



Rare Diseases Task Force

**Centres of Reference  
for rare diseases in Europe:**

**State-of-the-art in 2006  
and recommendations  
of the Rare Diseases Task Force**

**A technical and scientific report from  
an expert group  
of the Rare Diseases Task Force**

**To**

**The High Level Group  
on Health Services and Medical Care**

*December 2006*

<b><u>INTRODUCTION</u></b> .....	<b>3</b>
<b><u>ANALYSIS AND RECOMMENDATIONS</u></b> .....	<b>6</b>
<b>1. METHODOLOGY</b> .....	<b>6</b>
<b>2. RESULTS</b> .....	<b>6</b>
2.1. RATIONALE FOR ESTABLISHING A EUROPEAN COLLABORATION FOR THE DELIVERY OF HEALTH CARE AND MEDICAL SERVICES IN THE FIELD OF RARE DISEASES .....	6
2.2. THE CONCEPT OF CENTRES OF REFERENCE .....	8
2.3. CENTRES OF REFERENCE IN EUROPE.....	8
2.4. CENTRES OF EXPERTISE IN EUROPE .....	19
2.5. EUROPEAN NETWORKS OF CENTRES OF EXPERTISE .....	20
<b><u>ANNEX 1</u></b> .....	<b>23</b>
<b><u>ANNEX 2</u></b> .....	<b>29</b>
<b><u>ANNEX 3</u></b> .....	<b>33</b>
<b><u>ANNEX 4</u></b> .....	<b>37</b>
<b><u>ANNEX 5</u></b> .....	<b>38</b>

## Introduction

In the course of their work on European Centres of Reference (ECR), a Working Group of the **High Level Group** (HLG) on medical care and health services (comprised of representatives from member states) has decided to seek advice from an expert group on Centres of Reference on several specific issues. The expert group was charged with providing advice to the Working Group on technical and scientific aspects of issues concerning ECR, as set out in the report from the High Level Group to the Employment, Social Affairs, Health and Consumer Protection Council on 6-7 December 2004 (HLG/2004/21), as well as the synthesis document following responses to the questionnaire on ECR (HLG/COR/2004/7). The experimental phase of the work on ECR focused on the field of rare diseases, which clearly needs an EU approach. Therefore, at its meeting on the 16th of June 2005, the Working Group on ECR decided to mandate the SANCO Rare Diseases Task Force (RDTF) to provide technical and scientific input for this experimental stage. However, the final goal was to develop a general concept for a European system of centres of reference not limited to the area of rare diseases.

The **Task Force on Rare Diseases** established an *ad hoc* working group (Annex 1) in June 05 and issued a first report delivered to the HLG on September 05 (HLG/COR/2005/11). The conclusions of the RDTF working group were endorsed by the HLG (HLG/2005/16) and included the recommendation of the establishment of **European networks of centres of reference** (ENCR) and agreed on the following characteristics of the ENCR for the purpose of launching pilot projects:

- Hierarchy between national or regional networks of centres of reference should be avoided
- Networking of expert centres should be favoured, rather than isolated centres of reference
- In principle, expertise should travel rather than patients themselves. However, it should be possible for patients to travel to centres when necessary.

For the HLG, European networks of centres of reference should comply with the following criteria:

- Appropriate capacity to diagnose, to follow-up and manage patients with evidence of good outcomes when applicable
- Sufficient capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control
- Demonstration of a multi-disciplinary approach
- High level of expertise and experience documented through publications, grants or honorary positions, teaching and training activities
- Strong contribution to research
- Involvement in epidemiological surveillance, such as registries

- Close links and collaboration with other expert centres at the national and international levels and a capacity to network
- Close links and collaboration with patients associations where they exist
- Although a ENCR should fulfil most of the above criteria, the comparative relevance of these various criteria will depend on the particular disease or group of diseases covered

The HLG also noted that this list could be revised, with the outputs coming from the implementation and development of the expected 2006 pilot projects on ENCR.

Agreement at European level on the pathologies, technologies and techniques to be covered by ENCR was considered necessary by the HLG, drawing on national experiences and existing lists as many Member States currently have expert clinics but not any designated centres of reference. The priority areas should be determined on the basis of the following indicators:

- Diagnosis (when the diagnosis is difficult and is necessary for informed clinical management, to prevent complications and to set up treatment)
- Therapeutics and management when treatment requires expertise and specialised interventions
- Outcome when patients are at high risk of developing severe complications or disability that could be prevented
- Technology and therapeutic innovations.

Criteria for designation of an ENCR are set out above. Their application to specific situations, however, requires significant expertise and knowledge of the current international situation. Selection of such ENCR requires input from experts from relevant specialties in medicine, patients, and representatives of the health authorities. Continued compliance with the designation criteria should also be ensured.

The High Level Group invited the **European Commission** to test the feasibility and added-value of ENCR in 2006 through pilot projects. The 2006 Call for proposals within the framework of the Public Health Programme mentioned the establishment of European networks of centres of reference as a new priority and several applications were received in this area.

Alongside these pilot projects, the HLG proposed to pursue in 2006 issues which need further investigation, or which have not yet met a consensus. These include legal, financial and organisational issues raised by the designation of ENCR, including quality control and the general framework for European networks of centres of reference. The HLG noticed that the fundamental issue for ENCRs is their financial sustainability once they are identified, developed and established. Possibilities for integrating such financial support to the EU budget must be investigated. The objective was to propose a set of recommendations at the next meeting of the **Council of Health Ministers in December 2006**.

In order to disseminate the information about the current work, as well as to get a practical input “from the field”, the HLG invited representatives of other stakeholders to some of its meetings in 2006, including **EURORDIS** (European Organisation for Rare Diseases). EURORDIS is an umbrella organisation of patient associations that has a contract (RAPSODY) with DG SanCo to launch a dialogue on centres of references for rare diseases between stakeholders, based on the analysis of existing policies, to clarify definitions and concepts and to identify best practices.

The **RDTF** was also invited and proposed to issue this report on ECRs in Europe in order to incorporate all the discussions and contributions received since the last report and to contribute to the RAPSODY project.

## **Analysis and recommendations**

### **1. Methodology**

This report has been prepared by an expert group from the Task Force on Rare Diseases (RDTF).

The RDTF was set up in January 2004 by the European Commission's Public Health Directorate. It is led by Ségolène Aymé, a medical geneticist and Director of the Orphanet Database of Rare Diseases. The deputy leader is Helen Dolk, Director of the Eurocat Programme on Congenital Disorders.

The Task Force members are current and former project leaders of European funded initiatives related to rare diseases, member state experts and representatives from relevant international organisations.

The aims of the Task Force are to advise and assist the European Commission Public Health Directorate in promoting the optimal prevention and case management of rare diseases in Europe, recognizing the unique added value to be gained for rare diseases through European co-ordination.

The Task Force has three established working groups: on public health indicators, on coding and classification and on standards of health care. It was decided that the expert group on European Centres of Reference would be derived from the working group on standards of care which is led by Edmund Jessop from the UK Department of Health's National Specialist Commissioning Advisory Group.

The expert group met twice in 2005 to prepare a first report that served as a basis for the current report. The same group prepared the second report and discussed it during a workshop held on the 1st of September 06. The draft report was also sent for comments to all the members of the RDTF and to targeted experts.

The list of participants of the RDTF working group and of the consulted experts is attached as Annex 1.

### **2. Results**

#### **2.1. Rationale for establishing a European collaboration for the delivery of health care and medical services in the field of rare diseases**

Rare diseases are those affecting a limited number of people in the whole population, defined specifically as diseases that affect less than one person in 2,000. While the number of affected individuals seems small, it translates to approximately 230,000 in the 25 Member States for one disease with such prevalence. It is estimated that between 5,000 and 8,000 distinct rare diseases have been identified to date, affecting between 6% and 8% of the EU population in total. In other words, between 24 and 36 million people in the European Community are affected.

The European added-value of sharing expertise and resources at European level is especially well established for this group of diseases. As a result of the support of both DG SanCo and DG Research, good information systems have been developed and cooperation between expert centres has been encouraged in recognition of the unique added value to be gained for rare diseases through European coordination.

Developing European collaboration for the delivery of health care and medical services in the field of rare diseases has major potential in bringing benefits to European citizens by:

- Overcoming the limited experience of professionals confronted with very rare conditions
- Improving access for EU citizens to treatment requiring a particular concentration/pooling of resources (infrastructure and knowledge) or expertise
- Offering patients the highest possible chance of success through sharing of expertise and resources
- Maximising cost-effective use of resources by concentrating them where appropriate
- Helping to share knowledge and provide training for health professionals
- Acting as benchmarks to help develop and spread best practice throughout Europe
- And helping small countries with insufficient resources from their health care sector to provide a full range of highly specialised services of the highest quality.

Pressures for change in this direction are coming from all stakeholders:

- From the health professionals, as there is a long term shift towards much greater specialisation, which limits the number of conditions that an individual specialist is able to diagnose and treat.
- From the managers interested in cutting costs and improving the cost-efficiency of clinical centres, as there is evidence that multidisciplinary approaches produce better results at lower cost.
- From the patients who become better informed each day and have a growing consumer power, as they expect that European cooperation will provide an improved response to their needs.

However there are difficulties in establishing and funding such cooperation, as health services and medical care are not derived from a European competency and as any type of cooperation could have potential consequences on the national/regional health care systems.

**The RDTF recommends exploring all possible forms of cooperation between Member States in the field of health services and medical care for rare diseases.**

## **2.2. The concept of Centres of Reference**

The initial mandate given to the RDTF by the HLG was to explore the concept of "European Centres of Reference" (ECR) as a possible response to the needs of the patients.

The title "centre of reference" is a very intuitive one, defined as a place suitable for referring patients due to its expertise and scope of services. This implies that the distance between the patient's home and the centre should not be too large and that the centre is located in an area dependant on the health care system of the patient for reimbursement purposes, or in a more distant area but within the framework of an agreement between centres for health care delivery.

Outside such an arrangement, having to attend a clinic located in a foreign country can have several negative side effects. The patients would have to face an additional financial burden due to referral to distant clinical centre, obliging them to travel mostly at their own expense. They could suffer a psychological burden due to the consultation in a foreign language and the lack of support when far way from their family and community. The cost of care may not be covered at all by health insurances from their country of origin. The global cost of care may be much greater than it would be in a local clinic, without significant benefit for the patient.

The title "centre of reference" is, at the same time, quite ambiguous, as exemplified by its use by national health care systems in Europe.

## **2.3. Centres of reference in Europe**

With regard to centres of reference, there are three categories of countries: those which have a specific policy regarding rare diseases and have established centres of reference in this framework; those which have established centres of reference but not specifically for rare diseases and those which have no centres with these denominations, although they have centres with all characteristics of a centre of reference.

### **2.3.1. Countries with official centres of reference for rare diseases in Europe**

Only the following six European countries have officially adopted (or will soon adopt) the concept of centres of reference for rare diseases within the context of a national policy regarding rare diseases: Bulgaria, Denmark, France, Italy, Spain and Sweden. The situation in these countries stands as follows:

#### ***Bulgaria***

Bulgaria has a relatively quickly developing policy for rare diseases, with both national and regional importance. Currently, the new Bulgarian National Health Strategy (2007-2012) is under development. In the draft version of the document from April 2006, the establishment of a Reference Centre for rare and genetic diseases is anticipated (Strategic Aim 6). A separate expert group at the Bulgarian Ministry of health was also created in July 2006 with the task of creating a National Program for Rare Diseases.



## *Denmark*

Within the national health system, Denmark has a designation system for referral centres/ highly specialised centres for a number of different conditions (diseases or procedures). The system takes the form of a catalogue from the National Board of Health made in collaboration with the local health authorities and medical experts. The general criteria used in establishing such referral centres are rareness, complexity, multidisciplinary and costly diagnosis and treatment. This catalogue is revised regularly. The catalogue as a whole contains lists of about 300 – 400 different conditions ranging from groups of diseases as a whole to a single specific disease or procedure (Annex 2). Approximately 100 different referral departments are located in one of the five university hospitals. This system has functioned for more than 10 years in its present form. The number of centres for one condition depends on rarity (estimated number of patients) competence and available technology. A specific condition might thus be treated at only one university hospital department or up to five different university hospital departments. Some geographical considerations will usually play a role in the decision-making process if there is room for more than one centre. The designated departments are required to secure and develop their expertise, establish a quality improvement programme, document their activities and take part in teaching and research activities. The system is focused on treatment of patients.

As part of this general system, the Danish National Board of Health launched a special report in 2001 regarding rare diseases and recommended that two centres be established at the university hospital level (one west, one east) for rare diseases, each covering approximately 14 specific diagnoses which did not already have a designated centre. A survey of patient satisfaction in 2003 showed that 33% of rare disease patients are treated at these centres. There was a higher level of satisfaction in patients treated at these centres and patients with individual action plans were more satisfied with their treatment. However, patients encountered reluctance to be referred to the specialised centres. Possible reasons include financial implications and the wish of local clinicians to carry out the treatment themselves for experience and research. In addition, some knowledge is required at local level, in order to maintain diagnosis and follow-up skills. The correct balance between specialist and local centres remains in question. A new catalogue of expert centres is in preparation.

## *France*

France launched its National Plan for Rare Disease in November 2004 which will be in affect from 2005-2008. The plan includes a specific provision for care management of rare diseases. The provision was intended to improve the somewhat unstructured care situation which previously existed. Currently, criteria for national centres of reference are focused on their provision of expertise, not the provision of direct care as such. The calls for proposals for designation of centres of reference are intended only for university/teaching hospitals. Through the first three annual calls, 103 such centres were designated (Annex 3). Each centre is designated for five years, with a mid-term evaluation after three and again after five years. Centres receive a specific budget to run their coordination activities corresponding to approximately 2 or 3 additional staff. Decrees are currently in preparation to designate other expert clinics accepting to work in a network coordinated by the CR with the intention of increasing the geographical coverage of the CR and preventing unnecessary travelling of patients.

## *Italy*

In 1998, the Italian Government approved the National Health Plan in which rare diseases were indicated as a priority for public health. In 2001 the government approved a legislation that established the Italian National Network for Rare Diseases to tackle the problem of prevention, surveillance, diagnosis and treatment of rare diseases. It listed approximately 500 rare diseases for which patients are diagnosed and treated completely free of charge. The same legislation established the National Registry of Rare Diseases at the Istituto Superiore di Sanità (ISS), which is expected to receive epidemiological data from regional centres. Since 2001, more than 250 regional centres of reference have been established by official regional decisions following the governmental regulation on rare diseases. These centres do not receive an extra budget for their activity. The National Network is almost completed; although the criteria used by the regions to identify centres were highly heterogeneous throughout the national territory. Only centres established by regional decisions are officially recognised by the Italian Health System for the reimbursement of patients affected by rare diseases. In the future it is expected that a coordination centre will be established in each region. An official agreement between the Ministry of Health, ISS and each region has been established in order to coordinate and harmonise the regional network activities. The same national committee, established within the agreement between the Italian Government and the regions, is currently reviewing the list of conditions which will receive free diagnosis and treatment.

## *Spain*

The Ministry of health is developing a strategy for the designation of reference centres on rare diseases. This is being developed as a new decree in which the way of designation, time schedule, commitments and dissemination of the information will be defined. This decree is expected to be published at the end of 2006 and the process of setting up these centres will take between 6 to 12 additional months. A committee will be established to monitor the whole process.

## *Sweden*

Sweden defines rare diseases as those disorders resulting in extensive disability and affecting less than 1 in 10,000 individuals. Sweden's care system for rare diseases is concentrated in specialised centres within an overall decentralised system run at the county level (there are 20 counties in Sweden). The National Board of Health and Welfare, based on an agreement with the Federation of County Councils in 1990, sets out the providers of specialist care in a catalogue, which is intended to provide a reference point for local administrators. The catalogue lists around 75 of these specialist centres, which concentrate on clinical care - diagnosis and treatment of rare disorders – rather than research. Their services are offered to a broad geographical area, beyond their local catchment area, to ensure sufficient flow of patients. Counties can decide to buy in healthcare from centres located in other counties. In addition to the medical centres of reference, the catalogue also includes specialised regional resource centres. Recently a committee has been set up by the Swedish National Board of Health and Welfare to work on the future organisation of highly specialised medical care.

### **2.3.2. Countries with official centres of reference outside a national policy for rare diseases**

In eight countries, there are clinical centres designated as Centre of Reference in areas relevant for rare diseases, but they were established outside any specific policy regarding rare diseases. In these countries, the situation stands as follows:

#### ***Belgium***

In Belgium, several centres of reference are in place. The concept of reference is bound, however, to categories of diseases requiring specific multidisciplinary care with common characteristics rather than to the rarity of diseases. These centres function under a specific convention with the National Institute for Sickness and handicap. Among these centres, different groups deal with rare diseases: Creutzfeld-Jacob, neuromuscular diseases, Cystic Fibrosis, Autism spectrum, Chronic fatigue syndrome and metabolic diseases. Moreover, the Belgian regulation mentions eight Centres of Human Genetics which also manage rare diseases.

#### ***Croatia***

The Ministry of Health is responsible for certification of reference centres in medicine. Currently such certificate has been given to a reference centre for inherited and metabolic diseases in children at the Clinical Hospital Centre and School of Medicine in Zagreb.

#### ***Czech Republic***

There are two official centres of reference in the area of rare diseases: the Institute of Inherited Metabolic Disorders, which has a special status and is funded outside of the regular health insurance; and the National Cystic Fibrosis Centre, which was established in 1997 at the University Hospital Motol based on the Czech Government decree of September 8th, 1993, # 493, Section 3, §3i. It provides a comprehensive, highly professional and up-to-date diagnostic service and clinical treatment for CF patients within the entire Czech Republic.

#### ***Finland***

Finland has established a list of procedures that should be carried out in centres of reference (for example, neonatal cardiac surgery or bone marrow transplantation) rather than a list of rare diseases. Only centres for operative treatment of bone dysplasias (diastrophic dysplasia and achondroplasia) and treatment of retinoblastoma are mentioned according to a specific diagnosis. The list includes centres for treatment of broader groups such as craniofacial malformations and operative treatment of childhood glaucoma. All of these centres are found in departments of one of the five university hospitals. The departments for the different medical specialities of these five university hospitals act as reference centres for all kinds of rare disorders and are accepted as such by the Finnish medical community. As such, the centres of reference for rare disorders in Finland are organized mostly on regional basis covering the whole country.

## *Greece*

A national centre of reference for paediatric, rheumatology and immunity diseases (Thessaloniki) was appointed by the Ministry of Health based on the law number N.2519/1997, Article 19. There is also a Thalassaemia centre which has been appointed by WHO as a national reference centre for genetic diseases (in which tests are performed mainly on beta-Thalassaemia and Cystic Fibrosis).

## *Ireland*

The Irish Department of Health and Children does not maintain a specific list of "National Reference Centres", nor does it set standards for specific units to be considered "national". The Department of Health does, however, recognise that particular centres have particular expertise, and gives specific funds to support those specialist services. For instance, kidney transplants are only carried out at one hospital in the country, and thus this hospital is given funds to run the service. As such, some national centres can be considered *de facto* or "soit-disant" national centres, without being given a specialist distinct status by the government. The Irish government is currently introducing hospital accreditation. One of the issues which may be more specifically examined is the accreditation of hospitals which provide national specialist services.

## *Portugal*

There is no officially approved policy specific to rare diseases or to centres of reference for rare diseases in Portugal, although there are official networks of CR for a few specific medical specialities rather than for diseases. At the National Directorate of Health (NDH), rare diseases are under the authority of the Division of Chronic, Genetic and Geriatric Disorders. A great amount of legislation exists for some rare diseases, primarily in response to specific demands of affected patients or patient institutions/organizations, but no coordinated action or policy has followed. The diagnosis and treatment of most genetic metabolic diseases occurs at the national level by the Institute for Medical Genetics Jacinto Magalhães at Oporto, which also leads the national program for neonatal screening. Currently, a Committee for Rare Diseases is being established at the NDH. It is expected that this committee will consider the issue of centres of reference for rare diseases as well as other related issues, in the hopes of establishing and developing a coordinated national policy and strategy.

## *UK*

Since 1990, a separate system exists for providing funding to 71 specialised centres of reference for diagnoses or procedures of particular conditions within the national healthcare system (Annex 4). The definition of rare diseases is much stricter than that for the: 2 or fewer affected individuals per 100,000 and covers 18 diseases or groups of conditions, diagnoses or procedures (mostly genetic diseases of children). As this funding system has been running for over 15 years, it has been possible to observe effects after centres are designated. The centres are regularly reviewed and there has been a strong emphasis on defining patient outcome measures and publishing these data. Some measures, such as survival rates, are straightforward, but others, such as diagnoses, have been much more difficult to define. In the latter case, some centres have measured the time taken to provide a diagnosis and recorded

patients' comments. The centres are not distributed on a geographical basis (many centres are in London), but patients' ability to access centres is monitored and access is mapped. The system is a reactive one. There has been no specific call - centres have come to the Department of Health directly in order to access the funding stream for specialist treatment centres. Research and epidemiology are not funded under this system. Regional specialist services also exist for genetic diseases but these are funded separately. Separate arrangements exist within the UK for Scotland, Wales and Northern Ireland.

### **2.3.3. Countries with no official centre of reference for rare diseases**

In the remaining countries, no clinical centres are designated as "centres of reference" although many centres act as such. The situation in these countries is as follows:

#### ***Austria***

There is no official centre of reference in Austria yet, though some progress has begun. Recently, a few databases have been established to collect data on patients with rare conditions in the field of Lymphangio-leiomyomatosis, hereditary colon cancer and MEN syndrome.

#### ***Cyprus***

Cyprus has no official labelled centre of reference but has several centres established by reputation, such as the Cyprus Thalassaemia Centre for Haemoglobinopathies and the Institute of Neurology and Genetics for Rare Neurological Genetic diseases.

#### ***Estonia***

Due to Estonia's small population, there is no outpatient clinic purely dedicated to rare diseases. Two clinical genetics centres, one in Tallinn and one in Tartu, are responsible for the final diagnosis of rare diseases. The patients from all over Estonia with an uncertain diagnosis are sent to these centres.

#### ***Germany***

The German federal structure of the health care system is not easily compatible with the implementation of national centres of reference, since provision of sufficient structural resources for health care is solely a matter of the "Bundesländer" (states). At the level of the "Bundesländer", centres of reference have not yet been established. Legislation has only recently provided the basis for contracting of "Hochspezialisierte Versorgung" (highly specialised care) for a limited number of specified diseases, among which are a few rare diseases. Further diseases or groups of diseases may soon be added to the list. Contracts will be made between single regional centres and the health insurers. Networking will be encouraged but not funded on a national basis, except for a limited time span while building the networks. Currently, 9 networks on rare diseases are funded by the German Ministry for Research and Education for a total funding period of 5 years.

### *Hungary*

There is no officially approved centre of reference for rare diseases in Hungary, but discussions currently exist at the highest level. Health professionals have proposed an organisation with six regional centres allowing national coordination.

### *Latvia*

There is no official centre of reference in Latvia, although the Medical Genetics Clinic of Latvian State University Children's Hospital provides genetic services for the population of Latvia.

### *Lithuania*

There is no official centre of reference in Lithuania, although the Centre for Medical Genetics (CMG) of Vilnius University Hospital Santariškių Klinikos is acting as such and provides genetic services for the population of Lithuania.

### *Luxembourg*

No information to date.

### *Malta*

No information to date.

### *Norway*

No information to date.

### *Netherlands*

The Netherlands has no established policy for centres of reference. The eight university hospitals have ample expertise in diagnosis and treatment of many rare diseases, but their specific expertise is not yet recognised. A new initiative will be launched in September 2006 to establish the Dutch umbrella organisation for university hospitals (NFU). This organisation will perform an inventory of the expertise on rare diseases in the eight university hospitals, using a list with more than 1000 rare diseases. This list was created by a special committee that advised the Ministry of Health, Welfare and Sports about a deduction for national insurance, especially in the case of rare diseases. This committee made an inventory about the need for care, possibilities for treatment and future costs. University hospitals will add their experience in research, care and treatment to this list. The inventory of the NFU will give sound information on the expertise of each university hospital for the various rare diseases.

Alongside the eight university hospitals are special Healthcare and Treatment Centres in other hospitals for several diseases. In some cases medical (fundamental and applied) research is also performed in these centres. Some examples of these treatment centres are: 13 locations for treatment of haemophilia, with special centres for children and special centres for adults; seven centres for cystic fibrosis, fulfilling twenty quality criteria written by the Dutch Patient Organisation for Cystic Fibrosis; one expert/reference centre for Gaucher and Fabry disease (Patients with Gaucher disease are treated extramurally in their own region, but they have a regular check-up in this expertise centre. Their medical specialist in their own hospital or their general practitioner can get information about treating the disease at this expertise centre as well); one expert centre for Pompe disease where patients are treated.

### *Poland*

In Poland, health care of patients with rare disease is not organised. Significant progress was made as a result of the European Project of Centres of Excellence “PERFECT” *QLG1-CT-2002-90358*. The grant was coordinated by the largest Polish paediatric referral and research centre, The Children’s Memorial Health Institute in Warsaw. The grant programme included problems of rare paediatric diseases in the field of genetics, metabolism, gastroenterology, cardiology, immunology and oncology. In January 2007, a new EU grant *PRIOMEDCHILD* will start. One of the aims of this programme is the organisation of European and national networks of paediatric centres involved in clinical trials, including those concerning rare diseases.

### *Romania*

Romania has no Centre of Reference labelled as such by the Ministry of Health. There are some centres (in Iasi, Cluj, Oradea etc.) with all the characteristics of centres of references (multidisciplinary care, particular expertise) for rare disease, particularly for cystic fibrosis, Gaucher disease, Fabry disease and Mucopolysaccharidosis, rare malignancies, kidney diseases and kidney transplantation. As of 2001 there is a National Program for Health of Mother and the Child in which a sub-program for prevention of genetics diseases, neonatal screening, cystic fibrosis and haematological diseases exists.

### *Serbia*

There are no centres of reference for rare diseases in Serbia. There are only expert groups formed by the Ministry of Health dealing with haemophilia, diabetes, malignant diseases, psychiatric diseases, acute kidney failure, contagious diseases (vaccines and prevention), tuberculosis, transfusion, urgent medicine and obstetrics. They focus on the organisation of services and creation of policy and guidelines.

### *Slovakia*

No information to date



## *Slovenia*

The majority of patients with rare diseases in Slovenia are evaluated centrally at the University Medical Centre Ljubljana in which there is an efficient system for the referral of genetic, endocrine, metabolic, and neurodegenerative disorders, among others. Additionally, there is a Centre for Fabry disease in Slovenj Gradec. The Ministry of Health is currently establishing a working group with the aim of establishing a national policy on the nomination and organization of national centres of reference.

## *Switzerland*

Switzerland has not yet established its policy regarding centres of reference, although work is in progress in some areas of medicine, such as transplantation. Regarding rare diseases, a few centres have been established as centres of reference by reputation, such as the Centre for Retinoblastoma in Lausanne, the Centre for Malignant Hyperthermia in Basel and the Centre for Fabry disease in Lausanne. Officially designating these centres of reference is not easy in a country where there are 26 cantons (subdivisions) that each have a public health policy of their own.

## *Turkey*

Though no centres of reference for rare diseases currently exist, Turkey is planning to establish a national network for the prevention, surveillance, diagnosis and treatment of rare diseases. Projects to establish national centres of reference for rare diseases expected to start in late 2007. These centres will be part of the overall planning of healthcare in the country. The Ministry of Health and the different regional healthcare authorities will have to coordinate their approach and need to harmonise regional network activities.

### **2.3.4. Definition of a Centre of Reference in European countries**

There is no common definition of what a centre of reference is among member states which have established such centres.

Even among countries with official centres of reference, the definition of what is a rare disease varies between centres of reference. The UK uses 1 in 50,000, Sweden and Denmark use 1 in 10,000 whereas France, Italy and Spain use the European orphan drugs regulation definition of 1 in 2,000. Regardless of the definition used, a large prevalence of diseases qualifying as rare exists in Europe.

The number and geographical distribution of centres in each country also varies though not proportionally to the size of the population, reflecting differences in the organisation of the health care systems.

Among the larger countries, there is some consistency though differences continue to exist. The UK and the French approach is similar even though the disease prevalence used as the cut-off is different. Italy attributes the label of regional reference centre to over 250 clinics.



There is no attempt to systematically distribute the centres on a geographical basis in either the UK or France, while in Italy centres are distributed throughout the country to cover all regions.

Within the medium-sized countries, the approaches by Sweden and Denmark are similar to each other (though still different from the approach of the large countries): Sweden currently has 75 centres for 8.9 million people while Denmark has two centres for 5.4 million people. Sweden is currently considering reducing this number.

Among the countries analysed thus far, seven countries use a national approach (Bulgaria, UK, Belgium, France Greece, Norway and the Netherlands), whereas others, such as Finland, Italy, Spain, and Sweden have a more regional. The majority of countries have not yet started to identify their expert centres.

The centres of reference differ in form from one country to another, reflecting the heterogeneity of national health systems. In Sweden, the centres are expected to concentrate on clinical care, diagnosis and treatment, rather than research. In Denmark, they are supposed to carry out specialised diagnoses, treatment and monitoring, and to organise the overall planning of treatment, with daily care being provided locally. In Italy, the regional centres were established to be areas for diagnosis and treatment. In the UK and France, reference centres are mainly centres of multidisciplinary expertise with the ability to provide a service that cannot be delivered elsewhere with the same quality and that attracts patients from all over the country. Whereas France has a strong emphasis on clinical research, with centres expected to produce the best practice guidelines and provide expert opinion with preference given to patients travelling to the clinic from afar.

The number of diseases covered by each type of centre differs. In Denmark, each centre is supposed to be able to manage patients with several different diseases from various medical specialties. In Italy, the UK and France the centres are very specialised in one or a very small number of diseases (see Annex). France has currently 103 centres with a balance between medical areas (see Annex) and plans to have a few more in areas not yet well covered. Currently all French centres are disease oriented.

In the UK, half of the centres are disease oriented, covering all aspects of the patients' needs, from diagnosis to therapy. The other half is technology-oriented and provides a highly specialised service, mainly through surgery and transplantation (see Annex). In Denmark, the number of conditions which are covered by the centres is larger than that in France and the UK, and, in practice, the two centres dedicated to rare diseases accept referral of patients with any type of rare disease.

The current process to identify, select and designate centres of reference for rare diseases is also quite different from one country to another. In the UK, the centres must apply to the National Specialist Commissioning Advisory Group (NSCAG) to become a reference centre. There is no specific call for proposals and no overarching national strategy; the call is permanently open. NSCAG was established in 1996 to advise Ministers on the identification and funding of services where central intervention into local commissioning of patient services was necessary for reasons of clinical effectiveness, equity of access and/or economic viability. It superseded the Supra Regional Services Advisory Group.

In France, the centres apply annually through a competitive call for proposals. The applications are reviewed by an advisory committee (Comité National Consultatif de Labellisation des centres de référence de maladies rares (CNCL)) comprised of experts, patient representatives, and members of relevant societies and administrations. The selection criteria are transparent.

In Italy, the designation of reference centres is in the remit of the Regional authorities, although uniform criteria for definition have not yet been agreed upon. However, there is a national conference of the Regions, and a process toward the adoption of a more uniform set of criteria may be set in motion in the future.

Denmark has established two designated centres for rare diseases at university hospital level, in addition to 100 specialised clinics. The final selection was done by the National Board of Health after consultation of the learned societies, the administration and the patients' organisations.

The reason for designating centres of reference is different from one country to another. In principle, there are two main purposes for officially identifying specific resource centres. The first purpose is to provide a rating scheme to the consumers to allow them to identify the appropriate health care resource for their case. The overall objective of a rating scheme is to guide consumers to trustworthy health information and to empower consumers to accurately select high quality services for referral. A rating scheme has to establish its standards for interoperability of rating and description services and fosters a worldwide collaboration to guide consumers to high-quality information and services. It is for this reason that it is important to have an operational definition of a centre of reference and a clear understanding of how they are designated if the concept of CR is to be applied to many more European countries. The rating scheme in use should be the same in all Member States.

The second purpose of designating CR is for the health care managers to identify where to allocate specific financial resources in order to support the additional activities linked to the duties of a CR, as the designation of CR confers both rights and duties that require additional staff and resources. It is well established that the designation of a centre as a CR increases its referral rate, and the number of requests for expert opinion. In addition, designated CRs must be actively involved in clinical research, issue best practice guidelines and produce information leaflets for patients; all these activities require additional resources. For all these reasons, designating a clinical centre as CR has a direct impact on the health care system of the region where this centre is located. This is why designation of a CR should be left to the member states, which will ultimately have to support the cost of the extra activity. It is also a reason why member states should preferably not designate CR without providing them with the necessary financial support. When looking at the current situation in Europe, it appears that only France is allocating a significant budget to support the extra activities of the CR, whereas all the other countries only provide the funding linked to the clinical activity of the CR with no specific budget for expert opinion activity, teaching, training, information and coordination.

In conclusion, this overview of the situation of CR in the different member states shows (1) that only a few countries have official CR; (2) that the official CR cover different types of centres; (3) that the concept of CR is not used by some member states that have a regionally organised health care system and a low level of coordination between regions; (4) that many centres of expertise, acting as CR, are not labelled as such but are well established by reputation.

### **The RDTF recommends that:**

- **the wording "centre of reference" is not used in the future when referring to the nodes of a network to be established or when discussing a possible cooperation between member states in the field of health services and medical care for rare diseases. The preferred wording is "centre of expertise". Centres of expertise exist everywhere, whereas centres of reference are confined to a few countries.**
- **countries having a policy for establishing national or regional centres of reference for rare diseases agree as much as possible on an operational definition of what is a CR and on how to designate them. Countries with established centres of reference should be encouraged to share their experience and the results of their outcome measures.**
- **countries not having a policy regarding the establishment of centres of reference for rare diseases, find an appropriate way to organise their health care system to serve the needs of patients, either through the establishment of CR or through contracting with other CR or centres of expertise abroad (not too distant if possible), and developing electronic communication between local clinics and centres of expertise from all over Europe.**
- **the European Commission plays an important role in supporting the identification of centres of expertise and in the diffusion of the information about them.**

#### **2.4. Centres of expertise in Europe**

An attempt to identify expert clinics in Europe has been made by Orphanet ([www.orpha.net](http://www.orpha.net)), the European database of specialised services in the area of rare diseases. The selection was based on quality indicators including national reputation, high volume of relevant activity, appropriate capacity to manage patients, and a high level of expertise as documented through publications, grants and international collaborations.

There are currently 2197 expert clinics in Orphanet, identified in the 18 countries investigated so far: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Switzerland, and the UK. Not all of them can be considered as having the highest level of expertise possible, but all of them are delivering a service which qualifies them as a local, regional or national centre for referring patients in practice.

These, over 2,000, expert clinics can be classified into 133 types of expert clinic of which 76 are offering an expertise regarding a single disease or less than 10 diseases, 32 are offering a service for a group of less than 100 diseases, and 25 for a group of over 100 of rare diseases (Annex 5).

The list of types of expert clinics identified so far is given in Annex.

The data collection is going on in the other countries.

In conclusion, there is a rich selection of expert centres in European countries. Their cooperation could be organised to maximise the output of services through incentives to establish formal networks.

Such networks already exist in practice in the area of clinical research or in the area of public health. A list of identified European networks in the area of rare diseases is given in Annex.

**The RDTF recommends that:**

- **Networks of centres of expertise are identified and funded at European level. These networks would be better called "European Networks of centres of expertise".**

## **2.5. European networks of centres of expertise**

Both the RDTF 2005 report and the HLG report concluded that networking of expert centres should be favoured.

The scope of a European network of centres of expertise has already been defined by the HLG (HLG/2005/16), although with the title of "centres of reference". This is to ensure an optimal collaboration between centres, so that ultimately every European patient in every European country can benefit from optimal care.

A network consists of nodes plus links between the nodes. A network is a European network because its nodes (centres of expertise) are located in more than one European country, though not every European country. The network encompasses the whole of Europe because patients in every European country can benefit from the network. These networks constitute virtual centres.

The centres of expertise are the nodes, and the links between them are communications. Thus, a network of centres of expertise is characterised by communication between the centres of reference in the network. These communications may be electronic or face-to-face (at a meeting or conference). Communication in the network will normally be from any node to all other nodes *i.e.* from a centre of reference to all of the other centres of reference. Occasionally communication may be private, from one centre to a subset of the other centres, but this will not be the norm. Communication may be needed to develop a consensus on, for example, treatment protocols, or (with suitable arrangements for patient consent) to discuss the diagnosis and management of individual patients. Centres are members of the network because they communicate in this way. Centres which do not share ideas and opinions are not active members of the network. It is the sharing of expert opinion and ideas which provides the key benefit of the network.

Within the network the nodes are equal; there is no hierarchy between centres of reference, although one of them may act as coordinator on behalf of the others.

There should be separate networks for separate diseases or conditions to ensure optimal expertise as for expert centres, not a single network for all diseases or conditions.

Current developments in molecular diagnosis, imaging, video conferencing, robotics and communication are making virtual centres through networking a real possibility, allowing highly specialised care to be supported in remote locations.

In response to this recommendation, the 2006 Annual Work Programme for grants from the European Commission in the framework of the Programme of Community Action in the field of public health set the development of ENCRs for rare diseases as a priority, priority 2.1.4(e).

The results of its call for proposals intended to finance proposals for European reference centre networks for healthcare provision concerning a rare disease or a group of rare diseases starting in 2007 over a three-year period. Six networks of centres of reference for a specific rare disease or a group of rare diseases have been selected, spanning six EU countries. They are currently in the negotiation phase and will serve as pilot projects for reference networks of Centres of expertise:

- European Centres of Expertise Network for Cushing Syndrome (Dr Susan Webb, University of San Pau, Barcelona)
- European Centres of Expertise Network for porphyria (Prof. Jean-Charles Deybach, Paris)
- European Centres of Expertise Network alpha-1 antitrypsin deficit (Prof. Jan Stolk, Leiden)
- European Centres of Expertise Network for dysmorphic syndromes (Prof. Jill Clayton-Smith, Manchester)
- European Centres of Expertise Network for cystic fibrosis (Prof. Thomas Wagner, Frankfurt)
- European Centres of Expertise Network for hemorrhagic syndromes (Prof. Flora Payvandi, Milan).

It is interesting to see that these networks were established between expert centres that were not "official" centres of reference in their respective country, for most of them, underlining once more the necessity to modify the title of this type of network.

**The RDTF recommends that the European Commission:**

- **continues its financial support to networks of centres of expertise in the field of rare diseases until an evaluation of the output of the networking process demonstrates that it is not cost-effective (which is extremely unlikely).**
- **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.**
- **encourages, by all possible means, the development of electronic tools necessary for the development of telemedicine in the field of rare diseases.**

**The RDTF recommends that the member states:**

- **contribute to the identification of their expert centres and support them financially as much as possible**
- **organise healthcare pathways for their patients through the establishment of cooperation with all necessary expert centres from within the country and from abroad when necessary.**

# Annex 1

## Members of the Rare Diseases Task Force Expert Group

### Austria

**Dr Helmut POPPER**

Medizinische Universität Graz  
Graz AUSTRIA

### Bulgaria

**Dr Rumen STEFANOV**

Information Centre for Rare Diseases and Orphan Drugs  
BAPES  
Plovdiv BULGARIA

### Denmark

**Mrs Birthe HOLM**

Rare Disorders Denmark  
Copenhagen DENMARK

**Dr Marianne JESPERSEN**

National Board of Health  
Copenhagen DENMARK

### France

**Dr Ségolène AYME (chair)**

Orphanet  
INSERM  
Paris FRANCE

**Marc BRODIN**

President of the French National Consultative Committee for Certification (CNCL)  
Hôpital Robert Debré  
Paris FRANCE

**Prof Jean-François CORDIER**

Hôpital Louis Pradel  
Lyon FRANCE

**Dr Alexandra FOURCADE**

DHOS  
Ministère de la Santé et des solidarités  
Paris FRANCE

**Mrs Aude MARLIER-SUTTER**

DHOS  
Ministère de la Santé et des Solidarités  
Paris FRANCE

**Mrs Christel NOURISSIER**

Eurordis  
Paris FRANCE

## **Finland**

### **Dr Riitta SALONEN**

Väestöliitto Department of Medical Genetics  
Helsinki FINLAND

### **Dr Mauno VIHINEN**

Institute of Medical Technology  
University of Tampere  
FINLAND

## **Germany**

### **Dr Thomas WAGNER**

Klinikum der Johann-Wolfgang Goethe-Universität  
Frankfurt GERMANY

### **Dr Cornelia ZEIDLER**

Medizinische Hochschule  
Hannover GERMANY

## **Italy**

### **Pr Bruno DALLAPICCOLA**

Istituto CSS-Mendel  
Roma, Italy

### **Dr Nicolino RUPERTO**

IRCCS G. Gaslini  
Genova, Italy

### **Dr Arrigo SCHIEPPATI**

Mario Negri Institute for pharmaceutical research  
Ranica, Italy

### **Dr Domenica TARUSCIO**

Centro Nazionale Malattie Rare  
Istituto Superiore di Sanita  
Roma, Italy

## **Spain**

### **Dr Miguel DEL CAMPO**

Hospital Materno-Infantil Vall d'Hebron  
Barcelona SPAIN

### **Dr Manuel POSADA**

Instituto de Investigacion en Enfermedades Raras  
Instituto de Salud Carlos 3  
Madrid SPAIN

### **Dr Joan Lluís VIVES CORRONS**

Red Cell Pathology Unit  
University of Barcelona  
Barcelona SPAIN

## **Sweden**

### **Pr Anders FASTH**



Gothenburg University  
Gothenburg SWEDEN

## **United Kingdom**

### **Prof Dian DONNAI**

St Mary's Hospital  
Manchester UNITED KINGDOM

### **Dr Edmund JESSOP**

National Specialist Commissioning Advisory Group  
Department of Health  
London UNITED KINGDOM

### **Mr Alastair KENT**

Genetic Interest Group  
London UNITED KINGDOM

### **Dr Michael RIGBY**

Centre for Health Planning and Management  
Keele University  
Keele UNITED KINGDOM

## **Observers**

## **European Commission**

### **Mr Martin DORAZIL**

DG Health and Consumer Protection  
Health Strategy Unit  
European Commission

### **Mr Nick FAHY**

DG Health and Consumer Protection  
Health Strategy Unit  
European Commission

### **Mr Antoni MONTSERRAT**

Public Health and Risk Assessment  
DG Health and Consumer Protection  
European Commission

## **France**

### **Mrs Kathy BEUZARD-EDWARDS**

Orphanet France  
Paris FRANCE

### **Mrs Carole CRETIN**

Direction Générale de la Santé  
Ministère de la Santé et des Solidarités  
Paris FRANCE

### **Mrs Emmanuelle JEAN**

Direction Générale de la Santé  
Ministère de la Santé et des Solidarités  
Paris FRANCE

### **Dr Frédéric SICARD**

International and European Affairs

Ministère de la Santé et des Solidarités  
Paris FRANCE

**Dr Ana RATH**

Orphanet France  
Paris FRANCE

**Dr Valérie THIBAudeau**

Orphanet France  
Paris FRANCE

**Mrs Lydia VALDES**

Direction Générale de la Santé  
Ministère de la Santé et des Solidarités  
Paris FRANCE

## Contributors

**Dr Till VOIGTLANDER**

Medical University of Vienna  
Institute of Neurology  
Vienna AUSTRIA

**Prof Jean-Jacques CASSIMAN**

Centre of Human Genetics  
University Hospital Gasthuisberg  
Leuven BELGIUM

**Prof Ana STAVLJENIC-RUKAVINA**

Zagreb University School of Medicine  
Diagnosis Center  
Zagreb CROATIA

**Dr Violetta ANASTASIADOU**

Archbishop Makarios III Medical Centre  
Clinical Genetics Department  
Nicosia CYPRUS

**Prof Milan MACEK**

Institute of Biology and Medical Genetics  
Department of Molecular Genetics and National Cystic Fibrosis Center  
Prague CZECH REPUBLIC

**Prof Andres METSAPALU**

Tartu University  
Institute of Molecular and Cell Biology  
Tartu ESTONIA

**Prof Joerg SCHMIDTKE**

Medizinische Hochschule  
Institut für Humangenetik  
Hannover GERMANY

**Dr Lina FLORENTIN-ARAR**

AlfaLab Molecular Biology and Cytogenetics Center  
Athens GREECE

**Prof Gyorgyi KOSZTOLANYI**

University of Pecs  
Department of Public Health  
Pecs HUNGARY

**Prof Andrew GREEN**

National Center for Medical Genetics  
Our Lady's Hospital for Sick Children  
Dublin IRELAND

**Prof Rita LUGOVSKA**

Medical Genetics Clinic of Latvian State  
Children's University Hospital  
Riga LATVIA

**Prof Vaidutis KUCINSKAS**

Department of Human and Medical Genetics  
Vilnius University  
Vilnius LITHUANIA

**Prof Martina CORNEL**

VU University Medical Center  
EMGO, BS7, D423  
Amsterdam NETHERLANDS

**Prof Ewa PRONICKA**

Children's Memorial Health Institute  
Division of Metabolic Diseases  
Department of Paediatrics  
Warsaw POLAND

**Dr Margarida REIS LIMA**

Instituto de Genética Médica Jacinto de Magalhães  
Porto PORTUGAL

**Prof Mircea COVIC**

Disciplina de Genetica Medicala  
Universitatea de Medicina si Farmacie Iasi  
Iasi ROMANIA

**Dr Dragica RADOJKOVIC**

Institute of Molecular Genetics and Genetic Engineering  
Laboratory for Molecular Biology  
Belgrade SERBIA

**Prof Borut PETERLIN**

University Medical Center Ljubljana  
Division of Medical Genetics  
Department of Obstetrics and Gynecology  
Ljubljana SLOVENIA

**Dr Miguel DEL CAMPO**

Unitat de Genètica  
Hospital Materno-Infantil Val d'Hebron  
Barcelona SPAIN

**Dr Loredana D'AMATO SIZONENKO**

Service de Génétique Médicale  
Centre Médical Universitaire  
Genève SWITZERLAND

**Prof Ugur OZBEK**

Istanbul University  
Institute for Experimental Medicine  
Istanbul TURKEY

**Christina GREEK-WINALD**

Swedish Center for Rare Diseases  
Gothenburg SWEDEN

## Annex 2

### National Referral Centres Designated by the National Board of Health of Denmark

(Conditions/Procedures Organised by Medical Specialty and the number of each type of centre included where available)

#### **Anesthetics**

Nervus frenicus pacemaker	1
Malignant hyperthermia	1
ECMO (adults)	2
ECMO (children)	1
Neuromuscular disease with chronic Respiratory insufficiency	2
Neonatal anesthesia	4

#### **Child and adolescents**

##### **Psychiatry**

Severe complicated cases of	
- neuropsychiatric disease	
- Gilles de la Tourette syndrome	4

##### **Dermatology**

Angiomas and vascular malformation	3
Severe genodermatosis	2
Cutaneous lymphoma	4

##### **Radiology**

Embolisation of neurovascular malformations	1- 5
---	------

##### **Gynecology/Obstetrics**

Pregnant women with rare disease	2
Foetus with rare diseases	3
Special prenatal diagnostics	5
Rare gynaecologic cancers	4

##### **Hepatology**

Congenital liver diseases	1
Wilson disease	1

##### **Haematology**

Stem cell transplantation	1-2
Malignant leukemias	4

Myelofibrosis	4
Essential thrombocytosis	4
Amyloidosis	5
Neutropenias	5
Hemophilia	2
<b>Infectious diseases</b>	
Children with HIV	3
Imported rare infectious diseases and rare sporadic infectious disease (cholera, pest, rabies etc.)	5
Special multi-resistant infections	5
<b>Cardiology</b>	
Congenital heart disease	2
Marfan syndrome, Ehlers- Danlos	2
<b>Endocrinology</b>	
Adrenogenital syndrome (children)	1
Adrenogenital syndrome (adults)	4
Galactosemia	1
Prader Willi Syndrome	2
<b>Gastroenterology</b>	
Short bowel/ intestine syndrome	3
Severe inflammatory intestinal disease	5
<b>Pneumology</b>	
Multiresistant TB	1
Rare interstitial lung diseases	4
Mesothelioma	4
Sarcoidosis	4
<b>Nephrology</b>	
Kidney- transplantation	5
Rare metabolic kidney disease (cystinosis, oxalosis)	5
<b>Rheumatology</b>	
Para – tetraplegia rehabilitation	2
Rare inflammatory joint disease (Feltys syndrome)	3
Systemic Vasculitis	
Wegener granulomatosis,	
Periarteritis nodosa	
Churg-strauss syndrome	
Behcet syndrome	
Takayasu syndrome	3
Rare connective tissue diseases	3
Severe Sclerodermia	3
Thoracic surgery	5

Thoraco-abdominal aortaaneurysma (control and elective surgery)	1-2
Severe vascular diseases (surgery)	5
Artificial heart	1
Heart- / heart and lung transplantation	1
Livertransplantation	1
FAP	4
HNPCC	4
Severe colitis ulcerosa, mb. Chron	5
Oesophagal cancer	5
<b>Plasticsurgery</b>	
Outer ear malformations	1
Lip-gum-palate cleft	1
Craniofacial surgery	2
Uro-genital malformations	2
Myelomeningocele, spina bifida	3
Melanoma	4
<b>Transexuality</b>	<b>1</b>
Cancer of face, mouth and throat	4
Bladder extrophy	2
Intersexconditions	2
Analatresia	2
Wilms tumor	2
<b>Genetic counselling</b>	<b>6</b>
<b>Neurosurgery</b>	<b>5</b>
Epileptic surgery	1
Implantation of n. vagus stimulator	1
Acusticusneurinomas	2
Deep brain stimulation, Parkinson	2
Intracranial cancer (children)	3
Arterio-venous intracranial malformations	2
<b>Neurology</b>	
Early intensive rehabilitation of severe traumatic brain damage	2
Rare Neuromuscular diseases (muscular dystrophia, spinal muscular atrophia )	2
Neurofibromatous Recklinghausen	2
Rare polyneuropathics	
<b>CIDP</b>	<b>2</b>
<b>Ophthalmology</b>	
Congenital glaucomas	1
Ophtalmic oncology	2
Retinoblastomas	1

Ophthalmic genetic counselling	1
Spielmeier- Vogt	1
<b>Oncology</b>	
Rare cancers medical treatment	6
Choriocarcinomas	2
Oncologic radiation therapy	6
<b>Orthopedic surgery</b>	
Special replantation surgery of limbs	1
Plexus brachialis lesions	1
Surgical treatment of dwarfism	1
Osteogenesis Imperfecta	2
Revisionsurgery of special alloplastics (shoulder, elbow)	3
Primary malignant bone tumors	2
Congenital deformities of back and limbs	3
<b>Oto-rhinolaryngology</b>	
Severe stenosis and malformations of larynx, trachea	2
Deafness - Cochlear implantation	2
<b>Psychiatry</b>	
Mental health service for deaf	1
Severe sexual disturbances (forensic)	3
Special secure forensic mental health care	1
<b>Pediatrics</b>	
Cystic fibrosis	2
Severe immunodeficiencies	1
Phenylketonuria	1
Malignant haematological disease (children)	4
Malignant cancers (children)	4

## **SCIDS**

National referral centres specific for rare diseases:



## Annex 3

### List of National Centres of Reference in France

#### **Autoimmune Diseases & Systemic Rare Diseases**

Centre of Reference for auto-immune systemic rare diseases- STRASBOURG  
Centre of Reference for Langerhans histiocytosis- PARIS  
Centre of Reference for primitive amylosis and other rare diseases with immunoglobulin deposits- POITIERS  
Centre of Reference for juvenile arthritis- PARIS  
Centre of Reference for amylosis of inflammatory origin & familial Mediterranean fever- PARIS  
Centre of Reference for vascular sclerodermia- LILLE  
Centre of Reference for lupus and antiphospholipides syndromes- PARIS  
Centre of Reference for the Rendu-Osler-Weber disease- LYON  
Centre of Reference for necrosing vascularitis and systemic sclerodermia- PARIS

#### **Cardiovascular Rare Diseases**

Centre of Reference for complex cardiac malformations- PARIS  
Centre of Reference for rare vascular diseases- PARIS  
Centre of Reference for hereditary cardiac diseases- PARIS  
Centre of Reference for cardiac rhythm problems of genetic origin- NANTES

#### **Embryonic Development Anomalies of Genetic Origin**

Centre of Reference for embryonic developmental anomalies of genetic origin- DIJON  
Centre of Reference for odontological manifestations of rare diseases- STRASBOURG  
Centre of Reference for non syndromic, fixed mental deficiency of genetic origin- PARIS  
Centre of Reference for anomalies in embryonic development of genetic origin- RENNES  
Centre of Reference for anomalies in embryonic development of genetic origin- MONTPELLIER  
Centre of Reference for anomalies in embryonic development of genetic origin- LILLE  
Centre of Reference for mental deficiency linked to chromosome X and X-Fragile Syndrome- LYON  
Centre of Reference for rare dysmorphic syndromes with mental deficiency- MARSEILLE  
Centre of Reference for anomalies in embryonic development of genetic origin- BORDEAUX  
Centre of Reference for anomalies in embryonic development of genetic origin- PARIS

#### **Rare Dermatological Diseases**

Centre of Reference for auto-immune bullous diseases- ROUEN  
Centre of Reference for rare skin diseases- BORDEAUX et TOULOUSE  
Centre of Reference for genetic diseases with cutaneous manifestations- PARIS  
Centre of Reference for neuro-fibromatosis- CRETEIL  
Centre of Reference for acquired toxic immunological bullous dermatosis- CRETEIL

#### **Rare Endocrinological Diseases**

Centre of Reference for rare sexual development diseases- LYON  
Centre of Reference for pathologies in hormonal receptivity- ANGERS

Centre of Reference for pituitary deficiency- MARSEILLE  
Centre of Reference for endocrinology of rare growth diseases- PARIS  
Centre of Reference for adrenal rare diseases- PARIS  
Centre of Reference for Prader-Willi Syndrome- TOULOUSE

### **Hepato-gastroenterological Rare Diseases**

Centre of Reference for congenital & malformation affections of the oesophagus- LILLE  
Centre of Reference for rare vascular liver diseases in adults- PARIS  
Centre of Reference for atresia of the bile ducts in children- PARIS  
Centre of Reference for Wilson's disease- PARIS  
Centre of Reference for hereditary rare diseases in hepatitis metabolism- CLAMART  
Centre of Reference for intestinal digestive diseases- PARIS  
Centre of Reference for inflammatory diseases of the bile ducts- PARIS

### **Benign Hematological Rare Diseases**

Centre of Reference for sickle cell disease- POINT A PITRE  
Centre of Reference for haemophilia & other haemorrhage-related constitutional diseases- LYON  
Centre of Reference for Willebrand disease- LILLE  
Centre of Reference for thrombocytic microangiopathies- PARIS  
Centre of Reference for thalasseмии- MARSEILLE  
Centre of Reference for rare constitutional medullar aplasia- PARIS  
Centre of Reference for constitutional thrombopathia- PESSAC  
Centre of Reference for adult auto-immune cytopenia- CRETEIL  
Centre of Reference for genetic erythrocyte & erythropoietic diseases (excluding sickle cell disease) - PARIS  
Centre of Reference for major drepanocytic syndromes- PARIS

### **Hereditary Metabolic Diseases**

Centre of Reference for hereditary metabolic diseases- NANCY  
Centre of Reference for mitochondrial pathologies- NICE  
Centre of Reference for mitochondrial diseases- PARIS  
Centre of Reference for hereditary metabolic diseases- LILLE  
Centre of Reference for hereditary metabolic diseases- PARIS  
Centre of Reference for children's metabolic diseases- MARSEILLE  
Centre of Reference for neurological lysosomal diseases- CLICHY  
Centre of Reference for Porphyria- COLOMBES

### **Rare Neurological Diseases**

Centre of Reference for narcolepsia & idiopathic hypersomnia- MONTPELLIER  
Centre of Reference for multiple system atrophy- TOULOUS  
Centre of Reference for rare peripheral neuropathies- LIMOGES  
Centre of Reference for neurogenetic diseases- PARIS  
Centre of Reference for rare types of epilepsy- PARIS  
Centre of Reference for neurogenetic & mitochondrial diseases in adults- ANGERS  
Centre of Reference for rare hypersomnia conditions- PARIS  
Centre of Reference for leucodystrophy- PARIS  
Centre of Reference for rare vascular diseases of the central nervous system & retina- PARIS  
Centre of Reference for familial amyloidosis neuropathies- LE KREMLIN BICETRE

Centre of Reference for Huntington disease- CRETEIL  
Centre of Reference for Ondine Syndrome- PARIS

### **Neuromuscular Diseases**

Centre of Reference for neuromuscular & neurological rare diseases- FORT DE FRANCE  
Centre of Reference for rare neuromuscular diseases- STRASBOURG  
Centre of Reference for rare neuromuscular diseases- NANTES  
Centre of Reference for rare neuromuscular diseases- SAINT ETIENNE  
Centre of Reference for amyotrophic lateral sclerosis- PARIS  
Centre of Reference for rare neuromuscular diseases- LILLE  
Centre of Reference for muscular canalopathies- PARIS  
Centre of Reference for rare neuromuscular diseases- GARCHES  
Centre of Reference for rare neuromuscular diseases- PARIS  
Centre of Reference for neuromuscular diseases and amyotrophic lateral sclerosis- NICE et MARSEILLE

### **Rare Pulmonary Diseases**

Centre of Reference for rare respiratory diseases- PARIS  
Centre of Reference for cystic fibrosis- LYON  
Centre of Reference for cystic fibrosis- NANTES  
Centre of Reference for acute pulmonary hypertension- CLAMART  
Centre of Reference for orphan pulmonary diseases- BRON

### **Rare Ophthalmological Diseases**

Centre of Reference for rare ophthalmic diseases- PARIS  
Centre of Reference for keratoconus- BORDEAUX et TOULOUSE  
Centre of Reference for hereditary retinal dystrophy- PARIS  
Centre of Reference for genetic ophthalmological affections- STRASBOURG

### **Rare Renal Diseases**

Centre of Reference for idiopathic nephrotic syndrome- PARIS  
Centre of Reference for rare renal diseases- TOULOUSE  
Centre of Reference for rare hereditary renal diseases- PARIS  
Centre of Reference for rare hereditary renal & metabolic diseases- LYON

### **Rare Bone Diseases**

Centre of Reference for fibrous bone dysplasia - LYON  
Centre of Reference for craniofacial dysostosis- PARIS  
Centre of Reference for constitutional bone diseases- PARIS

### **Rare Immune Deficiency**

Centre of Reference for hereditary immune deficiency- PARIS

### **Diseases of the Connective Tissue**

Centre of Reference for Fabry disease & hereditary diseases of connective tissue with cutaneous-articular manifestations- PARIS  
Centre of Reference for Marfan Syndrome- PARIS

## **Congenital & Genetic Deafness**

Centre of Reference for Genetic Sensorial Affections- PARIS

Centre of Reference for congenital & hereditary deafness- MONTPELLIER

## **Other Rare Diseases**

Centre of Reference for *non-histaminic* angioedema- PARIS

## Annex 4

### List of centres of reference in UK by type of centre

#### Disease-centred

- Amyloidosis
- Bladder exstrophy
- Choriocarcinoma
- Epidermolysis bullosa service for adults
- Epidermolysis bullosa service for children
- Liver disease service for children
- Lysosomal storage disorders\*
- Ocular oncology
- Ophthalmic pathology
- Personality disorder
- Primary malignant bone tumours\*
- Pulmonary hypertension
- Rare neuromuscular diseases
- Retinoblastoma
- Severe combined immunodeficiency and related disorders (SCIDS)
- Severe intestinal failure

#### Treatment centred

- Craniofacial surgery
- Deep brain stimulation for severe Parkinson's Disease
- Extra-corporeal membrane oxygenation (ECMO) for adults
- Extra-corporeal membrane oxygenation (ECMO) for children\*
- Extra-corporeal membrane oxygenation (ECMO) for neonates and infants
- Heart and lung transplantation service for adults and children
- Liver transplantation service for adults and children
- Mental health services for deaf children & adolescents (inpatient)
- Pancreas transplantation
- Pseudomyxoma peritonei surgery
- Pulmonary thromboendarterectomy
- Reconstructive surgery in adolescents for congenital malformation of the female genital tract
- Secure forensic mental health service for young people
- Small bowel transplantation for adults and children
- Stem cell transplantation for juvenile idiopathic arthritis and related connective tissue disorders
- Ventricular assist devices for adults
- Ventricular assist devices / extra-corporeal membrane oxygenation (bridge to transplant) for children

## Annex 5

### **Different scopes of expert clinics for rare diseases In Europe, as identified by Orphanet (August 06)**

Adult primary immunodeficiency clinic	Hemophilia and other coagulation defects clinic
Adult rare renal diseases clinic	Hereditary amyloid-related neurological diseases clinic
Amyloidosis clinic	Hereditary cardiac diseases clinic
Amyotrophic lateral sclerosis clinic	Hereditary cardiac rhythm defects clinic
Angiomas and vascular malformations clinic	Hereditary metabolic hepatic diseases clinic
Antiphospholipid syndrome clinic	Hereditary rare eye diseases clinic
Antirabies clinic	Hereditary retinal dystrophies clinic
Autoimmune and systemic rare diseases clinic	Huntington disease clinic
Autoimmune cytopenias clinic	Ichthyosis clinic
Behcet disease clinic	Keratoconus clinic
Biliary atresia clinic	Langerhans cell histiocytosis clinic
Biliary inflammatory diseases clinic	Leukodystrophies clinic
Bladder exstrophy clinic	Lupus clinic
Bone diseases clinic	Lymphedema clinic
CADASIL clinic	Lysosomal diseases clinic
Congenital anomalies of limbs clinic	Malignant hyperthermia clinic
Congenital neutropenias clinic	Marfan syndrome clinic
Constitutional medullar aplasias clinic	Mastocytosis clinic
Constitutional thrombopathies clinic	Melanoma clinic
Creutzfeldt-Jakob clinic	Memory disorders clinic
Cutaneous lymphoma clinic	Metabolic diseases clinic
Cutis laxa clinic	Mitochondrial diseases clinic
Cystic fibrosis clinic	Moebius syndrome clinic
Cytogenetics clinic	Movement disorders clinic
Deafness clinic	Multiple sclerosis clinic
Down syndrome clinic	Neurodegenerative diseases clinic
Dyslipidemia clinic	Neurofibromatosis clinic
Dysmorphology clinic	Neuroimmunology clinic
Ehlers-Danlos clinic	Neurometabolic diseases clinic
Endocrinological rare growth disorders clinic	Neuromuscular diseases clinic
Epidermolysis bullosa clinic	Oncogenetics clinic
Fabry disease clinic	Ondine syndrome clinic
Facial anomalies clinic	Osteogenesis imperfecta clinic
Familial mediterranean fever clinic	Osteopetrosis clinic
Fibromuscular dysplasia clinic	Paediatric primary immunodeficiency clinic
Gaucher disease clinic	Paraneoplastic neurologic syndromes clinic
Genetic counselling clinic	Pediatric haematology clinic
Genetic red cells diseases clinic	Pediatric hepatology clinic
Hemoglobinopathies clinic	

Pediatric oncohaematology clinic  
Peroxisomal diseases clinic  
Phenylketonuria clinic  
Phosphocalcic metabolism diseases clinic  
Poliomyelitis clinic  
Porphyria clinic  
Prader-Willi clinic  
Premature menopause clinic  
Pseudomyxoma peritonei clinic  
Pseudoxanthoma elasticum clinic  
Pulmonary hypertension clinic  
Rare adrenal diseases clinic  
Rare bone tumors clinic  
Rare bullous autoimmune diseases clinic  
Rare central nervous system and retinal vascular diseases clinic  
Rare diseases of the skin clinic  
Rare epilepsies clinic  
Rare genetic neurological diseases clinic  
Rare intestinal diseases clinic  
Rare paediatric cancer clinic  
Rare paediatric neurological diseases clinic  
Rare paediatric rheumatological diseases clinic

Rare paediatric renal diseases clinic  
Rare Parkinsonian syndromes clinic  
Rare pulmonary diseases clinic  
Rare scalp diseases clinic  
Rendu-Osler syndrome clinic  
Retinitis pigmentosa clinic  
Retinoblastoma clinic  
Scleroderma clinic  
Shwachman-Diamond syndrome clinic  
Sickle cell anemia clinic  
Sjögren syndrome clinic  
Sleep disorders clinic  
Spina Bifida clinic  
Teratology clinic  
Toxic and immune bullous dermatosis clinic  
Tuberous sclerosis clinic  
Turner syndrome clinic  
Vascular liver diseases clinic  
Vascular medicine clinic  
Vasculitis clinic  
Von Hippel-Lindau disease clinic  
Wilson disease clinic