:

1. **Identification and designation of a Centre of Expertise should be undertaken at a national level** within each Member State, due to the variation in population size and in the diversity of healthcare structures between Member States (EUCERD Q. CoE Rec. 14).

2. **The core functions of a Centre of Expertise should include:** coordination of a specialised multidisciplinary team (EUCERD Q. CoE Rec. 4); building healthcare pathways from primary care (EUCERD Q. CoE Rec. 5); elaborating and disseminating good practice guidelines (EUCERD Q. CoE Rec. 8); providing education and training (EUCERD Q. CoE Rec. 9); developing information adapted to the specific needs of patients and their families, of health and social professionals (EUCERD Q. CoE Rec. 10); contributing to research (EUCERD Q. CoE Rec. 13); liaising with other CoEs at national and European level (EUCERD Q. CoE Rec. 15).

3. **Invest in designated Centres of Expertise to enhance** their capacity to deliver these core functions and increase their ability to meet the local population needs and strengthen the foundation of ERNs (EUCERD Q. CoE Rec. 17, 19, 21, 23 and 24).

4. **Healthcare organisational arrangements for rare diseases in each Member State should facilitate access** to these centres and services (EUCERD Q. CoE Rec. 33).

5. **Member States should provide adequate information** to professionals, citizens and patients organisations concerning the conditions of access to health care at national and international levels in the field of rare diseases (EUCERD Q. CoE Rec. 44).

Where are we now

Whilst the EUCERD Recommendations on the Quality of Centres of Expertise were expertly used in the formation of the EC ERN Delegated Decision [12] and the EC ERN Implementation Decision[13], [14] they were not consistently implemented across Member States. Today only a handful of countries[3] have a formal designation process for Centres of Expertise, which is different and should not be mistaken with the softer 'endorsement' given by Member States to the hospitals that wish to join the ERNs. The remit of Member States´ endorsement should be restricted solely to the ERNs membership application process and should not become "de facto" a national designation process for CoEs.

Different infrastructures and organisational arrangements are required in each country to address the healthcare needs of its rare disease population in an effective way. This also results in countries requiring different things when connected to the ERNs. In large countries national networks of Centres of Expertise may hold the local expertise to serve the needs of the <390 rare diseases that affect 98% of the rare disease patient population. On the other hand, the needs of smaller countries for the same patient population will likely require access to cross-border healthcare for diagnosis and treatment (face-to-face and/or ERNs expert virtual advice). The 2% of the people living with very rare diseases in any country will always require cross-border networked care, and this 2% of the population is therefore bound to benefit the most from the ERN model.

Regardless of the disease prevalence, certain aspects related to highly specialized healthcare, such as the development of international standards of care, are better informed and addressed through European or pan-European clinical networks. Likewise, rare disease research will always need to have a European or international dimension.

Different infrastructures and organisational arrangements are required to address these needs in an effective way. The new paradigm of cross-border networked care initiated by the European Reference Networks is an excellent infrastructure to support the delivery of highly specialized care, diagnosis, and research for rare diseases. However, in large countries and for the most prevalent conditions, national networks of Centres of Expertise anchored to the ERNs could be more effective at addressing specific needs.

[3] Denmark, France, Spain, The Netherlands, Sweden, U.K and more recently Austria, Germany

EURORDIS recognises the significant progress made by Member States representatives and the European Commission, working together at a European level to set up the Networks. **Now it is critical to shift some of the political, financial and administrative focus to the national level, progress on the integration of ERNs into national healthcare systems and strengthen the support provided to the Expert Centres** to enable them to contribute to the work of the ERNs, but also to work on their behalf at national level.

Challenges & Recommendations

1. **Endorsement to join the ERNs falls short of the benefits of national designation of Centres of Expertise.** Whilst some EU Member States have developed national designation process for rare diseases and highly specialised healthcare services (e.g.: Denmark, France, Spain, The Netherlands, Sweden, U.K and more recently Austria, Germany), many countries still do not have a national process in place. National designation of RD CoEs holds significant value for clinicians and patients alike, as it is undertaken with clearly defined and approved designation criteria and a transparent designation process, for a specific local population, and as such can support access to national highly specialised healthcare services (EUCERD Q. CoE Rec. 34). The designation of CoEs at Member State level ensures that the designated centres have the capacity and the resources to fulfil the obligations attached to the designation (EUCERD Q. CoE Rec. 37). The identification and selection of expert centres in each EU Member State is paramount for the patient community and should always be undertaken in close consultation with the national rare disease patient community, to ensure transparency and build confidence in the process but also to ensure that the selected centres are assess based on the needs of their respective patient community [15].

RECOMMENDATION

Member States should define common guiding core principles for the endorsement of their national Centres of Expertise to participate as HCPs members in the ERNs.

Target deadline 2022

Member States must define a process to identify and designate national Centres of Expertise where there is none; which integrates the opinion and needs of the patient community, through its representatives being a key stakeholder in the prioiritisation and decision making process.

It is important for Member States to continue to develop the existing national designation process, with a quality improvement approach, ultimately to progress towards a model based on benchmarked health outcomes of clinical services, similar to the one adopted in Sweden [16].

Target deadline: 2025

2. **National workshops on integration should be organised to stimulate local discussions and activities.** 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, to ensure that all patients with a rare disease or complex condition across Europe can benefit from the ERNs model. The ERN Board of Member States Statement on Integration [16], [17] and EURORDIS Recommendations on the Integration of European Reference Networks into National Health Systems[18], set out clear, concrete actions in five areas – i. Member State support to CoE and awareness raising; ii. Development of national networking between ERNs members and local healthcare providers; iii. Defining the referral pathways to HCP Members and to the ERNs; iv. Using the Networks´ knowledge assets – guidelines and consensus statements, training webinars, virtual consultations etc.; and v. Development of national care pathways for rare diseases.

The European Commission should support Member States to implement the actions outlined in the ERN BoMs Statement on Integration of ERNs into national health systems, specifically by funding national multi-stakeholder workshops, with the national patient community, clinical leads and national authorities, to facilitate discussions and actions on integration into each of the EU27 national health systems.

Target deadline: 2021

3. **Support and strengthen Centres of Expertise capacities.** Member States must strengthen the capacities of their Centres of Expertise to enable them to undertake the core functions set out in the EUCERD Recommendations. To do so, EU structural funds could be used to complement national health budgets. Enhancing the capacity of Centres of Expertise is a win-win for both the Member States and the Networks; it will build the health systems competencies to address the needs of people living with a rare disease locally, while increasing at the same time the ERNs collective capacity and knowledge. Each Member State should also review their health system capacity and expertise to assess if the combined scope of all CoEs covers all RD patients' needs, even if they cannot provide a full range of services with the same level of expertise for each RD (EUCERD Q. CoE Rec. 3).

Member States should strengthen their CoEs competencies and capacities and invest the resources required to fulfil the vision set out in the EUCERD Recommendations on Quality of Centres of Expertise and increase or adjust the skill mix of their health workforce to address the needs of its rare disease patient population.

Target deadline: 2025

4. **Enable networking at national level, develop national care pathways and referral pathways to the ERNs.** Having a well-organised network-like national approach to rare disease diagnosis, treatment and care is essential for the proper functioning of healthcare pathways for people living with a RD (e.g. the national Filières Santé Maladies Rares). Well-organised national or regional networks for rare diseases can complement, streamline support and connect national healthcare systems with the efficient operations of ERNs (which should complement but never unnecessarily replace national pathways for patients). National networks of Centres of Expertise would also provide a structure for patients and clinicians in each Member State to work more closely across administrative boundaries and areas of expertise. As well as reducing the weight of membership under the Networks, making them more streamlined and manageable.

Ultimately, the same rationale that underpins the ERN system is also valid at national level: pooling together resources and expertise on rare diseases at national level, could contribute to improve the delivery of healthcare and reduce the disparities in access to care for RD patients that we see in some Member States.

RECOMMENDATION

Member States should create, in partnership with the rare disease patient community and other key stakeholders, national rare disease reference networks, thereby extending the ERNs locally through a 'hub-and-spoke' model; update their RD National Plans or Strategies and engage with clinicians and patients to set them up and drive their implementation. Countries with a decentralised health system and regional networks of CoEs, should put in place a strong coordination mechanism to ensure that all people living with a rare disease in these countries get the same quality care, regardless of where they live.

Target deadline: 2025

Each Member State should have clear and effective transition pathways that support the smooth transition of affected individuals to adult services and to the ERNs, providing continuity of care. They should develop referral pathways and national care pathways and identify shared care arrangements between ERNs members and local care services

Target deadline 2022

PART 3

STRUCTURE AND SCOPE OF THE EUROPEAN REFERENCE NETWORKS

PART 3. STRUCTURE AND SCOPE OF THE EUROPEAN REFERENCE NETWORKS

Vision

The EUCERD vision and recommendations about the structure and extension of the ERNs [19], [20] are a good starting point to build an ambitious, all-encompassing long-term strategy for the Networks to ensure that ultimately all RD patients will find a 'home' within an ERN.

> "The overall **vision of RD ERNs** is that they will provide the framework for healthcare pathways for RD patients through a high level of integrated expertise. RD ERNs will enable networking of centres on a European level, and promote that the appropriate healthcare professionals have access to the tools and guidelines provided by the RD ERN and to the knowledge of the networks. **This will cover in a step-wise approach all rare disease patients, including those in the process of seeking a diagnosis or in whom a final diagnosis is not yet confirmed"** (EUCERD Rec. 1) [20]

1. Inclusive approach but limited number of ERNs to avoid establishing potentially thousands of individual networks. The EUCERD recommended to cluster ERNs according to broad diagnostic and therapeutic areas around the concept of medical specialties and body systems (Rec. 19) [19]. The rationale behind this approach was to ensure that **all rare disease had a "home" within an ERN** as well as to avoid fragmentation and duplication. In addition, the EUCERD **recommended including within each individual ERN paediatric and adult to ensure continuity of care for patients** [20].

2. Cross-ERN collaboration is key for success. The Networks' grouping follows the traditional organisation of healthcare services by medical specialty, as this is how Centres of Expertise have emerged in Member States. However, the EUCERD acknowledged from the outset that the "success of this framework will be ensured by effective cross-links between the different RD ERNs so that the multi-systemic needs of most rare diseases would be well-addressed" [20].

3. Progressive expansion of the ERNs to cover all rare diseases, other centres, expert groups and patient groups by 2025. "By the end of the Health for Growth Programme (in 2020), the 20 to 30 RD ERNs should be established and covering a wide range of RD. These first established RD ERNs (…) will then progressively expand in order **to cover all RDs** by the end of the two next EU Public Health Programmes (**by 2025**), through integration of appropriate centres and expertise (Rec. 19)[19]. Each thematic RD ERN would still need to expand over the course of its first five years of designation to include **other centres**, expert groups, **patient groups** and **ultimately diseases"** (EUCERD Rec. 18)[19].

4. A step-wise strategy for the designation of new ERNs. A step-wise strategy for RD ERN designation should be delineated so that all patients with a rare disease will have access to an appropriate RD ERN in a defined period of time (EUCERD Rec. 17) [19].

5. Funding mechanisms for ERNs need to be adequate and long-term. Sustainable and long-term funding processes are needed, as RD ERNs are likely to remain necessary for the near future. Based on satisfactory evaluation against agreed indicators, funding should be for at least 5-year periods (EUCERD Rec. 12) [19].

6. Collaborate closely with other centres of expertise and networks at national and international level. Specifically, to exchange and disseminate knowledge and best practices; communication tools, and methodologies to develop clinical guidelines and protocols; exchange clinical information in accordance with EU data protection provisions and national implementing measures; develop training alternatives and models and operation and coordination practices (Delegated Decision – Annex I (7)).

Where are we now

Rare and complex conditions were thematically grouped under **24 Networks**, each covering a wide range of diseases and encompassing adult and paediatric care, with the only exception of EURACAN and PaedCAN that cover solid tumor cancers for the adult and paediatric cancer population respectively. Additionally, three cross-ERN working groups have been established in areas of common interest for various Networks: Working Group on Pregnancy and family planning, Study Group on Paediatric Anaesthesia and Working Group on research in surgery.

TABLE 3: NUMBER OF EUROPEAN REFERENCE NETWORKS PER AREA OF EXPERTISE

Rare diseases	Rare cancers	Highly specialized healthcare[4]	Complex Conditions (other than RD)[5]
19 ERNs	4 ERNs	5 ERNs (TransplantChild, eUROGEN, ERNICA,CRANIO, EpiCare)	Unclear[6]

Source: Own elaboration

[4] Highly specialised healthcare' means healthcare that involves high complexity of a particular disease or condition in its diagnosis, treatment or management and high cost of the treatment and resources involved [12].
[5] Complex disease or condition' means a particular disease or disorder which combines a number of factors, symptoms, or signs that requires a multidisciplinary approach and well-planned organisation of services over time because it implies one or several of the following circumstances: a large number of possible diagnoses or management options and comorbidity, difficult interpretation of clinical and diagnostic tests data, a high risk of complications, morbidity, or mortality related to either the problem, the diagnostic procedure or the management [12].
[6] There are some ERNs that currently cover complex conditions, other than rare diseases, but this is currently not clearly captured at the moment. For example, ReCONNET covers Lupus and Sjogren that are not considered rare in all countries and eUROGEN covers uro-recto-genital diseases and complex conditions in which two or more organ systems and experts are involved (such as for example, urologist, gynecologist and colorectal surgeon).

Geographic coverage of the ERNs

The **geographic coverage** of the ERNs has gained traction with the enlargement process that started in 2019[7]. As a result of this process, 247 Affiliated Partners joined the Networks in 2019, representing around 25% of the total clinical units participating in the ERNs[21]–[23]. Thanks to the inclusion of these centres, the geographical coverage of the networks increased from 44% to 74% [24]. This has resulted in an increase, from 3 to 10 Member States that have centres in all 24 ERNs. In addition, 4 Member States have designated a National Coordination Hub to engage with all established Networks - Malta (Mater Dei Hospital), Luxembourg (Centre Hospitalier du Luxembourg), Hungary (Semmelweis University) and Slovenia (Clinical Institute for Genomic Medicine). Further expansion in terms of geographic coverage is expected when the new full members join the ERNs in 2021. Also, once this process will be closed, national health authorities are expected to appoint new Affiliated Partners or National Hubs in their countries to cover the remaining geographic gaps.

An important formal aspect that the Board of Member States in collaboration with the ERNs should address by 2021 is the development of a clear set of rights and obligations for the different types of membership, as well as common process for termination for each kind of membership. Certainty around this aspect, will allow the hospital managers to have a clear understanding of the commitments that their units are assuming when they join a Network, either as full member or Affiliated Partner.

The existing forms of affiliation do not ensure enough inclusivity. While a full member might hold expertise in one or several conditions that fall under the scope of a single Network, it will very seldom have the expertise to cover all the conditions grouped under that ERN. However, the current rules prevent Member States to designate Associated Centres to join a Network if there is already a full member from that country participating in the ERN. Member States should be able to designate Associated Centres when a country has a full member in a given Network, as long as these centres bring in complementary expertise to that of the full members established in their country. At the same time, the Networks could further expand their geographic remit by building partnerships with expert centres that have not been endorsed or designated as Affiliated Partner by their national health authorities. As long as there is a transparent process agreed by the Network Board defining the criteria and governance of these partnerships, all ERNs should have the opportunity to establish these peer-to-peer collaborations. These type of arrangements would yield important benefits to the rare disease patient population of certain countries that are reluctant to endorse their healthcare providers.

[7] Public information on the geographic and disease coverage per ERN is available here

Disease Coverage of the ERNs

Regarding the **disease coverage**, with the information available today it is difficult to have an accurate picture of the real coverage of the +6,000 rare diseases. In their original applications, all the Networks identified the Thematic and Sub-thematic areas that they intended to cover. They also developed specific criteria and thresholds to assess the expertise of the centres to treat and diagnose around 1,000 rare and complex conditions. Sometimes these criteria refer to a group of diseases, for example, all vascular anomalies, and others they refer to a specific disease. We may consider these 1,000 diseases as the **operational disease coverage of the Networks**, where the ERN members that were assessed against the specific criteria are actively developing collaborative activities.

On the other hand, we may consider that the **strategic coverage of the Networks** includes all the conditions under the sub-thematic groups of rare diseases included in the ERN original applications and the ones added later, right before the 2019 call for membership. This would imply that today the strategic coverage, and ambition, of the Networks would cover almost all rare diseases. A preliminary analysis performed by Orphanet showed that some groups of very rare diseases remain outside the strategic scope of the Networks, and would need to be mapped to one of the 24 existing ERNs, and that the two main gaps refer to gyneco-obstetrics and rare benign tumours.

FIGURE 3: OPERATIONAL AND STRATEGIC DISEASE COVERAGE

Source: own elaboration based on the information provided in 2019 call for ERN members on the scope, criteria and thresholds of the diseases covered by each of the 24 ERNs.

There are a few diseases that today fall under the operational scope of more than one Network, where two or more Networks have developed specific criteria to assess the expertise to manage different manifestations of the same disease (see Table 4).

TABLE 4: EXAMPLES OF OPERATIONAL DISEASE OVERLAPS

DISEASE	EUROPEAN REFERENCE NETWORKS		
Cutis marmorata telangiectatica congenita	Skin ERN	VASCERN	
Maffucci syndrome	Skin ERN	VASCERN	BOND
Marfan Syndrome type 1 and 2	ERN Eye	VASCERN	
Sturge Weber syndrome	EpiCare	Skin ERN	
Turner syndrome	eUROGEN	VASCERN	
Ehlers Danlos	ReCONNET	VASCERN	
Spina Bifida	ITHACA	eUROGEN	
Von Hippel-Lindau syndrome	ErkNet	EURACAN	GENTURIS
Alpha-1	Liver ERN	Lung ERN	
Fabry	GuardHeart	MetabERN	ERKNet

Familial multiple nevi flammei	VASCERN	ERN Skin	
Hennekam syndrome	VASCERN	RITA	
Autosomal dominant polycystic kidney disease/Cystic Liver Disease	ErkNET	Liver ERN	
Tuberous Sclerosis	EpiCare	ErkNET	
HPP	BOND	ITHACA	
XLH	BOND	ENDO ERN	ERKNet
Thyroid cancers	EURACAN	ENDO ERN	

Source: own elaboration based on the information provided in 2019 call for ERN members on the scope, criteria and thresholds of the diseases covered by each of the 24 ERNs. This is a non-exhaustive list, there might be other operational disease overlaps but the information is not available.

These Networks have not yet articulated the mechanisms to enable a permanent cross-ERN collaboration in these instances. As of today, only some ERNs have started discussing how to organise cross-ERN collaboration for a few conditions:

- eUROGEN and ITHACA: joint working group for Spina Bifida (strong involvement of the ePAG representatives) and designated clinical leads from both networks are already collaborating.
- Rare Liver, PaedCan and EURACAN: have organised a joint workshop on liver tumors but a permanent group has not yet been set up.
- eUROGEN and ERNICA: a cross-ERN joint working group has been established chaired by leading experts and ePAG representatives from both ERNs.

Is there an adequate size for a European Reference Network?

Currently, the number of full and affiliated members in each Network varies, ranging from 83 in ENDO ERN to 25 in TransplantChild. With over 800 applications for full membership submitted in the second call, the membership of all ERNs, as well as the number of Member States that are represented in all 24 ERNs, is expected to increase significantly in 2021.

Achieving a comprehensive geographic and disease coverage of the Networks whilst ensuring that they remain manageable, is a legitimate concern for the Commission as well as for the ERN Coordinators. Until there is no evidence supporting **an ideal number of members,** each ERN should have the flexibility to decide its own size, based on their specific needs and interest, as long as it can guarantee that all countries and all diseases are well covered, rather than having a common standardized rule on size for all the Networks. Standardisation, in this and other areas, should only happen if based on evidence. The ERNs 5-year evaluation should provide evidence to guide the decisions on the optimal number of ERN members. By looking into the relationship between ERN members, economies of scale and impact it should determine whether there is something such as "an ideal" number of ERN members, or rather other factors have a greater influence on outcomes (such as an adequate support infrastructure, perceived leadership of the ERN Coordinator, etc.).

The Court of Auditors also highlighted last year the difficulties around **sustainable funding** and called on the Commission to define by 2022 a sustainable and long-term funding framework for the ERNs [25]. The public funds to sustain the ERNs' operations should have a direct link and be proportionate to the size and scale of ambition and activities, through a 'cost and volume' model, combining a fixed payment for all Networks of the same amount regardless of size (core structural costs, including administrative and management support, translation, etc), complemented with an additional payment proportionately based to the size of the Networks (networking activities and logistics). Additionally, ERNs still lack the policies and mechanisms to channel funding from other sources

(industry, private donations, CSR, etc). **The long-term funding framework for the ERNs should take into consideration all possible sources of funding and define any central functionalities and policies to support ERNs' financial management and governance.**

The analysis of the progress until today in terms of the ERNs scope and structure, shows that there is still work to be done to achieve full disease and geographic operational coverage. At the same time, it is clear that any expansion strategy will require action at EU as well as at national level, and must be accompanied by increased resources and new funding arrangements.

Patient engagement

The Addendum to the EUCERD Recommendations on ERNs states that "due to the specificity of RD the role performed by RD patients is actually more fundamental; therefore, a higher level of involvement of patients in decision and opinion-making processes is essential to ensure the successful development of RD ERNs". This Addendum is the mandate for patient representatives to be included in the ERNs as equal partners. Whilst patient representatives are not 'legal members of the ERNs', patients have now been de facto accepted as members, sitting on ERNs Boards, clinical committees and working groups.

The lack of recognition of patient representatives as ERN members in the legislation, left a gap regarding rules for patient engagement, role of patient representatives in the ERNs and resources to support their involvement in the Networks. EURORDIS, its members and the patient community, have worked together to organize and ensure that patient involvement in ERNs was optimized, instead of leaving it to personal relationships or chance. EURORDIS and the rare disease patient community set up the European Patient Advocacy Groups (ePAGs) to optimize the involvement of patients and ensure unity, solidarity and equity of patient representatives of the rare disease in the 24 ERNs. In this context, the role and value of the European Federations should be emphasised, as their representatives have a clear community to engage with in terms of surveying needs across the EU Member States.

Today the formal recognition and organisation of patient engagement in the different ERNs varies. In some ERNs the European Patient Advocacy Group has not yet been integrated into the ERN formal governance organisational structure, whereas others have formally integrated the European Patient Advocacy Group or Patient Board into their governance structure. One ERN has gone a step further in terms of formalizing patient engagement by granting patient organisations the status of "associated partners". Having the patient group formally integrated into the ERN governance structure does not guarantee per se a good cooperation between patient representatives and clinicians, but it is a first step to legitimise the role of patient representatives in the Networks.

Patient representatives work on a voluntary basis for the Networks, they are not compensated for their work nor the time invested in ERN activities, and the large majority of the ERNs lack the resources to support patient engagement. To cover this shortfall, EURORDIS is supporting the operations of 19 ePAGs (secretariat, preparation of meetings, training, exchange of good practices, governance, guidance, assessment).

International Collaboration

The Delegated Decision clearly sets out the legal requirement for the Networks to foster international collaboration with other national centres and networks in countries outside the EU, however this has

not yet been operationalised. As is the case for rare diseases, with rarity of patients also comes scarcity of experts, with leading international expertise needing to collaborate globally.

On 23 September 2019, all 193 UN Member States adopted the historical Political Declaration on Universal Health Coverage[26] including a commitment to strengthen efforts to address rare diseases. ERNs are the main vehicle for the EU countries to make meaningful headway in honouring this political commitment within the WHO European Region.

The ERN model has inspired the development of the WHO Collaborative Global Network for Rare Diseases that will connect Global Rare Disease Hubs and patient organisations around the world in the different WHO Regions. Now is the time for the Networks to extend their international reach and impact, starting with the WHO European Region through piloting collaborations with the 59 Member States, to pool knowledge, data and efforts in tackling the public health needs of rare diseases.

Challenges & Recommendations

1. **Individual ERNs lack a strategy to extend their operational disease coverage to reach full strategic ambition by 2025.** The stepwise expansion recommended by the EUCERD requires each Network to define its timeline and work programme to reach full disease coverage. At the same time, the Board of Member States needs to agree how to best manage this expansion. Future calls for new members should be exclusively targeted to cover geographic and/or disease gaps in each Network. Members States should commit to respect the scope of the targeted calls and restrain from endorsing expert centres that do not cover an identified gap. On another note, this should go hand in hand with regular calls for membership and an improved application and assessment process for new members.

Clinicians and patient representatives in each ERN should develop a step-wise expansion roadmap with a detailed action plan, timeline, milestones and resources required to develop gradually the specific criteria for each new disease and achieve a comprehensive disease coverage in their respective thematic groupings. The Board of Member States, ERN Coordinators and the Commission will need to specify and publish a protocol for disease expansion across all 24 ERNs.

Target deadline: 2021

2. **The formal inclusion of a disease in a given Network should correspond with a proportionate increase in networking activities linked to that disease**, to avoid offering the rare disease patient community false hopes. Therefore, alongside the definition of specific criteria to identify expert centres, the Networks should define clear commitments concerning concrete networking activities that the centres will be required to undertake once they join. Each ERN needs to develop a roadmap of care pathways and a suite of clinical guidelines, clinical decision-making tools and patient information on diagnosis, care and treatment, and other collaborative activities for each

rare disease covered under its operational scope. These key deliverables and reference documents should be jointly developed by clinicians and patient representatives through strong patient-professional-partnership.

All ERNs should have identified for the diseases that they claim to cover a set of specific time-bound commitments that the clinical units commit to develop, if they have not done it so far. Thereafter, when an ERN proposes to extend its disease scope, it should propose a set of specific commitments that the clinical units will be required to undertake once they join the Network.

All these commitments would need to be supported by an adequate level of funding to ensure the implementation of these activities.

Target deadline: 2022

3. **The EC should launch a call for new Networks to cover the existing disease gaps, after having engaged with the rare disease community to identify relevant gaps**. The Commission has already explored the opportunity of setting up new ERNs for three large disease groups that are not covered by any of the 24 ERNs: rare communicable diseases, mental health diseases and gyneco-obstetrics. Specifically, a standalone Gyneco-Obstetrics European Reference Network for rare and complex gynecological and obstetrical conditions would respond to a well-identified cross-cutting need for rare disease patients, and contribute to build the evidence for the adequate management of complex pregnancies and the effect of pregnancy on the health of women during pregnancy and post-partum.

   The new Network should be linked to all 24 ERNs and would complement the work the individual Networks in this area by strengthening the collaboration between disease-specific multidisciplinary teams with obstetricians-gynaecologists specialized in rare and complex gynecological and obstetrical conditions, while building the capacities of these centres at national level to deliver evidence-based care to women affected living with a rare disease. This ERN would also be instrumental in pooling data and developing reliable registries on pregnancies that could support the development of prospective studies required to identify risk factors for possible exacerbation. Finally, the Network should build early on a partnership with the EMA to collect in a systematic way information on outcomes and adverse effects for pregnant women in clinical trials and after approval.

EURORDIS would welcome that the new ERN for rare and complex gynecological and obstetrical conditions would bring together expertise on complex pregnancies, teratogenicity, genetic counselling and ethics. As such, it should bring together University Hospitals' units specialized in rare and complex gynecological and obstetrical diseases and the national centres for teratogenicity.

Target deadline: 2023

4. **Regular cross-ERNs collaboration is not yet well established.** A main priority over the five next years should be to create effective and permanent mechanisms to build cross-talk between the different Networks and cross-ERN working to address the multi-systemic needs of most rare diseases. Likewise, multi-disciplinary collaboration at Network level is practically inexistent and this is preventing the Networks to deliver on their full potential. The EUCERD recommendations refer to **diagonal networking** when different specialties such as social, rehabilitative, psychological, physiotherapists etc, work together. The multidisciplinary collaboration that exists at the level of the expert centres must be transferred to the discussions and activities at a Network level, through the active participation of other specialists and health professionals in ERNs the collaborative activities and meetings.

Permanent cross-ERN working groups should be in place with a clear annual work plan for benign tumours and all the diseases that formally fall under the scope of several ERNs (such as for example, Cutis marmorata telangiectatica congénita, Maffucci sindrome, Marfan Syndrome type 1 and 2, Sturge Weber syndrome, Turner syndrome, Spina Bifida, Von Hippel-Lindau syndrome, Alpha-1, Fabry, Familial multiple nevi flammei, Hennekam syndrome, Autosomal dominant polycystic kidney disease/Cystic Liver Disease, Ehlers Danlos, etc.). A set of measures to assess the work of these cross-ERN working groups should be developed, so that the work of these first cross-ERNs groups can be monitored and assed as part of the ERN assessment, monitoring and evaluation system.

Target deadline 2021

All Networks should have in place the mechanisms to integrate health professionals from other disciplines and should be running multidisciplinary collaborative activities on a regular basis, including developing decision support tools, research, education and training. Specifically, a cross-ERN working group on integrated care should be established in partnership with European Resources centres for rare diseases as a gateway to build joint guidance on collaborative approaches for the provision integrated care to people living with a rare disease [5].

Target deadline: 2023

5. **Patient involvement in the ERNs must be fully legitimised and supported.** The existing governance structure and support for patient engagement in some ERNs falls short to recognise and legitimise the role of patient representatives in the Networks. This situation will need to be re-assessed to ensure that the participation of patient organisations and their representatives in the ERNs is well organised and has an impact. ERNs could envisage different levels of involvement that could go from "individual ad-hoc commitment" – for example, for the development of a clinical practice guideline - up to "associated partners". In each case the process to apply, the criteria and the rights and obligations of patient organisations and their representatives should be

clearly defined. ERNs should transparently inform patient organisations about cooperation opportunities and the efforts involved.

At the same time, even if the principle remains that patient representatives are involved in the ERNs on a voluntary basis, their involvement needs to be adequately supported by the ERNs and fairly compensated where appropriate. In the same way as the EMA has a framework for the interaction with patients' organisations and their representatives and a policy to reimburse the expenses of patient experts, ERNs should have a common set of policies to improve and streamline patients' involvement in their activities.

Based on existing experience, ERNs should develop clear and transparent rules for patient engagement, adequately support the involvement of patient organisations and their representatives in the different ERN activities and fairly compensate patient representatives.

Target deadline: 2021

6. **International collaboration between clinical network structures is a mandate of the legislative acts** [12] **but will not happen spontaneously.** It must be well organised with a mechanism possibly formalised under the current governance structure of each Network. Connecting with other global and regional clinical networks is vital to achieve excellence in highly specialised healthcare, maintain the Networks' capacities and multiply their impact. Typically, international cooperation with other networks will be formalised through bilateral or multilateral agreements for scientific cooperation focusing in one or more areas related to highly specialised care and research.

The ERN Board of Member States should develop strategic guidelines on international collaboration and define the role and remit of an "ERN international partner". It should define a common strategy on ERNs international collaboration and partnership, defining the rights and obligations of international partners under an ERN, as well as investing resources in joint projects, infrastructure and initiatives.

Target deadline: 2022

The European Commission should collaborate with the WHO European Regional Office to set up a number of pilots to establish international collaborations between the ERNs and non-EU Member State centres of expertise.

Target deadline: 2025

PART 4

OUR VISION OF A MATURE ERN SYSTEM

PART 4. OUR VISION OF A MATURE ERN SYSTEM

Introduction

The hallmark of rare diseases is that due to their low prevalence, and incidence in the case of rare cancers, expertise and knowledge is scarce, evidence is limited and care is often fragmented. Taken together these factors diminish healthcare services' capacity to respond to the complex, multisystem needs associated with these diseases, and result in poor access to basic, adequate and effective care.

Due to these unique characteristics, rare diseases have been recognised as a shared EU public health need that must be addressed through cross-border collaboration in the field of healthcare and research, as no-one country alone can meet the needs of this vulnerable community. As a result, the Cross-Border Healthcare Directive created the ERNs as a mechanism for EU collaboration to improve diagnosis, care and treatment options for people living with a rare disease. While European collaboration in RD research has long been well established, cross-border collaboration in RD healthcare is an emerging area where all EU27 RD healthcare systems need to gain experience and explore new ways of working together[8].

ERNs have already been recognised as a concrete example of cross-border EU collaboration; they received the European Ombudsman Award for Good Administration in 2017 and have built a reputation as a flagship initiative that demonstrates EU added value in the health sector. And they continue to guide and support healthcare professionals through the COVID-19 crisis, offering a tested and trusted system to exchange knowledge, discuss cases and improve training. This can be expanded further to create greater cooperation and more flexible healthcare systems that can respond and adjust to the needs of EU citizens, weatherproofing European health systems against future health crisis. However, it is worth recalling that the Networks are still in deployment mode and will only move to full service operations towards the end of their first five years in 2022.

The information and knowledge sharing linked to the activities developed by the Networks make each ERN a learning system, each with an emphasis on different areas (treatment options, surgical procedures, diagnosis, research, therapies, quality of life, etc.) depending on the characteristics of the rare diseases and complex conditions that fall under their scope.

The core services and building blocks of the Networks as set out in the EC delegated legislation [12] include:

1. Care delivery
2. Knowledge generation
3. Training and education
4. Research

[8] One exception to this are paediatric cancers, where cross-border cooperation has been established for over 50 years. Today, European clinical trials groups (ECTGs), part of the Clinical Research Council of SIOP Europe, cover all paediatric tumour types and work closely together with the ERN PaedCan in the framework of a united childhood cancer community.

The following sections of this paper, explore these core functions under three headings - the original strategic vision; progress to date; identification of gaps and our recommendations.

4.1 Care

Vision

ERNs are first and foremost about healthcare. The Networks' *raison d'être* is to improve access to diagnosis, treatment and to provide high-quality healthcare for patients who have a condition that requires a particular concentration of resources or expertise [12], [28]. This central philosophy is encapsulated in the Networks signature – Share, Care and Cure. The rare disease community shares this vision of the Networks. A vision where all rare diseases have a home under one of the ERNs, where experts are recognized, visible and accessible, and where expertise travels, not the patient.

For the ERNs to deliver their mandate – to Share, Care and Cure – through the expertise traveling, not the patients, they need to deliver the following functions detailed in the EC Delegated Decision [12]:

1. **Provide high quality, accessible and cost-effective highly specialised healthcare,** through experienced, highly skilled and multidisciplinary healthcare teams; where their Members demonstrate that they:
    a. can guarantee that healthcare is provided according to the highest quality criteria and available clinical evidence;
    b. hold the expertise related to the scope of their Network.
2. **Efficiently and securely exchange health data** and other patient information as well personal data of the healthcare professionals in charge of the patient.
3. **Promote good quality and safe care** and develop and maintain a **quality, patient safety and evaluation framework**.
4. **Offer and promote high level of expertise and support healthcare providers in order to bring local, regional and national provision of healthcare** closer to patients.
5. **Produce and implement cross-border patient pathways**.
6. **Design and implement outcome and performance indicators.**

The establishment of the ERNs has given the EU the opportunity to address the healthcare needs of rare diseases and strengthen national health systems competencies in highly specialised healthcare by harnessing the collective expertise and knowledge of leading expert centres. Ultimately, ERNs have the potential to put an end to the diagnostic odyssey, improve access to effective treatments, and alleviate the disease burden on the daily lives of people living with a rare disease. The Networks should also offer a gold standard for rare disease care delivery, one that is patient centred care, characterised by patient-clinician partnership, informed co-decision making, multidisciplinary and evidence-based care.

The concentration and centralization of resources and expertise under this new 'Networked Care' model, offers the opportunity for high-cost interventions and highly-specialised services to be better targeted, thereby reducing inappropriate and ineffective, costly interventions and the healthcare burden of rare diseases on hospitals' resources (see Part 2. Healthcare systems arrangements to meet Rare Disease population care needs).

However, the Networks can only fulfil their mission **through coordinated multi-stakeholder EU action that is guided by a clear 10-year strategy. A strategy that delivers on the weight of unmet needs of rare diseases, as ERNs are now the most important vehicle to tackle this EU public health priority.**

Where are we now

The ERNs are implementing a new way of delivering healthcare for rare diseases based on care coordination by multidisciplinary teams of experts who are part of a network of centres, instead of part of a single hospital team. ERNs are formalising this paradigm shift from multidisciplinary care to networked care for rare diseases, which previously existed on an informal basis. The establishment of the ERNs has provided a new, and much needed, cross-border infrastructure for rare diseases and highly specialized healthcare. Despite this development, there remains a clear visible gap in both investment and implementation, from where the ERNs are now to fulfilling the original vision of the rare disease community.

The added value of the Networks should not and cannot be measured solely by their performance in providing specialist advice through the Clinical Patient Management System (CMPS). The Networks have successfully conducted over 1,000 virtual cases discussions; however, even when considering these cases to be the more complex and rare presentations, these are only catering for the 'tip of the iceberg' needs of a community of 30,000,000 people living with a rare disease in the EU.

The CPMS expert panels are clearly an important feature of the new system and provide a much-needed secure platform to deliver networked care, but the Networks, through their Members, need now to extend their reach and drive improvements in their respective local health systems. It is reasonable that in this early phase the Networks have focused in launching and establishing their operations. However**, unless relationships and connections are made with national, regional and local hospitals and primary care physicians, the ERNs will remain an island of expertise inaccessible to these 30M EU citizens.**

With the long-awaited completion of the second round of applications in 2021, we will successfully conclude the first phase of the Networks' development, securing comprehensive coverage of all Member States in all Networks. All stakeholders involved in the successful development of ERNs, will now need to make the 'gear change' from development mode to full deployment mode to anchor and implement the networked care model within the national health systems. This implies a mindset shift for all stakeholders.

1. **Health authorities** will need to shift efforts and resources from the endorsement of healthcare providers to join an ERN, to adopting and implementing the ERN system at national level to support the organization of healthcare for rare and complex conditions. The footprint of a mature ERN system will revolve around the Networks' members that are formally recognised within their national healthcare system as Centres of Expertise through a national process for identification, assessment and designation. However, as previously mentioned, many Member States still do not recognize the full spectrum of experts in their own healthcare system and lack a national designation process.

2. **Hospitals and expert teams that are members of the Networks** will need draw on the ERNs knowledge assets (innovations, emerging best practice and clinical practice guidelines) and implement them locally in their clinics as well as share it with other hospitals in their own country. Support from local hospital managers, both from ERN and non-ERN hospitals, will be essential to implement successfully service improvements, redesign clinical templates and clinical protocols based on new knowledge and insights from the Networks; and to coordinate and connect with other hospitals within their country through formal and informal networks.

3. **Patients, Patient Organisations and their representatives** will need to collaborate with the Members of the Networks and national 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 their national health system 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 best organized locally to meet their needs.

Challenges & Recommendations

To fulfil the ERNs mission and support the establishment of a mature ERN system over the next ten years all stakeholders need to focus and invest their energies and resources on three priorities:

1. **Safeguard ERNs as a mark of quality and safety**

The Networks were carefully established through an evidence-based independent assessment process. The assessment of ERNs and their Members gave a level of assurance at a point in time, however, it is critical that the EC and Member States continue to build the ERNs as a mark of quality and maintain public confidence, as the capacities and competencies and areas of expertise of the centres change over time. Good oversight and continuous assessment is critical.

Immediately following the 2021 assessment of new full members, the EC, the Networks and their respective patient advocates, should continue to review and revise the Networks' specific criteria. The granularity of the specific criteria should reflect the prevalence and complexity of each rare disease.

Target deadline 2021

In addition, the EC should maintain a continuous cycle of peer review and independent assessment of full members, to ensure they maintain their competency and safeguard public confidence in the ERNs as a quality mark. Finally, the EC should conduct a full review of the assessment framework to strengthen the assessment and approval of EU 'light-houses' of expert centres in rare diseases.

2. Consolidate the ERN model of cross-border healthcare

The rollout of the ERNs online expert advice service is constrained by the current functionalities of the CPMS platform and the administrative burden linked to the operation of the virtual panels. Beyond improving these aspects, the EC and the BoMs should explore how to expand the routes for securing second opinion and specialist advice under an ERN, with other alternative models and IT tools. New methods could include direct online advice for patients, in their local language (as currently delivered in ERN LUNG); access to cross-border high-quality newborn screening; virtual 'online outpatient' clinics (scheduled patient-to-doctor outpatient appointment); etc. These new models of direct virtual cross-border care might well require reviewing the current EU legislative framework for cross-border healthcare.

The lack of a funding mechanism to reimburse the expert teams for their time and services, poses a significant risk to the Networks' sustainability and is a barrier for patients and hospitals to secure specialist advice under the ERN model. The fact is that the lack of a payment model for doctor-to-doctor virtual case discussions (using the CPMS) and patient-to-doctor virtual consultations both under an ERN and within each national health system, is lagging behind the necessity and the urgency. One hopes that in the shadow of COVID-19, appetite and perceptions about the value and need for virtual healthcare has changed and that the EC and BoMS will now develop a clear payment system for the ERNs.

The Networks should fully exploit digital technologies to enable patients and their families to access the right expertise, as close to home as possible and promote self-management. These tools also offer the Networks an opportunity to facilitate mobility of expertise and develop effective shared care arrangements through their Members, under a 'hub-and-spoke' model [27] to connect with their hospitals in their local regions.

The EC, BoMS, ERN hospital managers and the ERNs IT WG should agree on a digital roadmap to develop progressively the suite of digital tools and services to consolidate the 'Networked Care' model and support the expansion of cross-border clinical services.

Target deadline: 2025

The EC should support Member States to develop a fair, transparent pricing and reimbursement model and establish a funding mechanism for the virtual expert advice consultations and other ERN services under a Networked care model, thereby safeguarding the ERNs sustainability.

Target deadline: 2030

3. Enable access to highly specialised healthcare, breaking down the barriers and connecting the care chain from ERNs to the local health systems

Currently there is a significant lack of referral pathways and supporting public and professional information mapped out both at a Network and national level. The BoMS statement on integration[17], [18] recommended the development of referral pathways and information and guidance for local communities, but this remains an ambition and not a reality. The role and relationship between ERNs and the national health systems still needs to be defined at local level with clear rules throughout the care pathway, including follow-up of patients whose case or treatment has been discussed by the ERN and the role of the National Contact Points for Cross-Border Healthcare, that should have a specific responsibility on advising how to access the ERNs.

Referral management into the ERNs is a critical function that should be available in all Member States. However, only four Member States have endorsed an ERN National Coordination Hub, with the specific mandate to be a referral management centre for the Networks. The role of Full Members and National Associate Centres is focused on sharing expertise, conducting networking activities (e.g.: guideline development, research etc.) and these centres might not have the capacity or the interest to act as an ERN referral management centre in their respective countries.

There is a pressing need for each ERN to select one healthcare provider per country to act as a National Coordinator, as some ERNs have already done. The National Coordinators for each ERN in each country, should work in partnership with the local patient community as well as build relationships with the national professional societies and the national research leads.

All ERNs should agree and publish a common referral pathway into the Network describing the different referral alternatives and produce with its patient advocates information and advice on accessing specialist advice under an ERN.

Target deadline 2022

All Member States should endorse a hospital as a National Coordination Hub as the central referral management centre to enable access to ERNs specialist advice.

Target deadline 2025

4.2 Knowledge sharing

Vision

A common characteristic for rare diseases is the limited volume of published literature and finite body of evidence. The rarer the disease area, the fewer the experts and scarcer the knowledge. The volume of evidence is unlikely to ever reach a fraction of the evidence generated for diseases that are more common. These unique factors increase the level of uncertainty in diagnosis care and treatment, resulting in isolated pockets of expertise and knowledge, which remain largely untapped and inaccessible, as well as a lack of available treatment for the majority of rare diseases (>95%).

However, published literature in rare diseases is not an accurate reflection of the wealth of experts' experience. Whilst there is, and probably always will be, a lack of published evidence due to the low prevalence of cases, the collective knowledge and experience of EU experts does provide a huge opportunity to build the knowledge base in rare diseases and offers many people living with a rare disease the chance to access higher quality healthcare. Evidence has shown that collaboration and learning together is a key feature of successful, effective networks[28]–[33]; it is no coincidence that knowledge sharing is the driving force of European Reference Networks and sits at the very heart of their mission.

The ERNs have been clearly positioned to address the shortfall in published literature with three (out of eight) objectives set out in Art.12 of the Cross-border Healthcare Directive [28], specifically focusing on knowledge generation and sharing:

- contribute to the pooling of knowledge regarding sickness prevention;
- facilitate mobility of expertise, virtually or physically, and to develop, share and spread information, knowledge and best practice and to foster developments of the diagnosis and treatment of rare diseases, within and outside the networks;
- encourage the development of quality and safety benchmarks and to help develop and spread best practice within and outside the network;

This ambition from the CBHCD, is further articulated in the EC Delegated Decision [12] that requires the Networks to offer a high level of expertise and have the capacity to produce good practice guidelines and to implement outcome measures and quality control, and more specifically to:

- exchange, gather and disseminate knowledge, evidence and expertise within and outside the Network, in particular on the different alternatives, therapeutic options and best practices with regard to the provision of services and the treatments available for each particular disease or condition;
- promote expertise and support healthcare providers in order to bring local, regional and national provision of healthcare closer to patients;
- develop and implement clinical guidelines and cross-border patient pathways;

- design and implement outcome and performance indicators;
- develop and maintain a quality, patient safety and evaluation framework.

Where are we now

Since their launch in 2017, the Networks and their Members have invested time and energies in forming new partnerships, getting to know each other experiences in their respective fields of expertise, and building trust and relationships. The Networks, however, have not yet fully drawn on their true potential in sharing their experiences and expertise in a structured way within and outside each Network.

1. **Knowledge sharing within the Network.** The overwhelming response to the first and second call for full members clearly demonstrated that there is the will to collaborate and share between clinicians. However, these experts need to be supported by the EC, their Member States and their hospital management, to have the capacity to act and invest their time in developing evidence for rare disease healthcare and knowledge.

   Guideline development, as well as, and arguably of greater value due to the lack of published literature, other clinical decision support tools and expert consensus statements, are one of the most important outputs of the Networks. The consolidation of experience and knowledge within the Networks into expert consensus statements, clinical practice guidelines and clinical pathways, offers all stakeholders and partners a great opportunity to quickly 'level-up' the systems' knowledge and capabilities across the EU27.

   Some Networks have begun to develop clinical practice guidelines and consensus statements, but this activity is time intensive and requires additional financial and administrative support to move it from a 'small-scale' ad-hoc activity to a production-line of internationally recognised guidelines. In this area of work, it would be good if ERNs would build on or, where possible, endorse the existing international guidelines or standards of care to avoid duplication of efforts, speed up processes and ensure that patients benefit from optimal clinical standards. In this sense, it will be critical that the process for developing ERN guidelines is aligned and developed in cooperation with professional societies. In addition, ERNs need a common methodology that goes beyond the value of GRADE and is adapted to the specificities of rare diseases. A methodology that balances the weight of both published evidence and the wealth of expert experience and knowledge within the Networks. The EC contract for services to provide the Networks with additional capacity to develop guidelines is welcome; however, additional resources directed to the Network themselves are needed to continue developing this work in the long-term.

   A similar picture emerges when it comes to clinical pathways that remain undeveloped for the majority of the diseases. Some ERNs have started to develop clinical pathways but they lack a clear common methodology to guide the development of uniform and connected cross-border clinical pathways. The Networks will require targeted funding to support the development of a common methodology to develop cross-border clinical pathways.

2. **Transforming data into knowledge.** As long as data is not being systematically collected, ERNs will not be able to transform it into knowledge. The ERN Coordinators Monitoring Working Group has defined a continuous monitoring strategy. The first stage included the development of a set of 18 common indicators whereas the collection of disease-specific outcome measures was planned for a second stage. It has proven challenging for the Network members to collect and report the agreed 18 indicators, let alone outcome measures. Clinical leads will need the support from the hospitals' managers to report consistently on both the common and specific disease measures.

   Defining and collecting disease-specific outcomes is central to develop a culture of sharing and learning; one that celebrates the variation in clinical practice and surgical philosophy, as this is the hotbed for innovation, and at the same time will help ERNs to identify emerging best practice. Disease-specific outcome measures provide a structured way for experts to share and compare experiences and performance, enabling the teams to quickly identify and learn when one practice is more effective than other. In short, it enables them to connect the dots, identify patterns, and transform data into insights and knowledge.

   Collecting outcome measures in a consistent and interoperable manner is an essential foundation to build the Networks' ability to foster learning from the leading experts under an ERN. Greater coordination in the development of the ERN registries is a major priority, due to the multi-system needs of many rare diseases. An integrated ERN registry infrastructure is essential (i.e. common rules on data collection, standards, access policies, etc.) to build the integrated quality improvement system envisaged in the ERNs Assessment, Monitoring and Evaluation Quality Improvement System (AMEQUIS). The successful outcome of the long awaited AMEQUIS tender for services will be critical in shaping the ERN system as a continuous quality improvement system.

   Eventually the Coordination and Support Action for the coordination of clinical research activities of the ERNs will help to lay the grounds for an integrated ERN registry infrastructure, but without clear interest and continuous support from all stakeholders, the Networks capacity to share and to learn will quickly diminish over time.

3. **Knowledge sharing outside the Network with the medical and patient communities, as well as the general public.** The ERNs ability to share knowledge outside the Network is critical in supporting national healthcare systems to develop their competencies to treat rare disease patients locally, enabling expertise to travel, not the patient! However, this relies on the Networks' members acting as national coordination centres, on behalf of their Network, to build relationships and collaborations between the ERN, their national health system and scientific societies. As such, ERNs' members have a two-fold obligation to share knowledge with the medical community:

   - within the Network to share their knowledge and experiences with other Members and Associated Centres;
   - outside the Network, within their hospital to implement new practices and guidelines for their own patients and within their own health system to promote expertise and support other hospitals, disseminate knowledge and best practices to other centres to bring local, regional and national provision of quality healthcare closer to patients. Whilst the role of ERN National Coordination Hubs has been formally established as the interface between the ERNs and all stakeholders within their country, this function is not clearly articulated nor understood by the Networks' members.

   Beyond reaching out to the medical community, ERNs should be the "go-to" trusted source of information on rare diseases and healthcare for patients, family members and the general public, and adequate funding should be allocated to fulfil this role. They should also enable peer support and networking between patients, family members and healthcare professionals. Patient representatives involved in the ERNs are playing an important role in this regard, but further work and resources to support this activity are needed. At a minimum, all ERNs should share basic information on all the diseases under their operational coverage, map expertise throughout the EU in a way that is accessible for patients and families, offer clear guidance on their structures, their work, what are the services provided by the ERN and how they are organised, as well as information about their progress and outcomes. It would also be useful to have annual meetings of ERN members, health authorities and the rare disease patient community in each country to synchronize the efforts needed specifically for the country's health care system.

1. **Generation of new evidence, best practice and knowledge.** Networks should celebrate the variation in clinical practice across their members, through the establishment of a culture and system for quality improvement based on sharing and benchmarking disease specific clinical outcomes and publishing innovative and emerging best practice.

   The collective knowledge and expertise under the ERNs has not yet been fully harnessed to drive the development of evidence and quality improvement for rare disease and highly specialized healthcare. Where this is not yet the case, the Networks' annual meetings should gradually move from away from administrative topics to multi-professional Clinical Summits that provide an opportunity for sharing, learning, presenting new evidence and stimulate clinical discussion.

   The ERNs should be supported to develop a library of evidence-based guidelines and expert opinions that cut across the whole care pathway from diagnosis to long-term follow up for all rare diseases included in their operational scope. A common dedicated 'in-house' Guideline office should provide support in the assessment and endorsement of existing guidelines and consensus statements and the development of new clinical decision support tools.

RECOMMENDATION

Urgently, the Networks need additional direct funding to support the development of new guidelines and consensus statements in partnership with patients, so that by 2025 they will have developed guidelines and/or other clinical decision support tools for each of the rare diseases included in their operational scope.

Target deadline: 2021

2. **Transforming data into knowledge and information.** The Networks have implemented the first part of the ERN continuous monitoring framework, collecting a common set of indicators. The next planned step is the development and collection of disease-specific outcome measures. Benchmarking these outcome measures, is critical to facilitate continuous improvement and learning from differences in clinical practice of Members within the Network. Expert centres should increasingly share their outcomes and analyse the differences in clinical practice to further develop the evidence base for each rare disease.

   The identification and collection of outcome measures should be undertaken following a common methodology. The quality of the Networks' registries is the cornerstone of the ERNs structure that will unleash the potential of knowledge sharing to improve the quality of care for people living with a rare disease. Additional investment is needed to improve and further develop the ERNs registries and link them to other research infrastructures such as biobanks.

All the Networks should be collecting and publishing disease specific outcome measures and patient reported outcome measures that are relevant for patients, for all rare diseases that are included in the operational scope of each Network.

Target deadline: 2022

ERNs must ensure open access to all peer-reviewed scientific publications related to their results and achievements. To do so they must at least ensure that any scientific peer-reviewed publications can be read online, downloaded and printed. Likewise, all Networks should provide easy access to the information that they curate as well as a comprehensive mapping of its Centres of Expertise, members and Affiliated partners, per disease. An internet-based web-portal should serve as a central access point to information generated by the ERNs.

Target deadline: 2022

All Networks should hold annual multi-professional and multi-stakeholder clinical summit conferences, to present their outcomes, in a standardised format to enable comparisons, and use this data to facilitate learning and identify new emerging best practice and advancements in surgical philosophy.

Target deadline: 2025

3. **Identification and implementation of best practice at local level.** National health authorities should agree on a common methodology to develop ERN clinical guidelines, patient pathways and other clinical decision support tools and define the mechanisms to implement into local services. Following a validated methodology will fast track the adoption and implementation of these clinical tools in Member States and their local services. With adequate support from their hospital management, ERNs members should implement ERN clinical decision support tools and patient pathways and monitor adherence of care prescribed within their clinics, measure the outcomes of care under these pathways and use findings and results to make ongoing quality improvements within their hospitals.

The BoMs, ERN members and ERN hospital managers should agree on how to facilitate uptake and implementation of patient pathways and clinical decision support tools at local level.

Target deadline 2022

Member States, after engaging with the ERNs and professional societies, should validate methodologies for the development of clinical practice guidelines and other clinical decision support tools and clinical pathways to 'pre-approve' tools developed by the ERNs under these methodologies as ready for implementation within the ERNs' members. These CoEs, supported by their hospital management, should implement these tools leveraging collective knowledge and expertise to enhance evidence-based clinical practice.

Target deadline: 2025

4.3 Training and education

Vision

European Reference Networks can be focal points for medical training, information dissemination and evaluation for rare diseases. Specifically, to provide training for health professionals and organise teaching and training activities [28].

Facilitating the mobility of expertise and delivering training within and outside the Networks are two of the core objectives of the ERNs [34]. The EC Delegated Decision requires them to organise teaching and training activities, including i. identify and fill training gaps, and; ii. encourage and facilitate the development of training and continuous education programmes and tools for healthcare providers involved in the chain of care (within or outside the Network) [12].

The ERNs members should also be active in medical training and education, specifically:

1. For patient empowerment, members must provide training for patients and their families, educational and engagement strategies to ensure patients' right to be empowered and to participate in their care is respected (EC Delegated Decision Annex II 1.a.i);
2. For healthcare professionals, members must hold training capacities to provide academic, university or specialised level training (Annex II 1.c.i); carry out teaching and education activities related to the area of expertise aimed at improving the knowledge and technical capacity of the healthcare providers involved in the same chain of care within and outside the provider facility, such as continuing medical education and distance learning (EC Delegated Decision Annex II 1.c.iv)
3. To ensure good quality, safety services, members should undertake evaluation of services, specifically training and education activities on clinical incidence and learning from medical errors (EC Delegated Decision Annex II 1.e.ii).

With the weight of ERN members coming from 5 large Western European Member States (Germany, France, Italy, Spain, The Netherlands), these centres have the opportunity and responsibility to secure increased knowledge and share their expertise with health professionals throughout all EU Member States. These activities can significantly contribute to build the EU health systems capabilities and position the EU as a global leader on rare diseases. Certainly, the achievements in this area will be a key measure of success when the Networks are evaluated at the end of their first 5-year term, under the new integrated assessment, monitoring, evaluation and quality improvement system (AMEQUIS).

Where are we now

The Commission and the Networks have begun to take concrete action to enhance and share their knowledge and expertise outside the Networks, through the Expert Educational Webinar Programmes, as well as inside the Networks through the Short-term Mobility and Exchanges of Healthcare Professionals.

Over the last year, all ERNs have prioritised education and training activities. They have rolled-out open-access expert webinar programmes and some Networks are offering formal teaching courses for non-Members. With the expert webinar programmes drawing high attendance from an international audience, the webinars are a clear sign of the need for ERN-led training activities in the field of rare diseases and is a mark of success!

However, currently funding opportunities remain restricted to grants for short-term exchange of medical professionals with no specific funding to develop the webinar programmes. For the Networks' experts to share meaningfully their knowledge and support the development of the local health care systems capabilities they will require additional financial, administrative, and technological support.

Notably, training activities for patients and their families, and internal clinical governance training on lessons learnt and medical errors, both remain neglected in the Networks' priorities and their work plans. They are also lacking adequate financial support, despite this being a requirement in the EC delegated acts.

Challenges & Recommendations

1. The ambition (and potential) for the Networks to promote and deliver medical training and educational activities along the chain of care in all Member States remains yet to be fulfilled. Significant increased support, resources and e-training tools are needed to unlock this potential and support the development of local healthcare systems competencies in rare disease.

   On the other hand, the bilateral agreements between the ERN Coordinating Centres and the Affiliated Partners are being formalised but the collaboration has not yet started. Likewise, the links between the Networks and the European and national professional societies and medical training institutes has started to develop, but co-funded joint working still needs to take off to develop targeted and effective educational and training initiatives that will require country and disease-specific prospective analysis of requirements.

The Networks should expand their educational and teaching activities, jointly with Member States, professional societies, rare disease patient community and medical training institutes to support the development of local healthcare systems competencies in rare diseases and develop the next generation of experts, specifically to raise the awareness of rare diseases in medical students of the red-flag symptoms of rare diseases.

Target deadline 2025

Once the new Members join the Networks in 2021, full Members and Affiliated Partners should establish formal twining partnerships to develop the specific knowledge and expertise of the Affiliated Partners in providing highly specialised interventions, surgery and supra-specialised capacity.

Target deadline 2021

2. Virtual collaborative work, whether in the delivery of healthcare or training, has become the new reality for everyone following the impact of the COVID-19 pandemic. However, there has been a lack of opportunities under Horizon 2020 and the European Health Programme to develop innovative training in supra-specialised expertise and knowledge, despite this being highlighted as an area of value for cross-border voluntary cooperation (Maltese EU Presidency, 2017).

The EC should provide more funding to develop innovative training modules and interactive tools to support the ERNs training and education activities. It should aim to establish an integrated educational strategy for the development of cross-border supra-specialised training e.g.: empowering patients and families for self-care and management; virtual surgical e-learning techniques and tools by formalising partnerships with different EU and national initiatives in the fields of education, research and health.

Target deadline: 2025

The ERN Board of Member States should agree on the ERNs strategy for International Collaboration with other centres of expertise and networks and include training and educational activities between international partners to learn from other networking initiatives.

Target deadline: 2025

3. Clinical governance of the services provided by ERNs Members sits solely under the clinical governance policies of their respective hospitals, and is key for the provision of safe, good quality and sustainable services. As such, clinical governance is a clear candidate for extensive internal training and exchange within the ERNs, at Network level, yet this area is not well covered by the Networks' activities.

Networks should provide an integrated and connected clinical governance framework, extended from their individual Members to learn from each other's clinical practices. Specifically, in the areas of risk management, clinical audit, continuous professional development, evidence-based care, patients' and carers' experience with and involvement in healthcare.

Target deadline: 2025

4.4 Research

Vision

The majority of rare diseases lack a cure and there is no approved treatment available for at least 95% of these conditions. This is why timely, equitable and affordable access to treatments following regulatory approval is a cross-cutting need for rare disease patients. In the rare diseases field, clinical research is a natural extension of healthcare and RD patients have the expectation that ERNs will contribute to make significant progress in clinical research. A first step towards building and fostering ERNs clinical research capacity may be realised by embedding Clinical Research Networks in the ERNs and facilitating international collaboration in this area, drawing from the vision and experience of the US rare disease Clinical Research Networks (US RDCRN).

Clinical Research Networks (CRNs) embedded in the ERNs will allow pursuing an integrated approach where clinical settings will regularly inform clinical research activities, such as the design of the studies or the selection of endpoints that are useful for clinicians and relevant for patients. At the same time, they will contribute to accelerate the uptake of therapeutic innovations in real world clinical settings.

The overall vision is that these CRNs will provide a framework for clinicians, scientists and their multi-disciplinary teams and patient representatives to work together to **advance collaborative research on rare diseases by providing support for clinical studies and facilitating study enrolment and data sharing.**

Drawing again on the experience of the US RDCRN, ERNs should build a common research structure to provide services around 4 domains:

1. Clinical Research to promote high-quality collaborative research and excellence.
2. Data Management to reduce the cycle time from data collection to knowledge and research insights.
3. Engagement and dissemination to reach out to the ERNs stakeholders.
4. Administrative support to coordinate the clinical research operations.

A key service under the Clinical Research domain would be to provide guidance on how to work with industry partners. For this to happen, first the BoMS must adopt a clear set of rules for ERNs to partner with industry to develop research activities. This model could build on some of the operating principles and policies developed by the European Organisation for Research and Treatment of Cancer (EORTC):

- Regardless of trial sponsorship, EORTC's principles of independence always apply.
- A comprehensive set of policies govern their research activities, including a Code for Ethical Conduct, a Conflict of Interest Policy that addresses financial and non-financial interests, Research Misconduct, Data sharing, and a Protocol Development Process, Selection and Approval Procedures for EORTC Studies. The model allows to deal with funding coming from 5 different sources of funding (public foundations and national cancer leagues, private donations, CSR programmes, EU projects and industry funding).
- All studies conducted by EORTC are reviewed and approved by a Board-appointed panel of independent experts.
- Databases are managed by EORTC staff, and EORTC controls access to biological material collected during each trial. EORTC HQ specialists manage the analysis of study endpoints and publication of primary results, unless it is an "intergroup" clinical trial and another independent research group takes the lead.

TABLE 5. SERVICES OF THE COMMON RESEARCH SUPPORT STRUCTURE FOR ERNS

1	**Clinical Research do to promote high-quality collaborative research and excellence**	• Study Protocol development and management support/advice • Guidance on the design and implementation of natural history studies that can be used to support the development of treatments for rare diseases • Biostatistics and study design support and advice • Support in establishing ethics committees • Support and guidance on the translational research process • Information, policies and guidance for ERN members on cross-ERN clinical research issues such as working with industry or navigating the regulatory process • Coordination of training activities that cut across topics relevant to multiple ERNs • Support and guidance to assist the ERNs in identifying relevant patient-centered outcome measures and tools to find existing measurement instruments
2	**Data Management Core to reduce the cycle time from data collection to knowledge and research insights.**	• Management system for data collection, storage, and quality control of ERN-derived research data • Common policies for data collection and data processing • Clear principles on how and who should have access to the data • A web-based platform that allows for real-time tracking of data quality and completeness and that facilitates remote monitoring • Tools for research scientists and clinicians to access and manage their own data • A portal and tools to share information both within and outside the ERNs in a manner that meets all data safety and data sharing requirements • Cloud computing services and engineering support for facilitating computing and data services across the Networks and to the broader research community
3	**Engagement and Dissemination Core to reach out to the ERN CRNs community stakeholders**	• Patient engagement framework on clinical trials • A broad ERN-CRNs outreach plan that extends to basic and clinical researchers, academic and practicing physicians, patients, and the general public engagement strategy to facilitate the interactions of ERNs researchers with research infrastructures (BBMRI, EATRIS, ELIXIR, Infrafrontier, EORTC, etc.) and the International Rare Disease Research Consortium (IRDiRC) • An internet-based web-portal to serve as a central access point to information generated by the ERN Clinical Research Networks
4	**Administrative Core to coordinate the ERN CRNs operations**	• Overall coordination for the ERN Clinical Research Networks and management of activities, including ERN research working group meetings • Oversight and coordination of all four Cores • Support for patient representatives meetings • Coordinate the draft of the ERNs Strategic Research Agenda (horizon scanning to identify common areas of strategic interest). • Preparation of annual reports

Source: own elaboration based on the core services provided by the US RDCRN Data and Coordination Center.

Where are we today

Although ERNs primary focus revolves around improving access to diagnosis and the provision of highly specialised healthcare for rare diseases and complex conditions, Article 12 of the Cross-Border Healthcare Directive[34] specifically refers to research and epidemiological surveillance as one of the focal points for the Networks' activities. At the same time, the delegated legislation also requires the Networks' members to have research capacity and demonstrated research experience or production, at national and international level.

Clinical research conducted today by individual ERN members focuses on three main areas: improvement of diagnostics; identifying disease modifiers (including natural history studies and biomarker studies) and developing novel therapies. Also, almost all of them are conducting clinical research and many are involved in all types of research (basic, translational and clinical).

Today almost all ERNs have a group specifically dedicated to coordinate colaborative research activities. In addition, a cross-ERN Research working group supports the Networks in areas of common interest such as registries or clinical trials. This group serves as an observatory for ERNs collaborative research; disseminates relevant information; helps build synergies with the European Joint Programme on Rare Diseases (and projects such as Solve-RD, Solving the Unsolved Rare Diseases) and provides a multidisciplinary approach to research. The working group also plays a role as the ERNs focal point for the European Medicines Agency (EMA) and rare disease research infrastructures (ECRIN, BBMRI, EATRIS etc.). This group has also been tasked to work across ERNs on registries, developing a common strategy and building on the experience of the 5 ERNs that started developing their registries back in 2017 (ErkNet, PeadCan ERN, ERN LUNG, MetabERN and ENDO ERN).

There is also a strong record of collaborative research in the field of rare adult cancers supported and facilitated by EORTC over the last 10 years. In paediatric cancers, the SIOP Europe ECTGs have established long-term successful cross-border clinical research collaborations. The ERN PaedCan is working in partnership with these entities to develop disease-specific roadmaps and standard treatment protocols which will be implemented across Europe. Most Networks have dedicated the past two years to identify research gaps and map research infrastructures such as registries and biobanks. A few have already started developing collaborative research projects and clinical trials and the most research-mature Networks have an annual Research Agenda. Regarding data, at least one ERN has selected two Patient Reported Outcomes measures for testing and deployment; some Networks have started advancing the work in this area by harmonising data collection, agreeing on common data sets and preparing the disease specific registries to interoperate. Also, since January 2019 all ERNs are collaborating with other stakeholders to establish a rare disease research ecosystem in Europe via the EJP. All 24 Networks have received seed EU funding to set up their registries. A Horizon 2020 Coordination and Support Action will also support the ERNs to build the foundations of the Clinical Research Networks in 2021-2022.

1. Sustainable funding to support the ERNs-Clinical Research Networks. The ambition to embed Clinical Research Networks into the ERN structure is a realistic goal that can be achieved over the next five years. By 2030 all ERNs could be performing high quality collaborative research that complies with the expected standards required by regulatory and HTA bodies provided that (i) they have the support of a centralised research support structure and (ii) there are clear rules that enable ERNs to partner with industry and ensure the greatest degree of independence for ERNs to set their research strategic agendas.

RECOMMENDATION

The Coordination and Support Action funded by the H2020 programme to support the creation of Clinical Research Networks should lay the ground to set up the core services of a common research support structure covering 4 domains: clinical research, data management, engagement and dissemination and administrative support. Additional funding will be required to gradually deploy these core services so that they will be fully operational by 2025. The BoMs should agree on the mechanisms to provide sustainable funding to support the operations of the ERNs-Clinical Research Networks. Any funding mechanism must ensure the independence of the ERNs to establish their own strategic research agenda.

Target deadline 2025

2. A common framework for patient engagement should be built into the operations and governance of the individual Clinical Research Networks to facilitate a real partnership between patient representatives, researchers and clinicians in this specific domain.

RECOMMENDATION

ERNs must have the necessary capabilities for patient engagement in research, including policies, tools, processes and governance mechanisms to enable clinicians, researchers and patient organisations and their representatives to work together on different research activities, including the identification and systematic collection of outcome measures.

Target deadline 2023

3. In the short term, each ERN should agree on specific commitments around the development of strong natural history studies that provide insights into the causes and progression of the diseases, ways to measure outcomes of treatments and biomarker studies.

Each individual Network should commit to study 80% of the diseases that are under their operational coverage within a given timeframe. Over the next two years, they should develop a minimum of 5 new natural history studies to get ready for clinical testing and improve their chances to secure funding to develop clinical trials.

Target deadline 2022

4. A comprehensive data strategy for ERNs and implementation plan are necessary to support collaborative research, but also clinical decision-making[35]. This strategy should be driven by the principles of collaboration and open science to avoid creating new data siloes, in line with the European Open Cloud Science vision, and integrated with the European Health Data Space.

To enable the re-use of clinical data for research purposes respecting patients' preferences, ERNs should be able to rely on a suite of ERN-wide integrated and high quality services to manage the data lifecycle, from search data accessibility to data curation and data analysis. Researchers need to be able to find and access the data stored in registries or other databases, have clear rules around how and who can access this data. At the same time, these services will need to ensure the completeness, consistency, accuracy, conformity and integrity of the data. Finally, researchers should have a suite of services and tools to perform their analysis, share insights and innovative ways of analysing data. Governance of this data structure would require the participation of clinicians, researchers and patient organisations, all of them participating in equal grounds and with equal partnership in decision-making.

ERNs should develop a comprehensive data strategy and implementation plan envisaging the necessary activities across 6 action lines: architecture - cloud computing services and engineering support for registries and other databases; data collection protocols; data curation services, data management tools (services and tools to search, access and share data, tools to manage own data) data analytics tools and services and governance.

Target deadline: 2022

CONCLUSION

EURORDIS, and the rare disease patient community, believes in the potential of the European Reference Networks to improve care and the quality of live for the 30 million people living with a rare disease in Europe.

From the beginning, the vision of European Reference Networks as a system to tackle the public health needs of the 30 million people living with a rare disease in all EU Member States was extremely ambitious. The rare disease patient community believes that this vision is still relevant. This comprehensive coverage can and should be achieved as long as the ERNs supplement and bridge the existing gaps in care, knowledge generation, training and research. Therefore the depth of this coverage per disease will necessarily vary, depending on how well these areas are serviced for each disease by national health systems and international healthcare arrangements. This approach that builds on the principles of equity, solidarity and cooperation, in a progressive, step-wise approach, is a preferred option to the alternative that would entail targeting only a limited number of rare diseases, which would exacerbate existing health inequalities. Instead, we believe on a comprehensive catalogue of ERNs services and collaborative activities, supplementing national health systems offerings for ALL diseases and affected individuals, leaving no one behind.

There is one key aspect that cannot be overstated: without recognition of the time and effort required to deliver their functions and the currently limited funding available, the ERNs will be under considerable pressure to fully deliver on their potential. Likewise, the complexity and ambition of the ERNs should be met by a comparable set of organisational structures, governance and management policies. A mature ERN system should have a vocation of stability and permanence and have more lean and simple structures and streamlined funding mechanisms to allow the Networks to focus on their core tasks and objectives, with long-term security and sustainability.

Secondly the system will only be successful and deliver tangible results for people living with a rare disease if the European and national dimensions are understood as components of the same system. One cannot exist without the other. This requires a clear commitment of Member States to implement the necessary structural changes in their health systems to use, adopt, and where necessary adapt, the ERNs recommendations, guidelines, care pathways, standards of care and educational resources. Having a national process to identify, designate and assess centres of expertise, should be part of this commitment as well as strengthening their capacities to perform their functions and be active members in the Networks.

Third, a sound assessment, monitoring and evaluation and quality improvement system will ensure quality assurance and lead to continuous improvement and learning. In the next five years these should be the main objectives of the AMEQUIS system. Connecting ERNs funding with performance measurement should only come at a later stage, the Networks are in their early stages of development and they still need time, resources and a protected environment to innovate.

Finally, we must praise the dedication, solidarity and drive shown by the clinicians and patient representatives that have been involved in the Networks in these first four years. They grasped the opportunity that the ERNs offered and have worked hard to build the foundations and get the system up and running. It is now our collective responsibility to move the gear up to drive the progressive change initiated in 2017.

Our vision is for a mature ERN system that leaves no person living with a rare disease in uncertainty regarding their diagnosis, care and treatment.

With this paper EURORDIS and the community of people living with rare diseases hope to bring its vision for a mature ERN system to reality, and thus bring the benefits of the Networks to all.

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RECOMMENDATIONS TO ACHIEVE A MATURE ERN SYSTEM IN 2030

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"Our vision is for a mature ERN system that leaves no person living with a rare disease in uncertainty regarding their diagnosis, care and treatment."

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