Overview of current Centres of Reference on rare diseases

in the EU

Report from
an expert group
of the Rare Diseases Task Force

To

The High Level Group
on Health Services and Medical Care

September 2005

EXECUTIVE SUMMARY

ESTABLISHMENT OF THE EXPERT GROUP

In the course of their work on European Centres of Reference (ECR), the High Level Working Group on ECR has decided to seek advice from an expert group on Centres of Reference on certain specific issues. The expert group was expected to provide 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 ECR work will first focus on the field of rare diseases which obviously needs an EU approach. Therefore, at its meeting on 16 June 2005 the Working Group on ECR decided to mandate the SANCO Rare Diseases Task Force (RDTF) as the expert group for the experimental phase of this process. However, the experience gained in this experimental phase may also be applied in the future to other areas beyond rare diseases

The expert group met twice: on 3 June and 12 September 2005. It included most of the members of the Rare Disease Task Force as well as other opinion leaders in the field and a number of national representatives of the High Level Group and representatives of the European Commission.

TERMS OF REFERENCE

The expert group was asked to adhere to the Terms of Reference agreed by the High Level Group (HLG/COR/2005/5/REV 1).

RESULTS

Six European countries have officially adopted the concept of centres of reference for rare diseases: Sweden, UK, Denmark, Belgium, France and Italy, among the MS which have participated in this mapping exercise (we had no information from The Netherlands and Greece, and from the new MS).

The Orphanet database of rare diseases currently lists 88 types of outpatient expert clinics dedicated to rare diseases covering 1472 clinics.

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

The definition of what constitutes a rare disease varies between countries with official centres of reference, although there is a well defined prevalence in Europe qualifying a disease as rare.

The number of centres per country is quite different from one country to another and not proportionate to the size of the population reflecting differences in the organisation of the health care system.

Among the countries analysed so far, three countries have a national approach to the concept (UK, Belgium, and France) whereas others have a more regional approach. Most of the countries have not yet started to identify their expert centres.

Currently, three MS (France, Germany and Spain) have national programmes dedicated specifically to funding research networks in the field of rare diseases.

DG Research (FP5 and FP6 programmes) supports several networks in the field of rare diseases. DG Sanco funds European information networks. As with the national networks, they are dedicated to research activities but many of them are also based in major clinical centres which can be considered as potential reference centres.

PROPOSAL FOR TECHNICAL AND SCIENTIFIC ASPECTS OF THE ROLE OF ECR ON RARE DISEASES

The Expert Group agrees that the concept of ECR is a good one which will benefit patients and health professionals alike.

There is a need for a systematic identification of the expert centres which could qualify as ERC. These are the centres providing a service which is of indisputably higher quality than a regular teaching hospital clinic in the specialty, either because the technical platform is unique, or the organisation multidisciplinary and the expertise of the clinicians of international stature.

The estimated number of potential ECR is around **800 centres of reference in the field of rare diseases necessary to serve a population of 450 million Europeans.** It is very important not to restrict overly the number of Centres of Reference (CR) to avoid pushing the patients to consult abroad when this is unnecessary. In view of this high number of potential centres of reference, there is enormous scope for networking these centres and rationalising the provision of some highly specialised services such as molecular diagnosis. They could share case management systems, establish common repository of cases, establish a unique portal to access expert advice and share the diversity of their expertise. The following criteria should be applied for selection of reference centres:

- appropriate capacities to diagnose, to do follow-up and manage patients with evidence of good outcomes when applicable
- attractiveness measured through the volume of activity which needs to be significantly larger than anticipated from the prevalence of the diseases and the catchment area, the catchment area being the loco-regional area normally served by the hosting hospital for non-rare diseases; or national coverage
- capacity to provide expert advice on diagnosis and management
- capacity to produce and adhere to good practice guidelines and to implement outcome measures and quality control
- demonstration of a multi-disciplinary approach
- high level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities
- strong contribution to research
- close links and collaboration with other expert centres at national and international level and capacity to network

- close links and collaboration with patients associations where they exist

Even if the criteria qualifying a centre of reference are delineated, their application to specific situations requires significant expertise and knowledge of the current international situation. It is suggested that an ad hoc committee is set up for the designation as ECR of existing centres meeting these criteria. This ad hoc committee should be composed of top experts from relevant specialties in medicine, of patients representatives, and of representatives of MS health authorities.

RECOMMENDATIONS

To achieve the goals defined in the introduction, this expert group recommends:

- that MS use the EU definition of rare disease which is any disease with a prevalence less or equal to 1 in 2,000 in the European population
- the adoption of a list of specifications that ECRs should adhere to
- that MS contribute to the establishment of lists of expert centres and facilitate access to CR and reference networks where they exist
- that the criteria for qualification of centres as ECR are applied to expert centres and networks in priority areas to be defined
- that progress in Europe is regularly assessed
- that funding is provided or continued in the following areas:

Mapping of existing expert centres to contribute to the empowerment of consumers. This could build upon projects already in place.

Networking of expert centres. Funding should be targeted at supporting the coordination activities.

Development and management of shared case management systems and expert systems (telemedicine, on-line diagnosis, shared repository of cases, meeting of experts).

Designation of ECR through a formal process involving European experts, patients representatives and national health authorities. This has to be set up on a step by step basis, after a priority list of groups of diseases has been established and the mapping of expert centres completed.

Dissemination of information on ECR and Reference networks in all MS to all possible types of media so as to reach all stakeholders

OVERVIEW OF CURRENT CENTRES OF REFERENCE ON RARE DISEASES IN THE EU

1- ESTABLISHMENT OF THE EXPERT GROUP

In the course of their work on European Centres of Reference (ECR), the High Level Working Group on ECR has decided to seek advice from an expert group on Centres of Reference on certain specific issues. The expert group was expected to provide 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 is first focussing on the field of rare diseases which is an area where there is a large consensus on the benefits of a cross-border/EU-level approach and added value. Therefore, at its meeting on 16 June 2005 the Working Group on ECR decided to mandate the SANCO Rare Diseases Task Force (RDTF) as the expert group for the experimental phase of this process. However, the experience gained in this experimental phase can also be applied to other areas beyond rare diseases in the future. The expert group was asked to adhere to the Terms of Reference agreed by the High Level Group (HLG/COR/2005/REV 1).

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 currently has 36 members comprising 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, in recognition of 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 Reference centres would be derived form 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: on 3 June and 12 September 2005. The list of participants of the working group is attached as Annex 1.

2- OBJECTIVES OF THE EXERCICE

2.1 To establish the need for European Centres of reference on rare diseases

Respecting the principle of subsidiarity, and the responsibility of Member States for the organisation and management of their healthcare systems, European centres of reference could bring a concrete added value for citizens, through cooperation between Member States.

European centres of reference could:

- improve access for EU citizens to treatment requiring a particular concentration/pooling of resources (structures, equipment, financial, knowledge) or expertise and to offer patients the highest possible quality of care;
- help to maximise a cost effective use of resources by concentrating them where appropriate;
- help to share knowledge
- act as benchmarks to help develop and spread best practice throughout Europe
- help small countries with an insufficient number of patients to provide a full range of highly specialised services of the highest quality.

More broadly, European centres of reference can help to foster research activities and to keep Europe at the forefront of medical developments, to facilitate medical education and training, and can help to foster a sense of common European citizenship and solidarity.

Centres of reference should provide equal access for all citizens, regardless of their country of origin and personal resources, in accordance with the principles of equity, universality of access and solidarity.

2.2 To define the concept of ECR for rare diseases

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

The European added-value of sharing expertise and resources at European level is especially well established for this group of diseases. In addition, thanks to the support of both DG Sanco and DG Research, good information systems have been developed and cooperation between expert centres has been encouraged. The Rare Diseases Task Force is already acting to promote the optimal prevention, diagnosis and treatment of rare diseases in Europe, in recognition of the unique added value to be gained for rare diseases through European co-ordination.

At its June meeting, the expert group re-affirmed its commitment to a number of principles:

- avoid “hierarchy” between national (or regional) and European centres
- favour networking of expert centres rather than isolated ECRs
- favour travel of the expertise (professionals, samples, information) as opposed to patients travelling

- support the possibility of 'patients moving to doctors' if necessary

The expert group also considered that the experience gained with ECR for rare diseases will be transposable to other fields in medicine in the future.

3- MATERIAL AND METHODS

The expert group had at its disposal four sets of information:

- Information on "official" reference centres in European countries where a procedure to designate them is already in place. The data were reviewed during the first meeting of the expert group on 3 June 05.

- Information on "specialised clinics" for rare diseases in European countries participating in the Orphanet project (www.orpha.net). The data were reviewed during the second meeting of the expert group on 12 September 05.

- Information on existing national funded networks of professionals in the field of rare diseases from countries where there are calls for proposals in that field. These networks are considered as national Reference networks of expert centres.

- Information on European networks in the field of rare diseases funded either by DG research or by DG Sanco. These networks are considered as European Reference networks of expert centres.

3.1 "Official" reference centres in European countries

Only six European countries have officially adopted the concept of centres of reference for rare diseases: Sweden, UK, Denmark, Belgium, France and Italy, among the MS which have participated in this mapping exercise (we had no information from Greece, and from the new MS). The Swiss cantons are working on an "intercantonal" coordination of highly specialised health services. The agreement is in consultation in the cantons for ratification.

3.1.1 Sweden

Sweden uses as a definition of rare diseases 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. The ministry is currently considering re-centralising some specialised services, though this is quite a political issue and still under discussion.

3.1.2 UK

Within the national health system, a separate system exists for providing funding to 71 specialised centres of reference for diagnoses or procedures of particular conditions, since

1990. The definition of rare is much rarer than for the EU definition of rare diseases: 2 per 100,000 or lower, which covers 18 diseases or groups of conditions, diagnoses or procedures (mostly genetic diseases of children). This system has been running for over 15 years, so has also had a chance to review what happens when centres are designated. The centres are reviewed constantly and there has been a strong emphasis on defining patient outcome measures, and publishing these data. Some measures are straightforward (survival rates), but some have been much more difficult to define (e.g. diagnoses). In the latter case, some centres have monitored time to produce a diagnosis and 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.
The list of centres is given in Annex 2.

3.1.3 Denmark

Within the national health system, Denmark has a system of designation of referral centres/ highly specialised centres for a number of different conditions, diseases or procedures, in the form of a catalogue from the National Board of Health made in dialogue with the local health authorities and the medical expertise. The general criteria for establishing such referral centres are rareness, complexity, multidisciplinarity and costly diagnosis and treatment. This catalogue is revised regularly. The catalogue as a whole contains lists of about 300 – 400 different conditions from groups of diseases as a whole to a single specific disease or procedure. About 100 different referral departments are located in one of the five university hospitals. In its present form this system has functioned for more than 10 years. 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 if there is room for more than one centre. The designated departments are obliged 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 National Board of Health launched a special report in 2001 regarding rare diseases recommending that Denmark established two centres at 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 encounter reluctance to be referred to the specialised centres (possible reasons include financial implications or 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 question arises of what the correct balance between specialist and local centres should be.

3.1.4 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. Among these centres, three groups at least deal with rare diseases : Creutzfeld-Jacob, neuromuscular diseases and metabolic diseases. Moreover, the Belgian regulation mentions centres for genetic diseases which also manage rare diseases (See Annex 3).

3.1.5 France

France launched its National Plan for Rare Disease in November 2004, running from 2005-2008. The Plan includes specific provision for care management of rare diseases. This was intended to overcome the somewhat unstructured care situation which existed up until then. Criteria for national centres of reference are focused on their provision of expertise, not the provision of direct care as such. The first call for proposals in 2004 for designation of centres of reference was addressed only to university/teaching hospitals. Thirty-four such centres were designated in the first call, of which 20 are in Paris. Each centre is designated for five years with a mid-term evaluation after three years and at the end of five years. A specific budget was attributed to the 34 centres in the first call and a similar amount will be available for the annual calls planned until 2007. One problem is to implement clinical pathways between these designated centres of reference and other health services. In future calls, there will be a focus on trying to increase geographical coverage to 5-7 areas. The list of centres is given as Annex 4.

3.1.6 Italy

In 1998 the Italian Government approved the National Health Plan in which rare diseases were indicated as a priority in public health. In 2001 the Italian Government approved legislation that established the Italian National Network for Rare Diseases to tackle the problem of prevention, surveillance, diagnosis and treatment of rare disease. It listed about 500 rare diseases for which patients have diagnosis and treatment completely free of charge. Since 2001 228 regional centres have been established by official regional decisions following the governmental regulation on rare disease. The criteria used by the 21 Regions to identify centres were not homogeneous and each region has adopted a different model for the organisation of the regional network. In each Region a Coordination Centre has been (or should have been) created in order to coordinate the initiatives of regional centres. An agreement between the Ministry of Health, Istituto Superiore di Sanità (ISS) and the Regions has been established in order to co-ordinate and harmonise the regional network activities In addition, the ISS has to manage the national register of rare diseases, which receives the epidemiological data from regional centres. The same national committee, established within the agreement between Italian government and regions is currently reviewing the list of conditions which will have free diagnosis and treatment.

3.1.6 Finland

Finland has established a list of procedures that should be done in centres of reference (like neonatal cardiac surgery or bone marrow transplantation) rather than a list of rare diseases. Five university hospitals act as reference centres and are accepted as such by the Finnish medical community.

3.1.7 The Netherlands

The Netherlands are not familiar with the term centre of reference nor labelling. However, some specific medical interventions, or the treatment of specific diseases are concentrated in a few centres.

Special medical services Act, Wet Bijzondere Medische Verrichtingen: By means of the WBMV, special medical services are designated and licence required. In general, the services designated are concentrated in a limited number of hospital (om het iets meer te specificeren) centres. The number depends on the frequency of the treatment. Services that require a licence are either highly complex (organ transplantation), highly rare (children's heart rhythm interventions) or are regulated because of ethical considerations (IVF).

3.2 Specialised clinics in Orphanet

Orphanet is a database of rare diseases available on the Internet at www.orpha.net. Its aim is to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases. It is accessed daily by more than 10,000 users.

Orphanet includes a rare disease encyclopaedia, which is expert-authored and peer-reviewed, and a directory of services. The Orphanet Directory of services provides information on specialised clinics including reference centres, clinical laboratories, research projects, registries, clinical trials and support groups in connection with rare diseases. The data collection is performed by local teams and validated at the country level with standard operating procedures which are common to all national teams.

The initial data collection is still in progress in most participating countries as it has only started recently. The participating countries are: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Romania, Spain, Switzerland and United Kingdom.

Orphanet was established in 1997 by the French Ministry of Health (Direction Générale de la Santé) and the INSERM (Institut National de la Santé et de la Recherche Médicale). Both agencies are still funding the core project. The European Commission funds the encyclopaedia and the collection of data on specialised clinics, clinical laboratories and support groups in European countries (since 2000 DG Public Health and Consumer Protection grants No S12.305098; S12.324970; SPC.2002269-2003220 (www.orpha.net) and since 2004 DG Research grant No LSSM-CT-2004-503246 (www.orphanplatform.org) funds the data collection on research projects, clinical trials, registries and research networks).

The types of clinics which are collected for the directory of services are established in consultation with the experts sitting on the scientific advisory committee of Orphanet.

Outpatient clinics mentioned in Orphanet have to deliver a service with a quality that is indisputably higher than a standard hospital service in the relevant speciality. By definition all the reference centres qualify for inclusion in Orphanet.

Candidate clinics are identified by asking the experts in each country about potential candidates and by using all relevant documents. Applicants have to complete a questionnaire (see Annex 6) in order to document the following items:

- total number of patients they have seen at that clinic with the specific disease in question and total number of new patients seen during the last year. This is to judge whether the activity is larger than expected for a teaching hospital clinic, knowing the prevalence of the disease and the normal catchment area.
- Technical platforms at their disposal and type of organisation, especially multidisciplinary as this is necessary for most rare diseases.
- Publications, grants and commitments in the field of rare diseases, especially with regard to patients organisations.

When completed, the application is reviewed by the scientific advisory committee member of the specialty to validate the information and decide on the inclusion in the database. Consistency within countries and between countries is reviewed weekly. The information is updated once a year.

Currently, 88 types of outpatient clinic covering 1472 clinics are listed.

3.3 National Reference networks

Currently, four MS (France, Germany, Italy and Spain) have national programmes dedicated specifically to funding research in the field of rare diseases. There are similarities as well as differences between the four programmes, but their common goal is to enhance networking among scientists and to pool knowledge and resources in co-operative networks. The German, Italian and the Spanish programmes aim to form large-scale interdisciplinary research networks which comprise basic science and clinical science to the profit of both groups of researchers and the patients. The main activity within the French programme is to promote new disease orientated research networks and research projects, the scale of the networks being smaller than the German networks. Although these networks were designed for research purpose, they generally include the best expert clinical centres in the field (see Annex 7).

3.4 European Reference networks

DG Research (FP5 and FP6 programmes) supports several networks in the field of rare diseases. As with the national networks, they are dedicated to research activities but many of them are also based in major clinical centres which can be considered as potential reference centres.

DG Sanco tackled rare diseases in a precursor programme until 2002 which financed several networks. RD are still a priority in the EU Public Health Programme 2003-2008 and the areas where funding is provided include information exchange through existing European information networks and co-ordination at EU level to encourage trans-national cooperation.

The list of networks currently supported by either DG Research or DG Sanco is in Annex 8. Some of them have developed interesting case management systems leading to improved diagnosis and management of patients.

4- RESULTS OF THE MAPPING EXERCICE

4.1 Mapping exercise of the Centres of Reference

4.1.1 National definitions of Centres of Reference

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

The definition of what is a rare disease varies between countries with official centres of reference, although there is a well defined prevalence in Europe qualifying a disease as rare. The UK uses 1 in 50,000, Sweden and Denmark use 1 in 10,000 whereas France and Italy use the European orphan drugs regulation definition of 1 in 5,000. (see Annex 9)

4.1.2 Number and geographical distribution of Centres of Reference

The number and geographical distribution of centres per country is quite different from one country to another and not proportionate to the size of the population (see size of population in MS in Annex 10), reflecting differences in the organisation of the health care system.

Among the large countries, although there is some consistency between the UK and the French approach even though the disease prevalence used as the cut-off is different, Italy attributes the label of regional reference centre to over 200 clinics. There is no attempt to distribute the centres in either UK or France on a geographical basis (most of the centres are in London and in Paris), while in Italy there has been an attempt to distribute the centres throughout the country to cover all regions.

Among the medium size countries, the approaches by Sweden and Denmark are close but different from the approach by large countries: Sweden currently has 75 centres for 8.9 million people while Denmark has about 100 centres for 5.4 million people. Sweden is currently considering reducing this number.

Among the countries analysed so far, three countries have a national approach to the concept (UK, Belgium and France) whereas others have a more regional approach. Most of the countries have not yet started to identify their expert centres.

4.1.3 Different forms of Centres of Reference

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 do specialised diagnoses, treatment and monitoring and organise the overall planning of treatment, with daily care being provided locally. In Italy, the regional centres were established to be the points for diagnosis and treatments. In UK and France, reference centres are mainly centres of multidisciplinary expertise able to provide a service which is not delivered elsewhere with the same quality and which attract patients from all over the country. In addition France has a strong emphasis on clinical research, with centres expected to produce best practice guidelines and provide expert opinion in preference to patients travelling to the clinic.

4.1.4 Areas covered (including pathologies, technologies and techniques)

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. In Italy, the UK and France the centres are very specialised in one or a very small number of diseases (see Annex 2 and 4). France has a prospective plan for up to 100 centres with a balance between medical areas (see Annex 4). 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 are technology-oriented and provide a highly specialised service, mainly through surgery and transplantation (Annex 11). In Denmark, the number of conditions which are covered the centres is larger than in France or UK, and, in practice the two centres dedicated to rare diseases accept referrals of patients with any type of rare diseases.

4.1.5 Process of identification or selection and designation of Centres of Reference on rare diseases in the Member States.

In the UK the centres have to 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 call for proposals which is competitive. The applications are reviewed by an advisory committee (Comité National Consultative de Labellisation des centres de reference de maladies rares CNCL) composed of experts, patients' representatives, members of learned societies and of relevant 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 been agreed upon yet. 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 soon.

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

4.2 Mapping exercise of the specialised clinics identified by Orphanet

4.2.1 National definitions of specialised clinics in Orphanet

The selection of specialised clinics which are listed in the Orphanet directory of services is based on quality indicators which include national notoriety, high volume of relevant

activity, appropriate capacity to manage patients, high level of expertise, and international collaborations. The eligibility criteria are the same in all participating countries.

4.2.2 Numbers and geographical distribution of specialised clinics in Orphanet

There are currently 1472 specialised clinics in Orphanet, classified in 88 categories. These categories were agreed on by the partners, based on an analysis of the notifications of clinical activities by the experts and for consistency between countries. These categories reflect the type of patient needs as well as the available expertise in Europe. The number of categories is expanded every time a new type of specialised clinic is notified to the database after verification that the concept applies to most other countries as well.

The distribution of these clinics within European countries is shown in Annex 12. The data collection is still on-going. Therefore the numbers reflect the number of clinics already identified, not the total number of existing specialised clinics.

4.2.3 Forms of specialised clinics in Orphanet

The list of types of specialised clinics is given in Annex 13, classified by main medical specialty domain, although this is somewhat artificial as many diseases require multidisciplinary management.

Most of these clinics provide care for both children and adults. Only 12 types of clinics are strictly dedicated to children.

Half of the types of clinics (44/88) are specialised in just one disease +/- related diseases while the others are open to a wide range of conditions. The number of diseases per type of clinic is displayed in Annex 14.

4.2.4 Process of identification and selection of specialised clinics in Orphanet

The identification of candidate clinics is done by the Orphanet team in each country. It is an ongoing proactive process. Clinicians can also apply by filling in a questionnaire which is available on the Orphanet website. The selection is done by the Orphanet team on the basis of the information provided in the questionnaire. The list of selected clinics is submitted to the scientific advisory board of the country for approval.

4.3 Mapping exercise of the reference networks of expert centres

The national and European information or research networks which are currently funded are covering rare diseases where centres of reference do exist. They reflect the necessity of sharing data and joining forces to make progresses in research and develop high quality information.

5- PROPOSAL FOR TECHNICAL AND SCIENTIFIC ASPECTS OF THE ROLE OF ECR ON RARE DISEASES

5.1 Role of the European Centres of Reference on rare diseases

5.1.1 Role of CR at national level

The first step is to question the role of CR at national level, as it is at that level that they start developing. In fact the perspective is very different depending on the size of the population of the country. In Europe, among the current member states we have four groups of countries with respect to the size of the population:

- The large ones: Germany, France, UK, Italy, Spain, Poland
- The medium ones: Netherlands, Greece, Belgium, Portugal, Czech republic, Hungary, Sweden, Austria
- The small ones: Denmark, Slovakia, Finland, Ireland, Lithuania, Latvia, Slovenia, Estonia
- The very small ones: Luxembourg, Cyprus, Malta

Only the large countries have enough professionals to be able to identify at least one clinic for each rare disease or group of rare diseases if their prevalence is larger than 1 in 100,000. For the rarest diseases, even in large countries, it is unlikely that there will be one national expert for each category. For these large countries, it makes sense to try to organise the available resources in order to maximise the benefit for the patients and to contribute significantly to research. However only 2 of the 6 large countries (France and UK) have adopted such a policy. The current regional Italian CR are heterogeneous. Germany has no formal process to identify expert centres at the national level, mainly because health care provision is organised at the regional (Bundeslaender) level. The only official support is to ten research networks currently funded by the federal government which include expert clinics. Spain has some non-officially labelled reference centres, well recognised at national and international level. As in Germany, 12 large research networks are financially supported in the field of rare diseases, including over 100 teams, many of them being clinical. These countries would be in favour of wider European collaboration as no one country has all the necessary expertise to serve all patients with rare diseases.

Medium size countries are in a position to have quite a few CR but also need to refer patients abroad when the expertise is not available at the national level. They are potentially interested in knowing where reliable clinics in other close countries are located and/or where language links exist.

Small and very small countries are likely to have very few potential reference centres and to have a strong need to refer patients to expert centres abroad. For these countries a comprehensive mapping of the expert centres in Europe would help enormously. It is also unlikely that they will have a national procedure for selecting the CR. It is here that the Community added value could be greatest.

5.1.2 Role of Centres of Reference at EU level

Centres of reference should tackle rare diseases or other conditions requiring specialised care and volumes of activity, serving also as research and knowledge Centres, which

update and contribute to the latest scientific results and treat patients from other Member States. They also reflect the need for services and expertise to be appropriately distributed and constantly improved across the enlarged European Union. In fact what is needed is a systematic identification of the expert centres providing a service which is of indisputably higher quality than a regular teaching hospital clinic in the specialty, either because the technical platform is unique, or the organisation multidisciplinary and the expertise of the clinicians of international stature.

This definition matches what Orphanet has been collecting since 2001 as well as the official centres of reference in UK and France and some of the Swedish centres. Of course not all the specialised clinics listed by Orphanet can be considered as potential reference centres.

The proportion of them which could qualify is probably around 17% (45/261) of the Italian specialised clinics and 10% of the French ones (100/941), the only two countries which have data on their specialised clinics and have done a estimate of how many of them could qualify as CR (Orphanet survey, unpublished).

This gives an estimate for Europe of around **800 centres of reference in the field of rare diseases necessary to serve a population of 450 million Europeans**. These centres would be the ones qualifying to be attended by patients from other regions on the basis of the quality of delivered services. It is very important not to restrict overly the number of CR to avoid pushing the patients to consult abroad when this is unnecessary. By not selecting one unique centre for Europe for each disease or each group of diseases, this is avoided.

5.1.3 Role of networks at EU level

In view of the high number of potential centres of reference, there is enormous scope for networking these centres and rationalising the provision of some highly specialised services such as molecular diagnosis. They could share case management systems, establish common repository of cases, establish a unique portal to access expert advice and share the diversity of their expertise. One of the areas where this networking approach is particularly relevant is the provision of services from childhood to adulthood. While some centres have the expertise and experience for serving patients from any age, most centres are either paediatric or adult centres. Therefore they need to work together to ensure continuity of care and transfer of experience.

5.2 Areas to be covered by the Centres of Reference on rare diseases

Agreement at European level on the pathologies, technologies and techniques to be covered by ECR is needed, drawing on national experiences and existing lists, especially as many MS do not currently have any centres of reference at all, although they have expert clinics.

On the basis of the sets of data already available, i.e. the list of Reference Centres in some member states, the list of specialised clinics from the Orphanet database, the list of networks of expert centres, a proposal for a list of main groups of pathologies (priority rare diseases or priority groups of rare diseases based on the possibility and existence of diagnosis and treatment), technologies and techniques to be covered by ECR on rare diseases is given in Annex 15. This proposal has to be further validated and diseases prioritised within the list.

The following indicators can be used for prioritisation of diseases:

- diagnosis (when the diagnosis is difficult and is necessary for informing clinical management, to prevent complications and to set up treatment). In addition diagnosis of genetic diseases is a necessary step to accurately inform families about the risk to each of its members of being affected by the disease or being a carrier of the risk.
- Therapeutics and management (when treatment requires expertise and specialised interventions). Examples of rare diseases treated with a costly drug is given in Annex 16.
- Outcome (when patients are at high risk of developing severe complications or disability which are preventable)

There is no reason to further prioritise as the main goal is to provide information to patients and health professionals about where consultations exist if there are no specialised clinics in their own region.

5.3 Criteria which should be fulfilled by the Centres of Reference on rare diseases

5.3.1 Criteria for selecting the ECR and Reference Networks of expert centres

The following criteria have to be applied for selection of reference centres:

- appropriate capacities to diagnose, to do follow-up and manage patients with evidence of good outcomes when applicable
- attractiveness measured through the volume of activity which needs to be significantly larger than anticipated from the prevalence of the diseases and the catchment area, the catchment area being the loco-regional area normally served by the hosting hospital for non-rare diseases; or national coverage
- capacity to provide expert advice on diagnosis and care
- capacity to produce and adhere to good practice guidelines and to implement outcome measures and quality control
- demonstration of a multi-disciplinary approach
- high level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities
- strong contribution to research
- close links and collaboration with other expert centres at national and international level and capacity to network
- close links and collaboration with patients associations where they exist

Whilst all these criteria should be applied to qualify a centre or a network, their comparative relevance depends on the disease or group of diseases covered

5.3.2 Peer review system

Even if the criteria for designation of a centre of reference are delineated, their application to specific situations requires significant expertise and knowledge of the current international situation. It is suggested that a committee is set up for the designation as ECR

of existing centres meeting these criteria. This committee should include top experts from relevant specialties in medicine, patients representatives, and representatives of MS health authorities, health insurance companies, and of the EC. The committee could also have a role in ensuring continuing compliance with the criteria once the centre has been designated. A review after three or five years could be envisaged, for example.

6- RECOMMENDATIONS

To achieve the goals defined in the introduction, this expert group recommends:

- that MS use the EU definition of rare disease which is any disease with a prevalence less or equal to 1 in 2,000
- the adoption of a list of specifications that ECRs should adhere to
- that MS contribute to the establishment of lists of expert centres and facilitate access to CR and reference networks where they exist
- that the criteria for designation of centres as ERC are applied to expert centres and networks in priority areas to be defined
- that progress in Europe is regularly assessed
- that funding is provided or continued in the following areas:
  - **Mapping** of existing expert centres to contribute to the empowerment of consumers. This should build upon projects already in place.
  - N**etworking** of expert centres. Funding should be targeted at supporting the coordination activities.
  - **Development and management of shared case management systems** and expert systems (telemedicine, on-line diagnosis, shared repository of cases, meeting of experts).
  - **Designation** of ERC through a formal process involving European experts, patients representatives and national health authorities. This has to be set up on a step by step basis, after a priority list of groups of diseases has been established and the mapping of expert centres completed.
  - **Dissemination of information** on ERC and Reference networks in all MS to all possible types of media so as to reach all stakeholders