



# **Workshop Report**

## **From Centres of Expertise for Rare Diseases to European Reference Networks**

**11 & 12 May 2015, Madrid**



Co-funded by  
the Health Programme  
of the European Union

## Introduction

The workshop was organized by CIBERER, within the scope of Work Package 7 (WP7) of the EUCERD Joint Action (EJA): Working for Rare Diseases, (DG SANCO 20112201, EU Health Programme). It was held at the Spanish Ministry of Health, Social Services and Equality in Madrid on 11<sup>th</sup> and 12<sup>th</sup> May 2015 and it was attended by over forty experts in the field of rare diseases, representing the various stakeholder groups (see annex 1).

### **Specific questions to be addressed**

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- To present the final results obtained by WP7 of the EUCERD Joint Action on Quality of Care / Centres of Expertise.
- To provide a forum for Member State Representatives to discuss these results and how they might be used to improve the quality of care in Centres of Expertise (CEs) for Rare Diseases (RD).
- To explore Member States' current plans and readiness to support the participation of Centres of Expertise for RD in European Reference Networks (ERNs).
- To identify main criteria of Quality of Care in CEs and discuss their impact in future ERNs.

## Agenda

### **Day 1**

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- 13:00 - 13:15 Welcome (Paloma Casado, Spanish Ministry of Health, Social Services and Equality)
- 13: 15 - 13:30 Overview of EJA WP7 (Francesc Palau, CIBERER)
- 13: 30 - 14:00 EUCERD Recommendations for Centres of Expertise – the European perspective (Victoria Hedley, University of Newcastle)
- 14: 00 - 14:30 WP7 General Results (Richard Woolley, INGENIO)
- 14:30 –15:00 Challenges and Opportunities for CEs (Richard Woolley, INGENIO)
- 15:00 - 15:30 Challenge 1: How to provide continuity of care (Francesc Cardellach, Hospital Clinic of Barcelona / CIBERER)
- 15: 30 - 16: 00 Coffee break
- 16:00 - 16:30 Challenge 2: Integrating Genomics technology into clinical practice (Luis Pérez-Jurado, Pompeu-Fabra University / CIBERER)
- 16:30 - 17:00 Challenge 3: Multidisciplinarity: what does this mean for a CE for RD (Eduardo Tizzano, Vall d’Hebron Hospital / CIBERER)
- 17: 00 - 18: 00 Plenary Discussion: Challenges for CEs and suggestions for addressing these

### **Day 2**

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- 08:50 - 8:55 Summary of Day 1
- 08:55 - 09:15 Designating and networking Centres of Expertise for Rare Diseases – the French Experience (Jean-Baptiste Rouffet, French Ministry of Health)
- 09:15 - 09:35 State of the play of the implementation of ERNs: Legal criteria and conditions for the establishment of ERN (Enrique Terol, European Commission)
- 09:35 - 09:55 State of the play of the technical proposal for an assessment manual and toolbox contracted by the European Commission (Enrique Terol, European Commission)
- 09:55 - 10:10 Designating and networking Centres of Reference for Rare Diseases – the Spanish Experience (Maravillas Izquierdo, Spanish Ministry of Health, Social Services and Equality)
- 10:10 - 11:30 Round Table: CE Designation status and plans for Centres’ participation in ERNs
- 11:30 - 11: 50 Coffee break

- 11:50 -12:10 Quality of Care in the future ERNs: Potential efficiency criteria (Miriam Schlangen, National Action League for People with Rare Diseases-NAMSE)
- 12:10 - 12:25 Addendum on RD ERNs – what does this mean for CEs wishing to engage in RD ERNs? (Kate Bushby, University of Newcastle)
- 12:25 - 13:15 Open Discussion: Readiness for ERNs and Quality of Care
- 13:15 - 13:30 Closing remarks

## Brief Description of Each Presentation and Round Table

### DAY 1

#### **Presentation 1: Overview of EJA WP7 (Francesc Palau)**

In the opening presentation, Francesc Palau, leader of WP7, summarized the main objectives of this Workpackage, which is to identify:

- Actions which could improve access to higher-quality healthcare in rare diseases, enhancing quality of life for patients.
- Initiatives across the EU Member States (MS) which address the quality of care for rare diseases, with the objective of identifying and sharing good practices in healthcare.
- How healthcare systems organize themselves to accommodate RD policies and patients.

A brief summary of the methodology used was also presented, which is based on ethnographic research, an online questionnaire and semi-structured interviews with expert RD stakeholders.

Dr. Palau emphasized that work of WP7 has also been aimed at supporting the Expert Group on Rare Diseases by providing evidence and insights regarding the processes of alignment of different national and disease settings and the EUCERD recommendations on Quality criteria for Centres of Expertise for rare diseases.

#### **Presentation 2: EUCERD Recommendations for Centres of Expertise – the European perspective (Victoria Hedley)**

In this presentation, Victoria Hedley, University of Newcastle, provided an overview of the EUCERD Recommendations for Centres of Expertise, covering the following aspects: framework, aims, mission and scope.

She explained in detail all aspects related to the criteria for designation and evaluation of CEs, taking into account the need for networking, the European dimension and the Status Quo in 2015.

Finally she highlighted two different approaches to the nomination of CEs, by summarising the French and Danish experiences, and shared some overarching conclusions:

- many CEs are based in University hospitals.
- several Member States opt for a national coordination centre (either alongside or in place of disease-specific CEs) which in theory addresses all RD patients' needs: this is an alternative to attempting to set-up CEs for all disease areas.

- some MS –particularly the smaller countries- only have a single CE for RD (in the form of a major hospital or Medical Genetics Centre), which raises the question of how to integrate with ERNs arranged on disease-specific lines (i.e. would such a centre seek to join all ERNs, and if so, would it have the requisite expertise in all diseases areas?).
- there are already some well-established networks linking national and regional CEs.
- despite the variety in designating CEs/recognising national/regional excellence in RD confidence in quality criteria for CEs will be critical to the success of ERNs.

### **Presentation 3: WP7 General Results (Richard Woolley)**

In this presentation, Richard Woolley, Institute of Innovation and Knowledge Management, (INGENIO CSIC-UPV), provided a detailed description of the approach and methodology followed by the team and presented the work concluded to date.

Dr. Woolley started by recalling the contribution of Work Package 7 to the Joint Action and explained the basis of the framework under which the analysis of the information collected has taken place, the Quality of Care (QoC) model and the dimensions of QoC related to the EUCERD Recommendations for CEs.

He then presented the main outcomes of WP7 relating to the following thematic areas:

- CE activities (identification of those core activities developed by CEs).
- Quality of Care (pragmatic CE activities and EUCERD Recommendations from a QoC perspective).
- CE activities in implementing the EUCERD Recommendations.

Finally, he presented some conclusions related to CEs (organization, research activity, patient-centred practices, networking, and interaction and future perspectives) and regarding the opportunity and readiness to move from CEs to European Reference Networks.

### **Presentation 4: Challenges and Opportunities for CEs (Richard Woolley)**

In this presentation, Dr. Woolley provided an overview of the CE context focusing on the major challenges identified by the study:

- Human resources – next generation of specialists, specialised support staff, training adult specialists, IT specialists.
- Technical change – finding cost effective ways to exploit new technologies (NGS, -omics) and data sharing potential.
- Continuity of care – from paediatric contexts of relatively holistic patient-centred care to (emergent) adult contexts.

- From a QoC perspective, efficiency remains a challenge.
- Integration in ERNs – potential Efficiency dividend from linking consolidated expert system and linking to promote consolidation.
- Telemedicine or e-services – recognition that this is an underutilised potential tool to improve QoC.
- Other: CE Governance, networking, disease grouping in ERNs, designation criteria.

#### **Presentation 5: Challenge 1: How to provide continuity of care (Francesc Cardellach)**

In this presentation, Francesc Cardellach, Hospital Clinic of Barcelona / CIBERER, shared his experience of the challenges of transitioning from pediatric to adult age, a process which involves purposeful, planned efforts to prepare the pediatric patient to move from caregiver-directed attention to disease self-management in the adult unit, accepting responsibility for his/her disease management.

Dr. Cardellach suggested several steps be followed:

1) *Transition to patient transfer* (preparing the teenage patient and providing sufficient patient-care information to the receiving adult service);

2) *Transfer characteristics* (it should be individualized, agreed with patient and family; carried-out in a period without crises, after completing a school period; taking into account other specialists and considering financial factors);

3) *Transition process* (information provision should begin at 12-14 years of age and should take place gradually; it should be directed by experienced (senior) clinicians and support professionals should be assigned; there should be both a generic and individualized transition plan that include parents, other family members, boyfriends/girlfriends; informal visits to the adult service should be allowed; participation in group sessions with other young people who are about to transition should be facilitated; tools to aid in the acquisition of disease self-management skills should be provided);

4) *Transition itself or transfer to the adults clinic* (transfer clinic specialists should be assigned, including an internal medicine specialist, nurse and social workers; written and verbal information of all multidisciplinary aspects of the young person's care should be given; and, the young adult patient should be prepared for his/her autonomy).

Dr. Cardellach also focused on the objectives and challenges experienced in the particular case of the Unit of Adults with Inborn Errors of Metabolism at the Hospital Clinic of Barcelona to which pediatric patients from the Sant Joan de Deu Hospital are transferred. Amongst the key challenges mentioned were the lack of experience and low patient/family reliance in “new” physicians; the lack of young motivated physicians for RD; the issues related to organizing “one time” multidisciplinary clinic; the lack of clinical guides for emergency events; the time restrictions for outpatient consultation; getting a formal (official) engagement of institutions and agreements among institutions and the Health Department for expensive treatments; or, to design research projects and establish an official training program and getting financial support for it.

**Presentation 6: Challenge 2: Integrating Genomics technology into clinical practice (Luis Pérez-Jurado)**

In this presentation, Dr. Pérez-Jurado, Pompeu Fabra University / CIBERER, explored another important challenge faced by CEs and ERNs: that posed by the integration of genomics technology into clinical practice.

The major challenges highlighted were:

- Evidence of clinical validity and proven clinical utility and their impact on communication and counselling.
- Necessity of having trained professionals with a deep knowledge and expertise in genetics for clinical interpretation of data and genetic counselling.
- Technology availability and investments required as far as:
  - Equipment (Next Generation Sequencing-NGS).
  - Data storage and integration with medical records.

4) Warrant provision of services and sustainability.

**Presentation 7: Challenge 3: Multidisciplinary: what does this mean for a CE for RD (Eduardo Tizzano)**

Eduardo Tizzano, Vall d' Hebron Hospital / CIBERER, presented the challenge of setting up CEs with a multidisciplinary approach.

In this presentation, Dr. Tizzano provided details regarding the composition and structure of the RD interdisciplinary clinic he leads in Barcelona, which integrates experts from different backgrounds and specialties, trained nurses, case managers and psychologists, among others. This clinic is able to provide personalized, complete medical care at a single location for any RD referred to it (although the pilot experiences have been with 22q-, Rasopathies - Noonan and related disorders-, neurocutaneous, metabolic, and neuromuscular disorders). So far, this Clinic has attained sustainability by using a multidisciplinary approach, broadening the case-material, extending the adequacy of the diagnostic tests and adapting treatment and protocols. In addition, the Clinic participates in teaching and training programs alongside translational research activities.

He concluded by enumerating the main challenges faced: coordination of multiple hospital teams (agenda, visits, protocols, studies and therapies) to optimize the grouping of diseases; training and recognition of case managers for each group; adaptation of the database and patients' registry; coordination, follow up and support to primary care centres and local hospitals; defining transition protocols for different groups of rare diseases; consolidation and sustainability; the use of telemedicine; and collaboration with advocacy groups.

**Plenary Discussion 1: Challenges for CEs and suggestions for addressing these**

Following the afternoon presentations a space for discussion was opened to talk about the different topics approached. Participants were invited to formulate questions which may have arisen during the previous session presentations.

The specific issues discussed may be summarized as follows:

– Rare Disease Grouping:

A participant from the rare cancer field raised the question of how to balance RD grouping with expertise and commented on her experience with rare cancers, where a major effort to group has been made, but noting that it is not always possible given the high number of rare cancers. She asked the rest of participants to share their opinions.

The EJA Coordinator confirmed that a lot of thinking has been done regarding this matter, specifically around the need for grouping diseases in order to create workable European reference networks for rare diseases. She emphasized that it is a different issue if we are talking about grouping expertise in a single clinic hospital for other purposes. The rationale behind grouping is that it is not feasible to have hundreds of rare disease ERNs, so it is necessary to look for a pragmatic way to bring together some already existing smaller groupings. From this it was decided to look at how different countries group rare diseases, how Orphanet groups rare diseases and how the different classification systems group them. The idea was to develop a consensus from across these different groupings, to try and develop a potentially functional list - within which every rare disease will 'find a home'. Quoting her, *"in the end, what is desirable at the individual expert level is having a workable structure that allows us to share resources and share expertise wisely at a European or even global level"*.

Another participant, a MS Representative, added that it is necessary to differentiate between grouping at the level of a Centre of Expertise and grouping at the level of European Reference Networks. Also, the idea of the Reference Networks is to accumulate expertise since not every country will have centres of expertise for all the very specific groups.

– Case managers:

The usefulness of and need for case managers in the Centres of Expertise was attested, whilst acknowledging the difficulty to incorporate this figure, mainly due to economic restrictions.

The experience of WP7 members during the interviews carried out at different CEs was that the CE Directors working in the field for many years could point to a threshold moment when they hired specialized nurses or case managers in particular. As one of them put it, *"it's almost like a critical mass making possible to carry out all of the administrative work, dealing with health authorities, dealing with social services, working with the patient organization, etc.. It is crucial to have someone who can actually dedicate his/her energies to building the personal relationships which absorb a lot of time and opportunity for the clinical specialists"*. When CE Directors were asked what was the most crucial and important improvement made in the Centre, most of them agreed it was the fact that they hired a specialized nurse, someone who took over case management.

– The utility of the EUCERD Recommendations

A WP7 member was asked to define his overall impressions regarding the usefulness and the utility of the EUCERD Recommendations related to CEs on RD. The response was that a close alignment was found between what Centres that had emerged and grown were doing and

the strategic vision set by the Recommendations. He also highlighted the networking practices between those Centres, which have consolidated a certain amount of knowledge and expertise and other less experienced Centres even in the same region.

– Problems encountered by small countries

The group discussed the main problems faced by small countries when dealing with rare diseases. For these countries the organization model for CEs and ERNs represents a big challenge: for instance, in Malta there is only one university hospital and they need to send patients abroad via bilateral agreements, to the UK in particular. The whole concept of ERN for small country has to be tailor made.

– Centralized vs Federal Health Systems

The issue of how different MS approach social and healthcare depending on whether they follow a centralized or a federated model was raised by the Malta Representative, in the sense that perhaps small countries such as Malta should look at regional models (such as those implemented in Germany, France or Spain). At this point, the German representative clarified the difference between type A and type B centres designated in this country. Type B is a centre of expertise for a specific group of rare diseases and it corresponds more or less to the concept of CEs, whereas type A centres are somehow a fusion of several type B centres that provide additional services.

– Improving system efficiency

A question was raised regarding how a Centre that is focused on the patient, on safety and effectiveness could improve its efficiency.

It was pointed out that it depends on the degree of consolidation of systems of practices, of networks, of organizations, et cetera and that it would be appropriate to start thinking more seriously about monitoring and evaluation processes at that level.

It was also suggested that ERNs, linking up consolidated, larger centres with a lot of expertise, could start to share standard monitoring processes and work towards forms of evaluation leading to increased efficiency.

Some participants argued that it is too early to ask for evidence of efficiency because it is not just about the Centre: CEs are integrated into healthcare systems and their pathways, the functioning of which influences certain processes at the level of the centre like for instance the time to diagnosis.

Another participant and MS Representative shared a good practice example of efficiency in the context of Next Generation Sequencing (NGS), where they have been able to double the diagnostic efficiency over the last few years without an increase in their budget, having a double impact, both economical and professional. This example of using internal capabilities to improve effectiveness but also to introduce efficiency corroborates a key principle raised in one of the presentations regarding the main challenges facing CEs: it is more efficient to share knowledge, network and have good pathways in place than to duplicate facilities.

Other participants stressed this last point regarding the need for collaboration and sharing of expertise. It was suggested that once European Reference Networks are constituted, it would be helpful to create e-medicine or tele-medicine platforms in order to maintain close and interactive links among the different expert centres. Therefore, implementation of tele-

medicine and learning platforms is seen by some as one of the best ways to increase efficacy and efficiency.

– Next Generation Sequencing

Linking with the NGS presentation, a question was raised regarding the interpretation of results generated by these new technologies. This concern –on the role and reliability of NGS and bioinformatics- seemed to come up many times during the interview phase carried out by WP7 at CEs. Participants were asked to share any insights about how precisely this capability or the skills involved can be built with the existing workforce in order to deal with this new type of information.

According to the invited speaker, what seems to be particularly important when using these techniques is the ability to communicate findings with the patients and to be able to provide them with all the necessary information. Also, there is no question that there is a need for qualified people and expert knowledge to interpret the data. However, that is much easier now than three or four years ago.

A related challenge now is to establish population specific variant databases. A participant explained that in Slovenia they were able to reduce the complexity of interpretation by ten-fold, by having a comprehensive database of genetic variants.

An additional question related to NGS data storage was raised. A participant asked if CEs would be the most appropriate place to store the genetic information generated. Storing all the information is extremely demanding as far as computer space. Right now this is done through consortiums with specific centres at the regional or national level. However, if all the information generated is stored, it will present a problem a few years from now. In addition, if data generated is shared by a network, further discussion is necessary to determine where that data is stored, who is going to be in charge of it, who will have access to it, etc. One participant suggested that even though there should be country-specific solutions, ERNs should provide guidance (if not the actual infrastructure).

Participants discussed whether there is in fact a need to store all the information generated by NGS, when it would be less costly to repeat the sequencing of the exome or genome in the future, if needed. It was even suggested that each patient stores his/her own data. It is possible that with the advent of web computing and storage in the web, storing NGS generated data won't be such a problem.

Other issues:

– Recommendation regarding research activity in Centres of Expertise

It was emphasized that whilst research was a very strong point at pilot networks, this probably this won't be the case for European Reference Networks, where there should be contribution to research, but the main focus will be care. It was argued however that there is no reason for a Centre not to participate in ERNs if it does not have a significant level of research activities. Providing small number of patients for a clinical study in a multi-disciplinary approach or multi-national approach should be enough.

– Lessons learnt from WP7 work

The EJA Coordinator closed this Plenary Discussion with a reflection regarding the positive lessons extracted from WP7 fieldwork. Although much time was spent thinking about the difficulties faced by CEs, there are many examples of very good centres everywhere in

Europe. WP7 showed that whether you go to large or small countries, or focus on large or small disease areas, it is possible to find real beacons of excellence and dedication everywhere. You can see that people are forward thinking and passionately committed to their work.

Quoting her: *“This work package has shown that there is a very good body of work out there that we should be building on. It hasn't grown in a way that anybody has prescribed because the use of recommendations or even thoughts about centres of expertise of rare diseases only came up when many of these centres were already developing. So, I think that we focus a lot on challenges and problems but we've actually got a lot of really positive things to learn from the work done in WP7 as well.”*

## DAY 2

### **Presentation 8: Designating and networking Centres of Expertise for Rare Diseases – the French Experience (Jean-Baptiste Rouffet)**

In this presentation, Jean Baptiste Rouffet, French Ministry of Health, reviewed a decade of experience related to France's RD health care system, integrated by Centres of Reference, Centres of Competence, University Hospitals and RD networks or “Filières” according to the directions provided by two successive National Plans.

Dr. Rouffet

described the CEs designation and assessment process, the criteria for which are very similar to those outlined by the EUCERD Recommendations. Centres of Reference are both single site and multi-site in France. The first round of evaluations for Centres of Reference entailed a self-assessment process. Details were provided regarding the establishment of the 23 “Filières” created so far.

To conclude, a summary of future actions to improve the French RD System were presented and key messages were provided to the audience.

### **Presentation 9: State of the play of the implementation of ERNs: Legal criteria and conditions for the establishment of ERN (Enrique Terol)**

In this presentation, Dr. Terol, European Commission, detailed the general and specific criteria and capacities applying to networks and members that shall be taken into account for the proposal preparation and self assessment.

He also provided some insights regarding the assessment and improvement of networks and emphasised the key roles that Member States should play during the process, describing the current status and timelines of ERNs. It will be necessary for all actors to amend our current practices somewhat, move outside existing ‘boxes’ to make ERNs a success.

**Presentation 10:** *State of the play of the technical proposal for an assessment manual and toolbox contracted by the European Commission (Enrique Terol)*

In this presentation, Dr. Terol provided some detail and preliminary results related to the work being done by the PACE-ERN Consortium (EURORDIS, HOPE & Accreditation Europe (Canada)) towards delivering an Assessment Manual and Tool Box for the upcoming ERN Call. Key deliverables of this project are:

- Translational of the legal criteria into operational criteria
- Tools and guidance for both the call and assessment process tools and guidance for the networks proposals.

Preliminary results of the mapping exercise carried out by means of a literature review and project and a written consultation were shared, which included key considerations and challenges.

In regards to upcoming actions, mention was made of the ERN IT platform, the ERN services study and the communication and awareness activities. Disease-specific groups should begin to network and organise themselves in preparation for the first call.

**Presentation 11:** *Designating and Networking Centres of Reference for Rare Diseases – the Spanish Experience (Maravillas Izquierdo)*

This presentation by Dr. Izquierdo, Spanish Ministry of Health, Social Services and Equality, was centred on the situation of CEs in Spain and the “Reference Centres, Departments and Units (CSUR) of the Spanish National Health System” Project and provided information related to the CSUR project aims, requirements, procedure, designation committee and expert group, specialization areas, diseases and procedures, current status and future actions.

**Round Table 1:** *CE Designation status and plans for Centres’ participation in ERNs*

This round table gave the opportunity to all Member State Representatives attending the workshop to briefly describe the situation in their own countries regarding CE designation and readiness to participate in the upcoming ERN call.

The conclusion of this round table was that, as we already know and has previously been reported by EUCERD (and many other stakeholders), the European landscape is very heterogeneous, given the differences in size, population, health system organization (centralized vs. federal), adoption of a national plan or strategy for RD and a CE designation process in place, etc. Thus, rather than detailing the situation in each country it is preferable to summarize the main issues and concerns expressed by the participants:

Regarding the existence of CEs

We find these different situations:

- Countries without CEs
- Countries with CEs specific for RD groups
- Countries with CEs specific for RDs in general
- Countries with CEs that are not specific for RDs organized around procedures.

Many countries have identified clinics and/or hospitals where RD patients are referred but are not constituted as centres of reference.

In general, bigger countries and/or most highly populated countries tend to have centres where RDs are grouped, while in smaller and/or sparsely populated countries, centres tend to be common for all or most rare diseases.

In some countries with CEs, these are integrated in networks at a national level.

Smaller countries and/or countries with added physical barriers (such as Malta and Iceland) are very dependent on collaboration agreements with other European countries.

Some MS are currently working to elaborate a list of rare diseases and seeking to develop a grouping proposal, as well as working on indicators to identify possible CEs.

#### Regarding the existence of a CE designation process

- Countries with a CE designation process
- Countries in the process of defining the designation process
- Countries which are putting a designation process in place with the sole purpose of nominating CEs to participate in the ERN call.

In general, countries without a designation process (which seem to be the majority) are trying to accelerate the process in order to participate in the ERN call. Just a few Member States feel they are ready to nominate CEs to be included in a network.

Some Member States have constituted RD Boards, National Advisory Committees or working groups to deal with CE designation.

MS working on a designation process are concerned about defining an assessment process as similar as possible to the one that will be used to assess ERNs, and expressed a desire to coordinate somehow, to avoid the need to 'designate' twice, as it were.

Many countries expressed concerns regarding the coexistence of self-designated and officially designated CEs, though this won't represent a problem in the context of ERNs since being officially nominated is a compulsory requirement to participate. However some MS believe that it is possible to use a bottom-up approach to include some centres identified through patient organizations and professionals as long as quality of care can be guaranteed.

#### Regarding the organization of the health system

- Centralized
- Decentralized or federal

MS with a federal system commented on the challenge and added difficulties to designating centres in comparison to centralized systems. The main issues are: the inability of the Government to make decisions concerning all the centres included in their territory; coming to an agreement regarding the designation of CEs in different geographical areas whilst trying to avoid duplicating efforts and resources; and putting mechanisms in place to attend to patients coming from other regions or councils.

**Presentation 12:** *Quality of Care in the future ERNs: Potential efficiency criteria* (Miriam Schlangen)

Miriam Schlangen, National Action League for People with Rare Diseases (NAMSE), centred her presentation on the definition of quality criteria for centres of expertise for RD.

Dr. Schlangen provided details regarding the quality criteria set by the NAMSE Plan for type A, type B and type C centres, the process and requirements for each one of them and the care pathways defined. Also, a summary of results of a 2015 feasibility study including 18 type A and 50 type B centres was presented. The aims of this study were to analyze the current situation according to the quality criteria developed by NAMSE and getting feedback to practicability, plausibility and completeness of the criteria catalog. Amongst the aspects assessed were: structure of the centre, patient management (several items), diagnostics, provision of care and knowledge management (research and training).

To conclude, the process to define quality criteria and the development of a scoring system were presented.

**Plenary Discussion 2:** *Readiness for ERNs and Quality of Care*

The last round table of the workshop was devoted to the future design and implementation of European Reference Networks and was preceded by a presentation by Kate Bushby, EJA Coordinator- University of Newcastle. Since the content of this presentation was quite relevant for the final discussion, a summary of the main points has been included here:

**Presentation 13:** *Addendum on RD ERNs – what does this mean for CEs wishing to engage in RD ERNs?* (Kate Bushby)

- The original EUCERD Recommendation acknowledged that updates might be needed in the future, specifically around the areas of ERNs.
- The Addendum to the original Recommendations is a way to provide extra criteria for the rare disease field to help interested parties to organize and be able to respond to the call for ERNs. The Addendum was presented to the March Expert Group meeting, and hopefully will be adopted without any further major amendment.
- The Addendum does not challenge existing structures. It's about ensuring that every rare disease patient should have a 'home' in the new system.

- The Expert Group agreed last November that two topics should be revisited and elaborated at this stage:
  - grouping of rare diseases into networks
  - need for a patient centred approach.
- The Board of Member States highlighted that some specific criteria should be deployed in order to help to avoid fragmentation, increase efficiency of the networks and decrease inequality for patients.
- With that in mind, it was suggested to group healthcare providers that focus on related rare diseases or conditions in a thematic network. It was also advised to create age inclusive networks avoiding, for example, having a childhood network on a certain disease area and an adult network on a certain disease area since this would encourage fragmentation. Furthermore, it will be increasingly important at the level of the CE to provide a seamless transition between pediatric and adult care.
- In order to advise on RD grouping, the Expert Group has compared possible lists and classifications of rare diseases, examined the pragmatic ways that networks have evolved in different places, and considered alternate classifications. What has been presented to the Commission is a synthesis of the most consensual/overlapping ways of grouping rare diseases.
- It seems likely there will be more than one call for ERNs, which might give flexibility to some of the less developed networks to combine themselves, observe what happens in the first call and enter in at a later date.
- Members of a given ERN will not all be at the same level of expertise for all of the rare diseases within that ERN, but organizing ERNs at this level will help to close those gaps.
- It is also important to remark that networks don't manage patients, centres manage patients. Centres of expertise and their own smaller networks will continue to perform the functions that they currently do. ERNs will be an overarching structure, which will provide access to a greater level of expertise and hopefully also tools to help with the exchange of information.
- In terms of the designation process, it will not be necessary for the healthcare providers or centres of expertise to be designated or re-designated to align precisely with one of the overarching themes.
- Regarding the second part of the Addendum related to the necessity of patient-centred involvement in RD ERNs, the EUCERD Recommendations for ERNs and CEs already emphasize the critical role of patient representatives and patient organizations as experts through experience and as co-producers of knowledge. Furthermore, in the Delegated Acts, a strong push towards patient empowerment and patient-centred care already exists. However, with this Addendum, the Expert Group intended that it was recognized that the role performed by RD patients can be in some scenarios even more fundamental and involved than would be seen in other disease areas.

## Discussion

The first topic of discussion was the rare **disease grouping**, focusing on the particular case of primary immunodeficiency diseases (PIDD) as an example. It was suggested that they should be included with the rest of hematological diseases. The benefit for the patient would be that if a CE specialized in PIDD is included with other hematological expert centres within the same ERN, patients not having access to PIDD in their countries of residence could be managed through the ERN.

This example served the purpose to initiate discussion regarding the different concepts of networks envisaged by the participants. Many believe that networks should integrate many centres with different backgrounds and expertise so that there is an additional value to ERNs. It was mentioned that if we take into consideration the fact that many patients do not arrive at a CE with a definite diagnosis, it is an advantage not to have too-restrictive disease groupings. In the end, the goal would be that the ERN will add efficiency and new tools for sharing expertise across different places and countries.

On the other hand, questions were raised regarding the **integration of broader centres** into ERNs based upon these disease Groupings: centres to which a wide spectrum of RD are referred, such as those in the Danish model or in countries with a low and sparsely distributed population might struggle to identify with a particular Group. This kind of centre was compared to the 'Type A' centre concept in Germany. From some participants' point of view, these centres should not be full members of an ERN. However, it was remarked that there will be three different types or **modalities of participation** in an ERN. One is to be a full partner meaning that the centre has the expertise, the capacity to provide advice to other centres and even the capacity to receive patients from abroad and treat them. The second option is to be associated and the third to collaborate, which could apply, for instance to diagnostic laboratories linked to ERNs.

Concerns were expressed as to how **small countries** without CEs participating in an ERN could still benefit from the ERNs expertise. It was clarified that patients from any country could be assisted, taking into account that the ERNs won't be able to facilitate anything that isn't already in place in terms of cross-border healthcare. *"The systems are already in place through the E112 treatment abroad scheme and the Cross-border Healthcare Directive for patients to travel if certain conditions are met. That won't change in a financial way because of the ERN. What will hopefully change is signposting to the best areas and to the best resources"*.

The question of whether the Board of Member States had decided on the **number of centres** that could be designated by a country to participate at a given ERN was raised- there is a mandatory minimum as per the Acts, but no legal maximum number of member healthcare providers. Participants expressed the opinion that information and guidance from the Board would be desirable so that there isn't too much expectation on behalf of the CEs about being nominated to participate. In addition, as things stand, each individual country is free to nominate as many centres as it considers appropriate. The general feeling was that all these issues should be approached and somehow regulated by the Board, since it wouldn't be operational to end up with very large ERNs or without representation from small countries.

On the other hand, other participants expressed the view that if a country wishes to nominate several centres based on their excellence and expertise they should not be restricted from doing so, since their participation would provide added value to the network. A possibility could be to have a few officially designated ERN centres which maintain collaborations with other centres within the country.

Attention was brought to the fact that there are **pilot networks** that have been functioning quite efficiently and which have experience that should be used to the advantage of ERNs. As one participant put it *“perhaps we need to think a little bit more outside of our traditional boxes to make ERN strong overall while respecting the expertise that's there and not bulldozing these sometimes quite fragile networks that we already have”*.

One participant asked for clarification on the term ‘**centre accreditation**’ and whether this refers to a quality standard. It was explained that the term used by the Commission is not about accreditation, but designation. However, harmonization and quality standard implementation are necessary and this is the reason for the development of an assessment manual and toolbox for ERNs. The European Commission is looking for institutions with a strong background in health technology assessment to evaluate whether nationally designated centres nominated for inclusion in a network comply with quality standards.

Finally, the pertinence of having a dedicated **genetics ERN** was discussed. This question was previously raised in the context of the EJA workshop on cross-border genetic testing of RD in Newcastle in December 2014. It was suggested that a genetics ERN could have quite clearly defined services in terms of expertise particularly in the genomics area. Also, it would potentially constitute a logical ‘home’ for undiagnosed patients and for patients that don’t fit well into disease categories. Some participants believe this would complicate matters because 80% of rare disorders are genetic disorders. Quoting one of the participants, *“if we had a special ERN for genetic diseases, then everything would be integrated into that ERN”*. It was clarified that the proposal is to constitute an ERN for genetic testing, as opposed to genetic diseases. However, it was argued that genetic testing varies according to the type of disease and that all ERNs should integrate genetic testing anyway. Additionally, genetic testing is such a fast changing field that a network built upon current expertise could be obsolete in a few years as technology is moving too quickly to be included into routine work. Others pointed out that there are a lot of well-established networks in the genetics field already, such as DYS CERNE and EuroGentest.

Nonetheless, it was reported that at the December 2014 workshop, geneticists could see a role for an ERN in many of these different areas, although quoting one of the participants *“the representative from the Commission was not very supportive of the idea because a genetics ERN would be transversal and, at the moment, we are not thinking transversely, we are thinking more horizontally”*.

To conclude, it was mentioned that it seems that there is potential for a second call for ERNs where a genetic ERN could find a place considering that, by then, *“we may be at a more stable position knowing where next generation sequencing really sits”*.

## **Closing Remarks**

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The workshop was closed by Dr Palau, who summarized the most relevant points covered during the two day event and thanked all participants for a fruitful workshop.

## Annexes

### Annex 1. List of participants

Last name, name	Country	Organization
Agius, Francis	Malta	Ministry of Health
Agra, Yolanda	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Ancochea, Alba	Spain	The Spanish Federation of Rare Diseases (FEDER)
Arias, Carmen	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Arlés, Martín	France	ORPHANET
Balciuniene, Anzelika	Lithuania	Ministry of Health of the Republic of Lithuania
Bartsocas, Christos	Greece	Medical School of Athens University
Bergström, Jonas	Sweden	Ministry of Health and Social Affairs
Bescós, Mónica	Spain	Centre for Biomedical Network Research on Rare Diseases (CIBERER)
Bushby, Kate	United Kingdom	University of Newcastle (UNEW)
Cardellach, Francesc	Spain	Clinic Hospital of Barcelona
Cardoso, Patricia	Portugal	Instituto Nacional de Saúde Doutor Ricardo Jorge
Casado, Paloma	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Corrochano, Virginia	Spain	Centre for Biomedical Network Research on Rare Diseases (CIBERER)
Cruz, Jordi	Spain	The Spanish Federation of Rare Diseases (FEDER)
Dan, Dorica	Romania	EURORDIS
Evangelista, Teresinha	United Kingdom	University of Newcastle (UNEW)
Gómez, Beatriz	Spain	Centre for Biomedical Network Research on Rare Diseases (CIBERER)
Gómez, Veronica	Portugal	Instituto Nacional de Saúde Doutor Ricardo Jorge
Einarsson, Ingolfur	Iceland	The State Diagnostic and Counselling Centre
Hedley, Victoria	United Kingdom	University of Newcastle (UNEW)
Isidro, Gloria	Portugal	Instituto Nacional de Saúde Doutor Ricardo Jorge
Izquierdo, Maravillas	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Kleina, Biruta	Latvia	Latvian Member of the Board (ERN)
Kovacheva, Irina	Bulgaria	Medical Activities Directorate Ministry of Health
Lukkarinen, Heikki	Finland	Turku University Hospital
Nogueira, Paulo	Portugal	Ministry of Health
Palanca, Inés	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Palau, Francesc	Spain	Centre for Biomedical Network Research on Rare Diseases (CIBERER)
Pérez Mateos, Carmen	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Last name, name	Country	Organization
Pérez-Jurado, Luis	Spain	Pompeu- Fabra University
Peterlin, Borut	Slovenia	University Medical Centre Ljubljana
Posada, Manuel	Spain	Institute of Health Carlos III (ISCIII)

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Rouffet, Jean-Baptiste	France	French Ministry of Health
Saiz, Isabel	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Schlangen, Miriam	Germany	Nationales Aktionsbündnis für Menschen mit Seltene Erkrankungen (NAMSE)
Seppänen, Mikko	Finland	Helsinki University Central Hospital
Severin, Emilia	Romania	Universitatea de Medicina si Farmacie
Soler, Pilar	Spain	Ministry of Health, Social Services and Equality (MSSSI)
Terol, Enrique	Belgium	European Commission
Tizzano, Eduardo	Spain	Hospital Vall d'Hebron
Trama, Annalisa	Italy	RARECAREnet
Valdmane, Antra	Latvia	Ministry of Health
Vives-Corróns, Joan Lluís	Spain	Hospital Clínic de Barcelona
Voigtländer, Till	Austria	Ministry of Health
Weinman, Ariane	France	EURORDIS
Woolley, Richard	Spain	Ingenio-CSIC

**Annex 2 Documents circulated to participants**

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EUCERD Recommendations. *Quality Criteria for Centres Of Expertise For Rare Diseases In Member States*.

[http://ec.europa.eu/health/rare\\_diseases/docs/eucerd\\_Centresexpertise\\_en.pdf](http://ec.europa.eu/health/rare_diseases/docs/eucerd_Centresexpertise_en.pdf)

EUCERD Joint Action Workshop. *Centres of Expertise for Rare Diseases: Improving Practices and Networks*. Madrid, 31 st March - 1 st April, 2014. Summary Report.

[http://www.eucerd.eu/?page\\_id=54](http://www.eucerd.eu/?page_id=54).