EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH

(EXPH)

Opinion on
Application of the ERN model in European cross border healthcare cooperation outside the rare diseases area

The EXPH adopted this opinion at the [to be inserted]h plenary of [to be inserted]

About the EXpert Panel on effective ways of investing in Health (EXPH)

Sound and timely scientific advice is an essential requirement for the Commission to pursue modern, responsive and sustainable health systems. To this end, the Commission has set up a multidisciplinary and independent Expert Panel which provides advice on effective ways of investing in health (Commission Decision 2012/C 198/06).

The core element of the Expert Panel's mission is to provide the Commission with sound and independent advice in the form of opinions in response to questions (mandates) submitted by the Commission on matters related to health care modernisation, responsiveness, and sustainability. The advice does not bind the Commission.

The areas of competence of the Expert Panel include, and are not limited to, primary care, hospital care, pharmaceuticals, research and development, prevention and promotion, links with the social protection sector, cross-border issues, system financing, information systems and patient registers, health inequalities, etc.

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The opinions of the Expert Panel present the views of the independent scientists who are members of the Expert Panel. They do not necessarily reflect the views of the European Commission nor its services. The opinions are published by the European Union in their original language only.

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SUMMARY

European Reference Networks (ERNs) were created by the Directive on the Application of Patients’ Rights in Cross-Border Healthcare. They offer a means by which patients with rare and complex diseases can gain access to highly specialised knowledge from across the European Union. The Expert Panel has been asked to advise on areas that can benefit most from the ERN model, options for the new networks in the longer term and the roles that they might assume, and how best national health systems could integrate networks into their national frameworks.

ERNs are still a very new concept, having been launched in March 2017. So far, 24 have been established, bringing together over 300 hospitals from 26 Member States. Given the short time that they have been operating, the Expert Panel concluded that it was premature to draw any conclusions on their effectiveness. Instead, it sought to understand how other networks with similar goals have operated within member states and the lessons that have been learned, coupled with interviews with two of the coordinators of existing ERNs.

The Expert Panel concluded that, while ERNs have considerable potential to improve the care of patients with rare diseases across the EU, both through advice on the management of individual patients, as well as through collaboration on research and development of guidelines, it is not yet possible to ascertain the extent to which these goals will be achieved. The Expert Panel also identified several issues which, even at this stage, appeared to need to be addressed, including long-term financial sustainability and the implementation of effective IT systems.

Turning to the specific questions asked of the expert panel, we firstly concluded that the current criteria for establishing a ERN, as a means of improving the management of patients with rare and complex diseases, was appropriate. The ERN concept does not address other issues raised for our consideration, such as remote areas and border regions, or the development of new medicines or interventions, for which there are alternative and more appropriate mechanisms. We were also asked about the scope to extend the scope of ERNs to other areas such as the care of people who are homeless or emergency situations. In both cases, we believe that there are better alternative mechanisms to achieve the intended goals. Secondly, we examined the scope of the ERNs, and in particular their relationship with research and guideline development. Given the current state of implementation, it is not possible to come to a definitive conclusion, but we were persuaded by the arguments that there is considerable scope for incorporating these additional roles beyond the immediate objective of providing advice on individual patients. This will, however, require dedicated resources, some of which will have to come from other sources. Thirdly, while reinforcing the importance of ERN is to link with national health systems, the diversity of systems within member states makes it impossible to provide detailed guidelines for how this can best be made to work. This is another area where it will be important to monitor the implementation of the existing ERNs and disseminate the lessons that arise from their experiences.

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1. BACKGROUND

Member States seek to give their citizens access to the best possible health services. This has led to various arrangements for cooperation between them. The European Union, on the basis of Article 168 of the TFEU, plays an important role in complementing and supporting national health policies, encouraging cooperation among Member States and promoting coordination between their programmes. This general mandate was further defined in Directive 2011/24/EU on the application of patients' rights in cross-border health care.

The European Reference Networks (ERN)[1] are a prime example of structured and voluntary collaboration among the EU Member States in the field of healthcare.

These cross-border networks bring together healthcare providers across Europe to tackle rare and complex diseases that require highly specialised healthcare knowledge. The ERNs give access to a much larger, cross-border pool of expertise and knowledge, increasing the chances of patients receiving the best advice to treat and diagnose their diseases. By assembling a large pool of patient data, they will, in the longer term, facilitate large clinical studies to improve the understanding of diseases or support the development of new medicinal products. Commissioner Andriukaitis highlighted the many opportunities for cooperation provided by the ERNs, referring to them as a backbone on which a European health data eco- system could be built [2].

Although the Directive makes particular reference to rare diseases, it has been suggested that other conditions requiring specialized resources or expertise could also benefit from the idea of networking to provide high-quality and cost–effective care [3]. Could the experience gained in cross-border collaboration on rare diseases be transferred to other health topics? To answer this question, it is necessary to assess what the gain in cross border cooperation is, what areas might potentially be amenable to this approach and what possibilities exist to realise this potential, as well as what the financial implications would be.

Rare diseases affect 6-8% of the population and as a group are an important public health problem. Many of the more prevalent diseases with the highest mortality rates in Europe, such as cardiovascular diseases (accounting for 34% of all deaths among men and 40% among women), cancer (30% men, 24% women) and respiratory diseases (9% men and 8% women) [4], are successfully treated at national level, although there are likely to be specialised areas where European cooperation could bring further improvements in outcomes. There are also specific treatment or diagnostic challenges (e.g. genetic testing or access to expensive infrastructure, such as positron emission (PET) imaging and proton beam therapy) as well as the delivery of services in border areas, where cross-border collaboration brings added value [5]. There may also be further roles, with the Council Conclusions of June 2017 suggesting that the ERNs could, within their current scope, assume a role in highly specialized training and continuous professional development for health professionals [6, Sec. 3a].

2. TERMS OF REFERENCE

The Expert Panel's opinion on the application of the ERN model outside the rare diseases area would help to prepare future calls for new networks, by presenting the possibilities, outcomes and expected difficulties of a broader cooperation.

The Expert Panel is requested to analyse the following:

(a) What are the areas that can benefit most from the ERN model of cross- border cooperation? Should the selection process take into account:

- the nature of disease (prevalence, complexity),
- resources of the geographical area (small countries, remote areas, border regions),
- medical intervention (treatment method or product),
- specific goal of such a cooperation (e.g. creating new medicine)?

(b) The panel should also address aspects related to the implementation of the ERN model and advise on the different options for the long term nature of new networks. Should the ERN model be used as a whole (covering diagnosis and treatment, research, training, knowledge generation…) or only include specific modules of collaboration depending on the need (e.g. only data gathering for Artificial Intelligence or genetic testing)?

(c) How would national health systems integrate such networks into their national framework? What are the difficulties to expect at national level? What would be the best national approach in the aspect of referral, financing and changes required in national legal systems?

3. OPINION

3.1. Introduction

Ever since the Treaty of Maastricht, the European Union has recognized the contribution that cooperation in health services can bring to the people of Europe, while respecting the rights of Member States to decide how they will organize health services within their own national borders. The 2011 Directive on the Application of Patient's Rights in cross-border care (cross-border directive) sets out the conditions under which a patient may travel to another EU country to receive medical care and reimbursement. It covers healthcare costs, as well as the prescription and delivery of medications and medical devices. In addition, the directive established the principle of voluntary cooperation between healthcare units in member states in highlight specialized healthcare. In accordance with the article 12 of the cross-border directive ERNs were established in 2017 as cross-Europe virtual health-provider networks, aiming to facilitate discussion on complex or rare diseases that require highly specialized knowledge or treatment. Although the Directive does not define these networks precisely, it envisages the creation of a means of sharing of knowledge and expertise, concentrating resources and patients, and thereby improving diagnosis and treatment for those whose conditions are sufficiently rare that it will be difficult to provide appropriate treatment, especially in small member states. Furthermore, article 13 of the cross-border directive aims to make patients, health professionals and those bodies responsible for the funding of healthcare aware of the possibilities offered by Regulation (EC) No 883/2004 for referral of patients with rare diseases to other Member States even for diagnosis and treatments which are not available in the Member State of affiliation.

The expectation of ERNs is that they will offer the following benefits:

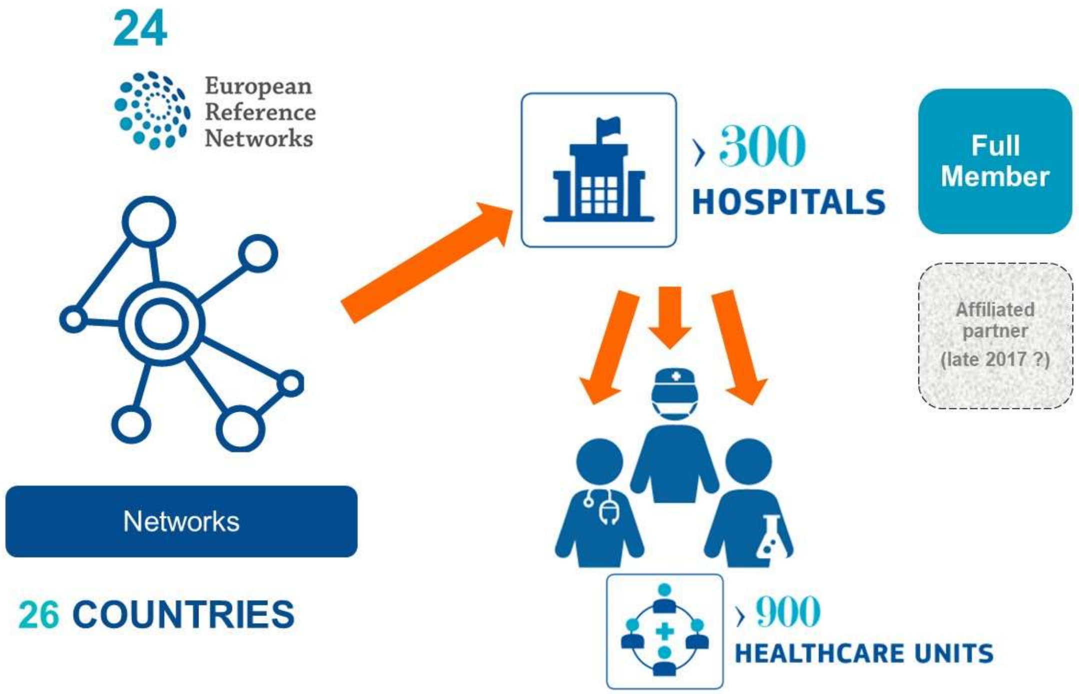
- access to a much larger, cross-border pool of expertise and knowledge, increasing the chances of receiving the best advice to diagnose and treat their diseases, particularly for small member states;
- bringing together patients and resources, enabling economies of scale for accessing treatment for rare diseases;

- gathering a larger pool of patient data, thereby, in the longer term, facilitate large clinical studies to improve the understanding of diseases or support the development of new medicinal products.

Historically, certain bilateral arrangements did exist, with varying degrees of informality, especially in the smallest member states such as Malta or Cyprus, or within the Nordic countries. However, the new concept offers a stronger European legal basis for this approach, enabling more people to access them.

Starting from March 2017, 24 ERNs have been established, bringing together over 300 hospitals from 26 member states (MS): the number of MSs participating in each ERN varies between 8 and 19, and the number of reference centres in each MS varies between 1 and 21 (with many reference centres taking part in more than one ERN) (Figure 1) [7].

Figure 1 The ERN concept



The names and disease areas of the ERNs are listed in Table 1.

Table 1 European Reference Networks

BOND ERN	Bone Diseases
CRANIO	Craniofacial anomalies and ENT disorders
Endo-ERN	Endocrine Conditions
EpiCARE	Rare and Complex Epilepsies
ERKNet	Kidney Diseases
ERN GENTURIS	Genetic Tumour Risk Syndromes
ERN-EYE	Eye Diseases
ERNICA	inherited and congenital anomalies
ERN-LUNG	Respiratory Diseases
ERN-RND	Neurological Diseases
ERN-Skin	Skin Disorders
EURACAN	Solid Adult Cancers
EuroBloodNet	Onco-Hematological Diseases
EUROGEN	Urogenital Diseases
EURO-NMD	Neuromuscular Diseases
GUARD-HEART	Diseases of the Heart
ITHACA	Congenital Malformations and Intellectual Disability
MetabERN	Hereditary metabolic diseases
PaedCan-ERN	Paediatric Cancer
RARE-LIVER	Hepatological Diseases
ReCONNET	Connective Tissue and Musculoskeletal Diseases
RITA	Immunodeficiency, AutoInflammatory and Auto Immune Diseases
TRANSPLANT-CHILD	Transplantation in Children
VASCERN	Multisystemic Vascular Diseases

The ERNs must meet certain criteria, set out in Box 1.

Box 1 Features and functions of ERNs

Key Features:

- The process and criteria for establishing an ERN and for determining eligibility of Centres of Expertise and healthcare providers to join are established in the Commission Delegated Decision (2014/286/EU)
- ERNs must fulfil criteria for implementation and evaluation, including being patient-centred and clinically led, with a minimum of 10 members in at least 8 countries, subject to robust independent third party assessment, and endorsed and approved by National Authorities.

Key Functions:

- To review a patient’s diagnosis and treatment, ERN coordinators convene ‘virtual’ advisory panels of medical specialists across different disciplines, using a dedicated IT platform and telemedicine tool called the Clinical Patient Management system (CPMS). This allows expertise travel to the patient, rather than vice versa.
- It allows sharing of expertise to diagnose, follow-up, and manage patients, and facilitates a multidisciplinary approach, as well as collaboration and learning across centres of expertise and networks at national and international level
- The focus is first on diagnosis and treatment by providing tools for collaboration and virtual consultations. However, there are clear potential research applications.
- These functions support the development of good practice guidelines and outcome measures for quality control, as well as contributing to research

All Networks and their Members should be periodically evaluated, at the latest every five years after their approval or last evaluation.

3.2. Legal basis

ERNs were created within the framework of European legislation on cross border care, presented in detail in the Expert Panel's report on Cross-border cooperation [5]. The key elements are summarized again in this section.

European Union policy in the field of health is aimed at complementing and supporting national health policies, encouraging cooperation between Member States and promoting coordination between their programmes. Article 168.2 of the Treaty on the Functioning of the European Union (TFEU) (European Union 2012) states: "*The Union shall encourage cooperation between the Member States in the areas referred to in this Article and, if necessary, lend support to their action. It shall in particular encourage cooperation between the Member States to improve the complementarity of their health services in cross-border areas. Member States shall, in liaison with the Commission, coordinate among themselves their policies and programmes in the areas referred to in paragraph 1. The Commission may, in close contact with the Member States, take any useful initiative to promote such coordination, in particular initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation. The European Parliament shall be kept fully informed.*"

The general mandate contained in the Treaty has been spelled out in Directive 2011/24/EU on the application of patients' rights in cross-border health care [5]. In addition to the objectives of establishing rules for facilitating access to safe and high-quality cross-border health care and ensuring patient mobility in the Union, the Directive aims to promote cooperation on health care between Member States (Recital 10). Recital 50 calls upon Member States to "*facilitate cooperation between healthcare providers, purchasers and regulators of different Member States at national, regional or local level in order to ensure safe, high-quality and efficient cross-border healthcare. This could be of particular importance in border regions, where cross-border provision of services may be the most efficient way of organising health services for the local population, but where* *achieving such cross-border provision on a sustained basis requires cooperation between the health systems of different Member States".*

The areas and modes of cooperation are further specified in Chapter IV of the Cross-border directive. They include, in the first place, an obligation for Member States to render mutual assistance to implement the Directive, *"including cooperation on standards and guidelines on quality and safety and the exchange of information, especially between their national contact points"* (Article 10.1). This also relates to exchanging information (through the Internal Market Information (IMI) system) on the right to practice of health professionals registered in one of the Member States (Article 10.4). In addition, Chapter IV creates a concrete basis for cooperation and action in specific areas that have been identified as particularly relevant: mutual recognition of medical prescriptions (Article 11), European Reference Networks (Article 12), rare diseases (Article 13), e-health (Article 14) and health technology assessment (Article 15). This does not, in principle, preclude cooperation in other fields as Article 10.2 also provides for a general commitment for Member States to facilitate cooperation.

Rather than providing an exact definition, Article 12 of Directive 2011/24/EU lists the objectives and characteristics for ERNs to qualify as such. Their functions and features are set out in the Directive (Box 1), and include provision of the knowledge and expertise to diagnose, follow-up, and manage patients, with evidence of good outcomes; employment of a multidisciplinary approach; possession of a high level of expertise, coupled with the ability to produce guidelines for good practice and to implement outcome measures and quality control; to contribute to research; to organize teaching and training activities; and to collaborate closely with other centres of expertise and networks at national and international level (Article 12.2).

While there is formally no legal obligation for Member States to engage proactively in each of the forms of cross-border collaboration, except in relation to some elements such as recognition of prescriptions issued in another member state, the European Commission (EC) is entrusted by the mandate to "*encourage cooperation between*

Member States in the areas set out in Chapter IV of this Directive and […]*, in accordance with Article 168(2) TFEU, take, in close contact with the Member States, any useful initiative to facilitate and promote such a cooperation"* (Recital 51). More specifically, Article 10.3 calls for the Commission to "*encourage Member States, particularly neighbouring countries, to conclude agreements among themselves*". This also includes specific action on border regions: *"The Commission shall also encourage the Member States to cooperate in cross-border health provision in border regions."* (Article 10.3 in fine). One way for the Commission to do so is "*by identifying major obstacles to collaboration between healthcare providers in border regions, and by making recommendations and disseminating information and best practices on how to overcome such obstacles*" (Recital 51). Furthermore, the Commission can adopt delegated and implementing acts to organise cooperation in certain areas, e.g. medical prescriptions and European reference networks.

3.3. What do we know about existing ERNs?

As has been noted, ERNs are a very new concept and experience in their operation is very limited. The existing ERNs have only been operational since 2017 and a relatively small number of patients have been referred, so it is too early to determine how effective they have been.

To inform our work we have undertaken interviews with two ERN co-ordinators, Franz Schaefer, coordinator of ERKNET: European Reference Network for Rare Kidney Diseases, a consortium of 38 expert paediatric and adult nephrology centres in 12 Member States, and Marissa Tejedor Botello, project manager for TransplantChild, the ERN for Paediatric Transplantation, including both Solid Organ Transplantation (SOT) and Hematopoietic Stem Cell Transplantation (HSCT). This ERN is concerned with a specific treatment (childhood transplants), rather than a single condition, since the conditions leading to transplants are diverse.

3.3.1. How do networks benefit patients?

We first asked how networks benefit patients. Two main ways were identified: the pooling of expertise and the pooling of patients. The pooling of expertise is achieved by convening specialists in member centres (which in theory improves management of all patients being treated in the centre due to knowledge sharing and development), and through uploading individual cases to an online Clinical Patient Management System (CPMS). Once a case is referred and uploaded, a panel of experts is selected, depending on the specific expertise needed. Clinical details are reviewed, and an online chat facility enables communication between the primary clinician and the expert panel. A report is then produced, providing the primary clinician advice for patient management.

This ability to pool and share expertise, resources, and experience for rare conditions requiring complex treatment was seen by both interviewees as the main benefit of the ERN model. Coordination of experts on rare diseases has resulted in the development of guidelines, with 39 new ones published by (ERKNET), as well as knowledge sharing and benchmarking.

The second main benefit is creating a critical mass of patients: collecting and coordinating experience in treating patients with rare conditions requiring complex treatment allows the development of registries (ERKNET) and provides a platform for research. Indeed, since the sample size required for studies can vary greatly, even the pooling of relatively few cases can result in new opportunities for research [8]; of course, the higher the number of cases registered, the wider the scope of potential studies. While TransplantChild is an ERN focused on a treatment rather than a disease, the conditions of rarity and complexity are satisfied. Moreover, given the rarity of childhood transplants, and due to the similarities in immunosuppression protocols and complications, regardless of the organ transplanted or underlying condition, pooling experience in treating patients yields invaluable economies of scale for advancing knowledge and expertise on rare and complex treatments.

Inevitably, members of networks will bring different degrees of expertise and capacity to contribute. In addition to those centres that join ERNs as full members, having satisfied the criteria of having the requisite expertise, others can join as ‘affiliates’ if these criteria are partially satisfied. This allows centres in countries without the means to create expert networks to gain access to knowledge in highly specialized centres in other European countries, through referral of patients, and participation in publications and registry activities.

3.3.2. What are the factors influencing the success of ERNs?

As noted, it is premature to undertake formal evaluations of the ERNs. We were advised that a working group is currently developing a monitoring framework for all ERNs. Agreed indicators (18 in total) aim to measure both patient-level and wider outputs, e.g.; numbers of case uploaded to the CPMS system, cases closed, and publications generated. Both interviewees indicated a need to assess potential challenges related to the online patient management component of the ERN scheme, including equity of access (i.e. is the system being used by referring centres who lack expertise and thus have the greatest need, or is it only being used by hospitals with sufficient capacity and resources to know how to use the new system?).

It is clearly too early to assess whether the ERN model has resulted in improvements to patient care. Looking to the future, interviewees remarked that evaluation frameworks should be extended to measure improvements in care for both patients referred to the CPMS, as well as the wider group of patients treated at participating centres.

We sought insights into factors that might influence the success or otherwise of the ERNs, while recognising the limited experience so far. In particular, it is important to recognise that there is no clear definition of what “success” means for ERNs: in extremely broad terms, they aim to improve treatment and care pathways for patients by sharing information among health professionals, but this goal has not yet been translated into specific, measurable indicators. This crucial issue is expanded on in the following sections (“How to evaluate the effectiveness of ERNs?”), while here we focus on the information gathered by asking about the effectiveness of ERNs in these general terms.

The first factor influencing the success of ERNs was that the condition or the treatment around which the network was developed should be both rare and complex. It was noted that the current ERNs are not limited to rare diseases. The TransplantChild network covers all cases of childhood transplants (i.e. a range of diseases/ conditions that lead to the need for transplant). While not a discrete ‘disease’, transplants require complex management, and post-transplants complications are similar enough to warrant treatment within the same network.

A second factor was that those who might interact with ERNs, as health professionals or patients, should be aware of their existence. Networks need to be active in promoting themselves, in order to ensure that the network fulfils the potential to share knowledge outside highly specialised centres. Coordinators remarked that in the initial stages of ERN setup, centres who join the network first were often those who need it least, since they were usually the centres with the highest concentration of expertise. ERKNET has observed that representation from Eastern European countries is lacking. The real need for knowledge-sharing comes from those outside the very highly specialised centres. Effort is therefore needed by the network itself, as well as engagement with board of member state representatives and national health systems, to promote awareness and increase engagement by less developed specialist centres who may still be eligible for membership or affiliate membership. TransplantChild has sought to increase awareness through engagement with professional organizations and meetings (e.g. the Meeting of Competent Authorities in transplantation), and by mapping children’s transplant centres in Europe.

A third factor was the need for well-functioning IT infrastructure. Interviewees raised concerns about the CPMS system and argued for significant extra human resources in order to facilitate uptake and use of the CPMS system by clinicians.

3.3.3. What issues should be addressed to ensure proper functioning of ERNs?

In addition, interviewees highlighted a set of criteria for effective working of the networks. There is a need for robust referral mechanisms within national health systems in order to ensure equitable access for patients to the centres in their countries that are participating in ERNs. This involves clarity about responsibilities and access to resources for patient management, particularly amid fears by national authorities about increased healthcare costs resulting from easier access to highly specialised treatments.

We were told that member states were increasingly seeing the added value of ERNs, given that in healthcare overall costs will often be saved if the best possible treatment is given early on. However, given the lack of studies and the necessity to consider the costs of operating ERNs, it is unclear to what extent this holds true for rare diseases – thus, cost effectiveness is another crucial aspect to consider when evaluating ERNs, as will be highlighted in the next section ("How to evaluate the effectiveness of ERNs?").

As mentioned above, adequate funding is a critical issue. Significant investment is needed in participating specialist centres, both for individual patient management and wider activities such as the development of guidelines and registries, which require additional resources beyond those provided as part of the ERN project. At present, interviewees felt resourcing responsibilities were unclear, with clinicians picking up the majority of the extra work, which was not necessarily being recognised by their host institutions. In the case of ERKNET, alternative funding streams from the Commission were used to finance registry development. The process of guideline development was highly labour intensive, and largely product of "clinicians' enthusiasm". Also with regards to other ERNs, the sources of funding are unclear [9], with private donors and patient-organized campaigns still playing an important role in providing economic resources [10]. In addition, it is unclear who will provide for the treatment offered through ERNs [11].

This has clear implications for the sustainability of the concept [11], [12]: how are ERNs supposed to treat patients and develop guidelines, let alone monitor the outcomes and set up mechanisms for continuous improvement (as would be required of them in order to assess their effectiveness)? Furthermore, how can they be expanded to other areas, if there is no clear, long term, sustainable method of funding neither for existing ones?

Therefore, these funding issues must be addressed to guarantee the long-term existence of ERNs, although we recognise that it is difficult for a variety of reasons. For instance, finding funds can be complicated because, at least in some cases, it entails high costs per se. In addition, it requires agreements between countries with very different healthcare systems and a variety of third-party payers, with risk of free-riding occurring – unless ERNs themselves set the price for treatments, which however can pose problems of equity. Notwithstanding these difficulties, funding remains a critical issue which must be solved in order for ERNs to continue functioning.

The final issue that has been highlighted in the discussion on ERNs is the need for a clear management system and mechanism of governance [13]. Indeed, the task of ERNs is extremely complex, since it entails gathering information from many different patients and clinicians in different countries, carrying out research projects, and ultimately gathering evidence on best practices and making it available to those involved in the subject in all member states. All these activities are extremely difficult to carry out on such a large scale, since there are few established systems for doing so within national health systems [14]. For these reasons it has been suggested that coordinators should ideally have expertise in networking, [12] with the ability to supervise all these different activities and ensure that the objectives of ERNs are being reached, which will often require support from a coordination team.

3.4. How to evaluate the effectiveness of ERNs?

As noted above, ERNs for rare diseases have been only implemented for one year: this is too short to evaluate their performance or identify ways that they could be improved. Thus, while in principle the ERN model can be a powerful tool to improve healthcare for European patients, more time and more and robust data are required to evaluate their impact.

Given the inability to reach conclusions about the effectiveness of the ERNs, some insights into the issues that should be considered can be gained from a review of the operation of reference networks that exist already within member states undertaken by the European Observatory [3]. This identified five dimensions relevant to gaining a better understanding of reference networks, their functions and the different shapes they assume.

Table 2 Dimensions of the operations of reference networks

Governance	Objectives	Function	Material scope	Geographical scope
• Formal • Informal • Peer structure • Hub-and-spokes • Organic	• Efficiency • Quality • Safety • (Equity) • Market position	• Referral of patients • Transferring knowledge	• Prevalence • Cost • Complexity • Rare • Critical • Chronic • Common	• EU-wide • Transnational • National • Interregional • Regional

Source: W. Palm, I. Glinos, B. Rechel, and P. Garel, "Building European Reference Networks in Health Care," *European Observatory on Health Systems and Policies,* 2013.

In addition, we propose a method that could be used to define what makes ERNs effective and evaluate them, drawing on examples of existing evaluation systems.

In order to define what is an effective network, the first step is to define its mission. In the broadest possible terms, ERNs seek to improve outcomes, experience, and care pathways for patients with rare diseases. These networks should be able to facilitate and enhance exchange of information and competences among health professionals, thus sharing best practices and creating a virtual care community. The goal is to produce a multiplying effect, that is, to achieve an improvement in the care of these patients greater than what would be expected by simply adding together the single experts' abilities. Indeed, the sharing of competence among network members should foster the creation of new knowledge, in the form of guidelines, new clinical practices and recommendations, or scientific literature, while also sharing advice on the diagnosis and treatment of patients in ways that would never have been possible had the health professionals worked alone.

A second, but nonetheless important, objective is the ability for networks to become integrated in the national health care systems. In other words, what is the use of enormous amounts of expertise if they remain confined to the individual centres participating in the network? These centres must be able to reach all patients in their territories – and in other member states, if no national reference centre has been established – in order to really make a difference to the care of these patients. Thus, ERNs are effective only in so far as they are inclusive, proactively reaching out to the populations they serve.

Finally, a third objective of ERNS is to make this process of improving treatment and integration cost-effective. Indeed, rare diseases raise considerable equity questions, since they require a great amount of resources for a small group of people; this in turn means that said resources cannot be used where they may have had more effect on the overall health of the population. Therefore, it becomes essential for ERNs to become as efficient and effective as possible, in order to compensate for the opportunity costs that they inevitably entail. As a side note, it can also be highlighted that cost effectiveness is also vital for the long-term sustainability and possible expansion of ERNs, given that their sources of funding are so scarce.

Once these objectives have been agreed on, the second step is identifying how they can be achieved and, therefore, which aspects need to be evaluated to define a network as successful. In this sense, some examples can be drawn from national networks [3] and from the experience of pilot ERNs [15], which have similar objectives and have focused on similar issues. For simplicity, we will follow Donabedian's well-known structure-process-outcome model, to have a clear framework in which to situate the actions undertaken. For each step, we will briefly summarize the specific objectives to carry out and indicate examples of how they have been applied to real-life situations.

1. Structure: in the first place, it is necessary to clearly define what are the resources needed in reference centres and in the network for them to be able to deliver the highest quality of care and to carry out their role in the network. Obviously, these resources vary depending on the disease and therefore need to be defined on a case-by-case basis. Such resources can be broadly divided into:

    a. Equipment, such as diagnostic imaging appliances, or laboratories for genetic testing. One particularly important requirement is the presence of an information system and the information tools needed to get contact other experts, since one of the fundamental characteristics of ERNs is to allow knowledge to travel, rather than patients or physicians. To allow this to happen, the CPMS has been put in place, so reference centres should have all the necessary resources to use it without difficulties.

While the equipment required will vary according to the subject of the network, an illustrative example is from the Spanish national health care system, where providers aspiring to become reference centres for familial cardiomyopathies must have, for example:

- Diagnostic and therapeutic techniques: 250 echocardiograms, 50 cardiac MRI scanners, 100 Holter monitors, 100 units to conduct exercise stress tests; capacity to perform Pharmacologic Induction Tests (flecainide, procainamide or adrenaline); and capacity to carry out Genetic Studies for the range of conditions included;
- Clinical consultations specially devoted to family cardiopathies.
- Other units/services: image diagnosis, echocardiograms and high quality MR Unit/Service; unit for electrophysiology, arrhythmias, and induction-unmasking techniques; genetics Service/Unit; haemodynamic Units (diagnostic and therapeutic procedures) including alcohol septal ablation; etc.

b. Human resources, i.e. the professional expertise needed to deal with these difficult cases.

Again, the Spanish health care system can give a fitting example with its reference centres for cardiomyopathies, where providers are required to have, for example:

- Human Resources: 2 cardiologists dedicated to familial cardiomyopathies; specialised nursing staff;
- Basic training for the members of the team: cardiologists with at least 3 years’ experience in familial cardiomyopathies; nursing staff with more than 2 years’ experience in cardiology tests and familial mapping.

c. Research capacity, i.e. scientific reputation of the team of professionals involved in the process of care, with reference to the quantity and quality of scientific production in the last 5 years.

2. Process: this would probably be the aspect that can benefit the most from ERNs. Indeed, most have focused on improving it by concentrating on common themes and problems, which, according to the EUCERD report[15], are:

a. Sharing expertise for patient management: including the creation of tools for case management, sharing expertise through IT media, and working with patients and non-expert professionals to produce and disseminate. This is especially important with rare diseases, where the patients themselves often know more about their condition than the physician, potentially creating tensions in their relationship [16]. Consequently, the type of expertise that needs to be shared is not related to information on the disease, but also to the ways in which patients can be engaged respectfully and productively.

The ERN for neurological diseases (ERN-RND) has published a very precise outline of its objectives, the specific goals each seeks to achieve, and the timing over which to achieve them [17]. Specific objectives for sharing of expertise include:

- Define currently available education and training resources, by compiling a web directory of currently available education and training resources for professionals/families, by month 12;
- Establish an alert mechanism for rapid dissemination of new information, by establishing a list of high quality meetings/conferences and alert reports, by month 36;
- Identify and fulfil patients' and professionals' future education/training needs in a survey of different stakeholders by month 12.

b. Developing standards of care: this includes producing best practice guidelines for diagnosis and clinical management and implementing these guidelines and providing training in their use.

Some examples from the ERN-RND include:

- Evaluation of existing guidelines and pathways by a trained guideline expert group, with a priority list for new pathways and guidelines, by month 12;
- Improve patient care through use of high quality patient guidelines, by publication of a guideline list, by month 48;
- Develop cross-border pathways, by a framework report on cross-border pathways, by month 60.

c. A third aspect, not mentioned by the EUCERD report but that is nonetheless important, is the creation of a clinical pathway for patient management. Indeed, the initial responses from the survey on integration [18] highlight how there is no agreed referral system for patients inside member states, but rather it is left to each physician to refer their patients. Therefore, it would be important to define a clear process through which patients are managed, from their primary care physician to highly specialized treatment, in order to optimise efficacy and efficiency at each step of care.

Some examples from the ERN-RND include:

- Consent and share diagnostic flowcharts, by month 12-60;
- Develop generic diagnostic pathway for genetically caused neurological diseases by month 36;
- Improve access to high quality care by a report on implemented awareness strategies for ERN-RND, by month 12-60.

d. In the process of care, networks could establish a system to share diagnostic and therapeutic processes, by providing second and/or multiple opinions for patients taking advantage of information technology.

3. Outcome: finally, it is necessary for networks to find a way to evaluate their work, highlighting problems where they exist, but also documenting improvements brought about by the network. The main focus in this phase is on the objectives of the reference networks, namely:

   a. The provision of high quality care: networks should be able to provide better care than that which would otherwise be available to the patient. This can be evaluated using outcome indicators, which need to be defined for each disease, but also patient reported outcome and experience measures.

   b. Equity in the provision of care: networks aim to ensure that all citizens are receiving quality care based on need, not geographical location, social status or income. This could be considered by evaluating the level of awareness by physicians of networks and referral processes, or the measures put in place by networks to make themselves better known.

   c. Cost-effectiveness in the provision of care: networks should ensure that resources are being spent in a responsible and effective manner, in order to actually benefit patients and make the use of resources for rare diseases, rather than for more prevalent conditions, meaningful. This assessment is more complicated, since it raises moral issues (what is the level of effectiveness which justifies the extra resources?), but one method could be confronting healthcare for patients with rare diseases before and after ERNs, in order to understand whether and how much it has improved.

The framework that has been outlined in the previous paragraphs can be useful in agreeing criteria to define how effective a network is. The core belief behind it is that it is necessary to find practical, measurable aspects to understand how well a network is performing. A second fundamental aspect is to make the entire evaluation process as public and transparent as possible, as numerous experiences have shown how reputation, more than economic incentives, is a key factor in driving performance in the health care sector [19].

The question of what an effective network is, therefore, has no clear answer: it is necessary to establish its goals and, from them, derive the objectives to pursue. The achievement of these objectives needs to be evaluated with measures of outcome, and the result of this evaluation can then form the basis for the development of new objectives and measures, in what (hopefully) becomes a virtuous cycle. Therefore, this framework can be used when evaluating ERNs as well as any further application of them, in part or as a whole: clearly, however, if the ERN model were to be adapted to other realities, a new discussion on its objectives would be needed, leading to different indicators measuring its success.

3.5. Are there other areas where European Reference networks might be appropriate?

One question that naturally arises when considering the results obtained by ERNs is: can a similar approach be used to tackle other healthcare problems? Can it be extended to other settings and to the treatment of other conditions? To answer these questions, first it is necessary to reflect on the reason for the creation of ERNs, the methods they have used, and whether there are sufficient similarities with other conditions to suggest that the ERN model might be appropriate. Second, it is necessary to ask, if there is a case for considering the ERN model, whether there are alternative, more appropriate mechanisms to achieve the relevant goals.

Fundamentally, the objective behind the creation of ERNs is to improve healthcare for patients suffering from rare diseases, in terms of quality of the services provided, efficiency, cost-effectiveness, and ease of access [20]. The need to resort to a European network, rather than implementing national measures in each country, has arisen because of the extreme scarcity of cases: it is very difficult to provide adequate health care for complex problems when there are extremely few patients, as is the case especially in smaller countries [16], [21]. Referral of all patients to a single network makes it possible to centralize knowledge and resources, and also accumulate a sufficient number of cases to evaluate outcomes and establish best practices [15], [22]. Indeed, since knowledge about rare diseases is scarce and continually evolving thanks to advances in research [23], one of the main activities of ERNs is the sharing of knowledge to improve treatment of patients [15]. For patients, this translates into better quality of care and easier access to treatment, since patients can benefit from a team of experts without having to move to distant hospitals [24].

However, the goal of improving healthcare is hardly exclusive to ERNs, but rather is one of the main objectives of all national health systems. Therefore, it is legitimate to ask whether a similar approach can be useful in other circumstances or settings, to improve other features of healthcare.

One element of ERNs is the exchange of knowledge on how to treat certain conditions. Without a structured system, such as that created by the ERNs, it is difficult to know whether different centres are providing care that is consistent with best practice, to the extent that this is known. In the absence of such a system, it is likely that there will be variation in models of care. This variation is not confined to rare diseases. It is widespread in all sectors of healthcare with unwarranted variation, i.e. service usage differences among providers and regions that cannot be attributed to differences in patient needs or preferences but to other factors [25], [26]. These differences can be due to unequal access to services, disagreement about the best medical practice (although treatments that have been proven effective have a great deal of regional variation as well), different medical practice styles, or availability of resources [25]–[28]. These unwarranted forms of variation have a negative impact on the efficacy and efficiency of healthcare [29]: for example, they can indicate lack of conformity to clinical guidelines, a lack of equity in access to care, or a waste of money in ineffective procedures [27]. For these reasons, reducing unwarranted variation is a priority for healthcare systems as they pursue their objective of providing universal and equal coverage of high quality [29]. Therefore, going back to the original question, one could ask whether the measures used by ERNs to solve the problems related to rare diseases can also be useful in addressing problems of geographical variation.

The approach adopted by ERNs to address the issues related to care for rare diseases, as outlined above, is knowledge sharing and benchmarking. This implies that performance of the healthcare system should be evaluated in a transparent and systematic manner in order to identify areas of best practice and those which need to be improved on [30]. Then the results must be disclosed to the public: making the results available offers the opportunity to share best practices and increases the physicians' awareness of the quality of their performance [31]. In addition, a "reputation effect" [19] is set in motion, encouraging professionals to take steps, where feasible, to improve their performance [32], including advocating for a better use of resources, by investing them where they can yield better results (which means, in the case of ERNs, directing them towards international cooperation rather than towards less effective national care pathways).

This can be done through benchmarking, i.e. comparing one's results with those of the best performer, learning how they are achieved, and applying the lessons learnt to improve [33]. These actions can lead to a significant improvement in both quality and economic sustainability of healthcare [30]; in addition, they have been shown to improve equity by providing means to reduce unwarranted geographical variation [27].

The question then is whether the ERN model might be appropriate as a means of reducing unwarranted variation, offering a forum in which those managing different conditions could share experience.

We do not find this argument persuasive. Except in small countries, there is no obvious need to create an international network to function: on the contrary, there are reports of implementation of these measures at a local and regional level [26], [34], with excellent results even for common conditions, such as diabetic foot [30]. In other words, once there is a sufficient number of cases, the methods used by ERNs can be easily applied at a national, regional or even local level, since the focus is not on gathering information per se, but rather on using the information to improve healthcare, and increasing the amount of information available is useful only if it can change decisions on treatment. Indeed, the necessity for international cooperation has only arisen for rare diseases because the volumes are too small to gather a reliable amount of data and identify differences in quality of care. Moreover, conditions with a higher prevalence can implement the same actions as ERNs without having to face all the challenges linked to international cooperation [11]. Even if there is a desire for international collaboration, for example to develop guidelines for complex conditions or indications for new treatments, this can often be achieved equally well by networks developed within other frameworks, for example by European scientific and professional organisations, many of which are already engaged in such mechanisms. While these activities can draw on the experiences from the ERNs in due course, they are substantially different: they are not defined by having a small number of cases, but rather by the fact that international cooperation would make tackling these issues much easier.

A second issue is whether the ERN model can promote access to healthcare for vulnerable communities (such as cross-border communities that are currently not adequately covered by national health services), small countries, remote areas, and/or EU border regions, all of which may suffer from inadequate access to high-quality healthcare that is not limited to rare diseases. Again, there are many other mechanisms that can address these issues, including the now numerous examples of cross-border collaboration and it is not clear what the ERN model would add to them.

There have also been several proposals to create ERNs for other conditions, issues, or population groups. We now review some illustrative examples of these proposals.

It has been suggested that it could be appropriate to create an ERN for humanitarian crises. However, that would, to some extent, duplicate the role of the existing European Emergency Response Capacity and the European Medical Corps. The panel was also informed about a range of bilateral and multi-lateral agreements to enhance disaster preparedness, such as those to ensure access to hospital beds in neighbouring countries in cases of earthquakes other disasters. Thus, there are many alternative, and more appropriate mechanisms that can be employed other than an ERN.

Another proposal is to create a network to improve the care of homeless people. Again, it is not clear how this relates to the ERN concept. Feantsa, the European Federation of national organisations working with the homeless, drew our attention to how, apart from

Finland and Norway, all EEA countries have seen a rise in homelessness with, for example, a 150% increase in Germany from 2014 to 2016, a 20% rise in the number of people in emergency shelters in Spain of the same period and an 8 % increase in Denmark between 2015 and 2017 [35]. The panel agrees that the extreme health inequalities homeless people face mean that homelessness is a health issue [36] and currently many health care systems across Europe are failing people who are homeless. However, the consequences of homelessness are likely to be highly context dependent, influenced by what services are available to homeless people and the pathways into and out of homelessness and it is not clear how the ERN would address this issue.

Although all these initiatives have something in common, they are all related to problems of rather small groups in the European Union (e.g. the homeless population counts for approximately 0.075% of the population at any given time in Europe), and in this sense there is a certain quantitative similarity with the situation of people with “rare diseases”, the panel does not think that it is appropriate to copy the ERN model to address those needs. The European Reference Network-model is a strong “sui generis”-approach, suitable for patients with “rare diseases” as it concentrates expertise and knowledge, and acts as a super-specialised advisory level to improve diagnosis and treatment of people with those diseases.

With other challenges (e.g. refugees, homeless people, disaster interventions) the needs of those affected should be addressed directly by offering appropriate service provision.

That being said, the panel urges member states and the European Union to optimise the care for these groups and the preparedness to provide acute responses, through the creation of platforms and “Learning Communities” in Europe with participation of multiple member states and experts in the different domains, in order to improve access in quality of these vulnerable people. This action certainly relates to the ambition of the recently adopted European Pillar of Social Rights. Creating these platforms and “learning communities” around these topics, providing the needed evidence through practice-based research, will enable health care providers in Europe to better serve the needs of these vulnerable nations. In other words, there are many possible ways to share information and undertake action to tackle healthcare and social issues: rare diseases have been addressed using the ERN framework, while other problems can benefit more from other forms of cooperation – and it is of the utmost importance that these communities and networks are put in place, in order to best deal with them.

In summary, the current criteria for establishing a ERN, as a means of improving the management of patients with rare and complex diseases, was appropriate. The ERN concept does not address other issues raised for consideration, such as remote areas and border regions, or the development of new medicines or interventions, for which there are alternative and more appropriate mechanisms. The Expert Panel was also asked about the scope to extend the scope of ERNs to other areas such as the care of people who are homeless or emergency situations. In both cases, there are better alternative mechanisms to achieve the intended goals. However, the panel does accept that improved responses are needed to meet the needs of homeless-people, refugees and other vulnerable groups, and to increase preparedness in relation to disaster-interventions through specific "European Learning Communities".

3.6. Should the ERN model be used as a whole?

The application of the ERN model as a whole or part of the model will depend on the needs to which the model is expected to respond. The ERN model can tackle one, several or all the main fields for action currently identified for rare diseases: research and innovation, generating and sharing evidence, developing guidelines, and training.

Research is of paramount importance in the field of rare diseases, given how little is known about them: ERNs should bring to a stronger EU research governance, based on systematically identified research gaps and priorities [14]. In the field of rare diseases an example is the EU funded project RARE-Bestpractices [37]. The project has produced a specific resource (RareGAP) that collates validated research recommendations for diagnosis and treatment of rare diseases, identified from high quality systematic reviews

[38]. These validated research recommendations can feed the research agenda on rare diseases.

In a similar way, an active cross-border network can be a valuable tool to pinpoint the need for generating new evidence also for conditions other than rare diseases. Consequently, it will be important to find a consistent way to feed the inputs of the ERNs, as research needs, into the EU research agenda.

Clinical guideline development can be highlighted as a priority topic**.** In fact, Directive 2011/24/EU [point (iii) of Act. 12(4)(a)], the Commission Delegated Decision 2014/286/EU and the Commission Implementation Decision 2014/287/EU require that ERNs and the health care providers wishing to join ERNs should have the capacity to develop and implement trustworthy clinical guidelines [20], [39], [40].

Production and implementation of clinical guidelines in the EU is far from satisfactory. Few countries have well-established systems in place, sustained by national or local regulations that provide mechanisms for quality assurance, implementation and use. Many countries still rely on sporadic initiatives based on unclear processes, others have insufficient capacity for evidence-based guideline development or, even if they have the capacity, they lack a coordination of a central agency [41]. The ERNs offer an excellent opportunity (albeit not the only one) to (i) consider the importance of devoting resources to build an efficient system for developing and implementing guidelines, and (ii) ascertain the actual capacity of healthcare providers to produce trustworthy guidelines according to international standards. Since ERNs are expected to pursue a cooperative approach aimed at sharing expertise, they can contribute to initiating processes to establish European cooperation structures. This in turn can contribute to the production of clinical guidelines in accordance to robust international standards, leading to more equitable care across countries and a wider access for patients to care.

However, it should be noted that the production of guidelines is hardly the only objective of ERNs, but rather it should be one of the end products of their activity. Indeed, clinical guidelines are known to be often ignored or misinterpreted, even in the case of the most common diseases: 30-40% of patients do not receive effective treatments, while up to 25% of them receive unnecessary or potentially harmful ones [42]. The varying degrees of guideline application can also be seen when examining geographical variation in healthcare, of which it is a main determinant [27]. Because of this, guideline development and dissemination are not the only focus of ERNs, but rather they also focus on other aspects of rare diseases where they can make a difference. Conversely, there are other ways to highlight the importance of sharing information and producing valid guidelines, without having to resort to ERN (such as highlighting unwarranted variation) [43].

Another characteristic of ERNs is the fact that training and e-learning are priority topics: the implementation of ERNs requires the availability of trained professionals at all levels of healthcare; therefore, ERNs might be focussed on up-to-date training of healthcare professionals across EU, possibly in conjunction with empowerment of patients and citizens.

Finally, a peculiar characteristic of ERNs, albeit one that has not been formally recognised, is the high degree of patient involvement: representatives of patients and their families are members of the boards of ERNs [44] and patient advocacy groups participate in ERN activities [24], up to the point of organising publicity campaigns [10]. Because of this, another focus of the "ERN model" should be to further increase the participation of patients in the diagnostic, treatment and follow-up processes, by registering and sharing their experiences, thereby improving their care. This can be facilitated with greater use of patient reported experience and outcome measures (PREMs and PROMs), already in use in various national health systems with varying, but generally good outcomes [45]. They would be especially useful in the field of rare diseases, since patients are highly involved in their healthcare [16] and can therefore give extremely important insights.

In summary, while it is not possible to come to definitive conclusions about the role of ERNs in we examined the scope of the ERNs research and guideline development, there would seem to be connsiderable scope for incorporating these additional roles beyond the immediate objective of providing advice on individual patients. This will, however, require dedicated resources, some of which will have to come from other sources.

3.7. How should national health systems integrate such networks into their national framework?

Properly implemented ERNs are not an obstacle to the overall functioning of the national healthcare systems; indeed, the added value of ERNs is evident as long as the focus is on information and knowledge exchange and as long as the patient is only treated in the "foreign" system when it is appropriate and justified. The main challenge is to provide evidence of the added value of these networks for all players, in particular the member states. For the first time, member states will not only cooperate with one or two others on the basis of framework agreements and using existing administrative arrangements, but with at least 8 member states whose health systems differ. We need to identify and monitor indicators of relevance for the individual players, especially health authorities and insurers in member states, in order to evaluate the entire process [46]. The diversity of systems within member states makes it impossible to provide detailed guidelines for how this can best be made to work. This is an area where it will be important to monitor the implementation of the existing ERNs and disseminate the lessons that arise from their experiences.

At this point it is important to consider the financial sustainability of the ERN model in the light of constraints facing some national health systems. At present, individual cross-border patient mobility takes place on a small scale. According to the May 2015 Eurobarometer, entitled "Patients' rights in cross-border healthcare in the European Union", only 5% of EU citizens obtained treatment abroad [46]. The consequences and the potential financial burden associated with the establishment of the ERNs need further investigation and more time [46]. The optimal way to finance ERNs in the medium-long term remains unresolved: as highlighted above, further elaboration will be needed to achieve long-term sustainability. This issue may be a problem for all EU member states, but especially so for some of them.

Finally, the ERN model could usefully be applied within a national health system, or even a regional section of a health system, when dealing with common diseases. Indeed, in some cases the application of the ERN model does not need an EU dimension: it might be translated with equal or higher effectiveness to a national or regional dimension [11].

3.8. Proposed criteria for establishing ERNs

In the light of the considerations described above, the panel proposes a set criteria for creating a European network. The panel considered that four criteria were relevant:

a) The condition/ intervention must be rare (however defined). The panel saw no justification for creating a pan-European infrastructure for common conditions where relevant expertise is widely available.

b) The condition must occur throughout large parts of the EU. Thus, a condition could be rare on account of its concentrating in a few families with a particular genetic anomaly but if they all lived in the same region then it is likely that expertise would also be concentrated and there would be little added value of a Europe-wide network. Similarly, if cases were concentrated in a few member States, bilateral of multi-lateral arrangements might be more appropriate. There may be some occasions in which a condition, especially infectious ones, that is not uncommon in some member states, such as tick-borne encephalitis, is seen in travellers who move to other countries where it is not endemic. However, again, there will be alternative mechanisms available and, in cases such as this, the surveillance networks working with ECDC may be able to play a role.

c) The condition must be complex and there must be incomplete knowledge, benefitting from consultation among specialists. A condition may be rare but its management may be straightforward and uncontentious. It would not justify a ERN model.

d) The establishment of a ERN should only be undertaken when there is no existing alternative mechanism to obtain access to relevant expertise or other forms of collaboration or where a simpler solution is not possible.

CONCLUSIONS AND RECOMMENDATIONS

ERNs have the potential to facilitate cooperation at the EU level in particular medical domains with a focus on areas where expertise is scarce, facilitating access to diagnosis and to high-quality health care, especially in the area of rare diseases. As such, the establishment of ERNs appears to have been, at least potentially, among the most important European cooperative initiative for decades.

ERNs seek to provide an important mechanism be powerful tools to support a consistent, up-to-date, cost-effective and evidence-based healthcare for those with rare diseases across the EU.

Potential points of strength of the ERN model include, in particular, the added value of knowledge sharing and the integration of the ERN system in the national health services of each MS.

The ERN model stems from the principle of subsidiarity and added value of action at European level: therefore, in principle, all those healthcare areas that may benefit from cross – border cooperation could be interested, including those caring for people with complex, high-prevalence diseases and cross-border communities with increased health risks (homeless, refugees, etc.). On the other hand, ERNs for rare diseases have been implemented for only one year. This is too short to make an evaluation of outcomes, costs and points for improvement.

ERN financing in the medium-long term is also a health policy issue; further elaboration may be needed to optimize the long-term sustainability of ERN. The sustainability issue may be a problem for all EU member states, especially for some of them. Moreover, ERNs require extended cooperation among at least 8 MS, whose health systems can be very different, making such cooperation challenging to achieve.

However, properly implemented ERNs are not an obstacle to the overall functioning of the national healthcare systems; indeed, the added value of ERNs is evident as long as the focus is on information and knowledge exchange. The main key challenge is to provide evidence, by means of adequate indicators, of the added value of these networks for all players, in particular the MS.

Based on the above considerations, the extension of the ERN model to diseases other than rare diseases is currently considered premature.

More data are required on benefits and costs of ERN for rare diseases, in order to achieve a more robust body of evidence to support the extension of the model to other health conditions. Such conditions likely have features that would call for adaptations of the ERN model currently implemented for rare diseases: such features include (but are necessarily limited to) relatively high frequency, multifactorial aetiology, multiple clinical phenotypes under the same diagnostic umbrella and multiple, sometimes divergent, approaches to diagnosis and treatment.

The application of the ERN model as a whole or part of the model will depend on the needs to which the model is expected to respond in fields other than rare diseases. Therefore, the ERN model can tackle one, several or all the main fields for action currently identified for rare diseases: developing guidelines, training, research and innovation, generating and sharing evidence. Clinical guideline development can be a priority topic as requested by the Directive 2011/24/EU. Indeed, the development [47], production and implementation [48] of clinical guidelines in the EU is far from satisfactory. ERNs can support initiating processes to establish European structures of cooperation in producing guidelines, pursued through structured knowledge sharing; this could lead to more equitable care across countries and a wider access for patients to care, including either rare and frequent conditions.

In addition, an active cross-border network can be a good means to pinpoint the needs for generating new evidence; it will be important to find a consistent way to feed the inputs of the ERNs, as research needs, into the EU research agenda.

It is recommended that well-designed, independent research is carried out on the impact of ERN on healthcare of rare diseases including the clinical (e.g., improved diagnosis), scientific (e.g., added value of shared knowledge) and social (e.g., benefits for patient's life quality, sustainability) aspects [20]; the adaptations that may be needed in order to fit the ERN model to diseases other than rare diseases.

Finally, the implementation of ERN, for rare diseases as well as for other conditions, requires the availability of trained professionals at all levels of healthcare; it is, therefore, recommended that the lessons learned from ERNs should be reported and disseminated in ways that can feed into in the undergraduate through to post-graduate and professional education of the healthcare professions.

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