



## **EUCERD WORKSHOP REPORT**



**National centres of expertise for  
rare diseases & European  
collaboration between centres of  
expertise**

**Luxembourg, 21-22 March 2011**

# AGENDA

**Monday, 21 March 2011, 14:00 – 18:00**

**Session 1: Centres of expertise for rare diseases**

*Co-chairs: Concepción Colomer Revuelta<sup>†</sup> & Gabor Pogany*

14:00 Welcome address by Antoni Montserrat

*Presentation: Overview of the concepts – Kate Bushby*

*Presentation: Which model for expert care? Examples: Spain (Concepción Colomer Revuelta), Austria (Helmut Hintner), Luxembourg (Yolande Wagener)*

*Discussion: Which model for expert care? Health care pathways versus coordinating centres and expert centres (Missions and financing)*

16:00 Coffee break

16:30 *Presentation: Overview of the concepts – Kate Bushby*

*Discussion: Defining the scope of expert centres: Disease coverage and links with university hospitals and medical specialties / recommendations for organisation by size of country*  
Conclusions and further steps

18:00 End of the workshop

**Tuesday, 22 March 2010, 9:00 –12:30**

**Session 2: European collaboration between expert centres, healthcare pathways and European Reference Networks**

*Co-chairs: Kate Bushby & Yann Le Cam*

9:00 *Presentation: Overview of the concepts – Kate Bushby*

*Discussion: Prioritisation of areas for European Reference Networks*

10:30 Coffee break

**Session 3 : Designation criteria for national centres of expertise**

*Co-chairs: Kate Bushby & Yann Le Cam*

11:00 *Discussion: Designation criteria of the HLG/RDTF and feedback from Member States on their application at national level*

12:30 End of the workshop

# SUMMARY REPORT

## General Introduction

One of the objectives of the European Union Committee of Experts on Rare Diseases (EUCERD) is the surveillance of initiatives and incentives in the field of rare diseases at European level and at member state level. A report has been produced detailing initiatives and incentives in the field at EU and MS level prior to 2009 and during 2009 entitled: *2009 Report on Initiatives and Incentives in the Field of Rare Diseases of the European Union Committee of Experts on Rare Diseases*<sup>1</sup>. The analysis this report led to the decision to explore in further depth the area concerning centres of expertise for rare diseases and European Reference Networks of Centres of Expertise (ERNs) for Rare Diseases. Centres of expertise and ERNs in the field of RD are mentioned in the High Level Group (HLG) on Health Services and Medical Care Report of November 2005, the Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of Regions on Rare Diseases: Europe's challenges (11.11.08) and the Council Recommendation on an action in the field of rare diseases (08.06.09), as well as in the recommendations for National Plans and Strategies for Rare Diseases (Europlan) and in Point 15 of the draft Cross-Border Healthcare Directive - the amendments of the European Parliament of this directive were approved by the Council of the European Union on 28 February 2011.

In order to build on previous work in the field of national centres of expertise and ERNs, there was a need to examine the experience of national centres of expertise, to examine the experience and outcomes of the pilot ERNs financed by DG Sanco and to revise recommendations and guidelines in these areas in the light of these experiences.

To launch this work, a workshop was organised on 8-9 December 2010 in Luxembourg which was attended by 32 experts. The first session of the December 2010 workshop concentrated on centres of expertise at national level in Europe with an overview of the concepts and current situation, followed by presentations on the application of the concepts in some Member States (France, Italy, Denmark, Germany and also Norway). For this first session, a draft Orphanet Report Series listing designated centres of expertise in Europe in the Orphanet database was provided to participants as supporting documentation. The second session was dedicated to European Reference Networks with an overview of the concepts and current situation, followed by examples of the application of the concepts in different European networks (Care NMD, EPNET, TAG). Prior to the workshop the participants

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<sup>1</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

received a draft preliminary analysis of the outcomes and experiences of pilot ERNs prepared by the Scientific Secretariat.

The discussions and conclusions of this workshop can be found in the workshop report which can be accessed via the EUCERD website<sup>2</sup>.

As a result of this workshop it was decided to hold a workshop on 21-22 March 2011 to discuss in further depth a number of priority topics identified during the December 2010 workshop. Firstly, the December 2010 workshop established a consensus that expertise needs to be identified at national level before networking of expertise at European level can take place. It was therefore decided to concentrate in greater detail on the organisation of expertise at national level including the following topics: the models of organisation of expert care at national level according to country size (health care pathways versus a system of coordinating centres and expert centres); defining the scope of expert centres in terms of disease coverage and links with university hospitals and medical specialties including reflections on recommendations for organisation by size of country; and quality designation criteria established by the EC Rare Diseases Task Force (RDTF) and HLG for national centres of expertise for rare diseases in view of the experiences of Member States (MS). It was also decided to discuss European collaboration between expert centres, healthcare pathways and European Reference Networks and reflect on this question in the light of the future Cross-Border Health Care Directive in which ERNs for rare diseases are explicitly mentioned in Point 15.

This workshop was led by Kate Bushby (Vice-Chair of the EUCERD, Treat-NMD) in the absence of Ségolène Aymé (Chair of the EUCERD, Orphanet) and Karl Freese (DG Sanco C2) represented the European Commission in the absence of Antoni Montserrat (Policy Officer for Rare Diseases and Neurodevelopmental Diseases, DG Sanco C2); both absences were due to health-related problems and the participants of the workshop transmitted their best wishes for speedy recoveries.

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<sup>2</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf>

## SESSION 1: NATIONAL CENTRES OF EXPERTISE FOR RARE DISEASES

### 1. Centres of expertise: Which model for expert care? (Kate Bushby)

Kate Bushby presented an overview of the concepts and consensus reached in the field of national centres of expertise for rare diseases.

One of the main issues highlighted was the need to analyse the experiences of countries with national centres of expertise for rare diseases and use this analysis to improve the provision of expert care for all patients with a rare diseases. The question of how to maximise the resources of centres of expertise, should also be revisited.

National centres of expertise have been highlighted in the Commission Communication "Rare Diseases: Europe's challenge" of 11 November 2008 and the Council Recommendation of 8 June 2009. There is a strong agreement that national centres of expertise should be established in the framework of national policy for rare diseases, however there has been no analysis so far of past experience in MS where there are centres of expertise in place, except in France.

National centres of expertise for rare diseases should provide healthcare services to patients with conditions requiring a particular concentration of resources and/or expertise, provide cost-effective, high quality care and provide focal points for medical training and research, information dissemination and evaluation.

The RDTF has produced two reports on national centres of expertise, *RDTF Report: Overview of Current Centres of Reference on rare diseases in the EU - September 2005*, and *RDTF Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – September 2006*. For this workshop, the Scientific Secretariat of the EUCERD has produced the following additional documents: Orphanet Report Series: *Designated centres of expertise for rare diseases in Europe* (February 2011); EUCERD Workshop Report: *Centres of expertise and ERNs for rare diseases* (December 2010); and the EUCERD supporting document: *Centres of expertise for rare diseases – Overview of situation at country level* (March 2011). These documents highlight that not all countries have a designation process in place and that expert care is organised differently from country to country. However there is an agreement on the following criteria for national centres of expertise for rare diseases established by the HLG and RDTF which fit the criteria used by countries who currently designate centres for RD:

- appropriate capacities to diagnose, to follow-up and manage patients with evidence of good outcomes , where applicable;

- sufficient activity and capacity to provide relevant services and maintain quality of the services provided;
- capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control;
- demonstration of a multi-disciplinary approach;
- high level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities;
- strong contribution to research and involvement in epidemiological surveillance, such as registries;
- close links and collaboration with other expert centres at national and international level and capacity to network;
- close links and collaboration with patients associations where they exist.

These designation criteria can be applied to national centres for different groups of diseases or specific diseases. There is also an agreement on the designation process: designation at country level can follow one of the following models: through a call for proposals (bottom/up), or a public health plan (top/down). The bottom/up method is more pragmatic whereas a top/down approach is more ambitious.

MS with no designation process in place should be encouraged to put into action either a designation or identification policy, or should establish contracts with expert centres abroad in order to provide care for all patients with a rare disease. MS with a designation process in place should share their experience with other countries and should harmonise their approaches and designation quality criteria for centres of expertise. This will be crucial in the context of the Cross-Border Health Care Directive as there must be an assurance that the quality of centres of expertise is the same from country to country for this system to work.

A consensus has also been reached that without some centres of expertise already existing at national level, there is no possibility for European networks. However, in issuing recommendations, the responsibilities of MS for the organisation, financing and delivery of healthcare must be respected. Recommendations must also take into account the diversity of health care systems and economies and the differences between large/ medium/ small size countries in respect of both geography and population.

The definition of what constitutes a national centre of expertise differs from one country to another, for example in countries with either a national or regional approach where the definition will reflect the heterogeneity of their national health care systems. Some countries have specialised centres (by disease or group) and/or generalist centres (for all RD): these different types of organisation reflect differences in the size of countries. Some national centres are uniquely clinical whilst others undertake clinical research, whereas others have a focus on technology and/or expert intervention (e.g. as is the case in the UK).

Some national centres of expertise focus on the management of patients whereas others focus on expert advice/ production of guidelines: many centres do both.

A number of issues therefore need to be further discussed around the themes of the missions of national centres of expertise and their financing. In terms of the missions of these centres, how should health care pathways at local/regional/national level be organised, should centres focus on the management of patients or on giving expert advice and producing guidelines (or both), and which European dimensions can be envisaged when expertise is not available nationally? In terms of the financing of centres of expertise, should this be done through the healthcare system or through an extra dedicated budget?

Following this overview, presentations of the organisation of expert care for rare diseases in three different sized countries were given, with the examples of Spain as a large country, Austria as a medium-sized country and Luxembourg as a small country.

## 2. Organisation of expert care for rare diseases in Spain (Concepcion Colomer Revuelta <sup>†</sup>)

In Spain, a Royal Decree of 2006 established the conditions regarding the procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish National Health System. Diseases must have the following characteristics in the framework of this Decree:

- a) Diseases that for their adequate care require preventive, diagnostic and therapeutic techniques, technologies and procedures of a high level of expertise requiring experience in their use, which can only be acquired and maintained through certain volumes of activity;
- b) Diseases that require high technology for their prevention, diagnosis or treatment and for which, in view of their cost-effectiveness and the available resources, the concentration of a minimum number of cases is required;
- c) Rare diseases which, because of their low prevalence, require a concentration of cases for their adequate care, which does not imply the ongoing care of the patient in the reference centre, service or unit, but can act as a support for diagnosis, therapeutic and follow-up strategies and as an adviser for the clinical units that usually treat those patients.

The aims of the CSUR are: patient safety, equitable access, quality of care, effectiveness/scientific evidence, efficiency and NHS sustainability.

In Spain, a Designation Committee has been established which is charged with studying identified needs and proposing pathologies or diagnostic/therapeutic techniques, technologies and procedures for which a CSU needs to be designated. Groups of experts are

appointed by the Autonomous Communities, scientific societies and the Ministry to define the criteria for each kind of CSU. Once the criteria have been agreed upon, a application period is opened and the Autonomous Communities can present proposals for their CSU through the Designation Committee. Once they have been admitted for processing, applications are sent to the Spanish NHS Quality Agency for audit and accreditation. Accreditation reports are sent to the Committee that studies them and submits its proposals for designation. The Ministry at the suggestion of the Designation Committee and with the prior consent of the Interterritorial Council, decides on the designation of the CSU.

Designation is for a maximum period of 5 years and can be renewed after a re-evaluation by the Spanish NHS Quality Agency.

The designation criteria are based on: professional experience (training, research, activity, multidisciplinary team work), human resources and facilities of the CSU, human resources and facilities of the hospital/others, outcomes and output indicators, and the information system (activity and evaluation of services).

From 2007 – 2010, 10 areas of specialisation have been selected (including ophthalmology, oncology, orthopaedics, cardiology including paediatric cardiac surgery, neurology including paediatric neurosurgery) and 221 experts have worked on the definition of criteria. 46 diseases and techniques have been agreed upon for CSU designation and quality criteria have been defined for them. 132 reference CSU have been approved for 35 diseases or techniques, and 27 reference CSU have been approved for rare diseases. Patient representatives have participated in the National Strategy working groups to define needs and identify the CSU that are reported to the Designation Committee. An information system for planning, following up and financing has been developed.

The Spanish approach to identifying and designating national centres of expertise can therefore be seen as a mix of the top/down and bottom/up approaches.

The aim of the Ministry of Health is for rare disease patients to be followed up as near as possible to their home and the principal mission of the CSU is to provide advice and second opinion.

The Spanish Rare Disease Strategy will thus focus on identifying groups of diseases and will examine where there are needs for diagnosis and for care and which type of service should be provided. What exists and what is lacking at national level will therefore be examined. A key priority for Spain is to direct the patient and provide proximate care.

### **3. Organisation of expert care for rare diseases in Austria (Helmut Hintner)**

In Austria there are three public medical universities one private one. And, as the public health system is of a high quality, patients with rare diseases are sufficiently cared for. However, experts believe that there is room for improvement.

In Austria there are several but unofficial, centres of expertise in place – one of them is for Epidermolysis Bullosa called 'EB Haus' at the Department of Dermatology at the Medical University of Salzburg.

This centre was established in 2005 at the initiative of a patient organisation founded in 1985. The establishment of the centre cost 1.7 million € and was funded by the Austrian Ministry of Health and other sponsors. The centre annual costs of 800 000 € are covered by patient organisations' active fundraising.

Multi-disciplinary care is provided by this centre on an outpatient basis, and if patients need to be admitted, they are admitted to the clinical centre. The centre has strong links with research, has an excellent laboratory and will start gene therapy trials in 2012. The centre runs training sessions and treats in total 281 patients from 18 countries, with many patients seeking a second opinion.

A coordinating centre for rare diseases was established by 1 January 2011 at the Austrian Health Institute (Gesundheit Österreich GmbH), funded by the Ministry of Health. One of its first tasks is to assess the needs of patients and health professionals regarding rare diseases and to continue the work on the National Plan for Rare Diseases that was started by Dr. Voigtländer, the national Orphanet coordinator. A number of meetings and conferences were held in Austria as well as attended by national experts, a helpline for rare diseases is open for 2 hours a week. There is currently no umbrella organisation for rare disease patients in Austria, but the foundation process is planned to commence in summer 2011.

### **4. Organisation of expert care for rare diseases in Luxembourg (Yolande Wagener)**

Luxembourg is a country with 500 000 inhabitants with no national plan or national programme for rare diseases. The results of a national survey were launched on 28 February 2011: this survey was carried out to discover the needs of rare diseases patients in Luxembourg. 202 rare disease patients replied representing 91 different rare diseases.

The results show that 53.9% of rare disease patients are treated in Luxembourg, but 95% of patients travel to neighbouring countries (in most cases to Germany) in order to receive health care.

Luxembourg has been coordinating with neighbouring countries' health insurance systems for many years now and the free circulation of patients is authorised following a request by

the patient or the medical prescriber which is then authorised on the basis of EC Regulation 883/2004. A number of agreements have been established with other EU MS and countries in the European Economic Area. Cross-border healthcare amounted to 17.5% of health expenditures in 2009. It was highlighted that patients with rare diseases also travel to Luxembourg in some cases to obtain better quality care.

In Luxembourg there is no 'entire' medical university, just classes for first year students. However, there are many medical universities in neighbouring countries, and there is a long tradition of close collaborations between Luxembourg and their neighbours in these institutions which reinforces links and collaborations.

However, there are problems with the coordination of care, with patients treated by a number of different doctors and 28% of rare disease patients replying that they felt as they were the 'coordinator' of their health care.

It can be seen that cross-border healthcare is ultimately organised through personal contacts and there are very few 'organised' collaboration conventions by disease with few interdisciplinary management projects for 'global care'.

Problems surrounding reimbursement were also highlighted: 18% of patients paid themselves for medical care and treatment and 10% of patients renounced psychological support. It was also seen that 20% did not access specific medical care. A significant percentage of respondents (71%) also cited the linguistic problems implicated in seeking health care in another country.

Discussions after this presentation highlighted that Luxembourg, as a geographically small country with a small population centrally placed in the European Union has the nearest to a 'European approach' with resident patients seeking treatment in neighbouring countries and residents of neighbouring countries seeking treatment in Luxembourg.

## 5. General discussion

Examples were given in the general discussion of the organisation of expert care for rare diseases in other countries.

In **Norway** centres of expertise are organised around disease clusters with some specific centres (i.e. Cystic Fibrosis) with a few coordinating centres. Norway seems to use both models of expert care organisation for rare diseases, health care pathways plus coordinating centres and expert centres.

In **Belgium**, the King Baudouin Foundation is preparing, on request of the Minister of Health and Social Affairs, a proposition for a Belgian Plan for Rare Diseases. This proposition is elaborated in two phases. In their proposition concerning the first phase of the plan they foresee a system of coordination centres and centres of expertise per group of rare diseases.

They have also formulated a set of criteria. But this proposition is still under discussion. Furthermore, Belgium already coordinates with other countries to enlarge their genetic testing offer and is willing to cooperate with other countries lacking such expertise.

Participants highlighted that patients needing expert care should not be left without a centre of expertise. The example of the Second **French** National Plan for Rare Diseases (2011-2014) launched on 28 February 2011 is an example of a pragmatic, bottom/up approach to designating centres of expertise for rare diseases (see presentation of the French approach in the report of the previous December 2010 workshop). The third and fourth calls for designations of national '*centres de référence*' in France focused on the diseases which were not already covered. It was also decided to create regional centres, closer to the place of residence of the patient, called '*centres de compétence*' during the First Plan. However, at the end of the First Plan, not all rare diseases were covered. The Second Plan therefore foresees the organisation of centres of reference and competence in around 20 different networks/health care pathways by medical field. These vertically organised networks will provide links between research and diagnosis, and between clinical and social care. Local experts and the designated centres of reference at national level will work in conjunction sharing common tools and resources (i.e. laboratories and registries). The key concept is think in terms of health care pathways and improving the possibility for patients to be well orientated and find expertise at national or European level. Participants highlighted that only by networking horizontally with other European countries can all rare diseases be covered.

The example of the organisation of care in **Hungary** was given: this approach is a pragmatic one, focused on patients' needs. Two main factors are to be considered for Hungarian national centres of expertise: the presence of equipment for diagnosis, and personal expertise of the medical professionals in the centre. In Hungary, the need for 5 rare disease centres playing a coordinating role has been identified. The 4 existing medical universities could play this role, but it has to be assured that the adequate expertise is provided in these centres. Healthcare pathways will be considered as will interdisciplinarity, which should be a key feature of the designated national centres of expertise in the Hungarian strategy. It was highlighted that the rarer the disease, the fewer evidence-based guidelines available and therefore there is an increased dependence on the personal expertise of professionals.

In **Germany** in 2010, the NAMSE group was established and 4 working groups on the areas of information, diagnosis, research, care and networks were established. The diagnosis working group noted that some people sometimes did not have a diagnosis. A number of self-designated centres of expertise have been established according to self-defined quality criteria. For Germany, the principal need now is to reflect on what a centre of expertise for rare diseases should be, and ideally these criteria should be flexible enough to accommodate developments at EU and national level and be transposable to the national framework.

In **Italy**, where health care is the responsibility of the regions, some regions are more advanced than others in the designation of centres of expertise for rare diseases. There is no homogeneity in the current designation process.

**Spain** also has a decentralised political structure, like Italy and Germany, and at national level, the experience is similar to what is happening at European level in the Member States. At state level, quality and equality is ensured through consensus as regions are not obliged to provide their services in a specific way, as is the case in Europe. Although at EU level we cannot dictate designation at EU level, it is possible to reach a consensus between nations, but we have to understand the complexity at national level and therefore a top/down approach will not be feasible but national systems can be built with the quality criteria recommended at EU level in mind.

In **Norway**, new recommendations concerning the regulation of hospitals are soon to be put into place, including criteria for centres of expertise. Norwegian centres would be very interested in joining ERNs.

It was drawn to the attention of participants that the next stage of the Europlan project foreseen in the context of the Joint Action on Rare Diseases (which will start in January 2012) will focus on analysing the current situation by country in terms of centres of expertise and designation criteria.

One of the discussions following the presentation discussed the possibility of examining the prevalence of rare diseases across Europe and determining where rare diseases patients are and how many centres are needed to cover all rare diseases and designating centres in a top/down approach. This approach is very ambitious: population registries do not currently collect the data to achieve this. It was also suggested that diseases not covered by the pre-existing centres could be 'attributed' to existing centres in order for all diseases to be covered at MS level.

It was generally agreed that centres of expertise need to be identified and designated using the concepts established by the HLG and RDTF, but that networks of experts also need to be considered and individual expertise identified at national level. The identification of individual experts may be more pragmatic in smaller-sized countries than the identification/designation of national centres of expertise, and that the identification of individual expertise may benefit patients with a disease without a centre and provide geographically close expert care where a centre could not have provided this. Some pilot ERNs have worked on identifying this individual expertise at the European level. The question of the criteria for identifying individual expertise should be raised, in this case.

Participants suggested that some very specific centres of single diseases or groups of diseases are needed (especially where specialised techniques and technology are needed to manage the disease) and that some generalised centres for rare diseases should be considered in order to coordinate the care of patients and orientate them in the health care

system. Commonalities between diseases should be sought in order to cover a maximum number of diseases when organising expert care at national level. The quality criteria for national centres of expertise should also be adapted to the disease/group of diseases dealt with by the centre. Participants suggested that it was unrealistic to provide uniquely disease specific/group specific centres as without more generalised rare disease centres it is probable that some patients will have difficulty obtaining the diagnosis which will orientate them towards the appropriate disease-specific expert centre.

Discussion on the subject of how to link what is done at national level to recommendations at EU level (and vice versa) also highlighted the need to link specific actions in the field of rare diseases with the existing missions of national health care systems and to find the best links between the two.

If there are guidelines for specific diseases, they should be disseminated to all health care professionals that may treat rare diseases and also encourage professionals to apply guidelines for both common and rare diseases.

Obtaining a diagnosis was highlighted as a key issue: even the larger countries in Europe are unable to provide a genetic diagnosis test for all rare diseases. Each MS should identify which diagnosis can be made in their country and then devise decision trees to determine what to do in these other cases where a diagnosis can perhaps be provided in another EU MS. Vertical networks should have the responsibility for following up on this diagnosis. The example of the UK was cited: in the UK there is a genetic testing network and information is provided on which tests are provided by which laboratories. Each laboratory has a budget for sending tests elsewhere to achieve a diagnosis.

There is a consensus that research and clinical care should both be missions of centres of expertise: it was highlighted that clinical researchers usually have European contacts whereas clinical practitioners sometimes do not, which are crucial for networking.

Concerning the quality criteria of centres of expertise, it was highlighted that in many countries criteria such as the HLG criteria have been applied, and in France the centres applying for designation must explain how they will reach these criteria if they are not already in place, and what they will do 5 years from the time of designation. They are also self-evaluated 3 years after designation and externally evaluated at 5 years against the objectives set at the time of designation by the centres themselves, to determine possible renewal of designation.

It was agreed that ongoing quality indicators for centres of expertise are needed. The example of the Care-NMD network was cited as an example of monitoring the implementation of guidelines for quality care in centres and ensuring centres of fulfilling quality criteria.

Concerning quality of care guidelines, the example of the European Association of Hemophilia was given: this association has prepared a consensus document with experts in the field and centres of expertise with guidelines to be applied to ensure expert care. It was suggested that a similar set of quality criteria should be established for each group of diseases derived from the quality criteria for centres of expertise established by the HLG and RDTF.

National plans for rare diseases must therefore consider this European dimension, especially in relation to the designation quality criteria for national centres of expertise. It should also be born in mind that disease communities are not sufficiently aware of what happens in the RD community, and vice-versa. The potential role of scientific societies should also be explored in greater depth.

## 6. Centres of expertise: Scope of expert centres (Kate Bushby)

The scope of expert centres in terms of disease coverage is an important issue, as at national and European level expert care should be provided for all rare diseases patients. In order to stimulate discussion on this topic, the EUCERD Scientific Secretariat prepared a scoping document detailing by medical speciality the specific diseases and groups of diseases for which an officially designated national centre of expertise exists or for which a national centre of expertise by reputation in a country has been identified. This information has been extracted from the Orphanet database.

Three or more countries have designated centres for the following diseases/groups of diseases and a consensus can be identified that centres are required, on the base of experience, for:

- Juvenile arthritis/rare paediatric rheumatological diseases
- Developmental anomalies and malformations/dysmorphology
- Rare dermatological diseases
- Epidermolysis bullosa
- Prader-Willi syndrome
- Haemophilia and other constitutional bleeding disorders
- Mastocytosis
- Hereditary diseases of the metabolism
- Lysosomal diseases
- Porphyrrias
- Rare epilepsies
- Neuromuscular diseases
- Amyotrophic lateral sclerosis
- Rare pulmonary diseases

- Severe pulmonary hypertension
- Cystic fibrosis
- Rare genetic kidney disease
- Rare cranofacial anomalies
- Rendu-Osler disease

Most CE fit into the traditional organisation of healthcare by medical speciality. The scoping document also shows the necessity of some grouping outside of traditional medical specialities (i.e. transversal), i.e. diseases of the connective tissue, rare bone diseases, neurofibromatosis, multimalformation syndromes with intellectual disability, any multi-systemic complex disease, etc.

Questions that need to be considered are: whether centres should be mainly organised by medical specialties, whether there should be a prioritisation of needs, and whether different methods of organising care should be suggested according to country size?

## 7. General discussion

The discussion following this presentation highlighted that the scope of national expert centres in terms of disease coverage is closely related to the organisation of health care in each country, and the discussions continued from the previous session.

Participants commented that the scoping document provided a number of interesting observations and it should be considered why the diseases which are present have a designated national centre, and why other diseases do not. Is this because some diseases do not need a centre because the treatment/medical management of the disease is simple? Is the best way to identify which groups of diseases or which more common groups need designated national centres?

Health care is traditionally organised by medical specialty in most health care systems, and expertise for rare disease is therefore most pragmatically organised along these lines. Participants considered the problems of a strong medical focus resulting from the organisation of expert care by medical specialities: for example, in the case of intellectual disability there are specific needs, and perhaps an organisation of care in clusters focusing on these needs could be another interesting, interdisciplinary approach. It was stressed, however, that specialisation is needed to make a diagnosis.

When considering an approach by medical speciality, which would capture most rare diseases, there has to be a degree of flexibility as some rare diseases/groups of rare diseases need specific skills and networks. Perhaps around 40 areas, either broad fields or specific diseases, could be suggested with links between medical specialities and these groups. The key consideration is flexibility, so as to group diseases in a way that leaves no patient out.

Participants voiced the opinion that a top/down approach aimed at covering all rare diseases should be treated carefully, as if, for example, a medical university department for pulmonary diseases is designated as the national expert centre, it is not necessarily true that the department has expertise in all rare pulmonary diseases.

Discussions highlighted the importance of interdisciplinary in the diagnosis and care of patients with rare diseases. If an organisation of national expert centres by medical speciality is to be recommended (as this seems to be the most pragmatic approach), so should interdisciplinary units as many rare diseases fall into a number of different medical specialties and adequate coordination should be provided between these specialties in order provide quality care for rare disease patients. The example of tumour boards was given where experts from a range of specialities meet to discuss specific cases as a way of coordinating between specialties. It was suggested that medical professionals need to be educated to look at the patient as a whole, like a paediatrician, as many specialists forget to do so.

Rare disease patients often have a range of different needs: medical, social, socio-medical, respite, research. The example of the organisation of national centres of expertise in France was given to illustrate that multidisciplinary is a key issue: in France, some patients (especially those with psychological problems) have to depend on a number of different 'centres de référence' for their specific disease.

The question of the hierarchy of expertise (and in particular, the question of whether expertise should be embodied by a centre or by an individual) was raised, including the issue of whether a centre should move with the head expert of the centre if this expert changes locations. It was highlighted that in WP6 of the FP7 project EuroGenTest has established core competence criteria for the designation of experts in medical genetics. Countries such as France have responded by organising their health care in a step-wise fashion, by first organising medical professionals (through reference centres and competence centres) in preparation for the organisation of European networks of national centres of expertise. Research then has to be organised, followed by social and medico-social aspects at local and regional level.

The question of rare cancers was also raised, highlighting the fact that the diagnosis and care of rare cancers may better fit into organ-specific specialties than oncology. It was also highlighted that for rare cancers, in Italy and France, these diseases are covered and designated in the framework of a national plan for cancers, and are not included in strategies for rare diseases. In France, the national cancer plan has a specific section on rare cancers, which was inspired by the first national plan for rare diseases.

It was highlighted that the lack of designated national centres of expertise does not implicate a lack of expertise in a country. Indeed, many non-designated centres fulfill many of the HLG/RDTF criteria and have proven to attract patients. Designation implies the

responsibility of the state, in terms of sustainability, financing and monitoring. Participants agreed that the stability of national centres of expertise, in terms of personnel and financing, is vital. Succession and transition planning should be a key requirement of centres of expertise, as should the coordination of care between specialties, with perhaps a dedicated coordinator in charge of this task.

It was highlighted that with the start of the Joint Action for Orphanet in April 2011, Member States' health authorities will be implicated in the governance of the database and the representation of centres of expertise in the database will be rethought to represent officially designated national centres and other centres which have been recognised as having expertise in order to better identify expertise at a national level.

Another issue highlighted was the continuity between childhood and adulthood care. In France, centres of reference must assure the transition between child and adult care by organising links with adult hospitals and establishing a consultancy team at the adult hospital in the first year of transition in order to transfer expertise from the paediatric to the adult hospital team.

Outcome indicators and guarantees of quality are key to monitoring and ensuring the expertise of a national centre and that expert centres maintain levels of quality. Also one expert can be the basis to designate a centre of expertise, but this is not the most sustainable solution, and sustainability and continuity are vital criteria to be considered.

It was also once again highlighted that not all rare diseases can be covered at national level by national centres of expertise and that European networking is the only possible solution.

The Cross-Border Health Care Directive was discussed as a possible legal framework for providing expertise for all rare disease patients in Europe. In the context of this Directive, explicit designation procedures for European reference networks are needed and homogenisation of criteria and designation of national centres of expertise across Europe is also necessary. Participants were reminded that, concerning the designation of ERNs for rare diseases, prevalence of the diseases will be the key criteria in this political framework.

It is vital to examine the organisation of expert care in each country and to reassure patients that they receive quality expert care. General quality criteria for national centres of expertise need to be confirmed, and afterwards so do specific criteria for specific diseases/groups of diseases. It is clear that specific criteria can be extrapolated for certain diseases/groups of diseases from the RDTE/HLG criteria for centres of expertise, and refining the definition of centres of expertise in the perspective of the disease group is a type of work already carried out by some disease-specific groups of experts and learned societies and this work should be built upon. Criteria for disease areas are needed to preserve this expertise. We should look at a way of saving the pre-existing ad hoc nuggets of excellence and not sweep them away with new designation processes at national level. RDTE/HLG criteria can be used as the starting point for designation of national centres of expertise, and these centres of expertise

in each MS will then work together as a European network to share tools, expertise, guidelines, etc.

It was highlighted that in many cases in the field of rare diseases, networks are generated in an almost spontaneous way; experts see patients, are identified as having expertise and see more and more patients, they talk to families, they help establish patient groups, they start research and they then realise there are other experts in Europe and start collaborating with these contacts.

It was suggested that networking for more common rare diseases should be between centres of expertise as these will be more easily established, and then networking of experts for more rare RD could be envisaged as networking between centres of expertise for these diseases is for the moment premature.

Individual expertise and centres must be identified at MS level, otherwise patients will seek care unnecessarily abroad where it may possibly exist at national level. Patients should only travel abroad to find real expertise, i.e. centres which are lighthouses for clinical care and research excellence in their domain. Even if centres are not established for each rare disease, but for groups of rare diseases, the diseases treated by these centres should be clearly indexed in Orphanet so that patients at national level know which centre treats their disease.

It was highlighted that the ENERCA network has a working group dedicated to the legal and ethical framework for referral between centres of expertise participating in a network and has carried out a comparative analysis which could be of use to the working group.

Quality management systems should be considered in the optic of national centres of expertise and ERNs for rare diseases. A preliminary European standard on quality management systems in health care services (prEN 15004 based on EN ISO 9001:2008) is currently being developed.

In conclusion, the scoping document shows us which areas based on experience require centres of expertise. We also need to take into account the priorities that can be signaled by patient organisations. We also need to consider the relative geographical size of countries and their populations in order to consider the need for Cross-Border Health Care in order to access expertise lacking at national level. However, it is important to note that national centres of expertise have a duty first and foremost to their citizens.

Participants agree that there is a need to capture all rare diseases, and having broader centres by medical group can achieve this, with specialised groups for complex diseases when needed which should link across specialties and be truly transversal. It should also be borne in mind that a diagnosis has to be made.

The organisation by speciality of expert care demands a better education of medical professionals so that they recognise rare diseases in their specialty to refer on to experts.

Ideally, each speciality's learned society should be involved in identifying a list of centres of expertise needed in their specialty to cover rare diseases along with the disease-specific quality criteria for these centres: some learned societies have already done this work in published guidelines.

## SESSION 2: NETWORKING BETWEEN CENTRES OF EXPERTISE, EUROPEAN REFERENCE NETWORKS AND HEALTH CARE PATHWAYS

### 1. European Reference Networks of Centres of Expertise: Overview of the Concepts (Kate Bushby)

An overview of the concepts in the field of European Reference Networks of Centres of Expertise was presented. Much work has already been carried out in this area by the RDTF and the HLG, including a report in 2008 of the RDTF entitled *European Reference Networks in the field of rare diseases: state of the art and future directions*. The EUCERD Scientific Secretariat has revised since the December 2010 workshop on centres of expertise and ERNs for rare diseases the draft of the *Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for rare diseases*, and has also provided a draft Orphanet Report Series listing designated national centres of expertise for rare diseases in Europe, and a Orphanet Report Series listing the networks in the field of rare diseases supported by DG Sanco and DG Research<sup>3</sup>.

The preliminary analysis of the ERN highlighted the following observations:

- ERNs' activities are extremely heterogenous with different types of networks for different needs;
- many networks have activities which are similar to those funded by DG Research, and many DG Research networks have care components so we must consider the output of networks not funding streaming;
- the geographical coverage of networks is heterogenous (not all EU MS are covered by each ERN);
- the challenge of durability of funding/sustainability of networks is a significant one;
- no analysis of the experience and outcomes of ERN has yet been conducted at EC level;

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<sup>3</sup> Orphanet Report Series - European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases & European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases - November 2010

<http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

- that the strategy of pilot ERNs is generally in line with the recommendations of RDTF/EUCERD that expertise (or experts) should travel, rather than patients.

It can be seen that research networks share data through systematic collection of patient data, share repositories of biological samples, and share expertise for research purpose. Public health networks mostly share clinical experience to sort out difficult cases, produce clinical guidelines /information and document the natural history of diseases.

Networking is foremost about collaboration and sharing, both sharing expertise (case management /tele-expertise, production of standards of care/ information packages / training / education, and multidisciplinary research, etc.) and sharing tools (ICT tools for sharing expertise, ICT tools for disseminating information, databases /cohorts/ biobanks, etc.)

A number of agreements have already been reached:

- there is a clear distinction between the missions of centres of expertise and of European Reference Networks;
- a ERN is not a supra-centre;
- the current networks are more networks of experts, not networks of designated national centres;
- expert care and clinical research go together and both activities belong in the same network;
- ERNs contribute to derisking R&D;
- the establishment of ERNs requires long term effort and is a process;
- it is waste of money to establish ERNs if renewal of funding is not feasible.

A number of other details need to be further considered, including the question of prioritisation. As funding will always be scarce, prioritisation for European Reference Networks will be necessary, but we need to tackle how to prioritise networks (should we consider a top/down approach or a bottom/up approach?) and how participating centres should be selected? The prioritisation criteria for ERN could include the European added-value of the network, the degree of complexity of the clinical management of the disease, the presence of innovative clinical research, the cost of management and the possibility to improve health outcome.

The composition of networks and their dynamic also has to be considered: should only designated centres of expertise be included and what should the expansion process be?

Also, we need to consider which designation and evaluation process needs to be established for ERNs and which body will do this with which indicators.

The question of sustainability is another key matter and the issue of which funding mechanisms and funding bodies should be considered.

Finally the implications of the Cross Border Health Care Directive in respects to these questions must be addressed, notably in the forthcoming Joint Action to implement the Cross-Border Health Care Directive.

Now we must consider which reference networks can and should be developed as well as the core group of activities that reference networks need to address. We should also consider the prioritisation of resources. Perhaps when considering sustaining existing networks, it should be taken into account whether the networks have made efforts to expand and how. The question of whether existing networks should be sustained at European or national level needs also to be addressed.

It was again highlighted that European networks should be a key component of national plans or strategies for rare diseases.

There are overlaps between research and public health networks, and there needs to be a flexibility to accommodate different models. It should be highlighted that research in the field of rare diseases can only take place with networking.

These pilot ERNs have been formed pragmatically, and group together recognised expertise, if not designated centres of expertise as at a national level designation has sometimes not yet taken place. European networks have to be dynamic to adapt to the situation at national level.

The designation of ERNs in a uniform way should be considered in the context of the Cross Border Health Care. ERNs should aim to reduce the need for patients to travel by sharing expertise. ERNs should also share expertise on networking with other aspiring networks.

It should also be highlighted that networks need a dedicated full time coordinator with expertise in networking.

The EU has invested financially in creating resources and networks and these resources and networks should now be fed into national plans for rare diseases and built upon.

In conclusion, higher priority should perhaps be given to diseases with complex clinical management and innovative clinical research, as there are a limited number of funding opportunities for networks. Although the prioritisation criteria and the validity of this idea have been discussed, this issue needs to be worked on further. In terms of the participating centres and groups in these networks, we currently observe a stepwise approach of self declaration, followed by acceptance by the network. The networks currently in place concentrate on training, producing information and guidelines as well as sharing resources such as registries and tools for teleexpertise. If the commitment of MS is to be sought, there is a real need to discuss the resources and infrastructures that can be shared instead of discussing networks of centres of expertise as it is too early to do so as many countries have

no designation process in place. Finally, it was highlighted that networks should also consider the use of outcome and process indicators to evaluate their activities.

## 2. General Discussion

The EUCERD can play a main role in the future of ERNs for rare diseases and possibly in the content of the foreseen Joint Action (TBC) to implement the Cross-Border Health Care Directive. Indeed, the EUCERD will play a role, not in setting standards for legislation, but by informing the European Commission on the implementation of recommendations and directives in the field of rare diseases and any need for further legislation in order to follow up recommendations and directives. In the context of the Cross-Border Health Care Directive, the field of rare diseases has informed debate on patient rights and cross border health care, although the Directive is aimed at all diseases. Participants commented that the criteria for national centres of expertise need to be concrete and defined for ERNs to be designated at European level with sufficient flexibility to take into account national health systems.

Quality criteria for national centres of expertise are crucial to ensuring comparable quality between countries, even if countries have different models for expert care. This consideration is especially important in the context of the Cross Border Health Care Directive. It was highlighted that under the Cross-Border Health Care Directive's article 12 there are two provisions:

- 1) the establishment of criteria for national centres of expertise and ERN through the delegated act;
- 2) the identification, establishment and evaluation of ERNs.

In the Cross-Border Health Care Directive, no difference will be made between public and private institutions as long as they fulfill the quality criteria for centres of expertise participating in ERNs.

From the criteria for designation of national centres of expertise proposed by the RDTF and HLG it is possible to extrapolate a core set of criteria for networks being established. The ERNs should attest to having these core criteria and there must be a greater reflection of what is expected of ERNs, including activities such as collaboration with patient groups, capacity building, patient registries and common tools, expert advice FAQs, best practice guidelines, etc, which have all been seen to have worked in the currently funded networks.

National centres of expertise have defined missions in their national health care systems and national plans: with the development of national plans, MS will work on the criteria for centres of expertise and the networking possibilities at EU level. MS will start to identify

expertise at national level, and will find ways to motivate national centres of expertise to be involved in the process at MS level, which will boost networking at EU level.

The scope of the activities of these networks should also be considered: should they focus on care, epidemiology, research, or all of these elements to constitute a 'comprehensive network'. We also have to consider whether all centres of expertise for a certain disease are included in the network, or whether just one centre from each country will be designated for the network. A lot of the ground work has been done, but much conceptual discussion is still needed, especially concerning quality management, monitoring and evaluation. Cooperation can now be seen between learned societies and pilot ERNs for rare diseases, which is an important step in sustaining the dynamics and geographical scope of a network.

We need to be open and flexible as pilot ERNs exist already although few countries have official designation procedures for national centres of expertise, and we must be open to accepting new self-declared national centres of expertise which are accepted according to the quality criteria networks are establishing themselves. However, as national policy advances, so will the approach at EU level.

Process indicators and quality indicators should be established at EU level and applied at national level to ensure the quality of centres participating in ERNs.

In terms of financing ERNs and networks, one possible approach is to levy MS as they have interest in these networks. It was highlighted that national centres of expertise must receive the necessary resources to take part in networks. It was also suggested that these networks be seen as the reference point for all patients in the European Union without the relevant expertise for their disease national level; however, it was highlighted that the duty of an expert centre is first and foremost to patients in their country.

In terms of prioritisation of networks for diseases, it was highlighted that for some countries this is a difficult ethical discussion. Concerning prioritisation of networks, applicants have to prove the real added value of their proposed networks: a list of criteria/indicators with a linked scoring system could be envisaged to assess which proposals are strong and should be prioritised. The French experience of prioritisation is that this does not work: 4 years was spent on this work in the context of the First French Plan for Rare Diseases, without any real pragmatic outcomes. It was much more realistic to start with what existed previously and to build on this, extend existing services and improve them with the aim of covering all needs.

The issue of making expertise travel despite language barriers was also highlighted as it is often neglected in these types of conceptual discussion. We need to think practically and pragmatically when dealing with the concepts of networking, and consider the adaptation of criteria for inclusion in networks to country specificities. The example of Treat-NMD's tool kits which are available to all countries to adapt to their national situation was given as an example of how networking can help capacity building in Europe.

Participants were reminded that the Council Recommendation can be used by every advocate for rare diseases patients to ask their national government where the structures are which are recommended in the document. It was noted that patient groups are often important starting points at the origin of networks and catalysts to extending networks.

It is clear that existing pilot ERNs have been established on an ad hoc basis and a degree of harmonisation is necessary in order to further construct ERNs for RD. Approaches to quality criteria at national level have to be shared and discussed at European level. The experience of networks also has to be shared at a national level. Questions concerning reimbursement also have to be considered.

In practical terms, networks need to be interoperable: shared information systems and registers should be shared and help given to those who wish to participate in a network to do so, all whilst ensuring quality standards are maintained. New networks should also take into consideration the experiences and outcomes of the pilot ERNs for rare diseases described in the *Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for rare diseases* carried out by the EUCERD Scientific Secretariat.

Participants highlighted that there cannot be two parallel systems: i.e. nationally designated centres of expertise, and the centres in ERNs. The centres of expertise in ERNs ideally should be nationally designated to avoid confusion and duplication of efforts.

Currently, many resources have developed without strict guidance, and these resources must be now brought together and incorporated into the new recommended structures, bearing in mind that different MS are starting from different points.

ERNs can also play an important role in collecting epidemiological data, as some pilot projects have already shown. The EPIRARE project, starting in April 2011 will establish a European platform for rare disease patient registries and will explore ways for integrating registries and linking data within the confines of data protection laws.

The future Joint Action for Rare Diseases to start in 2012 will carry out integrative work, based on experience of MS in the field of national centre of expertise and ERN, in order to define a common ground for criteria to be applied across MS.

It was also observed that it is difficult to isolate issues concerning expert care at national and European level in the field of rare diseases due to the rarity of expertise on diseases which demands European networking to provide expertise and expert care for all rare disease patients.

## SESSION 3: QUALITY CRITERIA FOR NATIONAL CENTRES OF EXPERTISE

### 1. Introduction

It was decided that the agenda of the workshop would be changed in order to discuss a priority topic in the context of the development of national plans or strategies for rare diseases: quality criteria for the designation of national centres of expertise for rare diseases. Participants highlighted that this working group should work further on the criteria for national centres of expertise as these are currently very conceptual, and very basic, pragmatic criteria are needed so as to be acceptable to all MS. There is a risk that extremely basic criteria will seriously lower the quality of the national centres of expertise.

It was decided to run through the criteria defined by the work of the HLG and RDTF and to examine whether these recommended criteria have been applied in MS who have a designation process in place (or who plan to put in place a designation process) and what differences can be observed: i.e. are there any more or less useful criteria, should extra criteria be added, can different degrees of fulfillment of criteria be observed, etc. Ultimately, it was suggested that these recommended criteria be examined, in the light of national experience, to see whether there is a need for them be adapted or developed further.

The criteria for national centres of expertise for rare diseases as defined by the HLG and RDTF are the following:

- appropriate capacities to diagnose, to follow-up and manage patients with evidence of good outcomes so far as applicable;
- sufficient activity and capacity to provide relevant services and maintain quality of the services provided;
- capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control;
- demonstration of a multi-disciplinary approach;
- high level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities;
- strong contribution to research and involvement in epidemiological surveillance, such as registries;
- close links and collaboration with other expert centres at national and international level and capacity to network;
- close links and collaboration with patients associations where they exist.

## 2. General Discussion

The discussion started with comments from Member State representatives on their experience concerning designation criteria, and their feedback on the HLG/RDTF criteria, before a more generalised discussion concerning criteria was embarked upon.

In **France**, the criteria of the HLG/RDTF were those used in the first phase of designation of the '*centres de référence*' of the first National Plan for Rare Diseases. In the Second National Plan these criteria will be reexamined and evaluated to see if they should be developed and/or adapted, taking into consideration ongoing work at EU level. In France, the designation criteria for '*centres de référence*' are mandatory and each centre must state which criteria they currently fulfill and their strategy for fulfilling the remaining criteria with the funding received. Three years after designation a self evaluation process takes place and five years after designation a specialist on rare diseases and a general health care expert evaluates the centre. In France, in the Second Plan, it is possible that centres which have not fulfilled the criteria they were supposed to fulfill will have their designation removed to allow for the establishment of a new centre. Many '*centres de compétence*' in France are currently unable to fulfill all of the HLG/RDTF criteria today, but their missions are different to those of the '*centres de référence*'. It was also highlighted that collaboration with other centres at national and international level, if they exist, is important. In France, collaboration between patient groups and existing centres was promoted and many French centres supported the establishment of patient groups as they wished to fulfill this criteria. Centres and patient organisations work together to produce information documents. In France, '*centres de référence*' already liaise with other expert groups and '*centres de compétence*' thus creating mini national networks by disease/ disease group. The issue of reimbursement was also raised: in France, patients' travel to a '*centre de référence*' or '*centre de compétence*' is reimbursed and the primo prescription of very expensive drugs is allocated to these centres.

In **Italy**, there are 20 regions which use differing designation criteria which are constantly revisited and revised at regional level. At central level, the CNMR should ensure that all regions have applied the appropriate criteria. In Italy, attractiveness of centres of expertise has been measured through the national registry of rare diseases by examining health migration within or outside the region. This enables health authorities to see where centres of expertise are situated and whether they are attractive or not. Migration can be seen within Europe and monitored if the appropriate tools are put into place.

In the **UK**, the recommended criteria are used in the planning of nationally commissioned services. In disease specific areas, patient organisations also adopt these criteria when examining the criteria for centres of expertise for rare diseases.

In **Spain**, there is a need to further establish these criteria. A multidisciplinary approach is suitable for some diseases, but not for surgical interventions. Some of the HLG/RDTF criteria are adhered to by designated centres, and some are not. There is close cooperation between centres treating patients and research centres and in some cases there is some overlap. The word 'attractivity' is problematic as there is a risk presented by self-promotion. In Spain, when there are social and medical needs, services work together to respond to those needs, and a team is set up to address all these areas to provide a coordinated approach. Coordination teams with dedicated coordinators to avoid unnecessary travel of the patient should be considered at national levels. In Spain, there are no other criteria to add to the list defined by the HLG and RDTF, but there are linked indicators to ensure quality. There are minimum requirements, but there is room for improvement. The designation is ultimately the decision of the regions and centres are allocated regional funding, with extra national funding for patients living outside the region.

Although multidisciplinary is crucial, funding of these activities, especially social activities is particularly difficult in the **German** health care service. The working group "care, centres, networks" of the national league for people with rare diseases (NAMSE) is considering these difficulties posed by a fragmented system based on specialties and sub-specialties. It is working on the problem that patients without a diagnosis will be looked at organ by organ and will need accompaniment. It is also important to provide support, via an umbrella organisation, for patients without a patient organisation for their specific disease. Furthermore rehabilitation is also an important component of the care of people with rare diseases which is financed through other sources than health care.

In **Sweden**, a new law has been adopted concerning patient safety: as such an extra required criterion would be a quality management system to ensure patient safety.

In **Hungary**, the national centres of expertise by reputation adhere to the criteria of the HLG and RDTF, with the strongest elements being research and diagnosis. In the Hungarian National Plan for Rare Diseases, the strategy will be to designate the four medical universities as centres of expertise due to the existing structure of the health system by speciality and the prominence and reputation of the medical university in terms of research, amongst other disciplines. In Hungary, there are expert groups outside of the medical universities who respect the criteria, but the ways of involving these groups into the existing structures needs to be examined. Hungary, therefore, is an example of the challenges to creating national centres of expertise within a traditional, specialised system.

The discussion then turned to a number of more general observations. Participants observed that there are clear experiences at national level of how to implement these criteria which should be collected in order to develop a set of guiding principles.

An appropriate evaluation process at national level for designated centres of expertise has to be considered and recommended. All designated centres in Norway, for example, have an evaluation process and must report to their authorities on how they are fulfilling criteria.

In the Care-NMD project, there are efforts to develop these criteria specifically for national centres of expertise for Duchenne Muscular Dystrophy to make them as concrete as possible. The project is also examining what exactly 'European cooperation' means and entails (i.e. guidance documents, sharing data etc.). The project has enabled a study of how different countries approach the treatment of DMD, i.e. through disease specific/ organ specific or generic rare disease centres.

We also need to consider that expertise is gained by seeing patients and a critical mass is needed for this. In France, the new networks by groups of diseases will enable this critical mass to be achieved.

It was highlighted that mobility between centres is not always possible in certain national health care systems based on catchment areas. Catchment protocols should thus also be considered when designating centres of expertise.

One main complaint of patients with a rare disease is the delay to diagnosis: participants discussed whether the criteria for centres of expertise therefore should therefore include the responsibility to improve this delay and to build healthcare pathways from primary care. Delay to diagnosis could also be improved by increased training of general practitioners at grass-roots level. The capacity to diagnose is of great importance and should be highlighted in the criteria.

It was highlighted that in some areas where diagnosis is difficult, there are still certain problems to be dealt with, i.e. intellectual disability.

Eurordis workshops on centres of expertise have highlighted the importance of multidisciplinary for patients to avoid going from doctor to doctor. In surgical cases, multidisciplinary is less important, but for other centres of expertise these criteria should be placed very highly.

Indicators are of great importance, to evaluate processes and outcomes and need to be defined for centres of expertise. Work has already been carried out by the Europlan project in its first stage on indicators for national plans for rare diseases, and now we need to observe how MS will implement measures and choose indicators for monitoring outcomes.

In conclusion, participants agreed that in the context of the Cross-Border Health Care Directive, national criteria for designation have to be congruent with the criteria for European Reference Networks at European level, and that clear standards and indicators are needed for the evaluation and auditing of national centres of expertise and European

Reference Networks. Participants suggested additional criteria for national centres of expertise:

- That these national centres must be open to European collaboration;
- That national centres must accept to be evaluated 3 or 5 years after their designation;
- Centres may not fulfill all the criteria when they are designated, but should have a strategy in place to attain quality criteria which they have not already reached;
- That the population and geographical size of the country be considered when organising expert care for rare diseases at national level, i.e. national centres of expertise should network with proximate centres, such as the French model of '*centres de compétence*';
- That centres should be responsible for improving the delay to diagnosis and for building healthcare pathways from primary care;
- That centres should have a quality management system in place to assure quality of care which takes into account European norms;
- That centres should adhere to good practice guidelines where they exist;
- That centres should be responsible for establishing health care pathways which both aid diagnosis and aid the coordination of care between different medical specialities;
- That quality of care indicators and process indicators should be developed and monitored;
- That collaboration with other expert centres at European/national/regional level if they exist is important;
- That the designation/quality criteria should be adapted to the national situation/ to the specificities of the disease/disease group;
- That centres should have a continuity plan in place for sustainability in terms of personnel;
- That continuity of care between childhood and adult care should be assured by centres;
- That centres should make appropriate arrangements for patient referrals from other countries.

Participants agreed that prevention is a difficult topic (as it can be interpreted as genetic selection), and that a criteria concerning prevention should not be added. The only approach would be to identify centres for genetic counselling and follow-up.

## Next steps

In conclusion, it was proposed that the discussions on the criteria for national centres of expertise would be used to fine tune the quality criteria defined by the HLG and RDTF to be proposed as a draft EUCERD recommendation for discussion at a workshop of EUCERD members before adoption at the next meeting of the EUCERD, which will help MS in their reflections or policy developments concerning national plans and strategies for rare diseases.

It was also proposed that this recommendation will be revised in around 2 years by the EUCERD based on the experiences of EU MS in the field.

It was proposed that a synthesis based on the Commission Communication and Council Recommendation, as well as feedback from Europlan, should be worked on to form a EUCERD strategic vision on health care pathways and networks, taking into account ERN and health care organisation at local, national and EU levels, to be presented at an upcoming meeting of the EUCERD for further consultation. This strategic vision could recommend creating pathways between childhood and adult care, that national centres of expertise act as reference points for countries where no expertise exists, that networks and pathways be organised around therapeutic fields such as is the plan in France, and that coordinating centres of general centres for rare diseases could be a way of resolving problems such as the organisation of health care for rare disease patients, or the provision of services for patients without a diagnosis.

Finally it was proposed that the EUCERD develop and adopt in the context of the Joint Action 2011 on RD (i.e. around 2012-2013) guidelines on ERN to provide a strategic vision and quality criteria for implementation in the field of rare diseases.

These proposed actions will ensure that experience generated at national level and by networks will be translated into beneficial and concrete proposals. The working group has also revised since the December 2010 workshop on this subject the '*EUCERD Report: Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for Rare Diseases*' which was sent following this workshop to the participants of the December 2010 and March 2011 workshops and members of the EUCERD for their comments/validation during a period of 4 weeks (until the end of April 2011).

## ANNEX 1: LIST OF PARTICIPANTS

**\*EUCERD members**

**Stein ARE AKSNES\*** - Norwegian Directorate of Health (Norway)

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## ANNEX 2: SCOPE OF DISEASES COVERAGE OF CENTRES OF EXPERTISE IN EUROPE BY MEDICAL SPECIALTY<sup>4</sup>

- = *group of diseases*
- = *single diseases*

### General centres of expertise for rare diseases

- **National rare diseases centre (DK)**
- **National rare disability centre (DK)**
- **National resource centre for rare disorders (NO)**
- **Centre for Treatment and Research on Rare Diseases (DE)**

### Group I: Rare systematic and auto-immune diseases (Internal Medicine)

- Rare auto-inflammatory diseases (FR, IT)
- Rare auto-immune diseases (FR, IT)
- Juvenile arthritis/rare paediatric rheumatological diseases (FR, IT, DE, GR, UK)
  
- Primary amyloidosis and other immunoglobulin deposit diseases (FR, UK)
- Lupus and antiphospholipid syndromes (FR)
- Necrotising vasculitis and vasculitis (FR, IT)
- Systemic sclerosis (FR, IT)
- Inflammatory amyloidosis and familial mediterranean fever (FR)
- Familial Mediterranean fever and periodic fever (IT)
- Cryopyrin Associated Periodic Fever – CAPS (UK)
- Langerhans cell histiocytosis (FR, DE)
- Behcet disease (IT)
- Stem Cell Transplant service for Juvenile idiopathic arthritis and related connective tissue disorders (UK)

### Group II: Rare cardio-vascular diseases

- Complex cardiac malformations (FR)
- Rare vascular diseases (FR, IT)
- Hereditary cardiac diseases (FR, IT)
- Genetic cardiac rhythm defects (FR, IT)
  
- Lymphedema (IT)

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<sup>4</sup> This analysis is based on an extraction of Orphanet database of officially designated centres of expertise and centres of expertise not officially designated but recognised at national level for their expertise (February 2011).

### **Group III: Malformations/Medical genetics/Neuropaediatrics**

- Developmental anomalies and malformations/dysmorphology (FR, IT, ES, SE)
- Short stature and skeletal dysplasias (DE)
- Neuropaediatrics (DE)
- Surgically congenital malformative pathologies associated to intrauterine diagnosis (IT)
- Malformations of the limbs (FR)
  
- Cri du chat syndrome (IT)
- Reconstructive surgery in adolescents for congenital malformations of the female genital tract (UK)
- Rare genital malformations in the female (DE)
- Bladder exstrophy (UK)
- Vein of Galen malformation in children (UK)

### **Group IV: Rare dermatological diseases**

- Rare dermatological diseases (FR, IT, DE)
- Rare genetic dermatological diseases (FR)
- Epidermolysis bullosa (FR, IT, AT, UK)
- Auto-immune skin bullous diseases (FR)
- Acquired toxic and auto-immune skin bullous diseases (FR)
  
- Cutaneous lymphoma (IT)
- Ichthyosis (IT)
- Cutis laxa (IT)
- Xeroderma pigmentosum (UK)
- Hypotrichosis (DE)

### **Group V: Rare endocrinal diseases**

- Rare metabolic diseases of calcium and of phosphorus (FR)
- Rare adrenal diseases (FR)
- Rare endocrine growth diseases (FR, IT)
- Rare endocrine diseases (DE)
- Hormone receptor diseases (FR)
- Rare pituitary diseases (FR)
- Rare sexual development diseases (FR, IT)
- Rare gynaecological diseases (FR)
- Hypothalamic-hypophyseal diseases (IT, ES)
- Rare forms of diabetes (IT)

- Prader-Willi syndrome (FR, IL, IT)
- Turner syndrome (IT)
- Multiple endocrine neoplasia (IT)
- Congenital hyperinsulinism (UK)

#### **Group VI: Rare hepatogastroenterological diseases**

- Adult vascular diseases of the liver (FR)
- Paediatric liver diseases (UK)
- Intestinal digestive diseases (FR, UK)
- Rare ano-rectal and pelvic malformations (FR)
- Congenital oesophagus complaints and malformations (FR)
- Paediatric autoimmune gut disorders (UK)
- Chronic cholestatic diseases (ES)
  
- Inflammatory bile duct (FR)
- Childhood bile duct atresia (FR)
- Inflammatory bowel disease (IT)
- Intestinal polyposis (IT)
- Hernia of the dome of the diaphragm (FR)
- Congenital intestinal atresia (DE)

#### **Group VII: Rare non-malignant haematological diseases**

- Haemophilia and other constitutional bleeding disorders (FR, BE, ES, DE)
- Haemoglobinopathies (IT)
- Major sickle cell anaemias (FR)
- Paediatric haematology (IT)
- Thalassemias (FR, GR)
- Rare medullar aplasias (FR, IT)
- Thrombotic microangiopathies (FR)
- Constitutional thrombopathies (FR, IT)
  
- Evans syndrome, haemolytic anaemia and severe auto-immune cytopenia (FR)
- Adult auto-immune cytopenia (FR)
- Mastocytosis (FR, IT, ES)
- Von Willebrand disease (FR, ES)
- Sickle cell anaemia (FR)
- Paroxysmal Nocturnal Haemoglobinuria (UK)

#### **Group VIII: Hereditary metabolic diseases**

- Hereditary diseases of the metabolism (BE, FR, IT, ES)
- Hereditary diseases of the hepatic metabolism (FR)
- Rare metabolic diseases (DE)

- Paediatric and metabolic diseases and malformative syndromes (IT)
- Lysosomal diseases (FR, IT, UK)
- Mitochondrial diseases (FR, UK)
- Porphyrrias (FR, IT, BE, ES, NO, SE)
  
- Wilson disease (FR)
- Rare genetic iron overload (FR)
- Phenylketonuria (ES)
- Mucopolysaccharidosis (IT)
- Gaucher disease (CZ)

#### **Group IX: Rare neurological diseases**

- Rare paediatric neurological diseases (IT)
- Neurogenetic diseases (FR, IT)
- Rare epilepsies (FR, BE, NO, DE)
- Rare dementias (FR)
- Intellectual deficiencies from rare causes (FR, IT)
- Brain inflammatory diseases (FR)
- Malformations and congenital diseases of the cerebellum (FR)
- Neurovascular malformation diseases (FR)
- Rare vascular diseases of the central nervous system and the retina (FR)
- Paraneoplastic neurological syndromes (FR)
- Leukodystrophies (FR, ES)
- Hereditary ataxias and paraplegias (ES, UK)
- Neurodegenerative and neurometabolic diseases (IT)
  
- Gilles de la Tourette syndrome (FR, NO)
- Narcolepsy (NO)
- Huntington's disease (FR, IT)
- Multisystemic atrophy (FR)
- Rare hypersomnia (FR)
- Tuberous sclerosis (FR, IT)
- Syringomyelia (FR)
- Neuromyelitis optica (UK)

#### **Group X: Neuromuscular diseases**

- Neuromuscular diseases (FR, IT, BE, NO, DE)
- Rare neuromuscular and neurological diseases (FR)
- Muscular channelopathies (FR, UK)
- Familial amyloid neuropathies (FR)

- Rare peripheral neuropathies (FR)
- Congenital muscular dystrophies and congenital myopathies (UK)
- Limb girdle muscular dystrophies (UK)
- Congenital myasthenic syndromes (UK)
  
- Amyotrophic lateral sclerosis (FR, IT, ES)
- Myaesthesia gravis (ES)
- McArdle's disease (UK)

#### **Group XI: Rare pulmonary diseases**

- Rare pulmonary diseases (FR, IT, ES, DE)
- Pulmonary vascular diseases (UK)
  
- Severe pulmonary hypertension (FR, CZ, ES)
- Cystic Fibrosis (FR, IT, BE, CZ, DE, UK, NO, SE)
- Ondine syndrome (FR)
- Chronic pulmonary aspergillosis (UK)
- Alpha 1 antitrypsin deficiency clinic (ES)
- Primary ciliary dyskinesia (UK)
- Pulmonary thromboendarterectomy (UK)

#### **Group XII: Rare sensory diseases including rare ophthalmological diseases and congenital and genetic diseases**

- Genetic ophthalmological complaints (FR, IT)
- Rare ophthalmological diseases (FR, DE)
- Genetic congenital deafness (FR, IT)
- Genetic sensory complaints (FR)
- Genetic retinal dystrophy (FR)
  
- Keratoconus (FR)
- Retinoblastoma (UK)
- Retinitis pigmentosa specialised clinic (IT)
- Jacobsen syndrome (IT)

#### **Group XIII: Rare kidney disease**

- Rare genetic kidney disease (FR, IT, BE, DE)
- Rare renal diseases and hereditary diseases of the metabolism (FR, ES)
- Paediatric renal transplant (ES)
  
- Idiopathic nephrotic syndrome (FR, ES)

**Group XIV: Rare bone diseases**

- Constitutional bone diseases (FR)
- Fibrous dysplasia of bone (FR)

**Group XV: Rare immune system deficiencies**

- Hereditary immune deficiencies (FR, SE)
- Neuroimmunology (IT)
- Severe combined immunodeficiency and related disorders (SCIDS) (UK)
- Primary immunodeficiency (DE)
- Congenital neutropenia (IT)

**Group XVI: Diseases of the connective tissue framework**

- Hereditary diseases of the connective tissue (FR, IT)
- Marfan syndrome (FR, IT)
- Fabry disease (FR, IT)
- Pseudoxanthoma elasticum (IT)
- Ehler Danlos syndrome (UK)

**Group XVII: Rare malformations of the head and neck**

- Rare ENT malformations (FR)
- Complex tracheal anomalies (UK)
- Rare malformations of the face and mouth cavity (FR)
- Rare maxillofacial anomalies (IT)
- Rare craniofacial anomalies (IT, ES, UK, DE)
- Rare craniomaxillofacial diseases (FR)
- Odontological manifestations of rare diseases (FR)
- Pierre Robin syndrome and congenital suction/swallowing defects (FR)
- Oral health in rare diseases (NO)
- Craniofacial dysostosis (FR)

**Group XVIII: Rare cancers**

- Soft tissue and internal organ sarcoma (FR)
- Oligodendroglial tumor (late stages) (FR)
- Resistant thyroid cancers (FR)

- Von Hippel Lindau disease and predispositions to kidney cancer (FR)
- Suprarenal cancers (FR)
- Peritoneal cancers (FR)
- Malignant sporadic and hereditary endocrinal tumours (FR)
- Gestational trophoblastic neoplasms and gestational trophoblastic diseases (FR)
- Rare ENT cancers (FR)
- Rare cutaneous lymphomas (FR)
- Rare ovarian cancers (FR)
- Primary lymphomas of the central nervous system (FR)
- Lymphomas associated with coeliac disease (FR)
- Malignant thymomas and thymic carcinomas (FR)
- Cancers developing during pregnancy (FR)
- Head and neck paragangliomas (ES)
- Primary malignant bone tumours (UK)
  
- Choriocarcinoma (UK)

#### **Group XIX: Other rare diseases**

- Autism and associated disorders (IT, NO)
- Paediatric haematology and oncology (IT)
- Developmental and perinatal disorders (PT)
- Rare allergic diseases (ES, DE)
- Deaf-blindness (NO, FR)
- Psychiatrically expressed rare diseases (FR)
- Rare congenital infectious diseases (DE)
  
- Alport, Cohen and Rett syndromes (IT)
- Alstrom syndrome (UK)
- Bardet-Biedl syndrome (UK)
- Barth syndrome (UK)
- Cluster headache (IT)
- Connatal and perinatal virus infection (DE)
- Malignant hyperthermia (IT)
- Neurofibromatosis (FR, IT, UK, DE)
- Non histamine-induced angioedema (FR, ES)
- Pseudomyxoma peritonei (UK)
- Rare neuroendocrine tumours (IT)
- Rendu-Osler disease (FR, IT, IL)
- Spina Bifida (FR, BE)
- Surgical treatment with stems cells for Mayer-Rokitansky Kuster-Hauser syndrome (IT)
- Twin to twin transfusion syndrome (FR)