European Union Committee of Experts on Rare Diseases

EUCERD REPORT

Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for rare diseases

May 2011

TABLE OF CONTENTS

Introduction 3

Analysis: 9

1. **Identifying expertise/networking** 9
2. **Sharing expertise for patient management** 15
3. **Building up standards of care** 20
4. **Improving clinical research** 24

Summary of the analysis 28

Conclusions and Recommendations 30

Annexes: 31

Annex 1: Description of the activities of the pilot European Reference Networks for rare diseases

Annex 2: Overview of pilot ERNs' actions

Annex 3: Country participation in DG Sanco pilot ERNs

Annex 4: Duration of pilot ERN financing by DG Sanco

Annex 5: HLG Document HLG/COR/2008/4: Summary of provisional responses of leaders of the pilot projects on European reference networks to the questionnaire

Annex 6: Comments from EUCERD Industry representatives on the *"Preliminary analysis of pilot European Reference Networks for Rare Diseases"*.

This draft report has been compiled by Ségolène Aymé and Charlotte Rodwell (EUCERD Scientific Secretariat) and has been revised according to the comments received during a consultation period of 4 weeks in April 2011 from the members of the European Union Committee of Experts on Rare Diseases (EUCERD) and the participants of two EUCERD workshops on the topic of national centres of expertise for rare diseases and European Reference Networks (ERN) for rare diseases held on 8-9 December 2010 and 21-22 March 2011 respectively.

To quote this document:

"EUCERD Report: Preliminary analysis of pilot European Reference Networks for Rare Diseases", May 2011.

http://www.eucerd.eu/EUCERD/upload/file/Reports/ERNAnalysis2011.pdf

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: *2009 EUCERD Report on Initiatives and Incentives in the Field of Rare Diseases of the European Union Committee of Experts on Rare Diseases*[1]. The analysis this report led to the decision to explore in further depth the area concerning national centres of expertise for rare diseases and European Reference Networks of Centres of Expertise (ERNs) for Rare Diseases. National centres of expertise and ERNs in the field of RD are mentioned in the High Level Group on Health Services and Medical Care Report of November 2005[2], 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[3] (11 November 2008) and the Council Recommendation on an action in the field of rare diseases[4] (8 June 2009), as well as in the Recommendations for National Plans and Strategies for Rare Diseases drawn up by the Europlan[5] project and in Point 15 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare[6].

Point 5 of the Commission Communication, focusing on 'Operational actions to develop European cooperation and access to high quality healthcare for rare diseases' recognises the European added-value of networks of expertise in the field of rare diseases, and cites the need to improve 'universal access to high quality healthcare for rare diseases, in particular through the development of national/regional centres of expertise and establishing EU reference networks' (5.1). The Council Recommendation gives an overview of the past work of the High Level Group on Health Services and Medical Care (HLG) and the RDTF:

(13) In July 2004, a Commission High-Level Group on Health Services and Medical Care was established to bring together experts from all Member States to work on practical aspects of collaboration between national health systems in the EU. One of this High-Level Group's working groups is focusing on **European Reference Networks (ERNs) for rare diseases**. **Some criteria and principles for ERNs have been developed, including their role in tackling rare diseases. ERNs could also serve as research and knowledge centres, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary.**

(14) **The Community added value of ERNs is particularly high for rare diseases by reason of the rarity of these conditions, which implies both a limited number of patients and a scarcity of expertise within a single country. Gathering expertise at European level is therefore paramount in order to ensure equal access to accurate information, appropriate and timely diagnosis and high quality care for rare disease patients.**

(15) In December 2006 an expert group of the European Union Rare Diseases Task Force issued a report 'Contribution to policy shaping: for a European collaboration on health services and medical care in the field of rare diseases' to the High-Level Group on Health Services and Medical Care. The expert group report outlines, inter alia, the **importance of identifying centres of expertise and the roles that such centres should fulfil. It is also agreed that, in principle and where possible, expertise should travel rather than patients themselves**. Some measures called for in the report are included in this recommendation.

[1] http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf
[2] http://ec.europa.eu/health/ph_overview/co_operation/healthcare/docs/highlevel_2005_013_en.pdf
[3] http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
[4] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
[5] http://www.europlanproject.eu/Home.aspx
[6] http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf

(16) **Cooperation and knowledge sharing between centres of expertise** has proven to be a very efficient approach to dealing with rare diseases in Europe.

(17) The centres of expertise could follow a **multidisciplinary approach** to care, in order to address the complex and diverse conditions implied by rare diseases.

(18) The specificities of rare diseases — a limited number of patients and a scarcity of relevant knowledge and expertise — single them out as a unique domain of very high added value of action at Community level. This added value can especially be achieved through **gathering national expertise on rare diseases which is scattered throughout the Member States**.

(19) It is of utmost importance to ensure an active contribution of the Member States to the elaboration of some of the **common instruments** foreseen in the Commission communication on rare diseases: Europe's challenges of 11 November 2008, especially on diagnostics and medical care and European guidelines on population screening. This could be also the case for the assessment reports on the therapeutic added value of orphan medicinal products, which could contribute to accelerating the price negotiation at national level, thereby reducing delays for access to orphan drugs for rare diseases patients.

As cited in the Council Recommendation, the RDTF, in collaboration with the HLG, has suggested the following criteria for centres of expertise participating in ERNs:

- appropriate capacities for diagnosing, following-up and managing patients, with evidence of good outcomes, where applicable;
- attractiveness measured through the volume of activity which needs to be significantly larger than anticipated from the prevalence of the diseases and the catchment area, the catchment area being the loco-regional area normally served by the hosting hospital for non-rare diseases; or national coverage;
- sufficient activity and capacity to provide relevant services at a sustained level of quality;
- capacity to provide expert advice on diagnosis and management;
- capacity 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, as documented through publications, grants or honorific positions, teaching and training activities, etc.;
- strong contribution to research;
- involvement in epidemiological surveillance, such as registries;
- close links and collaboration with other expert national and international centres, and capacity to network;
- close links and collaboration with patient associations, where they exist.

The RDTF also published in the 2008 RDTF Report *European Reference Networks: State of the Art and Future Directions: Third Report – July 2008* the following recommendations to the EC:

- the EC continues its financial support for the networking of national centres of expertise in the field of RD until an evaluation of the output of the networking process demonstrates that it is not cost-effective (which is extremely unlikely)
- the EC opens its call for proposals to the definition of a methodology to assess the benefit of such networks from the perspective of the different stakeholders

- the EC encourages, by all possible means, the development of electronic tools necessary for the development of telemedicine in the field of rare diseases.
- the EC encourages the production of legal and ethical guidelines for participants of any European network involving patients
- the EC with the cooperation of clinicians, patients, network coordinators, MS health authorities reconsiders the assessment of the added-value of ERN after:
    1) Additional findings from the experience of the pilot projects,
    2) Learning from the experience of existing collaborations in the field of RD,
    3) Continued identification of CE across Europe.

Taking into account these recommendations, the Council Recommendation on an action in the field of rare diseases recommends that Member States take these actions in the field of national centres of expertise and ERN:

IV. CENTRES OF EXPERTISE AND EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES

11. Identify appropriate centres of expertise throughout their national territory by the end of 2013, and consider supporting their creation.

12. Foster the participation of centres of expertise in European reference networks respecting the national competences and rules with regard to their authorisation or recognition.

13. Organise healthcare pathways for patients suffering from rare diseases through the establishment of cooperation with relevant experts and exchange of professionals and expertise within the country or from abroad when necessary.

14. Support the use of information and communication technologies such as telemedicine where it is necessary to ensure distant access to the specific healthcare needed.

15. Include, in their plans or strategies, the necessary conditions for the diffusion and mobility of expertise and knowledge in order to facilitate the treatment of patients in their proximity.

16. Encourage centres of expertise to be based on a multidisciplinary approach to care when addressing rare diseases.

The European Commission Directorate General for Health and Consumers (DG Sanco) has already financed a number (11) pilot European Reference Networks of Centres of Expertise (ERNs) through calls for proposals of the Executive Agency for Health and Consumers. Some of these pilot networks have reached the end of their grant agreement, and it is thus timely to examine their experiences and results.

The 10 pilot European Reference Networks for Rare Diseases financed by DG Sanco for a 36 month period are:

- **Dyscerne**: European Network of Centres of Reference for Dysmorphology (ended)
- **ECORN CF**: European Centres of Reference Network for Cystic Fibrosis (ended)
- **PAAIR**: Patient Associations and Alpha1 International Registry (PAAIR) (ended)
- **EPNET**: European Porphyria Network - providing better healthcare for patients and their families (ended)
- **EN-RBD**: Establishment of a European Network of Rare Bleeding Disorders (ended)
- **Paediatric Hodgkins Lymphoma Network**: European-wide organisation of quality controlled treatment (on-going)

- **NEUROPED**: European Network of Reference for Rare Paediatric Neurological Diseases (ended)
- **EURO HISTIO NET**: A reference network for Langerhans cell histiocytosis and associated syndrome in EU (on-going)
- **TAG**: Improving Health Care and Social Support for Patients and Family affected by Severe Genodermatoses – TogetherAgainstGenodermatoses (on-going)
- **CARE NMD:** Dissemination and Implementation of the Standards of Care for Duchene muscular Dystrophy in Europe (including Eastern countries) (on-going)

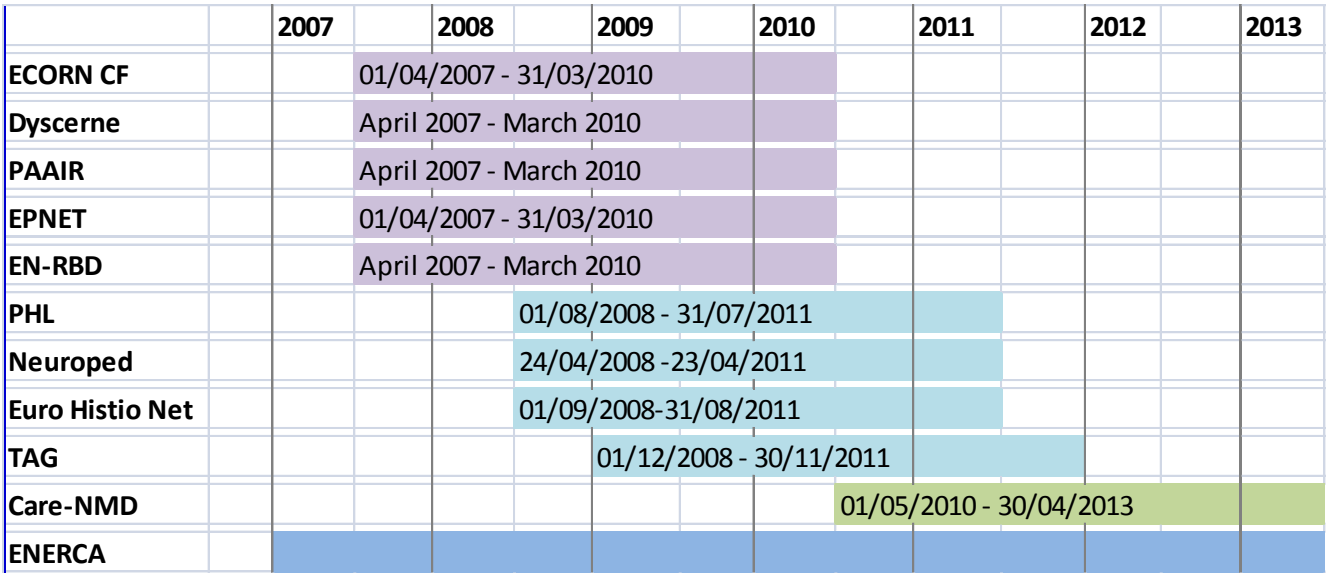


Fig. 1 Overview of financing of Pilot European Reference Networks for RD by the European Commission.

A summary of the actions of these networks can be found in Annex 1, along with a recapitulative table of their actions (Annex 2), their geographical distribution (Annex 3) and the duration of their EC financing (Annex 4). We have also examined the experience of the ENERCA project, a DG Sanco funded project, as the third phase of this project aims to define criteria for a European network of centres of expertise for rare anaemias.

The DG Sanco-funded European Reference Network pilot projects provide an opportunity to assess the relevance of the procedures and criteria proposed by the HLG Working Group on ERN and the RDTF. To date, the only analysis of the experience of these networks has been a questionnaire sent to pilot ERNs by the HLG in late 2007 during the initial stages of their establishment; the results were analysed and summarised in early 2008 (see Annex 5). The Scientific Secretariat of the EUCERD in the preparation of this preliminary analysis has gathered these completed questionnaires (some of which have since been updated) in addition to activity reports, workshop reports and data on project websites (when available) in order to gain an overview of the actions and experiences of these ERNs which are presented in this report. We have also taken into account the draft consensus paper[7] of the ENCE (European Networks of Centres of Expertise for Rare Diseases) CF-LAM-LTX working groups:

[7] http://www.ence-plan.eu/Downloads.16.0.html?&no_cache=1&cid=23&did=111&sechash=12f777f9 . This draft has since been finalised: http://www.ence-plan.eu/Downloads.16.0.html?&no_cache=1&cid=80&did=124&sechash=939414ee

ENCE is a DG Research FP7 project funded for two years (2009 – 2010) which aims to establish a blueprint for the establishment of European networks of centres of expertise for rare pulmonary disorders by examining experiences of existing networks and centres of expertise.

The present report concentrates on the experience of these pilot ERNs, seeking to define the concepts behind their actions, giving examples of how ERNs put these actions into practice and examples of the European added-value of these networks in the field of rare diseases. The report builds on three previous reports of the EC Rare Disease Task Force dealing with national centres of expertise and European reference networks of centres of expertise for rare diseases: *RDTF Report: Overview of Current Centres of Reference on rare diseases in the EU - September 2005*[8], *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*[9] and *RDTF Report: European Reference Networks: State of the Art and Future Directions: Third Report – July 2008*[10].

It should also be highlighted that a number of projects funded through the European Commission Directorate General for Research's 5th, 6th and 7th Framework Programmes for research, technological development and demonstration activities also include networking activities to improve clinical care for rare diseases, and therefore demonstrate some activities that also characterise public health networks. The introduction of the Council Recommendation (paragraph 13) also states that *"ERNs could also serve as research and knowledge centres"*, thus highlighting the importance of research activity in potential ERNs, therefore it is useful to consider the experiences of these networks. Some examples of these networks include:

- **ESDN**: European Skeletal Dysplasia Network
- **EUROCRAN**: European collaborationon craniofacial anomalies – Eurocleft clinical network
- **EUROCARE CF**: European coordination action for research in cystic fibrosis
- **EUROSCA**: European integrated project on spinocerebellar ataxias
- **EUROWILSON**: European network on Wilson disease
- **TREAT-NMD**: Accelerating Treatments for Neuromuscular Diseases
- **ENCE CF-LAM-LTX**: European networks of centres of expertise for CF (Cystic Fibrosis), LAM (Lymphangioleiomyomatosis), and LTX (Lung Transplantation)
- **LEUKOTREAT**: Therapeutic challenge in Leukodystrophies: Translational and ethical research towards clinical trials
- **CHD PLATFORM**: Establishment of a European parent- and patient-oriented information and communication platform on Congenital Heart Defects
- **GENESKIN**: European network on rare genetic skin diseases
- **EUROGLYCANET**: European network for the advancement of research, diagnosis and treatment of Congenital Disorders of Glycosylation.

Examples of actions from these projects, which although are not financed as pilot ERNs often concentrate on building networks for a rare disease/group of rare diseases which have similar aims to the criteria defined for ERNs, have been provided in this preliminary analysis when relevant, though these networks are not the primary focus of this document.

[8] http://www.eucerd.eu//upload/file/Publication/RDTFECR2005.pdf
[9] http://www.eucerd.eu//upload/file/Publication/RDTFECR2006.pdf
[10] http://www.eucerd.eu//upload/file/Publication/RDTFERN2008.pdf

This analysis considers the following general areas of action identified as having been undertaken by the pilot ERNs:

- Identifying expertise/networking
- Sharing expertise for patient management
- Building up standards of care
- Improving clinical research

Each section gives an outline of the European added-value in the field of rare diseases of each of the related actions, a brief definition of the concepts, and examples of these actions put into practice by the pilot ERNs and other EC funded networks for rare diseases.

The conclusion outlines some of the major observations derived from this preliminary analysis which were completed taking into account the discussions that took place during a session dedicated to ERNs at the EUCERD Workshop on Initiatives and Incentives in the Field of Centres of Expertise and ERNs for Rare Diseases (8-9 December 2010)[11]. A number of conclusions and recommendations made at the workshop by participants are also presented in the conclusions of this report.

Please note that this report does not deal with the topic of centres of expertise at national level treated during the first session of the December 2010 workshop: to aid the discussion at the workshop, a list of designated national/regional centres of expertise by country and town in the *Draft Orphanet Report Series on Designated Centres of Expertise in Europe* was provided to participants along with the three previous reports of the EC Rare Disease Task Force dealing with centres of expertise and European reference networks of centres of expertise for rare diseases: *RDTF Report: Overview of Current Centres of Reference on rare diseases in the EU - September 2005*[12], *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*[13] and *RDTF Report: European Reference Networks: State of the Art and Future Directions: Third Report – July 2008*[14] .

A full list of European networks in the field of rare diseases financed by DG Sanco and DG Research is provided in the *Orphanet Reports 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*[15].

[11] http://www.orpha.net/nestasso/EUCERD/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf
[12] http://www.eucerd.eu//EUCERD/upload/file/Publication/RDTFECR2005.pdf
[13] http://www.eucerd.eu//upload/file/Publication/RDTFECR2006.pdf
[14] http://www.eucerd.eu//upload/file/Publication/RDTFERN2008.pdf
[15] http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf

ANALYSIS

1. IDENTIFYING EXPERTISE/NETWORKING

"[Member States should] identify appropriate centres of expertise throughout their territory ... [and] foster the participation of centres of expertise in ERNs" – Council Recommendation on an action in the field of rare diseases, 8 June 2010

Building up of the network/identifying expertise

Networking is first, and foremost, a process: networks evolve through time, both in their nature (i.e. type of activities) and coverage (i.e. countries involved). Networks can only be envisaged when there are several expert centres at national level, with specific activities, in Europe. The establishment of national expert centres, and clinical research laboratories, is an essential step which precedes the establishment of European Reference Networks.

In order to build a network, the goals of the network should be defined, expertise should be identified, criteria for inclusion in the network should be established and an organisational structure and communication/organisational tools should be considered. The Council Recommendation highlights (§12 &13) the importance of the role to be played by Member States in the identification of centres of expertise and the fostering of their participation in ERNs, and the role of the EC and member states in ensuring *"appropriate funding and cooperation mechanisms"* adapted to *"the long-term sustainability of infrastructures"* such as ERNs.

Selection of pilot European Reference Networks and participating centres: The DG Sanco financed pilot ERNs were selected through competitive calls for proposals. However, these calls do not guarantee that the most appropriate centres of expertise at national level are initially selected to join the network. These collaborations are established because researchers have worked together well before and have similar interests and are able to draw up a successful proposition for financing. Often pilot ERNs are networks of experts rather than networks of expert centres. Respecting the principle of subsidiarity and taking into account the reality of networking in the field of RD, it is difficult to guarantee that the best centres of expertise at national level are included in the networks and apply for funding at EC level. It should also be noted that patient organisations who may wish to participate as partners in these ERN cannot apply for co-funding.

Mapping exercises to identify expertise: Most pilot ERNs have identified expertise in the field of their disease(s)/group of diseases, mostly through conducting a mapping exercise to identify potential partners for the network. This mapping also often includes the identification of existing resources and types of partner valuable to an ERN (e.g. expert clinics, registries, diagnostic laboratories) and other types of related networks of stakeholders (e.g. patient organisations, learned societies) who could contribute to the goals of the network.

Defining selection criteria: In addition to this mapping exercise, pilot ERNs decide on criteria by which to select participating centres/partners by considering the goals of the network: the

recommendations for selection criteria made by the RDTF and HLG were taken into account by many networks, but it can be observed that some networks were established before the adoption of these criteria and thus they were not taken into account. In addition to this, these networks are often established between centres which are not always officially designated as national centres of expertise in their respective countries: indeed, the heterogeneity of national approaches to centres of expertise and their identification is a key issue. Many pilot ERNs have highlighted that the willingness to invest in a project and a shared goal is of more importance in constituting a network than an official designation or compliance with the criteria recommended by the HLG/RDTF. Some ERNs have established other criteria for memberships, such as compliance with guidelines and a mutual understanding of goals and future progress. Some ERNs plan to define strict selection criteria in order to expand their initial pilot networks.

Hierarchy: The leading/ coordinating partner of the pilot ERN is responsible for coordination and supervision of the work of the committee, and is often supported by a steering or coordinating committee. Apart from the leading partner, there is generally no real hierarchy amongst the participating centres in an ERN: centres of expertise are nodes in the network and the links between them are communication and the ICT tools established by the network. It should be noted that in some cases (partly due to the nature of financing of pilot ERNs by the European Commission) some projects distinguish between two types of centre: associated partners and collaborating partners. These two types of centres often have different rights (i.e. access to data), obligations and financing. Existing networks have also highlighted that the creation and organisation of a network is a fulltime position for a non-medical expert in networking.

Expansion: Some pilot ERNs have tried to expand and include new centres/partners, but cost-related or administrative difficulties hindering the expansion of the ERN are often encountered. As previously highlighted, the willingness of a centre to invest in a project is of great importance in the expansion and evolution of the networks and their partnerships, and some ERNs are considering the selection criteria for including new members. The dynamic and evolution of pilot networks will be explored in the next section.

EXAMPLES

ECORN-CF: Partners were selected according to availability and willingness to participate in an EQA programme with the aim of educating partners to reach the standards/criteria set by HLG/RDTF rather than choosing partners less willing to participate but who have already 'proved' the quality of their services (i.e. officially designated centres). In this way partners willing to contribute to the network are not excluded, and this method also ensures that quality will be regulated to the best possible level, i.e. the level of the European Consensus on Care and corresponding to the requirements that have been provisionally set by the HLG/RDTF.

EPNET: Partners are required to complete a questionnaire which is then analysed before they are admitted to the network (for a 2 year period): partners are required to submit activity reports, subscribe to an EQA scheme, liaise with national scientific and patient networks, enter data into the patient registry and collect information about drug use by acute porphyria patients.

EN-RBD: At the start of the project an invitation and questionnaire was sent to the 870 Haemophilia Treatment Centres inventoried by the World Federation of Hemophilia bulletin (2005) in order to join the EN-RBD project. Sixty-one of these Centres replied to the survey sending information regarding the number of patients affected by each rare bleeding disorder they deal with, the type of treatment and if they were already contributed to a national registry. 26 of these centres were European and they were further contacted them in order to begin a collaboration for this new project, with the aim of setting up the on-line network. Nine of these Centres replied and were chosen as subcontracting 'collaborating partners' and have link with their National registry.

ENERCA: A list of identified expert centres and the services they provide for rare anaemias is already online http://www.enerca.org/Specialistcenters/tabid/57/Default.aspx. The 3rd stage of the ENERCA project will include sending a questionnaire to network participants establish a consensus on the criteria to be used to define ERNs for these diseases, in May 2012 a White Book on creation of ERN for rare anaemias is due to be published. The project also aims to study in depth the possibilities for transnational referrals of patients, biological samples and clinical information in order to identify barriers to 'physical' networking between centres.

Directory of expert centres/services: There are different types of directories of expert centres: directories of expert centres who are the partners of the ERN, and directories which include expert centres/services identified by a mapping exercise, and not necessarily in the core network, but with whom some kind of contact and collaboration has been established (extended network). These directories types are therefore neither exhaustive nor limited to expert centres designated at national/regional level. Some networks, for example, provide a more exhaustive list of expert laboratories for diagnosis, with details of the services they provide and contact details.

EXAMPLES

EPNET: This ERN provides an online list of specialist porphyria laboratories which follow a quality assurance scheme are able to distinguish, using biochemical testing, between all types of porphyria and are able to offer specialist detailed interpretation of results with clinical advice on management. Details are also provided on the clinical services offered by these laboratories/centres.

ENERCA: This network provides an online list of centres specialising in rare anaemias with details of the services they provide.

TAG: The list of centers of reference/expertise available on Orphanet and on Geneskin will be updated and completed particularly for the countries where these data are not yet available. Each associated partner will collect and update the data available in his own country and for the pathology they are responsible for: the coordinating partner will compile this data. In the final stage of the TAG project, efforts will focus on identifying which services should be provided by a European and international genetic cutaneous diseases network and where these infrastructures are available: rather than focusing on the criteria of the centres, the project will focus on the precise services the network should provide to patients and will identify the centres which can provide these services.

DYSCERNE: This network provides a list of experts in the network who form part of the expert review panel and a list of DDS submitting nodes.

ESDN: This FP5 funded network provides a list[16] of centres of expertise in the network and gives details of the molecular diagnoses for specific skeletal dysplasias offered by each centre with a link to the relevant service profile for the relevant skeletal dysplasia (i.e. reasons for referral, sample details, target turnaround time, cost etc.).

EuroWilson: This FP6 funded project provides a list of laboratories which have developed molecular diagnostic tests for Wilson disease: as part of the EuroWilson project, these laboratories have formed a network in which there is collaboration and a quality assurance scheme www.emqn.org. Techniques have rapidly improved, and there are now rapid methods for detecting the common mutations. This list gives details of the laboratory and contact details.

Dynamic/sustainability of the network

Expansion, continuing commitment/quality of participating centres, establishing collaborations and sustainability are key elements for maintaining the dynamic of an ERN. The experience of pilot ERNs gives examples of different approaches and factors which determine the dynamics and long-term functioning of the network.

Expansion: The European added-value of ERNs in the field of rare diseases is based on the rarity of the diseases, which implies both a limited number of patients and a scarcity of expertise within a single country: gathering expertise from as many countries and sources as possible is therefore of paramount importance in order to ensure equal access to accurate information, appropriate and timely diagnosis and high quality care for rare diseases patients. Geographical expansion in order to cover as many European countries as possible is therefore a main consideration in the dynamic and long term evolution of an ERN, as this means more expertise is gathered and more patients are implicated, therefore increasing the European added-value of the ERN for a specific disease/group of diseases. As highlighted in the previous section, expanding a network is often administratively complicated and costly as the coordination of a network demands time and resources, and a larger network is more costly to maintain than a smaller one. Also, expertise may not exist in a certain country, and so a suitable partner is difficult to identify/does not exist, and other approaches may need to be considered to provide services to patients in these countries.

Collaborations and partnerships: The dynamic of ERNs can also be increased/maintained by establishing collaborations, for example with learned societies, patient organisations and other ERNs: these collaborations can improve the sharing and dissemination of expertise (one of the principal missions of the ERNs) concerning the disease/ group of diseases. Sharing experiences of networking with other ERNs, and other types of rare disease networks (i.e. research networks, networks of excellence), can also potentially improve networking capacities.

Quality management programmes: For certain pilot ERNs, this is key method of maintaining their dynamic as quality management programmes serve to ensure that participating centres maintain the

[16] http://www.esdn.org/eug/About/Skeletal+Dysplasias+Diagnosis

standards of expertise expected of an ERN and to also monitor participants' commitment to the network.

Sustainability: A major concern in maintaining the dynamic of a network is sustainability as the infrastructure and coordination of an ERN engenders significant costs: currently, pilot ERNs are co-financed for a duration of three years by the European Commission (national co-funding has to be contributed in order to receive EC co-financing). Many ERNs have noted that the 'start-up' phase is lengthy and it takes these three years to establish a network and for partners to start to work together efficiently. After these three years of EU co-financing other solutions should be sought in order to finance these infrastructures if EU co-financing cannot be renewed, as ERNs will break down without proper, funded coordination. Some ERNs continue after the end of this initial financing due to the commitment of the participating centres and by seeking additional financing from other sources. A solution to this question of sustainability has to be found, both at EU and national level. The Council Recommendation highlights this in §20: *"[MS] together with the Commission, aim to ensure, through appropriate funding and cooperation mechanisms, the long-term sustainability of infrastructures developed in the field of information, research and healthcare [i.e. ERNs] for rare diseases".*

EXAMPLES

Care-NMD: This network plans to closely monitor partners of the networks and their compliance with best practice guidelines to assure quality of care and that there is no conflict of interest.

ECORN CF: The project's EU co-funding ended on April 30, 2010 after 36 months as planned. For the time being, the continuation of the ECORN-CF expert advice platforms in the different languages and the quality control of the Central Archive (in English) is supported by the German foundation 'Christiane Herzog Stiftung' and the German patient organisation 'Mukoviszidose e.V.' until the end of 2010.

NEUROPED: This project has held an extended network meeting (23 November 2010) to discuss with stakeholders the further development and extension of NEUROPED as a consortium operating beyond the initial funding provided by the EC for establishing a pilot ERN.

TREAT-NMD: This DG Research funded network of excellence is seeking different solutions in order to finance their activities as their EC co-funding is due to finish in December 2011; this includes a public consultation process launched in 2010 in order to define priorities for the future of the network and its evolution. The network also continues to diversify and develop related activities such as the DG Sanco funded project Care-NMD, a project promoting standards of care for Duchenne Muscular Dystrophy which contributes to the missions of Treat-NMD's Network of Excellence.

Promoting support networks: community networks and patient organisations

The evolution of the structure of ERNs can include promoting collaborations with other types of networks and helping improve support networks and mechanisms for patients with rare diseases.

One approach is to promote the creation of patient organisations where they do not exist (i.e. TAG and EPNET) by sharing networking expertise.

Another approach is to help improve/build community networks able to provide proximal care (i.e. non-expert centres close to the place of residence of the patient) by sharing networking expertise, which reduces the need for rare disease patients to travel, by making the expertise travel instead by establishing effective collaborations.

EXAMPLE

TAG: This network focuses on the treatment and care of patients with rare genetic cutaneous diseases in Mediterranean countries, aims to improve support and health care for these patients by helping to establish local community network of specialists, paramedics and nurses with the support of the local ministry of Health.

Communication and management of the network

All ERNs have highlighted the importance of internal newsletters, conference calls, meetings and workshops for improving networking, the dynamic of the network, communication and transfer of expertise. Although much can be done with ICT tools such as web and teleconferencing, initial 'face-to-face' contact with partners in the network greatly facilitates further cooperation. Many projects have held expert workshops in order to work on recommendations and guidelines, and later in the report we give examples of training sessions offered by ERNs to improve quality of diagnosis and care.

EXAMPLE

TAG: This network has organised a series of expert yearly working sessions where stakeholders of management and health care (specialists, paramedics, social workers, patients associations, pharmaceutical industries) on a European and Euro-Mediterranean At these sessions, experts then meet in working groups by specific disease meet to discuss the best strategies for the prevention and health care of patients as well as recommendations and guidelines.

2. SHARING EXPERTISE FOR PATIENT MANAGEMENT

"In principle and where possible, expertise should travel rather than patients themselves" – Council Recommendation on an action in the field of rare diseases, 8 June 2010

Telemedicine and teleexpertise

Telemedicine and teleexpertise are two distinct concepts: although both use information and communication technologies to facilitate the provision of healthcare, the participating parties differ: in the case of telemedicine the relationship is between a healthcare professional and a patient in different locations, whereas in the case of teleexpertise the relationship is between two healthcare professionals in different locations. Both concepts have a European added-value in the field of rare diseases as expertise and patients are dispersed in different locations across Europe. The use of ICT can help to pool scarce expertise and share expertise and information across borders and preventing, when possible, unnecessary travel by the patient. The Council Recommendation (§14) recommends that in the field of rare diseases Member States *"support the use of information and communication technologies such as telemedicine where it is necessary to ensure distant access to the specific healthcare needed"*.

1. **Telemedicine** is defined by the Communication from the Commission on telemedicine for the benefit of patients, healthcare systems and society (4/11/2008)[17] (COM 2008 689 final) as:

> "The provision of healthcare services, through use of information and communication technologies (ICT), in situations where the health professional and the patient (or two health professionals) are not in the same location. It involves secure transmission of medical data and information, through text, sound, images or other forms needed for the prevention, diagnosis, treatment and follow-up of patients. Telemedicine encompasses a wide variety of services. Those most often mentioned in peer reviews are **teleradiology, telepathology, teledermatology, teleconsultation**, telemonitoring, telesurgery and teleophthalmology. Other potential services include **call centres/online information centres for patients, remote consultation/e-visits or videoconferences between health professionals**. Health information portals, electronic health record systems, electronic transmission of prescriptions or referrals (e-prescription, e-referrals) are not regarded as telemedicine services for the purpose of this Communication."

   Telemedicine is a concept which implies first and foremost relationship between a medical professional and a patient using ICT in order to provide a health care service (i.e. teleconsultation, telemonitoring, telesurgery). The use of ICT tools can improve patient access to specialised care in areas suffering from a shortage of expertise, or in areas where access to healthcare is difficult. This is therefore a concept which is evolving quickly and which could greatly benefit the field of rare diseases: both expertise on rare diseases and the patients are dispersed and ICT allows for expertise to travel virtually, rather than the patients themselves, as put forward in the Council Recommendation.

2. **Teleexpertise** is the provision of expertise at distance through the use of ICT tools, from an expert professional to another expert or non-expert professional in different locations, by

[17] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0689:FIN:EN:PDF

sending information on a patient's case (i.e. X-rays, images, patient files). There is no direct contact with the patient (teleconsultation). The professional receiving the expertise then uses this knowledge to decide on a course of action in the diagnosis/treatment of their patient. Teleexpertise is therefore of value in the field of rare diseases where there is often scarce expertise on a rare disease, and it is preferable for this expertise to travel using ICT tools rather than the patients traveling themselves to be consulted by an expert.

The pilot ERNs adhere to the principal of expertise traveling rather than patients themselves: the analysis of ERNs' actions shows that currently the relationships in these networks are between professionals (teleexpertise) and not between a patient and a professional (telemedicine/teleconsultation). The expert professional shares their expertise on a certain rare disease or group of rare diseases with another professional (expert or non-expert) who then proceeds with the management of the patient's case using this expertise.

EXAMPLES

Dyscerne: This ERN has put in place a Dysmorphology Diagnosis System (DDS) which allows professionals experiencing difficulty in the diagnosis of a dysmorphic patient to submit case details an expert panel via a submitting node. The panel then examines the case and returns a case report to the submitting clinician with recommendations and their opinions on possible diagnoses. The DDS panel is made up of 37 experts from 32 centres of expertise in Europe.

Paediatric Hodgkins Lymphoma: This ERN has an interdisciplinary board of experts form a tumour board which meets weekly to evaluate 35-40 cases. The board assesses reference stage; necessary treatment intensity and response to treatment. A report is received by the treating physician within 3 days of the meeting. The treating physician may contact the board for further discussion/clarification. A secure high speed server is in place to send imaging data (CT, MRI, PET), and a web meeting facility GoToMeetings for regular discussions of teaching cases: the expert team can invite other attendees, such as treating physicians, to these teleconference for one-to-one consultation purposes and for knowledge transfer between the expert team and treating physicians throughout Europe.

Euro Histio Net: This ERN plans a meet the expert system with a session for case presentation and discussion. A web conferencing tool is to be put into place

ESDN: In the field of rare diseases, one of the first networks of expertise in the field of rare diseases to use ICT tools for the purposes of teleexpertise is the DG Research funded (FP5) European Skeletal Dysplasia Network : this network was one of the first to give expert opinions on X-rays sent to an expert clinical-radiological review group. The ESDN case manager has logged 1400 online referrals over the period 20032011 and has over 400 users in 45 countries.

Case management and case management tools

This concept is closely linked to that of teleexpertise. The management of rare diseases (i.e. diagnosis and treatment), due to the limited number of patients coupled with the scarcity and dispersion of expertise often across countries in Europe, is complicated and could be facilitated and improved by

adapted expert case management and case management tools in the context of a European network of centres of expertise sharing their expertise. The Council Recommendation recommends that ERNs take a lead (§13) in organising health care pathways for patients suffering from rare diseases: expert case management and associated tools are being used by some of the pilot ERNs to explore the European added-value of this concept in the field of rare diseases.

Case management is the monitoring and coordination of diagnosis and treatment rendered to patients with specific diagnoses or requiring high cost or extensive services, such is the case for certain rare diseases.

Case management tools are the ICT tools which allow for this coordination to be carried out.

EXAMPLES

Paediatric Hodgkins Lymphoma: This network uses a secure high speed server to send imaging data (CT, MRI, PET) to the expert tumour board and a web meeting facility GoToMeetings for regular discussions of teaching cases.

Dyscerne: This ERN has put in place a Dysmorphology Diagnosis System (DDS) which allows professionals experiencing difficulty in the diagnosis of a dysmorphic patient to submit case details an expert panel via a submitting node.

ESDN: This FP5 funded network has put into place a system called 'ESDN Case Manager' which allows for the management of referred cases.

EUROGLYCANET: This FP6 and FP7 funded network on Congenital Disorders of Glycosylation has adopted the 'case manager' software originally developed for ESDN and adapted it to the network's needs. It includes a sample tracing system and a mutation database. The network has also identified national expert centres for Congenital Disorders of Glycosylation which has the responsibility of the primary follow-up of samples and in supporting local physicians with diagnosis. They also manage the referral of interesting and complex cases to the network for further work-up and research.

ICT tools for sharing expertise within the network

Information and Communication Technology, as explained in the previous sections, helps experts and professionals in different locations (such as partners in an ERN) communicate without having to travel physically which is a great advantage in the field of rare diseases where expertise is scare and geographically dispersed. The use of ICT is recommended in the Council Recommendation (§14) in order to *"ensure distant access to the specific healthcare needed"* for rare diseases. It should, however, be noted that ICT tools are currently used by ERNs for experts to share their expertise (teleexpertise) and not to provide patient access to specific health care services at a distance (telemedicine), as is recommended *"when necessary"* in the Council Recommendation.

A variety of ICT tools are used by ERNs in order to share expertise:

- Discussion groups/forums: for case discussion between experts between a non-expert professional and another professional;
- Web/teleconferencing;
- Intranet sites: to be used as a repository for draft documents under discussion by experts

EXAMPLES

TAG: This network has set up an intranet site with a forum so that experts in different working groups can exchange on work in progress on recommendations for the improvement of the quality of care for patients and families affected by severe genodermatoses.

EPNET: This network set up a password protected website for EPNET members where draft documents under discussion were posted, as well as an email mediated discussion forum for members to allow for sharing of information, problem solving and project planning.

CARE-NMD: This network will provide and online forum for professionals to discuss guidelines for Duchenne Muscular Dystrophy and their implementation.

Producing and disseminating expertise and information with patients and non-expert professionals

The Council Recommendation states that MS should (§ 15) *"include, in their plans and strategies, the necessary conditions for the diffusion … of expertise and knowledge"*: pilot ERNs have demonstrated the suitability of these networks in diffusing such expertise and knowledge. The Recommendation is also in favour of facilitating patient access to updated information on rare diseases (§ 18). ERNs, as networks of expertise are often in contact with patients and patient organisations, and non-expert professionals, and can play a vital role in sharing information and expertise with patients and non-experts.

Information and expertise can be shared:

- by way of a **patient/professional FAQ**: this is a collection of frequently asked questions and expert validated answers either orientated to patients or non-expert professionals, which is then made accessible to patients and professionals, i.e. on a website, and if possible in different languages. FAQs allow for professionals' expertise to be shared with patients. (e.g. Euro Histio Net) ;
- through targeted **patient websites** (e.g. Euro Histio Net, EPNET, TAG) which contain information adapted to the needs of patients, parents and members of a patient's entourage, if possible in different languages;
- by **providing answers to experts to patient's specific questions** (ECORN-CF).

EXAMPLES

Euro Histio Net: Will provide a list of the most frequently asked questions about LCH and related syndromes on their website; one FAQ will be aimed at professionals and has been elaborated in collaboration with experts, and another FAQ will be aimed at patients/parents and general public.

ECORN CF: Patients and health care professionals can submit questions in their local language to a local expert team in the participating network. Answers are then published in their local language and are then translated into English for publication on a central archive.

EPNET: This project has been able to provide improved, evidence-based, information on the selection of drugs for use in acute porphyrias, which is now available for public consultation via an online database: www.drugs-porphyria.com. This information has been produced through collection of follow-up information by pharmacist (5071 reports were returned and through the analysis of data collection forms filled in by porphyria patients concerning their experiences (an important source of clinical data which has allowed theoretical evaluations to be confirmed).

CHD-Platform: This FP7 project aims to establish a European parent and patient-oriented, web-based information and communication platform which aims to help build up a large European network on congenital heart defects.

GENESKIN: This FP6 project provides information on various clinical, laboratory and social aspects of the genodermatoses in the five major groups of disorders (i.e. ectodermal dysplasias, and disorders of epithelial adhesion, keratinisation, connective tissue and DNA repair). Information on these pages is divided into two sub-sections. The first, free-access sub-section is for the general public, particularly patients and their relatives. It contains a general description of each of the five major groups of disorders, together with details of European centres offering clinical, diagnostic and research services, ongoing clinical trials, patients' associations and related websites. The second sub-section is restricted to professionals and requires registration. Here, each disease has a dedicated page with more detailed clinical and laboratory descriptions, including key clinical features, diagnostic tests and procedures, tools for laboratory diagnosis and genetic counselling. Research services, ongoing clinical trials, patients' associations and related websites are also documented.

EuroWilson: This FP6 funded project provides a FAQ for children suffering from Wilson disease, in French, and information on the disease, its diagnosis and treatment in English.

3. BUILDING UP STANDARDS OF CARE

"Gathering expertise at European level is therefore paramount in order to ensure [...] high quality care for rare disease patients"
- Council Recommendation on an action in the field of rare diseases, 8 June 2010

Producing best practice guidelines

Expertise in the field of rare diseases is rare, and it is essential (as stated in the Council Recommendation §17) to "*gather expertise at national level and support the pooling of that expertise with European counterparts"*: one of points of the recommendation is to support *"the sharing of best practices on diagnostic tools and medical care"* in order to mutualise expertise so as to build up and improve standards of care for patients with rare diseases. Although not specifically recommended in the Council Recommendation, ERNs are a suitable structure for sharing best practices and producing guidelines. Guidelines are of particular interest in the field of rare diseases where expertise is scarce and should be mutualised and shared whenever possible to increase knowledge of rare diseases and their management across Europe: these documents should be made easily accessible to professionals and the public (i.e. via ERNs websites, Orphanet). ERNs, as networks that already pool expertise, thus are ideally placed in the production and/or implementation of guidelines or consensus documents.

Clinical practice guidelines are recommendations designed to help a medical professional and patients make appropriate decisions about health care (from diagnosis to treatment) which should help improve standards of care. These recommendations are based on evidence from a rigorous systematic review and synthesis of the published medical literature (when available, if not by gathering expert opinion), and define the needs of most patients in most circumstances.

Diagnostic guidelines are recommendations specifically designed to help a medical professional diagnose a specific disease. Clinical practice guidelines also give diagnostic recommendations.

EXAMPLES

ECORN CF: This network has published a guideline endorsed by the ECFS[18]. A specificity of the approach within this network is the fact that the patients' questions are the driving force for the development of the specific guidelines, which is reflected in the usability of these guidelines for patients as well as and care team members.

Euro Histio Net: Several experts and teams worldwide have been producing guidelines for diagnosis, treatment and follow-up of LCH. One of the ambitious efforts of Euro-Histio-Net will be to review these works, to generate a synthesis of this information and to provide guidelines after approval of many involved specialists.

[18] J Cyst Fibros. 2010 Dec;9(6):385-399. Epub 2010 Sep 17.Travelling with cystic fibrosis: Recommendations for patients and care team members. Hirche TO, Bradley J, d'Alquen D, De Boeck K, Dembski B, Elborn JS, Gleiber W,Lais C, Malfroot A, Wagner TO; on behalf of the European Centres of Reference Network for Cystic Fibrosis (ECORN-CF) Study Group.

TAG: Aims to draw up guidelines specific/adapted to each country's situation (i.e. state of the art of health care).

EPNET: this project has been able to provide improved, evidence-based, information on the selection of drugs for use in acute porphyrias, which is now available for public consultation (online database: www.drugs-porphyria.com). This information has been produced through collection of follow-up information by pharmacist (5071 reports were returned and through the analysis of data collection forms filled in by porphyria patients concerning their experiences (an important source of clinical data which has allowed theoretical evaluations to be confirmed).

Neuroped: This ERN aims to surveys and registry data analysis to identify the main healthcare and social needs of the diseases covered by the network, so as to develop and disseminate guidelines.

Implementing/enforcing guidelines

Some pilot ERNs focus not only on diffusing guidelines and recommendations developed by experts at European (including those produced by ERNs) or International level, but also putting them into practice. ERNs thus play a role in sharing expertise and in some cases training non-expert medical professionals to follow these guidelines.

EXAMPLES

Care-NMD: This network aims to share and enforce best practice guidelines for Duchenne Muscular Dystrophy (DMD) by analysing the current treatment practices in Europe for this disease and by indentifying hurdles to the implementation of up to date recommendations in each country, especially in Eastern European countries. This will help stakeholders and decision-makers to take further actions to improve standards of care for DMD patients. Training workshops will be organised in centres to help enforce guidelines.

ECORN CF: This network aimed to enforce the consensus document of the European Cystic Fibrosis Society by closely monitoring and evaluating the expert replies. This network has also held quality round table meetings four times during the duration of the project.

EUROCARE-CF: This FP6 funded project has as one of its aims the promotion of good standards of care for all cystic fibrosis patients in European countries, through promoting the implementation of consensus guidelines, establishing clinical networks and providing specialist training. In the framework of this objective various experts have visited clinical centres across Europe to share their expertise, and training workshops have been organised. The project also seeks to develop a teaching tool for clinicians and healthcare professionals about the multi-disciplinary approach to CF patient care: this teaching tool would provide information on the minimum accreditation standards and clinical features for establishing a CF centre and a local clinic.

Providing training

Many ERNs have identified the need to hold workshops and training tools/training sessions in order to share and transmit expertise to participants in their networks, and to third parties (i.e. non-expert health professionals). In the field of rare diseases, where expertise is by nature scarce, it is important

to share and transmit this expertise where it is lacking, for example through specific training sessions and expert mobility. This transfer of expertise can greatly improve standards of care, and is encouraged in the Council Recommendation (§15): *ERNs should "include, in their plans or strategies, the necessary conditions for the diffusion and mobility of expertise and knowledge in order to facilitate the treatment of patients in their proximity".*

EXAMPLES

Care NMD: This network plans on holding national multidisciplinary training workshops in order to enforce good practice guidelines and raise awareness of the quality of standards of care.

Dyscerne: This network has developed educational resources for training purposes (i.e. "How to examine a foetus with a congenital anormality") and has also encouraged the implication of trainees in the discussion of cases evaluated through the DDS system.

TAG: As the health care of patients with genodermatoses requires special skills and competences, this project aims to organise training sessions in the second half of the project for specialists and nurses and to also encourage training in centers of reference/expertise throughout the project.

GENESKIN: In the same field as TAG, this FP6 project is active in training health professionals in the field of genetic skin diseases. Training is aimed at i) physicians and healthcare personnel and ii) laboratory personnel. Training focuses on diagnostic procedures, patient global care and treatment options in genodermatoses included in the GENESKIN project (i.e. epithelial adhesion disorders, keratinization disorders, ectodermal dysplasias, connective tissue disorders and DNA-repair diseases). Different areas of life sciences, information sciences and sociology will be covered through a multidisciplinary approach. Training allows for the transfer of knowledge about specific disease aspects beyond the participating centres to all European countries.

LEUKOTREAT: This FP7 project creating a research network for leukodystrophies has already organised a training session for students and young investigators on MRI pattern recognition in leukodystophies open to COST (European Cooperation in Science and Technology) participant countries[19].

EUROCRAN: This FP5 project, which incorporates the Eurocleft clinical network, has developed an interactive tool[20] designed for learning about cleft speech aimed at professionals, addressing previous lack of information concerning collection and documentation of such data. The tool provides suggestions on how to collect a good speech sample and more practically there are speech samples in different languages for professionals across Europe to develop their listening skills. It is therefore a listening exercise as well as a means of promoting good practice. The speech samples are not intended to be examples of good treatment outcomes.

EUROGLYCANET: This FP6 & FP7 project has organised 2 FOCUS courses, in collaboration with Orphan Europe Academy, specifically on Congenital Disorders of Glycosylation, for clinicians and laboratory scientists which develops links between clinical and basic researchers.

[19] The **27 EU Member States**, **EFTA Member States** (Iceland, Norway, Switzerland), **EU Candidate Countries** (Croatia, FYR of Macedonia, Turkey), **COST Cooperating States** (Israel), and Bosnia and Herzegovina and Serbia.
[20] http://www.eurocran.org/content.asp?contentID=1213&sid=132141

Implementing quality assurance and accreditation

Some networks implement External Quality Assurance schemes in order to improve quality standards, particularly for laboratory diagnosis, and in order to monitor the compliance of expert centres with guidelines. These EQA schemes are designed to ensure that centres participating in ERNs are fulfilling the necessary criteria in order to be considered as providing 'expert' services. Some ERNs use data reported from laboratories in order to assess the quality of diagnosis and analysis provided by participants in the networks. The EQA scheme of ECORN-CF has been implemented to ensure equal quality of expert advices given across all participating member states.

EXAMPLES

EPNET: This network has put in place an EQA scheme for laboratories participating in the network in order to develop uniform quality standards and to draw up consensus-agreed protocols for porphyria diagnosis and monitoring. Blood, urine and faeces samples were sent to laboratories to analyse with the methods they use, to provide a diagnosis, give information on how they would report the case to the requesting physician and give information about their diagnostic strategies. Feedback was given to participants and advice given to those who needed to improve their methods. There was in an improvement during the project in how results are reported to the requesting physician. A sustainable fee-paying EQA scheme for porphyria has been put in place at the end of the project, making it possible to monitor analytical and clinical performance at different centres.

EN-RBD: This project has as one of its aims the standardisation of laboratory methods (i.e. assays) for phenotype and genotype analysis according to the standard procedures ruled by International Society on Thrombosis and Haemostasis (ISTH). To do this, reports will be created using collected data which will be used to create guidelines for the evaluation, consultation and treatment of cases of rare bleeding disorders.

ECORN-CF: This expert advice system established an EQA system to assess the formal and content quality of the answers given thus enabling cross border quality assessment and improvement by quality feedback. Since there were significant differences in quality measures between participating partner countries, analysis of the underlying reasons and their correction was established.

ENERCA: One of this project's work packages is to increase quality assurance and improvement of accreditation laboratory systems across Europe. This will be achieved by harmonising existing diagnostic procedures and promoting the external quality assessment of specific laboratory methods used in the diagnosis of rare anaemias.

EUROGLYCANET: This FP6 and FP7 project has been running pilot schemes for the serum transferring assay that is the primary laboratory tool for the detection of Congenital Disorders of Glycosylation. The scheme has been formakku adopted by ERNDIM, an organization that provides external quality assessment for metabolic diseases.

4. IMPROVING CLINICAL RESEARCH

Databases - patient registry/cohort registry

Registries are one of the resources and sources of information on rare diseases cited by the Council Recommendation: *"Member States are encouraged to support registries and databases"* (§5). Disease-specific patient registries, and in particular European disease-specific patient registries (due to the limited number of patients), are an essential source of epidemiological and clinical data in the field of rare diseases which are a valuable resource for clinical research and trials. Pilot ERNs have provided the opportunity to mutualise resources such as databases. The end results/aims of sharing these resources are varied, e.g. to establish evidence-based diagnostic/treatment guidelines (EN-RBD), to establish an evidence-based list of safe/non-safe drugs when treating a patient affected by a certain disease (EPNET), or to analyse the impact of a patient organisations on the morbidity and mortality of patients with a specific rare disease (PAAIR). In order to reach these objectives, some of these ERNs have created a standardised and quality controlled database, sometimes based on an existing registry or combining the data of a number of registries, so as to collect new and/or existing data before analysis.

EXAMPLES

Euro Histio Net: An agreement between the international medical society for histiocytosis (Histiocyte Society) and the Euro-Histio-Net consortium has been was signed. This collaboration is aimed at jointly developing a safe and sustainable database. This database shall support a large data collection with a minimum mandatory dataset. Use of the database will be open to any data contributor (controller) who guarantees to comply with GCP and legal regulations (e.g. data safety and patient consent) and who is able to ascertain the data quality. Data controllers are not obliged to supply the whole catalogue of data but have to complete the mandatory patient registry. The database guarantees to data controllers full responsibility for the use of the data. Data specific to and directly pertaining to international clinical trial must not be published while the study is ongoing (concerning major endpoints, therapeutic arms, and data specified in the trials protocol), but the database can also be used without participation in an international clinical trial.

EN-RBD: The aim of this project is to establish a network of expert centres in the field of rare bleeding disorders in order to collect information on clinical, laboratory and treatment data regarding each single coagulation deficiency so as to analyse this data and make significant statistical interpretations concerning the clinical manifestations, treatment and genetic basis of rare bleeding disorders. An international database on RBDs (RBDD) was established in 2003 prior to the project, however, the data collected was not sufficient to extract useful information that can improve diagnosis and treatment of such disorders by providing evidence-based diagnostic and therapeutic guidelines. The aim of the EN-RBD project was to set up a European network among treatment centres, increasing the available data and ultimately filling the gap between clinical data and practice and providing a secure source of information for clinical surveys by national and supranational health bodies. A common tool for submitting data has been developed and a quality control of data has been performed, and national registry data has been merged into the database.

EPNET: this project established a central database (the European Porphyria Registry) in order to collect anonymised data so as to estimate the prevalence of selected severe complications of various porphyrias. This

data was collected by identified expert centres participating in the project. This study has enabled the project: to determine the incidence of inherited porphyria in Europe, to provide information on the main demographic and clinical features of inherited porphyria, to collect information about rare complications of porphyria, to determine the percentage of newly diagnosed patients with acute porphyria who will develop repeated acute attacks and require sustained management.

Patient Association and Alpha1 International Registry (PAAIR): The aim of PAAIR is to provide the EU with an example of how individuals involved in a rare disease can equip themselves with a comprehensive set of activities to improve diagnosis, care and treatment. Applicants collected and stored in an existing online database (Alpha1 International Registry) cross sectional, prospective data on general health- and disease-related items. This data will be analysed to evaluate the network's impact on the disorder's morbidity and mortality and early diagnosis.

Treat-NMD: This network has established two types of registry: 1) national patient registries containing the information needed to establish whether a particular patient might be eligible for a trial, together with the means of contacting them; 2) Care and Trial Sites Registry (CTSR) - a database of clinical sites and medical centres set up by the TREAT-NMD Clinical Trial Coordination Centre (CTCC) to provide a valuable and accurate source of information regarding the experience, facilities, equipment and personnel of sites worldwide caring for neuromuscular patients; the primary focus of the database is on collecting information that will enable the selection of sites with the expertise to take part in clinical trials.

Care-NMD: One of the aims of this project is to establish a care providers' database with information on patient cohorts, local infrastructure and current approaches to treatment, based on the web-based Clinical Trial and Care Sites Registry developed by Treat-NMD, and to analyse this data. This information will help with the implementation of best practice guidelines in the later stages of the project.

EUROSCA: This FP6 funded project has generated the world's largest collection of standardised data on SCA, the European Spinocerebellar Ataxias Registry (EUROSCA-R). This powerful tool will facilitate continuous recruitment of SCA patients throughout Europe for linkage analysis, identification of novel ataxia genes and natural history studies, in order to develop a treatment for this group of diseases.

Biobanks

Biobanks[21] are repositories of biomaterials: in the field of rare diseases, these biomaterials can be of great value for basic and translational research, especially when linked to clinical information. Biobanks are an important element of rare diseases networks as ERNs can potentially improve access to such biomaterials across Europe. None of the pilot ERNs have currently established collaborations with biobanks.

EXAMPLE

Treat-NMD: One goal of TREAT-NMD (FP6) is to improve the availability and the exchange of biomaterial among scientists across Europe, in collaboration with the already existing EuroBioBank network, a supranational biobank providing a network of biobanking facilities that will encourage the storage of

[21] ENCE blueprint/ BBMRI documentation

biomaterials for NMD patients and help scientists to obtain more easily the specific material they need for their experiments on neuromuscular diseases.

Clinical trial expertise and networks

European Reference Networks of centres of expertise are well placed to provide expertise for clinical trials in the field of rare diseases. A few pilot ERNs have approached this area of action.

Clinical trial design is a term which refers to the preparation of studies and trials in medical and epidemiological research, i.e. a certain drug or medical procedure. The design procedure includes the choice of type of trial (randomised/non-randomised), the doses and frequency of administration of drugs, the number of patients to participate in the trial etc.

Clinical trial management is the practical organisation of a clinical trial once it has been designed: this includes the recruitment of patients, the practical organisation of the trial, the collection of data from the trial etc.

Clinical trial networks are one of the types of expertise sharing networks which can greatly benefit the field of rare diseases due to the limited number of patients and scarcity of expertise in Europe. These networks work with pharmaceutical companies to facilitate every aspect of the trials process in Europe, as most trials are multinational due to the limited number of patients in a specific country. A clinical trial network usually aims to facilitate access to patients/patient data; to design and organise multicentre trials; to promote an interdisciplinary and international approach to clinical research and sharing of expertise; etc. Networks of centres of expertise can pool these resources and this expertise at European level, which is particularly useful in the field of rare diseases where expertise is dispersed.

Unique contact point for Industry: European networks for rare diseases regroup expertise and collect data, of high interest to Industry and some networks (such as Treat-NMD and their Clinical Trials Coordination Centre, see example below) have positioned themselves as a unique contact point for industry. Patient registries are of great interest to the pharmaceutical industry: these registries provide information concerning prevalence, treatment outcomes etc., therefore the networks which develop a European registry or regroup a number of registries can be useful contact point for pharmaceutical companies seeking expertise on a certain disease, and contact with the Industry can help improve access to orphan drugs, products and devices.

EXAMPLES

TREAT-NMD: TREAT-NMD has set up a Clinical Trials Coordination Centre (CTCC) to work with pharmaceutical companies to facilitate every aspect of the trials process in Europe. The network has implemented a Care and Trials Site Registry and a Regulatory Affairs Database and has conducted pre-feasibility studies which have produced valuable information about suitable centres and the patient cohorts available. All this vital groundwork will dramatically speed up the trial preparation process for companies wishing to conduct trials in this area. The CTCC is associated with the Neuropaediatric Department of the University Children's Hospital of Freiburg and the Clinical Trial Centre of the University of Freiburg. The Clinical Trial Centre can provide full clinical research organisation services and already has extensive experience in the planning, conduct and

analysis of multinational clinical trials for the pharmaceutical and medical device industry and scientific investigator initiated trials.

TAG: This ERN plans to approach pharmaceutical companies to help improve access to drugs and medical devices as well as cosmetics for patients affected by rare genetic genodermatoses.

EN-RBD: This ERN plans to approach industrials to promote the development/improvement of not yet available products (as FV and FX concentrates) and to make the network and its registry known to regulatory agencies planning new clinical trials.

ENRAH for SMEs: This FP6 project aims to establish a multidisciplinary research network for alternating hemiplegia of childhood (AHC) and set up a secured web-based registry of AHC cases in Europe: the network also aims to identify relevant SMEs, collect their research profiles and project ideas, and integrate them into the network's activities in order to promote research into therapies/clinical research.

SUMMARY OF THE ANALYSIS OF THE EXPERIENCES AND OUTCOMES OF PILOT EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES

A number of initial conclusions can be drawn from this preliminary analysis of the experience of EC-funded pilot European Reference Networks and other EC-funded networks for rare diseases: these initial conclusions were discussed by participants at the EUCERD Workshop on Initiatives and Incentives in the Field of Centres of Expertise and European Reference Networks for Rare Diseases (8-9 December 2010).

1. The activities of pilot ERNs reflect some of the specific actions needed at European level in order to improve the situation for patients suffering from a specific disease/group of diseases across Europe. As a result, the activities and aims of ERNs are extremely heterogeneous. The geographical coverage of these networks is also heterogeneous due to the choice of partners identified for the pilot and the availability/organisation of expertise from country to country. Despite this variability, the actions of these pilot ERNs have a European added-value in the field of rare diseases, as highlighted in the analysis, as their actions would not have been possible without European collaboration and networking. The pilot ERNs have thus explored various networking possibilities and the benefits of networking in the field of rare diseases. The ERNs do not cover all of the criteria established by the HLG/RDTF, and due to the variability of these networks' aims, it is very challenging to establish a common definition of ERN based on these experiences and to establish criteria for carefully selecting, creating or assessing ERN in a field where resources are limited. The experiences of the pilot ERN should be taken into account to assess the suitability of the criteria defined by the HLG/RDTF, and possibly revise these criteria.

2. The analysis of the networks previously and currently funded by DG Sanco shows that the most valuable resources developed by these ERNs are:
    - Shared databases/registries
    - Shared tools for teleexpertise
    - Guidelines and information
    - Training tools and training sessions

3. The analysis shows that the previously and currently funded pilot European Reference Networks are primarily networks of experts. These networks can include designated national centres of expertise, centres which are recognised as having expertise but without designation, laboratories and patient organisations.

4. This analysis has highlighted that the pilot ERNs have varying objectives and activities. Up to now, research networks have been funded at European level by DG Research, and DG Sanco funds public health networks, as stated in the 2008 RDTF Report *European Reference Networks in the Field of Rare Diseases: State of the Art and Future Directions*[22]. In fact, networking is a process, and there is a natural progression in the networking process:

[22] http://www.eucerd.eu//upload/file/Publication/RDTFERN2008.pdf

1. Basic research networks
2. Clinical research/trials networks
3. Clinical care networks
4. Information networks for patients/public
5. Comprehensive networks

Pilot ERNs do not currently follow this schema in developing their networks, but some comprehensive networks have developed from DG Research funded networks in this way. There is thus a need to harmonise and coordinate the approaches of DG Sanco and DG Research.

5. The analysis also shows that much of the networking currently practiced by ERNs and other networks with similar activities is virtual: expertise is shared at distance (teleexpertise) rather than physically (patients do not travel to expert centres in the network to receive care). Pilot ERNs practice teleexpertise, but not yet telemedicine as recommended by the Council Recommendation (§14) 'when necessary'. The exception to the virtual/physical mobility of expertise trend is that some networks promote travel by expert professionals to countries which lack certain expertise in order to share their experiences and certain specific treatment techniques, and many networks organise regular meetings of network partners in order to strengthen communication and cooperation in the network. Pilot ERNs, therefore follow the recommendation of the Council and the HLG/RDTF that expertise should travel rather than patients whenever possible, but they have not yet fully explored the potential of telemedicine.

CONCLUSIONS AND RECOMMENDATIONS

The conclusions and recommendations outlined below were drawn at the EUCERD Workshop on Initiatives and Incentives in the field of national centres of expertise and European Reference Networks for rare diseases (8-9 December 2010)[23].

The actions of current ERNs generally comply with the Council Recommendation. The adoption of the Cross-Border Health Care Directive will have an impact on the concept of ERNs.

It was agreed that the concepts concerning the field of national centres of expertise for rare diseases and European Reference Networks must be defined and stabilised for further work to be carried out. It was also agreed that expertise needs to be identified, and designated, at a national level before networks of expertise at a European level can be built.

ERN at European level should most importantly be infrastructures rather than just groups of experts, and should be coordinated by an expert in networking whose position is financed at European level. The type of infrastructures needed at EU level should be explored and the resources that can be mutualised and shared should be identified. Formal systems for sharing experiences should be envisaged.

An evaluation system for European Reference Networks should be established to assess their strengths and weaknesses in order to highlight directions for further improvement. This system could be linked to a financial sustainability instrument.

The question of how to support current networks (in particular the infrastructures developed) and identify new ones should be addressed:

- Bearing in mind the limited available budget, the question of prioritisation has to be answered at EUCERD level, as should the question of a suitable legal instrument to provide continuous support to ERN.
- A funding duration of 5 years would be more appropriate than 3 years. The joint action instrument should be envisaged: alternatively, the E-Rare ERA-NET instrument could be explored as a possibility.

Methods of financing and sustainability have already been explored by the HLG: this group produced a *Draft Procedure for the Identification and Development of ERN*[24] which should be considered in further depth in the light of the experiences of pilot ERNs.

[23] http://www.orpha.net/nestasso/EUCERD/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf
[24] http://ec.europa.eu/health/archive/ph_overview/co_operation/healthcare/docs/highlevel_2006_007_a1_en.pdf

ANNEX 1 : Description of the activities of the pilot European Reference Networks for rare diseases

This information is reproduced from the DG Sanco/EC Health Portal website (accessed November 2010) http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm .

European reference networks (ERNs) for rare diseases

European reference networks (ERNs) for rare diseases should serve as **research** and **knowledge** centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERN should also reflect the need for services and expertise to be distributed across the EU.

In 2005, the Rare Diseases Task Force Working Group on centres of reference submitted its first report: Overview of current Centres of Reference on rare diseases in the EU , including Annexes , to the Commission's High Level Group on Health Services and Medical Care. The report was used to feed a general reflection on the establishment of clinical centres of reference in Europe, based on the example of centres of reference for rare diseases.

In 2006, the Rare Diseases Task Force Working Group on centres of reference submitted its second report Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force .The report detailed the use of the concept of centres of reference and their functions.

1. Definition of centre of reference in European countries

There is no common definition of what a centre of reference is among those Member States which have established such centres. Even the definition of a rare disease varies between countries with official centres of reference, although there is a well-defined prevalence in Europe qualifying a disease as rare. The UK uses 1 in 50 000, Sweden and Denmark use 1 in 10 000, while France, Italy and Spain use the EU definition of 1 in 2 000.

The number and geographical distribution of centres per country vary from one country to another and are not proportional to the size of the population, reflecting differences in the organisation of health care systems. Some countries take a national approach to the concept (e.g. Bulgaria, UK, Belgium, France, Greece, the Netherlands), while others tackle a more regional one (e.g. Spain, Italy, Sweden). Most countries have not yet started identifying their expert centres.

2. Identifying and designating European reference networks

In 2005-2006, the High Level Group on Health Services and Medical Care. defined the main criteria for European reference centres.

- Work of the High Level Group on health services and medical care.
- Options for a procedure for identification and development of European reference networksT.

The aim is to give both health professionals and patients access to high level, shared expertise in a given field. The idea is that the expertise, rather than the patients, should travel - although patients should also be able to travel to the centres if they need to.

The suggested conditions for designation as a European reference centre are:

- sufficient activity and capacity to provide relevant services at a sustained level of quality;
- 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;
- multi-disciplinary approach;
- high level of expertise and experience, as documented through publications, grants or honorific positions, teaching and training activities, etc.;
- strong contribution to research;
- involvement in epidemiological surveillance, such as registries;
- close links and collaboration with other expert national and international centres, and capacity to network;
- close links and collaboration with patient associations, where they exist;
- appropriate arrangements for patient referrals from other EU countries;
- appropriate capacities for diagnosing, following-up and managing patients, with evidence of good outcomes, where applicable.

Although a European reference network should meet most of the above criteria, their comparative relevance will depend on the particular disease or group of diseases covered. New centres that meet all the conditions should be able to join a network at any time.

Another important principle is to respect the national governments' primary responsibility for organising, financing and delivering healthcare. As national authorities are best placed to oversee and keep regular contact with the expert/reference centres located on their territory, they should play an active role in the process.

3. Diagnosis and care: how can centres of reference best serve rare disease patients?

In the RAPSODY (Rare Disease Patient Solidarity) project, eleven workshops took place in Europe, during March and April 2007 , with the objective of opening or continuing dialogue between patient representatives, health policy makers and health care professionals about national centres of expertise and European reference networks of centres of reference for rare diseases.

After each meeting, a synthesis was written and the responses to the main questions addressed were presented at the European Workshop on Centres of Expertise and Reference Networks for Rare Diseases (July 12th-13th 2007). The reflection was based on the report from the Working group of the Rare Diseases Task Force first published in September 2005 and updated in December 2006.

Participants at the workshops were first asked to respond to the following questions:

- Needs and expectations for national rare diseases centres of expertise.
- Proposal for the evaluation of national centres of expertise in your country.
- Cooperation with other countries and recommendations for European reference networks.

From the patient's organisations point of view European Reference Networks (ERN) should:

(1) Have professional qualification and clinical and scientific experience;
(2) Be committed to cooperate & share information;
(3) Permit patient’s access to a multidisciplinary team of experts;

(4) Pay attention to coordination between professionals and a global approach (holistic, comprehensive) between medical and social levels;
(5) Agree best practice, standards and guidelines for diagnosis and treatment;
(6) Disseminate of European reference diagnostic and therapeutic protocols to ensure equity at EU level;
(7) Perform education, information, communication activities to empower patients;
(8) Collaborate with patient organisations;
(9) Be initially evaluated and accredited at EU level and regularly assessed; and
(10) Be aware of the importance of flexibility as to the types of centres belonging to the networks and their geographical location.

See Summary of Proposal (Draft for discussion) "Expectations and Eligibility Criteria for European Reference Network of Centres of Expertise for Rare Diseases". presented to the European Conference on Rare Diseases (Lisbon, November 2007).

See Final Report of the European Workshop on Centres of Expertise and Reference Networks for Rare Diseases (July 12th-13th 2007).

PROJECTS SELECTED FOR FUNDING AS PILOT EUROPEAN REFERENCE NETWORKS

A] Projects selected for funding in 2006 as reference networks pilot projects

Projects to develop networks:

1. European Centres of Reference Network for Cystic Fibrosis (ECORN-CF).

Project leader - Klinikum der Johann Wolfgang Goethe-Universität, Germany. This project facilitated access to specific healthcare aids for patients with rare diseases, in particular:

1. information on medical and psychosocial aspects of the disease,

2. advice for patients, relatives and the professional healthcare team,

3. expertise regardless of patient and/or healthcare professionals' place of residence and native language,

4. referrals to patient organisations and improvement of patient decision making aids,

5. accepted European guidelines and monitoring of adherence to them, and

6. quality assurance measures to raise levels of expertise to the highest European standards.

The general principles of this model can be extracted to formulate rules and construction guidelines. The financial figures can be extrapolated to calculate the possible costs and benefits of upscaling the model to cover either a number of rare diseases; all relevant rare diseases, or all diseases requiring specific expertise that can not be expected to be available in all EU countries.

See web site of the European Centres of Reference Network for Cystic Fibrosis (ECORN-CF)

2. European Network of Centres of Reference for Dysmorphology (DYSCERNE)

Project leader: University of Manchester, UK.

Main objectives were to:

1. Form a network of existing centres of reference for dysmorphology, raising standards for diagnosis, management and information dissemination and serving as a demonstration project for other networks,

2. Develop an electronic dysmorphology diagnostic network of expert opinions based on an EU-funded system for skeletal disorders that has been proven in practice and can serve as a model for networks covering other groups of rare diseases,

3. Develop and implement management strategies for selected dysmorphic syndromes,

4. Disseminate information on best practice in managing selected syndromes through existing European information networks and reference centres.

See web site of the European Network of Centres of Expertise for Dysmorphology

Projects including activities that aim to develop networks:

1. Patient Associations and Alpha1 International Registry (PAAIR)

Project leader: Stichting Alpha1 International Registry, the Netherlands.

The aim of PAAIR was to provide the EU with an example of how individuals involved in a rare disease can equip themselves with a comprehensive set of activities to improve diagnosis, care and treatment. To this end, the applicants collected and stored in an existing online database cross sectional, prospective data on general health- and disease-related items. The idea was to analyse the network's impact on the disorder's morbidity and mortality and early diagnosis. The strategic objectives were:

1. map the new EU countries to check eligibility for membership of the doctors' group (AIR) or the patient organisation (Alfaeurope),

2. compare the standards of the centres already in the AIR network and the centres identified in the new EU countries with the requirements for Reference Centres as defined by the Rare Diseases Task Force working group and adopted by the High Level Group on Health Services and Medical Care,

3. set up interaction between national patient and doctor/scientist bodies (AIR), to generate a model of doctor-patient interaction in three EU countries (the Netherlands, Italy and Germany),

4. establish a European patient body with legal status for the specific rare condition, and

5. investigate the AIR network's impact on the disorder's morbidity and mortality and early diagnosis, as compared with what is known from the literature.

See web site of Alpha One International Registry (AIR)

2. European Porphyria Network - providing better healthcare for patients and their families (EPNET)

Project leader: Assistance Publique - Hôpitaux de Paris, France.

The aim of the EPNET project was to set up a functional network of specialist porphyria centres, each conforming to agreed quality criteria. EPNET drew up consensus-agreed information on all porphyrias, translated it into patients' languages, standardised the evidence base for advice on drug use in porphyrias, monitored the diagnostic performance by external quality assessment, and collected epidemiological data for national public health authorities and the EU.

The overall aim was to (a) develop a common approach to the diagnosis and clinical management of porphyrias throughout the EU, so that patients, their families and healthcare professionals would have easy access to evidence based, consensus-agreed information and support in their own languages, and (b) provide national public health authorities and the EU with new epidemiological data on acute porphyrias.

The EPNET project had four key strategic objectives:

1. provide, on a dedicated website, up-to-date information on all porphyrias for patients, their families and healthcare professionals, in their own language,

2. provide improved, evidence-based, information on the selection of drugs for use in acute porphyrias,

3. promote better definition and classification of porphyrias by establishing a European network of diagnostic and clinical advisory centres, each conforming to agreed clinical and biological quality criteria, and

4. collect and pass on to national public health authorities and the EU epidemiological data on all porphyrias and their main complications.

The overall objective was to set up an effective and functioning network of specialist porphyria centres (EPNET) which, in each participating country, comprise of healthcare professionals in public hospitals and laboratory facilities that are fully dedicated to porphyria management.

See web site of the European Porphyria Initiative - European Porphyria Network

See web site of the Drug Database for Acute Porphyria

3. Establishment of a European Network of Rare Bleeding Disorders

Project leader - Università degli Studi di Milano, Italy

Treating patients with rare bleeding disorders during bleeding episodes or surgery is a challenge because of the lack of experience, paucity of data, non-availability of factor concentrates for some deficiency states and the possible occurrence of severe complications, which can be minimized by assessing the risks of bleeding and thrombosis and/or using haemostatic means other than blood components, or no therapy at all.

The international database on these disorders - the Rare Bleeding Disorders Database (RBDD) - is structured to report clinical, laboratory (specific and advanced coagulation tests), genetic (mutation detection, in vitro expression study, and requirements for prenatal diagnosis) and therapeutic data. However, the data collected is not sufficient to extract useful information that can improve diagnosis and treatment of such disorders by providing evidence-based diagnostic and therapeutic guidelines. Therefore the aim of the project was to set up a European network among treatment centres, increasing the available data and ultimately filling the gap

between clinical data and practice and providing a secure source of information for clinical surveys by national and supranational health bodies.

B] Projects selected for funding in 2007 as reference networks pilot projects

1. Improving Health Care and Social Support for Patients and Family affected by Severe Genodermatoses – TogetherAgainstGenodermatoses (TAG)

Coordinated by the Fondation René Touraine (FR)

The project aims at improving the delivery of health care and social support for patients and families affected by severe genodermatoses by getting together the stakeholders from the EU Member States and the candidate countries.

The project will identify and participate in three conferences of the main stakeholders, build multidisciplinary and European task forces for six groups of diseases, and exchange information on epidemiology, prevention, diagnosis and health care.

The project will structure national registries for epidemiology, define guidelines, list available resources and expertise and assess costs. TAG will also enter into discussion with the pharmaceutical companies; support development of community networks, a network of centres of expertise, and a network of patients' associations.

2. European network of paediatric Hodgkin's lymphoma – European-wide organisation of quality controlled treatment

Project Leader: University of Leipzig, Germany

Building on the experience from national trials for paediatric Hodgkin's lymphoma (PHL) experts from 12 EU countries decided on a common protocol to individualise PHL treatment. Treatment decisions depend on exact staging and early response assessment using CT, MRI and PET. Due to limited experience with this rare disease in local hospitals, participating countries decided either to join a central reference system (10 countries), successfully working in Germany since 1990, or to build up own systems (France and Poland). The project facilitates the establishment of a central reference system including all clinical, CT, MRI and PET data from all patients providing the basis for future guidelines.

3. European Network of Reference for Rare Paediatric Neurological Diseases (NEUROPED)

Project Leader: European Network for Research on Alternating Hemiplegia, Austria

NEUROPED focuses on a number of conditions, among which Alternating Hemiplegia of Childhood (AHC), Narcolepsy and Rare Surgically Treatable Epileptic Syndromes (RSTES) to include Tuberous Sclerosis, Sturge-Weber, Hypothalamic hamartoma, Landau- Kleffner syndrome and Rasmussen's encephalitis. A team of 13 partners from 9 European countries collaborate to:

(1) Establish a European Reference Network on Rare Nervous System Disorders in Children;

(2) Integrate Patients in the European Network;

(3) Identify main research, health care and social needs per each of selected diseases;

(4) Develop audited guidelines on diseases of rare nervous system in children with paroxysmal attacks;

(5) Build European-wide patient registries for prospective studies on AHC, Narcolepsy and RSTES;

(6) Identify specific ethical issues and Best Practice related to field, the Network and the use of patient registries; and

(7) Spread the Network expertise throughout Europe.

4. A reference network for Langerhans cell histiocytosis and associated syndrome in EU

Project Leader: Assistance Publique Hôpitaux de Paris, France

The EURO HISTIO NET 2008 project aims to set up a network for those reference centres organising care and clinical research for Langerhans Cell Histiocytosis (LCH) and associated syndromes in each individual EU country. It will share and disseminate the knowledge and experience of different European LCH centres through the realisation of 3 objectives:

(1) Set up a web portal to improve the quantity and quality of information exchange;

(2) Produce guidelines for diagnosis, follow up and therapy for LCH and associated syndromes and guidelines for tissue banking in order to enhance basic research in this field; and

(3) Set up an international data base in order to improve the level of knowledge about the epidemiology and risk factors for short term and long term sequelae, in order to determine better therapeutic measures.

See web site of the Euro-Histio-Net Project

C] Projects selected for funding in 2009

Projects including activities that aim to develop networks:

1. **Care-NMD: Dissemination and Implementation of the Standards of Care for Duchene muscular Dystrophy in Europe (including Eastern countries)**

CARE-NMD aims to implement best-practice standards of care for Duchenne muscular dystrophy across Europe, by bringing together a network of leading care centres. The project will evaluate existing treatment practices, implement newly agreed international consensus care recommendations, and evaluate their impact on patients' quality of life. By adopting an inclusive networking approach, targeting both care providers and patients, CARE-NMD will improve accessibility to best-practice care for Duchenne muscular dystrophy patients throughout Europe.

Project website: http://www.care-nmd.eu/

D] Other DG Sanco projects aimed at establishing networks for rare diseases (but not classed as pilot ERNs)

1. The EU ENERCA project (European Network for Rare Congenital Anaemias)

Under the coordination of the Hospital Clínic i Provincial de Barcelona, Catalonia (Spain), ENERCA is a source of information about rare congenital anaemias including:

- a detailed list of centres which specialise in these illnesses,
- definitions of all the rare congenital anaemias, including congenital red cell enzyme deficiencies, congenital red cell membrane defects, congenital haemoglobinopathies, congenital erythropoyesis defects, etc,
- information about national and international organisations for every country involved in the project, and
- standardised services for these diseases to ensure that the correct tests are performed and a correct diagnosis is made.

In addition to congenital anaemias the ENERCA-II Project covered all rare causes of anaemia, either hereditary or acquired. Other objectives were to:

- establish referral laboratories or experts to provide professional assistance and information,
- make information about their disease readily available to patients,
- facilitate a prompt response in emergencies,
- provide an officially endorsed website and restricted access database giving professionals an on-line forum and member newsletters,
- carry out epidemiological data studies to monitor the occurrence of congenital anaemias at national and local level and create a registry for rare congenital anaemias,
- carry out systematic neonatal screening in European countries without existing databases,
- promote the exchange of information between different research groups in order to improve the understanding of molecular and genetic mechanisms of congenital rare anaemias,
- prepare European guidelines for the diagnosis and clinical management of rare congenital anaemias and
- establish a quality-control system for the laboratory diagnosis of anaemia and for thalassaemia
- Improve detection time and apply a uniform approach to the prevention, diagnosis and treatment of rare congenital anaemias.

Further reading:

ENERCA 2

ENERCA 1

Annex 2: Overview of ERNs' actions

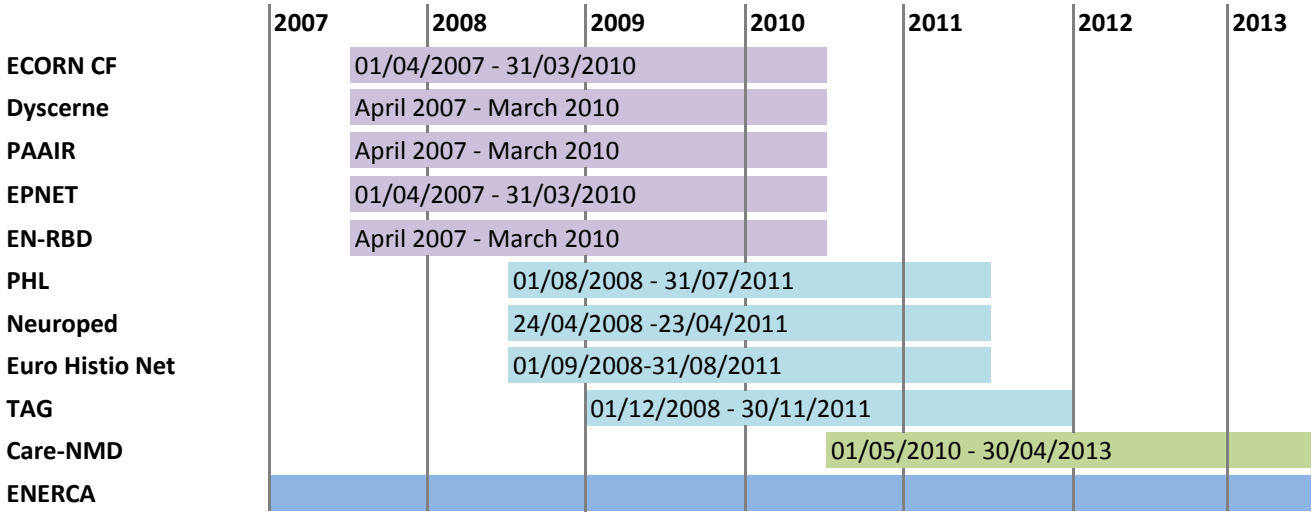
		finished					on going					
		DG Sanco funded pilot ERNs(2006)		*DG Sanco projects including activites aimed at establishing networks (2006)*			*DG Sanco funded pilot ERNs (2007)*				*DG Sanco funded pilot ERNs (2009)*	*DG Sanco funded RD network*
Type of activity		**DYSCERNE**	**ECORN CF**	**PAAIR** *(report not yet received)*	**EPNET**	**EN-RBD**	**Pediatric Hodgkins Lymphoma**	**NEUROPED** *(report not yet received)*	**EUROHISTIONET**	**TAG**	**Care NMD**	**ENERCA**
Identifying expertise/networking	Mapping exercise	Yes	No	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes
	List of partners	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Directory of expert services across Europe	No	No	?	Yes	No	No	?	?	?	Yes	Yes
	Establish collaborations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Encourage development of community networks/patient organisations	No	No	Yes	Yes	No	No	No	?	Yes	Yes	?
Sharing expertise/information	Telemedicine	No	No	No	No	No	No	No	No	No	No	No
	Teleexpertise	Yes	No	No	No	No	Yes	Discussion forum	Yes	Discussion forum	Discussion forum	Discussion forum
	Case management & tools	Yes	No	No	No	No	Yes	No	No	No	No	No
	Disseminating information for patients (i.e. website)	No	Yes	?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	Disseminating information for professionals (i.e. website)	Yes	Yes	?	Yes	Yes	Yes	Possibly	Yes	Yes	Yes	Yes
	Patient/professional FAQ	No	No	No	No	No	No	No	Yes	No	No	No
Building up standards of care	Producing best practice guidelines	Yes	No	?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
	Implementing/enforcing guidelines	Yes	Yes	No	Yes	Yes	Possibly	Yes	?	No	Yes	No
	Training	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes
	Implementing quality assurance and accreditation	No	No	No	Yes	Yes	No	No	No	No	No	Yes
Improving clinical research	Database (patient registry/cohort)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Biobank	No	No	No	No	No	No	No	No	No	No	No
	Clinical trial design	No	No	No	No	No	Yes	No	No	No	No	No
	Clinical trial management	No	No	No	No	No	Yes	No	No	No	No	No
	Unique contact point for industry	No	No	No	No	Possibly	No	Possibly	No	Possibly	No	?
Group of diseases covered		Rare dysmorphic diseases			Porphyrias	Rare bleeding disorders		Rare paediatric neurological diseases		Genetic skin diseases		Rare and congenital anaemias
Specific disease(s) covered			Cystic Fibrosis	alpha1-antitrypsin deficiency	CONGENITAL ERYTHROPOIETIC PORPHYRIA, Erythropoietic Protoporphyria, Porphyria Cutanea Tarda	rare coagulation disorders including afibrinogenemia, FII, FV, FVII, FV+FVIII, FX, FXI and FXIII deficiency, Haemophilia A and B, Von Willebrand disease	Pediatric Hodgkins Lymphoma	Alternating Hemiplegia of Childhood (AHC), Narcolepsy and Rare Surgically Treatable Epileptic Syndromes (RSTES)	Langerhans cell histiocytosis and associated syndromes	Epidermolysis bullosa, Inherited Ichthyosis, Palmoplantar keratoderma, Neurofibromatosis, Xeroderma pigmentosum (XP)	Duchenne muscular dystrophy	

Annex 3: COUNTRY PARTICIPATION IN DG SANCO EUROPEAN REFERENCE NETWORKS OF EXPERT CENTERS FOR RARE DISEASES

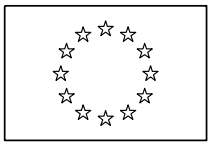
		DG Sanco Funded ERN										Networks of Action for RD - DG Sanco		
	COUNTRY	DYSCERNE (Dysmorphology)	ECORN CF (Cystic Fibrosis	PAAIR (Alpha1)	EPNET (Porphyrias) + EPI (European Porphyria Initative)	EN-RBD (Rare Bleeding Disorders)	Pediatric Hodgkins Lymphoma	NEUROPED (Rare paediatric neurological diseases)	EUROHISTIONET (Langerhans cell histiocytosis)	TAG (Genodermatoses)	Care-NMD (Duchenne)	ENERCA (Rare Congenital Anaemias)	Total # of projects participated in by country	Total # of project for which country is main partner
European Union Member States	Austria			X			X	Main	X				4	1
	Belgium	X	X	X	X	X		X	Collaborating	Collaborating		X	9	
	Bulgaria	X									X		2	
	Cyprus	X								X		X	3	
	Czech Rep.	X	X	X	X		X	X			X	X	8	
	Denmark	X		X	EPI	X	X	X			X		7	
	Estonia			X									1	
	Finland	X			X								2	
	France	X	extra language		Main	X	X	X	Main	Main	Collaborating	X	9	3
	Germany	X	Main	X	X	X	Main	X	Collaborating		Main	X	10	3
	Great Britain	Main	X	X	X	X	X	X	X		X	X	10	1
	Greece	X	X			X			Collaborating	X		X	6	
	Hungary				X						X		2	
	Ireland	X			X	X	X				Collaborating		5	
	Italy	X		X	X	Main		X	X	X		X	8	1
	Latvia	X		X									2	
	Lithuania		X	X									2	
	Luxembourg												0	
	Netherlands	X	X	Main	X			X	Collaborating		Collaborating	X	8	1
	Poland	X	X	X	X		X		Collaborating		X	X	8	
	Portugal	X						X		X		X	4	
	Romania	X	X							X	Collaborating	X	5	
	Slovakia	X									Collaborating		2	
	Slovenia	X				X		X		X			4	
	Spain	X		X	X		X	X	X			Main	7	1
	Sweden	X	X	X	X		X		Collaborating			X	7	
	Total by Network: EU countries	21	10	14	13 + 1 EPI	9	10	12	11	9	12	14		
Non- EU European Countries	Belarus										Collaborating		1	
	Croatia									Collaborating	Collaborating		2	
	Iceland							X					1	
	Israel	X			EPI								2	
	Macedonia	X									Collaborating		2	
	Morocco									Collaborating			1	
	Norway	X			X		X				Collaborating		4	
	Russia										Collaborating		1	
	Serbia					X					Collaborating	X	3	
	Switzerland	X		X	X							X	4	
	Turkey	X				X				X			3	
	Ukraine										Collaborating		1	
	Total by Network: EU and non-EU	26	10	15	15 + EPI 2	11	11	13	11	11	19	16		

Revised February 2011

Annex 4: Duration of ERN financing by DG Sanco



ANNEX 5 : Description of the activities of the pilot European Reference Networks for rare diseases



EUROPEAN COMMISSION

HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

HIGH LEVEL GROUP ON HEALTH SERVICES AND MEDICAL CARE

Document: Summary of provisional responses of leaders of the pilot projects on European reference networks to the questionnaire	
Date: 30/07/2008	**Reference:** HLG/COR/2008/4
To: Members of the working group.	**From:** Secretariat
Action: For information and consideration.	

On 1 February 2008 a questionnaire developed by the working group was circulated to the project leaders of five pilot projects on European reference networks supported under the 2006 Call for Proposals of the Public Health Programme. This paper summarises responses received until now (4 projects replied). These responses are only provisional ones, aiming to help the working group to better focus its further work in 2008 and beyond. However, the complete answers to all the questions in the questionnaire, based especially on the practical experience gained from the pilot projects, should be provided by the project leaders only in the later stage, once they were able to test sufficiently their plans and ideas in practice.

The questionnaire was also circulated to leaders of pilot projects supported under the 2007 Calls for Proposals, either from the Public Health Programme or from the 7th Research Framework Programme. Initial replies of these projects are expected later this year.

This paper provides only a general summary, question by question, of main features of most of the contributions. However, it does not necessarily always reflect every detail of the individual contributions. For more details it is recommended to consult individual contributions of the projects that are circulated together with this summary.

1. ESTABLISHING AND DEVELOPMENT OF THE NETWORK

1.1. How were partners of the network identified in the initial stage and how was the network formally established? Were the principles and criteria developed by the High Level Group so far taken into account[1]?

Generally, a core group of leading centres in a given field was initially identified, based mainly on their reputation. Subsequently the networks try to expand and to involve other centres..

HLG criteria were generally not taken into account as such, perhaps because they were not adopted yet in the time of establishment of the network or the network was not aware of them. However, most of the projects believe that they comply with most of the HLG criteria.

1.2. Is the network open for new partners and how are the potential new partners being identified or selected?

Generally yes. However, sometimes there is a cost or other difficulties related to expansion of the network.

1.3. What are the criteria to become a partner in the network?

Most of the networks do not really use structured criteria for the moment. Aspects such as reputation and being a leading centre in the country, contribution to projects, publications and participation in conferences are

[1] See in particular documents Work of the High level Group on health services and medical care in 2005 (HLG/2005/18) and Report on the work of the High Level Group in 2006 (HLG/2006/8), both available at http://ec.europa.eu/health/ph_overview/co_operation/mobility/high_level_documents_en.htm

most often considered. Some projects require also "technical" ability to participate, such as ability to generate relevant quality data and ability to transfer these data into the web-based database.

1.4. How is a centre and its capacity to become a partner in the network being assessed?

As with the previous question, generally there is no structured mechanism or structured quality criteria for assessment in place for the moments. Some projects use peer reviews or evaluation by an expert panel, while some other projects indicated that they will try to develop more structured criteria in the future.

1.5. How does the information about the network get to the potential partners, to the patients and other stakeholders (health professionals, patient associations, health authorities)?

All projects have their own dissemination strategies, including websites, articles, conferences and collaboration with patient associations.

1.6. How is patient participation being ensured in the process of establishing and running the network?

Different approaches are being used. For some projects patient organisations are directly part of the network; for other projects patient organisations are invited to regular meetings; and for some projects the direct involvement of patient organisations is rather limited for the moment, but may be further developed in the future.

1.7. Can the network easily be expanded/transferred to other diseases?

All projects believe that yes. Obviously, this seems to be easier for projects aiming at creating common databases as the models of the databases could be used also for other diseases.

2. GOVERNANCE OF THE NETWORK

2.1. Is there a hierarchy among the participating centres/nodes in the network?

In general, there is no real hierarchy among the centres participating in the networks. However, two types of structure of the networks can be identifed:

- Most of the projects distinguish between two types of centres, leading (coordinating) partners and associated (collaborating) partners. These two types of centres have different rights (e.g. right to access, but not to modify data), but also different obligations.

- One project indicated that all partners in the network have equal rights.

2.2. Who is responsible for supervising continuous compliance of the network partners with the membership criteria established by the network and how are the quality standards of care (including diagnostics, other tests or procedures in case the patient is referred only to the consultation or diagnostics) being continuously assessed within the network?

Generally, it is the leading partner of the network that is responsible for supervising the work of the network. This responsibility is sometimes shared with a steering or coordinating committee. In some networks the compliance is checked against commonly agreed guidelines; other networks plan to adopt in the future clear membership criteria.

2.3. Is the continuing compliance with criteria and evaluation ensured in a similar way as described in the High Level Groups document 'Options for a procedure for identification and development of European reference networks'[2] (see attached)?

This is not obvious from the responses. Some projects indicated that they apply similar principles or methods as outlined in the HLG document. Some projects will only develop a structured mechanism for evaluation in the future, so it is not possible to answer the question for the moment. Some projects feel that this is not applicable to them as the selection of the participating centres is not based on the structured quality criteria.

2.4. Is an external independent evaluation foreseen?

A general answer is no.

2.5. Are there contacts established with other European networks of reference?

Some projects established informal contacts with other networks, other projects not yet, but plan to do so in the future.

2.6. Are the contacts established with other partners such as ORPHANET or EURORDIS, or others (please precise)?

Yes, all projects have established contacts with Orpahnet, Eurordis and other organisations active in the area of rare diseases.

3. QUALITY AND CONTINUITY OF CARE

3.1. Is there any quality management program established within the network?

Different answers to this question were provided. For some projects this is an essential part of the project already, some projects plan to work on this

[2] The document is also available at http://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/highlevel_2006_007_a1_en.pdf

issue in the future, some projects provided only a quite general answer without providing more details about the quality management program.

3.2. Have quality goals been assigned?

Similar variation of replies as for the previous question. Apparently, definition of quality goals is much easier for networks or diseases where there is already a European consensus or agreed guidelines.

3.3. Is there a benchmarking process established within the network? If so, who is getting the results?

Only one project has established a real benchmarking mechanism. They use structural, procedural and outcome quality benchmarks and all the partners get the benchmarking results.

3.4. How is the continuity of care ensured for patients who are referred to the network from other countries or from centres outside the network or from the network back to the home country?

All of the projects are only virtual networks, so no physical transfer of patients between centres is generally foreseen. Some projects encourage intensive communication between physicians if more than one centre is involved and instruct them to relay all relevant information about the patient to the treating physician.

4. INVOLVEMENT OF PATIENTS AND OTHER STAKEHOLDERS

4.1. What is the involvement of other stakeholders, including patients, health professionals, health care administration and public authorities and health insurers, in the work of the network?

All projects agreed on importance to involve a wide range of stakeholders, especially patients and health professionals, and they try to involve them in the activities of the network. Obviously the form and extent of involvement is different in each project.

4.2. What is the network's contribution to patient empowerment?

Most of the projects indicate that their networks will contribute to patients' empowerment by supporting patients in getting relevant information (medical, scientific, socio-economic).

4.3. How patient and professional satisfaction with the existence and operation of the network is being assessed?

All projects foresee some kind of evaluation tools, including online or paper questionnaires.

4.4. Which of the stakeholders will be able to receive network's results (outcome variables)?

Most of the projects apply very transparent policy and make the results widely available, especially to patients and health professionals.

5. SHARING OF KNOWLEDGE, BEST PRACTICE AND DISSEMINATION OF EXPERTISE

5.1. How is the transfer of knowledge and sharing of best practice ensured within the network?

Most of the projects emphasised importance of close and regular contacts being established and maintained between the centres within the network. Different means of communication, including emails, teleconferences and regular meetings are being used to that end.

5.2. How is the visibility of the network's results ensured?

Each project has developed its own dissemination strategy. These include electronic and paper publications, newsletters, devoted websites, participation in conferences, contributions to journals etc.

5.3. How is/can be the expertise and best practice disseminated outside the network in the relevant area (disease)?

Most of the networks intend to use the dissemination tools described under the previous question. One project indicated that they prefer to involve all relevant experts directly in the network, rather than disseminating the expertise outside the network.

5.4. Can the expertise and best practice gained within the network be also disseminated to and used for other areas beyond the particular disease (for example for common diseases)? If yes, how?

The answers were similar as to the question 1.7. Projects generally believe that their models and best practice developed within their networks can be used also in other areas. Obviously, this seems to be easier for projects aiming at creating common databases as the models of the databases could be used also for other diseases.

5.5. Are there arrangements in place within the network for mobility of health professionals between the network members?

No such arrangements are foreseen for two projects (DYSCERN and PAAIR). On the other hand, active transfer of persons (experts) and data within the network is foreseen for the RBD network. However, no further information is provided about how this works in practice. The ECORN network foresees some travelling for experts to attend quality round tables.

6. FINANCIAL ISSUES

6.1. What is the overall budget of the network and what is its structure (including exact figures where possible)?

Detailed information is provided in each individual contributions. The overall project budgets vary between 100.000 and 1.500.000 EUR.

6.2. How is the long-term financial sustainability of the project ensured (i.e. what happens after the first three years of the project?)?

The long-term financial sustainability seems to be a problem for all projects. Problem. Networks rely to a large extend on the EU funding. Alternative ways of generating income are currently being explored by some networks, but these do not seem to be sufficient to cover all expenditures of the networks.

6.3. What are the other sources of funding provided to the network?

Some additional sources were identified, including charity, national public budgets for salaries, consultancy activities and clinical trials.

6.4. Are there any links to other sources of Community funding, for example to projects funded from the Framework Research Programmes?

Generally no, but some networks received or applied for funding from the Framework Research Programmes for specific activities.

6.5. What are the arrangements in place for reimbursement of costs of services provided as part of the network activities (i.e. services for patients form other centres or countries)?

Not applicable to any of the networks.

6.6. Based on your practical experience with the network, what can be done at both, European and national level, to improve the situation related to financial issues?

Issues such as need for more resources from the EU budget, longer period for EU funded projects (at least 5 years) and difficulties with co-funding of projects were raised.

7. PRACTICAL AND ADMINISTRATIVE ISSUES

7.1. What are the practical problems and difficulties that the network has to face?

No major practical problems were identified. Only minor practical difficulties in initial stages of projects were mentioned, such as communication pronlems, difficulties with establishing the working groups, recruiting competent people etc. However, these problems seems to be overcome by now.

7.2. What is the language regime of the network? Do the language differences cause any problems (between the network partners, but also in relation to patients)? How are these language problems being addressed?

All networks use English for internal communication among the professionals. However, when patients are involved, most of the projects have arrangements in place for translations. No major problems were identified regarding the language regime.

7.3. Are there any arrangements in place for transfer of patients from other centres or countries in case of need?

No. All the projects are only virtual networks and they do not foresee physical movements of patients.

7.4. What are the financial arrangements in place for transfers of patients from another Member State?

Not applicable – see the previous question.

7.5. Based on your practical experience with the network, what can be done at both, European and national level, to improve the situation related to practical and administrative issues?

Not many suggestions made. An issue of extensive paper-work related to applying for EU funding was mentioned.

8. LEGAL ISSUES

8.1. Are there any legal difficulties and obstacles hindering the work of the network?

8.2. Have there been any difficulties related to data protection rules identified within the network?

8.3. If clinical data are generated, who possesses the data? Is there any patient participation in the control of the data gathered by the network?

8.4. Have issues of professional medical liability arisen in the context of the network and are there any arrangements in place in this respect?

8.5. Based on your practical experience with the network, what can be done at both, European and national level, to improve the situation related to legal issues?

In general, not many legal issues were identified under this Section of the questionnaire. Some minor problems were mentioned with regard to data protection and intellectual property rights. There is need to explore these issues further.

9. GENERAL COMMENTS

9.1. Which are the public health outcome variables (e.g. utilisation of healthcare resources)?

Most of the projects indicated that they will look at specific public health outcomes as the projects will develop, such as measuring of how use of the network influences the costs born by healthcare providers, prevalence of the disease, lifestyle factors influencing the disease etc.

9.2. Can the results of the project help in solving problems for other rare or common diseases? Which specific elements of your project can be adapted or transferred to other rare and/or common diseases?

Answers were similar to those provided under questions 1.7 and 5.4. Projects generally believe that their models and best practice developed within their networks can be used also in other areas. Obviously, this seems to be easier for projects aiming at creating common databases as the models of the databases could be used also for other diseases.

9.3. How can the network in your project be used as a model for European reference networks?

The answer is largely covered by the previous question.

9.4. Which impact does the network in your project have on the health care system in the different participating and not participating countries?

This is something that will need to be seen in the future. Projects generally expect general improvement of quality of treatment of the particular disease in the participating countries. However, it is difficult to asses the potential impact in the non-participating countries for the moment.

9.5. Are there any other comments that you wish to make?

No further issues were raised. One project reiterated that the paper-work related to applications for EU funding is a real burden.

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ANNEX 6 : Comments from EUCERD Industry representatives April 2011

Guiding principles & background

The main focus of Centres of Expertise (CoE) and European Reference Networks (ERN) should be to benefit patients. The involvement of all stakeholders in an appropriate way is crucial. Industry is ready and willing to play a constructive role and should be a key partner for CoE and ERN, beyond providing funding.

Identifying expertise / Networking

A clear distinction needs to be made between the mission of a **centre of expertise** – providing expert care for patients, comprehensive care, a knowledge centre for both patients and second-line treating physicians, availability and infrastructure – and that of **European Reference Networks** – sharing of expertise and of (registry) data, be a resource for centre of expertise, share information about diagnostic testing and screening, collaboration (create research and diagnostic partnership) on gathering clinical added value data for orphan medicines, input in policy-making and priority-setting at Member State level and through network at EU level, set up (international) treatment guidelines including advice on early start of treatment.

When establishing centres of expertise and from that, a comprehensive network in rare diseases, it is imperative to identify particular unmet needs for the disease in research and clinical care, but also with regards to public health issues. The network should agree on research priorities on a specific disorder and reach a consensus on minimum standard of care for patients.

It is a fact that centres of expertise are often dependent on one clinician. If this clinician moves out of the centre, accreditation should only continue if the expertise of the centre is maintained. To avoid this situation, it could be considered that an individual with a high level of experience and knowledge can be accredited, or only sites with a critical mass, the right infrastructure and processes are eligible for accreditation.

It is important to consider whether an individual centre should limit its expertise to cover one or two diseases and to a specific age group (paediatric, adults, adolescent) or whether it could cover all rare diseases and all ages. Rare genetic diseases, rare cancers and other rare acquired diseases (oncology, immunology, genetic....) may have very little in common and so the creation of categories of rare diseases could be an intermediate solution.

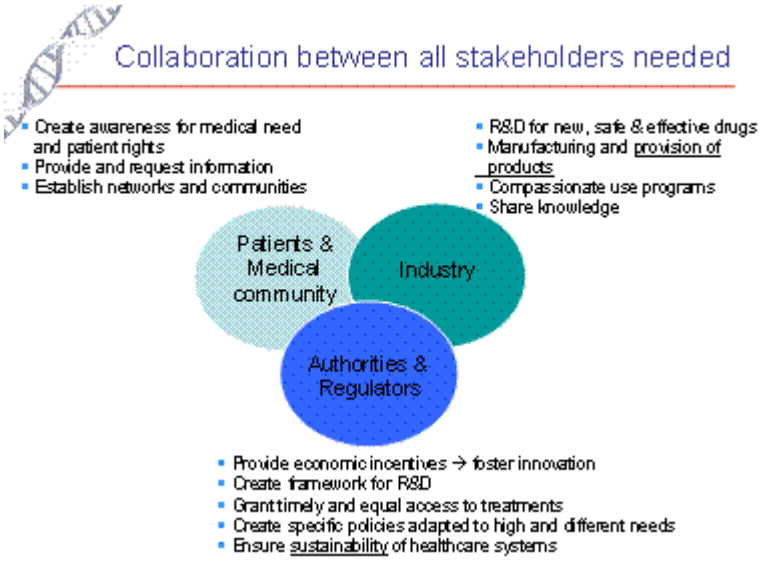
Consideration should be given as to how the centres could be grouped into networks, based on the expertise they have. For example, the network on skeletal dysplasia includes 100 diseases with common features (abnormal bones). Some networks are age-specific (pediatric network for Hodgkin disease) and some are

disease specific (CF, Duchenne etc..). The centres must not only have expertise in the treatment of a disease but also in the diagnosis. If not existent in the centre itself, there should at least be a partnership established (an "outsourcing model") with an expert body in this field. Ultimately, the European Reference Network should be in a position to be able to share information about diagnostic testing and screening.

It may be necessary to introduce a two-layer structure, differentiating between a few core, "driving, senior, confirmed centres", selected on proven expertise and "contributors, junior, emerging centres", selected on their willingness to contribute and ability to build expertise.

A consequent objective of ERN should be to support the "junior" centres (clinic and lab), to reach commonly-agreed standards of care. Less experienced centres could be granted conditional membership and a time period to improve standards and services provided. These centres will therefore benefit from the network meetings and knowledge transfer of being part of a ERN.

Currently, decision-making and advisory bodies are generally divided into three groups: the coordinator, a small steering group and the larger "advisory" network. Most of the day-to-day work is carried out by the steering group and this is an area where industry has a strong supporting role to play. Whilst pursuing their own goals, ERN should be able to make use of the expertise and skills developed by industry. In order to facilitate this cooperation and ensure transparency, a Code of Conduct could be developed, which would state key principles for collaboration and govern relationships between patients associations, industry and other partners.



Sharing expertise for patient management

ERN are fundamental hubs for all stakeholders interested in specific disease areas. They should be a one-stop shop for: a patient looking for a specialist, a healthcare professional looking for best practice, industry developing new therapies or scientists with a research idea. All patients should have access to information in their

own language. ERN's should encourage agreed patient information to be translated in all EU languages.

ERN should also transfer knowledge throughout the network, with a primary focus on processes, methodology, management and treatment modalities. Appropriate, effective technology is a very important component of ensuring an efficient transfer of knowledge. For ICT tools and telecommunication to work, dedicated resources must be in place and all centres and networks must have a similar level of ICT. If this is not the case, there is a danger that less well-equipped sites may not be able to function optimally. Before investment is made, however, it would be useful to understand the experience of the pilot networks in using ICT and the benefit to those making use of the centres and networks. For example, there is evidence to suggest that intranet sites tend not to be very successful, as busy clinicians do not use them actively. Therefore, when communicating with clinicians, it is easier and more cost-effective to use email.

The concept of telemedicine functions well, however, networks receive many requests for information about diagnosis and access to treatment from patients, families and carers from outside the European Union. This is an aspect that needs to be addressed when considering resources required by centres and networks.

Building up standards of care

Apart from establishing criteria for the definition of centres of expertise, other elements also need to be defined, such as quality of care indicators for the centres (setting up tools to evaluate the centres' effectiveness), assessing the centres and their capacity to become a partner in the network, and the potential of a network structure to be transferred to other diseases. The criteria should stimulate centres to improve care and to do research. Centres should be audited – and the work of the EUCERD and its stakeholder members will be to establish by whom and how this process will function.

European Reference Networks should make methodological resources or advice available to centres and innovate in methodology. A network should have a teaching and awareness mission: to develop sub-specialty networks (e.g., physiotherapists, nurses, etc.) with a similar mission.

Improving clinical research

Participation in (disease) registries is key to building the knowledge platform within centres and will help to address important questions: What is the epidemiology of the disease? What is its natural history? What are the long-term outcomes of treatment? How can patients achieve the best possible health outcomes?

Data can be gathered from various sources, including clinical trials and early / expanded access programmes. Legal aspects around compassionate use are especially challenging in rare diseases (data collection, but also access in early phase (limited evidence or off-label use) and late phase (patient outside of reimbursement criteria). Any possibility to improve this situation should be explored.

Recommendations

1. To have sufficient and sustainable funding for networking meetings that can include participation of less experienced centres. These network meetings are to share case studies, experience and knowledge management. Less experienced centres should have conditional membership.
2. ERN should encourage external quality assay schemes.
3. Encourage the translation of patient information into all European languages.
4. Involve industry in the early stages of expertise mapping exercises and general management of centres and networks. Industry members should sign a confidentiality agreement and make a commitment to the network.
5. ERN do not seem to have a natural progression from basic research to public health; the model would better be represented by a matrix.
6. There are clear challenges in creating formal indicators for the evaluation of networks. Outcome indicators are long-term and cannot be evaluated within a short-term project grant. We recommend producing a set of common indicators for the ERN which should be flexible on a case by case basis.
7. A common set of communication tools for ERN would be useful e.g. a public relations advisor, press releases etc. This could be an area where industry can support ERN.

Industry EUCERD members, April 2011