Centres of Expertise and European Reference Networks: key issues in the field of rare diseases. The EUCERD Recommendations.

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Background. Rare diseases, because of their intrinsic characteristics - large number of disorders and syndromes, low individual prevalence, severity, often limited information, lack of therapies - can benefit from collaboration and sharing of expertise while maximising the limited resources available for these conditions. Therefore, the development of Centres of Expertise (CEs) and European Reference Networks (ERNs) in this field is crucial.

The European Union Committee of Experts on Rare Diseases (EUCERD) has been charged to assist the European Commission with the preparation and implementation of activities in the field of rare diseases in Europe. In particular, EUCERD has assisted the EC in drawing up the recommendations issued in the Commission Communication and in the Council Recommendation. In this paper the authors focus on the EUCERD Recommendations on CEs and one on ERNs.

Materials and Methods. Recommendations on CEs and ERNs are the result of two different processes, developed through iterative reviews and discussions at workshops and EUCERD meetings, and according to the European Union documents.

Results. EUCERD has issued two complementary Recommendations, one on CEs (2011) and a second on ERNs (2013). Both address multiple targets (from Member States to Centres, and patient organisations), with the objective of helping them define and organise CEs and ERNs.

Conclusions. The establishment, designation, financial support, and evaluation of CEs throughout Europe allow RD patients and local health care providers to identify high-quality specialised services that can simplify disease management and improve patients' care. The EUCERD Recommendations are useful instruments to help and guide stakeholders in the development of CEs and ERNs and thus ensure equity of access to services and care for rare diseases patients across Europe.

Keywords: rare diseases, Centres of Expertise, reference networks, public health, policy.

Introduction

Rare Diseases (RDs) are defined in Europe as those that affect fewer than 5 in 10,000 people. They have specific characteristics as a low prevalence in the population, a multitude of different diseases and syndromes, the lack of general awareness, the difficulty in diagnosing and, for most of them, the lack of effective therapies. These conditions make them an exceptional field for collaboration and sharing of expertise. RDs represent one of the best examples where European cooperation can be a strong added value. Furthermore, only through the strengthening of international collaboration, it will be possible to maximise the scarce resources devoted to RDs and, at the same time, deliver the best quality of care to the RD patients. Therefore, the development of Centres of Expertise (CEs) and European reference networks (ERNs) in RDs is fundamental.

In November 1993, the European Commission (EC) published a Communication[1], defining the framework for action in the field of public health and describing the role of Community Institutions and of Member States (MSs). After this publication, the EC opened a wide consultation in the European Union (EU) on public health issues. In December 1993, experts were invited by the EC to submit proposals describing how they would seek to formulate draft policy proposals in some of the areas indicated in the framework document. In consultation with the Commission, five priority areas were identified, among them there was also "an EU programme for management of rare diseases".

It is worth noting that, even at that early time, the experts recommended "a system whereby the Commission might seek to encourage identification of centres of expertise on RDs and support the establishment

of networks for the development of research in appropriate fields". They underlined that *RD* "focal points (CEs on RD and networks with a central secretariat), should be identified, and the existing structures concerned with RDs within the MSs should form the backbone of the focal points[2]".

More recently, the need for the development of CEs and ERNs in the field of RDs has been highlighted in several EU documents[3-5], as a means of organising effective care for the thousands of heterogeneous RDs affecting patients scattered across Europe. Moreover, the Recommendations[6] of the European Project for Rare Diseases National Plans Development (EUROPLAN - www.europlanproject.eu) has reinforced the Council Recommendations[4] and has underscored the importance of MSs to identify national or regional CEs, to define good practices for their designation and evaluation, and to encourage their participation in ERNs.

Between 2004 and 2013, the European Union Committee of Experts on Rare Diseases (EUCERD[7] - www.eucerd.eu) - formerly the European Commission's Rare Diseases Task Force (RDTF) - was mandated to assist the EC with the preparation and implementation of community activities in the RDs field. In particular, EUCERD has assisted the EC in drawing up Recommendations, including those concerning CEs and ERNs for RDs, deriving them from the Commission Communication[3] and the Council Recommendation[4].

EUCERD was composed of 51 members: experts from MSs, current and former RD research project leaders, representatives from relevant international organisations (DG SANCO, DG Research, DG Enterprise, EuroStat, EMA, WHO, OECD), pharmaceutical industries, and representatives of patient organisations.

EUCERD has issued five Recommendations on the following areas:

- Quality Criteria for CEs for RDs in MSs (October 2011)[8];
- Informed decisions based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) (September 2012)[9];
- ERNs for RDs (January 2013)[10];
- RD Patient Registration and Data Collection (June 2013a)[11];
- Core Indicators for RD National Plans/Strategies (NP/S) (June 2013b)[12].

Materials and methods

The elaboration of the EUCERD Recommendations on CEs and ERNs was based upon the results of concepts defined by the High Level Group on health care and medical services (HLG)[13], EU projects documents[6], meetings with experts and other stakeholders, several reports investigating the state-of-the-art in the field of RDs, and on the previous work of the RDTF/EUCERD group[14-19].

In particular, the legal aspects associated with the Recommendations, as well as the political background, were established by the Commission Communication[3], by the Council Recommendation[4] and by the "Directive on the application of patients' rights in cross-border healthcare" (CBHCD)[5]. All draft Recommendations were elaborated by the EUCERD Scientific Secretariat, were sent to EUCERD members for comments, and the wording of the recommendations was discussed in dedicated workshops. The revised draft of the Recommendations was then submitted to EUCERD members for final approval prior to their meeting, where the Recommendations were unanimously adopted by the Committee.

Results

The main results concern the publication of the EUCERD Recommendations on CEs and ERNs, which are complementary, as they are elucidated below. They address numerous targets: MSs, the EC, other EC initiatives (e.g. projects and joint actions, Cross-Border Healthcare Expert Group, EUnetHTA, EPAAC), CEs in the field of RDs healthcare providers, RD experts and existing RD network co-ordinators and partners, patient organisations.

EUCERD Recommendations on CEs

The aim of these Recommendations is to help MSs in their reflections/policy developments concerning NP/S for RDs. Specifically, they are useful in addressing the organisation of healthcare pathways at national and at European level. Potentially, they are helpful for the CBHCD application in the context of ERNs development.

This document includes 45 Recommendations, concerning 4 main areas:

- mission and scope of CEs: definition, coverage, patient focus, core competencies, role in disseminating information and education, role in research;
- criteria for designation*:* leadership and credibility, multidisciplinarity and inclusiveness, capacity, links and collaborations, mechanisms for measuring performance/evaluation;
- process for designation: core principles of designation, designation criteria, duration of designation;
- European dimension: sharing experience and indicators at EU level, networking.

According to the EUCERD Recommendations, CEs are defined as physical highly specialised structures for the management and care of RD patients, with the mission of providing them with the highest standards of care and delivering timely diagnosis, appropriate treatment and follow up, on a regional, national, European or international level.

Each CE specialises in a single RD or in a group of RDs. It gathers or coordinates - within the specialised healthcare sector - multidisciplinary competences/skills, including paramedical skills and social services, in order to serve the specific medical, rehabilitative, palliative and social needs of RD patients. Multidisciplinarity and inclusiveness were defined as the capacity to deliver a multidisciplinary approach, integrating medical, paramedical, psychological and social needs and to ensure the continuity of care, from childhood through adolescence and adulthood, as well as in all stages of the disease. CEs should offer a wide range of specialised services: consultations, medical examinations, using specialised equipment, genetic testing, counselling and social care. They should also participate in building healthcare pathways, starting from primary care. Furthermore, they should contribute to research efforts through their participation in both data collection for clinical research and in clinical trials. They should collaborate with different stakeholders, including RD patient organisations. The focus of these Recommendations on CEs is on patients, so that all their needs may be effectively met.

The criteria for the designation of CEs should be based on leadership and credibility, multidisciplinarity and inclusiveness, as well as on their capacity to create links and collaborations and on the existence of an evaluation mechanism. Moreover, MSs are responsible for their designation and this should be done through the adoption of transparent designation criteria, the assurance of an on-going evaluation process and the facilitation of access to the patients. The designation process at MS level should ensure that the designated CEs have the capacity and the resources to fulfil their obligations according to the criteria and that they have a strategy in place to meet all the criteria during a set period of time. The CEs designation is an important step as it provides the base for its connection to the next level of collaboration, the ERNs level.

EUCERD Recommendations on ERNs

The general concept and the method of implementing ERNs are defined in Article 12 of the CBHCD.

The aim of these Recommendations on ERNs is to inform *(a)* the Commission's services and expert groups, working on the criteria for the creation and designation of ERNs on RDs specificities, in the context of the CBHCD; *(b)* MSs that are developing their healthcare pathways at, both, the national and the EU levels in the field of RDs, particularly in the context of NP/S for RDs.

This document includes 21 Recommendations, concerning 5 main areas:

- mission, vision and scope*:* providing a framework for healthcare pathways, covering core tools and activities;
- governance*:* robust and clearly defined governance, strong leadership;
- composition of RD ERNs*:* different forms of affiliation to allow inclusivity, linking CEs and stakeholders involved in the care management of patients;
- funding and evaluation: long-term sustainable funding mechanisms (MS competence);
- designation of RD ERNs: development of shared platforms across RDs, clear designation process, stepwise-strategy, defining and implementing a formal system for networking across all RD ERNs and sharing expertise.

According to the EUCERD Recommendations, an RD ERN is the physical or virtual networking of knowledge and expertise of national CEs in more than one European Country. The goal of an ERN is the improvement of the overall quality and management of care of a single RD or a group of RDs with similar health care needs, by complementing, supporting and providing added-value to the existing services and expertise at the national level. In these Recommendations, it is stated that designated CEs are the core participants, so RD ERNs should be flexible enough to be able to work with different national structures.

This networking activity among national CEs promotes the sharing and mobility of expertise rather than the movement of patients, and facilitates the travelling of patients to cross-border CEs when necessary.

In order to improve the delivery of care in an effective way, while reducing its costs, the ERNs need to facilitate the sharing of information and tools amongst CEs and other care providers. For instance, information on disease registries, communication of guidelines/best standards of diagnosis and care, training and education tools, quality assurance schemes, telemedicine, cross-border referral mechanisms should be shared among CEs and other interested parties.

The co-ordinating site(s) should be selected on the basis of proven leadership and capability to coordinate a network; it is not necessarily to be the best centre of expertise or the one with the largest number of patients. In the composition of RD ERNs different forms of affiliation (association, collaboration) can be foreseen. In small countries, where there may be a small number of CEs or no CEs at all, other healthcare providers can become affiliated members of an RD ERN. This allows an RD ERN to reach out of as many MSs as possible.

RD ERNs should have clearly defined mechanisms of governance and evaluation, and patient organisations should play an important role in the process. Patients in every European country can benefit from an RD ERN, even if in their country there may not be a CE

that is member of an RD ERN. The objective, in the next decade, is that RD ERNs cover all RDs grouped by diagnostic and systemic areas, using a step-wise approach.

Conclusions

There are currently more than 6,000 identified RDs[20], each of which affects fewer than 5 in 10,000 people, according to the EU definition. These diseases are thought to affect around 30 million people in the EU countries.

For the last 10 years, RDs have become one of the priorities of the EU health policies and the development of CEs and ERNs in the field of RDs was encouraged in several EC documents, as well as in EU projects, such as EUROPLAN[21].

The establishment, designation, financial support, and evaluation of CEs throughout Europe allow RD patients and local health care providers to identify high-quality specialised services thus simplifying disease management and improving patients' care. The MSs should promote and support CEs in order to guarantee equity of access to good quality of services and care to their citizens affected by RDs. CEs should reduce costs in healthcare systems by contributing to shorter delays in diagnosis, less adverse consequences, a reduction in misdiagnoses and subsequent unnecessary treatments and more adequately adapted care, as pointed out also by EURORDIS[22].

The political commitment of MSs to identify and financially support CEs is a prerequisite for the creation of ERNs. Moreover, the establishment of ERNs also allows health authorities to identify the best allocation of financial resources to support the activities linked to the effective management of RD patients.

Due to the differing health care structures, different definitions of a CEs and differences in the diseases they treat, each ERN, which consists of individual CEs, will also reflect this variability. CEs should be flexible to accommodate different stakeholders and healthcare providers with particular emphasis being placed on patients representatives.

Nevertheless, the establishment and the sustainability of ERNs, as indicated in the CBHCD, is a major opportunity for the RD community[23], especially for ultra RDs (by definition prevalence <1:2,000,000[24]-Table I) in which expertise may be available only in a very small number of European countries. Therefore, ultra RD patients may need to receive care across borders. The added-value[25] of ERNs is given by the existence of several multilateral cross border health care agreements, by many EC funded projects, documented by the EC HLG and by the currently funded EC pilot projects.

CEs and ERNs are a good example of how the field of RDs offers enormous and practical potentials for European cooperation. The specificities of these diseases - the limited number of patients and the scarcity of relevant knowledge and expertise - single them out as a prime area for cooperation, with a very high European added-value[26].

Table I - Comparison of the major characteristics of rare and ultra-rare disorders[25].

	Rare Disorders	Ultra-rare disorders
Prevalence	<1:2,000	<1:2,000,000
Number of affected newborns/disorder in Europe	5,000 or less	5 or less
Diagnosis	Centers of expertise (national); E-mail consulting.	Electronic database (international); E-mail consulting.
Follow-up	Centers of expertise	Local healthcare professionals; Virtual centres of expertise.
Provision of information	Text books; literature; sites (OMIM, Orphanet, etc.)	Wiki sites
Support groups	National	International
Research	Grants difficult	Grants extremely difficult

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