

**Report of the Rare Diseases Task Force
Working Group on Standards of Care
Expert Group Meeting on European Centres of Reference for Rare Diseases**

**Friday 3 June, 2005
Orphanet, Hôpital Broussais, 96 bis, rue Didot, 75014 PARIS**

Participants :

A detailed list of participants and apologies for absence is attached in Annexe 1

Presentation of the EC DG SANCO High Level Group on Health Services and Medical Care Working Party on Centres of Reference. Expectations from the Working Group on Centres of Reference for Rare Diseases

- ***Aude Marlier Sutter, French Ministry of Health, representing the High Level Group on Health Services and Medical Care***

The High Level Group on Health Services and Medical Care was established by the European Commission as a means of taking forward the recommendations made by the European Union patient mobility reflection process.

The High Level Group has moved the reflection process forward through working groups involving interested Member States on particular topics, with regular reporting of their work to the full High Level Group. One of the working groups, chaired by the French Ministry of Health, is focussing on European Centres of Reference (ECRs). Fifteen countries were initially involved in this working group: Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Malta, Poland, Slovenia, Slovakia and Sweden. The UK has since become associated with this group and the list of countries remains open.

The Working Group has met four times since its creation in 2004. In order to assess the views of the Member States on the concept of ECRs, a questionnaire was proposed by France, and adopted by the working group and the Commission. The questionnaire was sent to the 25 Member States and a synthesis document of answers was produced in October 2004.

The questions included:

- What would be the added value, at European level, of the concept of European Centres of Reference?
- Which criteria and definition should be used in order to identify European Centres of Reference?
- What should be the process for selection of Centres of Reference at European level?
- What should be the rules of referral for patients to a European Centre of Reference?
- How to ensure the dissemination of information on the centres of reference for citizens and the professionals? (website, database...)
- Which legal basis / instrument at EU level would you suggest in order to set up of European Centres of reference?

The Working Group decided to further discuss the issues raised by these questions and the answers received from Member States and made a decision to ask an expert group,

nominated by the Rare Diseases Task Force for clarification on some of the more scientific or technical questions.

The field of rare diseases was chosen as a model in which to test a number of pilot projects in the area.

Nick Fahy, DG SANCO, European Commission

The European Commission confirmed that issues relating to the legal framework and resources for European Centres of Reference would be addressed by the working group of the High Level Group; this expert group should assume that these issues would be appropriately resolved and focus on technical advice.

The Expert Group on ECRs for Rare Diseases is being asked to provide advice on criteria for selection and evaluation of designated European Centres of Reference. A call for proposals for pilot projects will be launched at the beginning of 2006 to see which models work in practice.

Presentation of the EC DG SANCO Rare Diseases Task Force and the Task Force Working Group on Standards of Care

• ***Ségolène Aymé, Orphanet, France and Leader of the Rare Diseases Task Force (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 disease. The deputy leader is Helen Dolk, director of the Eurocat programme on congenital disorders.

The RDTF currently has 36 members comprising current and former project leaders of European research projects related to rare diseases, member state experts and representatives from relevant international organisations.

The aims of the RDTF are to advise and assist the European Commission Public Health Directorate in promoting the optimal prevention and treatment of rare diseases in Europe, in recognition of the unique added value to be gained for rare diseases through European co-ordination. The specific objectives are:

- to widen access to high quality information on causes, diagnosis, screening methods, counselling and treatment for rare diseases
- - to promote the availability of high quality comparable epidemiological data across Europe regarding incidence, prevalence, survival and inequalities within and between countries
- to promote the creation of networks of excellence in relation to diagnosis and treatment
- - to promote the development of a classification and coding system for rare diseases to supplement the International Classification of Diseases
- - to promote effective surveillance, early warning and cluster response in relation to changing risk factors for rare diseases
- - to facilitate the consideration of different models of cross-border health care and health care funding
- - to promote the exchange of ideas and information regarding quality of life issues, and patient preferences and choice

In addition, the Task Force has a number of tasks in relation to the Public Health Directorate structures and processes:

- to communicate with the Network of Competent Authorities and Working Party on Morbidity and Mortality on all of the above
- to ensure that rare diseases are represented appropriately among Public Health indicators and linked into the European Public Health portal
- to assist the Commission in considering Rare Disease priorities for the annual work plans
- to help prepare the European Rare Diseases Conference in Luxembourg in 2005
- to consider the sustainability and long term funding of projects initiated under the Public Health programme
- to liaise with the Research Directorate concerning research priorities

- **Presentations from countries in Europe with existing centres of reference for rare diseases**

France: represented by Alexandra Fourcade, Ministry of Health

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 2005 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 budget of 10 million euros 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 7-9 regions.

Italy: represented by Domenica Taruscio, Istituto Superiore di Sanità, Rome

Italy has a national network for rare diseases established by governmental decision in 2001, in order to tackle the problems of prevention, surveillance, diagnosis and treatment rare diseases covering around 500 conditions. Free treatment for these conditions is only prescribed at designated centres. Rare disease centres are part of the planning of healthcare, and thus of agreements between central state and the regions which are responsible for healthcare provision and which designate centres within each region. However, the criteria used by regions to identify centres are not homogeneous and each region has adopted a different model for the organisation of the regional network. Moreover, although access to a basic level of care is guaranteed by the Italian state everywhere, different regions then add additional levels of care specifically for their region. Inter-regional centres have not yet been identified and the national network is not yet complete. The governmental decision also regulates the epidemiological flow from centres to the national registry of rare diseases, established at the Istituto Superiore di Sanità, to centralise surveillance activities. Finally, an agreement between the Ministry of Health, Istituto Superiore di Sanità and the Regions has been established in order to co-ordinate and harmonise the regional network activities; in particular, the same committee is reviewing a list of new conditions which will have free diagnosis and treatment.

Denmark: represented by Dorthe Lysgaard, Rare Disorders Denmark and Marianne Jespersen, National Board of Health

Denmark has a system of designation of referral centres/ highly specialised centres for a number of different diseases in the form of a catalogue from the National Board of Health made in agreement with the local health authorities and medical experts. The general criterias for establishing referral centres are rarity, complexity demanding special skills and costly diagnosis and treatment. In relation to this system, the National Board of Health launched a special report on rare diseases in 2001 recommending that Denmark established two centres for rare diseases in university hospitals (one west, one east), each covering approximately 100 different diagnoses. Other hospitals make the preliminary diagnosis and ensure follow-up, whilst the centres of reference do the specialised diagnostics, treatment and monitoring, and overall planning of treatment. A key issue is to ensure clear responsibility for overall coordination of treatment. A survey of patient satisfaction in 2003 showed that only 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 again more satisfied with their treatment. However, patients encounter reluctance to be referred to the specialised centres (possible reasons include financial implications, or desires of the 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.

Sweden: represented by Christina Greek Winald, Swedish Centre for Rare Diseases

Sweden uses a definition of rare diseases as those disorders or injuries resulting in extensive disability and affecting less than 100 in 1 million 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.

England: represented by Edmund Jessop, Department of Health

Within the national health system, a separate system exists for providing funding to specialised centres of reference (around fifty) for particular conditions (not necessarily rare diseases), diagnoses or procedures. The definition of rare is much rarer than for the EU definition of rare diseases; 2 per 100,000 or lower, which covers 30 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.

Spain: represented by Manuel Posada, Instituto de Salud Carlos III-, Madrid

After a period of research and development for networks on rare diseases, there are now some projects to establish national centres for rare diseases by 2007 – no system of rare disease provision currently exists. But there is a clear problem of disconnection between research (funded from national level) and clinical practice (which is a regional responsibility), which has hindered linkage between research and provision. Regional governments don't necessarily want central government involved in their healthcare policies.

The Catalanian government has also made a proposal to create a Commission with all rare disease specialists in Catalonia which will make recommendations on the possible creation of centres of reference. However, the problem of whether funding will come from the national or regional level is recurrent.

Discussion based on questionnaire (Annexe 2)

1. What would be the added value, at European level, of the concept of European Centres of Reference for Rare Diseases?

Added value would take the form of providing expertise and cross-border services in order to enable implementation of best practice at national level. There was a general view that European centres of reference should primarily be focused on providing expertise, not treatment, with the aim being to enable treatment to be provided within national systems, where patients can be treated in their own language, closer to home. However, treatment should be a possibility, especially for countries with limited national resources.

Expertise and European/cross-border services provided by the ECRs that would bring added value include:

- expert opinion
- production of guidelines
- individual patient plans/guidance on pathways where care has to be provided in the ECR
- clinical research
- increased knowledge of rare diseases – natural history and epidemiology

2. What defines a European Centre of Reference compared to a national one?

Similar aspects were mentioned as those that have already been discussed by the working group - high quality service reflecting current best practice and scientific advances etc – with national centres then taking that standard and translating it into clinical practice. The level at which making use of an ECR would be appropriate would vary for different countries and conditions (eg: small countries would make use of European centres of reference more readily than larger ones).

The ECRs should be capable of doing things that can't be done at the national level but both national and European centres should be considered as expert. It will be important to avoid hierarchy – an ECR should not be considered as higher than a national centre.

3. What kind of services / tasks should be provided?

Further to the above, services should include diagnostic services, second opinions, clinical research and development of general or individual treatment protocols, as well as actual provision of treatment. There was discussion of having different labels reflecting these different types of services, but in the end agreement was reached that in order to avoid confusion there should be a single label of European centre of reference, but with a description of each centre's services clearly accessible. Service provision needs to remain flexible as the capabilities of the ECRs will develop with experience.

Concerning the production of guidelines, those from national centres are often contextual and difficult to translate – they should not simply become European guidelines just because the centre is designated as an ECR. European guidelines need to be validated at the European level.

On-line diagnosis and tele-medicine should be developed to reduce patient travel. The European Skeletal Dysplasia network funded through DG Research was cited as a good example of this type of service. It was agreed that contact should be made with the EC Working Group on Telemedicine/E-medicine although it was pointed out that they are mainly focussing on technical developments in this area. There was general consensus that, as far as possible, samples should travel, not patients, and that, in addition, ECRs could be funded to send multi-skilled teams of experts around Europe, rather than getting patients to travel.

4. How to prioritise needs? For which categories of diseases should such centres be set up first?

It was agreed to focus on conditions where the involvement of a European centre of reference would make a difference to the course of the disease (diagnosis/survival/quality of life for the patient); centres would have to show how they do that. **Ségolène Aymé** agreed to prepare a list of conditions and groups of conditions on this basis after the meeting, which would be circulated to the expert group for approval. However, such criteria should not be set too precisely, as the expertise of making the diagnosis in the first place may be what is required. Many patients with rare disorders can only be diagnosed clinically because no molecular marker for their disease exists. This type of clinical diagnosis requires highly skilled experts and would benefit from European collaboration. The French list of 18 broad groups of rare diseases, used in the designation of their national centres was considered to be a useful model.

The Commission is looking for a small number of priority areas in which to test the approaches for a European system for centres of reference, on which a first call for projects would be focused.

5. Which criteria should be used to select European Centres of Reference?

It was agreed that the following criteria should be taken into account:

- **rarity of cases** (this could be based on the European definition of rare diseases, but there was not agreement on this – one person felt that this was too focused on pharmaceutical approvals). It was noted that in small countries, common rare diseases are often very rare diseases, and in other areas certain rare diseases are relatively common.

- **volume of cases** (the centre should deal with enough cases from the category of condition concerned to maintain their expertise – but what level this means in practice will have to be a case-by-case judgement);
- producing **protocols or guidelines**;
- whether the centre is part of a **network** (and how it is linked to local care and other centres of reference);
- being engaged in **research**;
- being engaged in **teaching/training**;
- focus on **patients** (involvement of associations, for example)
- **publication** of results and outcome measures (which could be defined by proposers themselves, as appropriate for particular conditions);
- **European added value** (perhaps building on existing networks, of which there are many in the area of rare diseases);

However, in many instances there simply is not a strong enough evidence base to justify direct application of these criteria. On this basis selection should be based on expert judgement of individual cases, using the above criteria as a guide.

6. The concept of Centre of Reference for Rare Diseases already exists at national level in some countries. Should any link exist between the concept of centre of reference at national and European levels? If yes, what about countries without national centres?

The question of whether only expertise that already exists should be labelled or whether expertise should also be built up in other parts of Europe was not completely resolved in the discussions. The general feeling was that there should be both, in which case the above criteria of existing networks would not hold true for all cases. Disparities in access to specialist care within Member States should be a dimension of cohesion which could be addressed by structural funds.

7. What should be the process for selection of Centres of Reference at European level? Should all centres which fulfil the criteria be appointed, or should there be some kind of co-ordination at EU level (for example a selection committee at EU level, a co-decision between the Commission and the Member States...)? Would you agree with the idea of a European "Quality Label" for Centres of Reference?

As it was not possible to set objective criteria which could be strictly evaluated, selection would have to be based on an expert judgement.

8. What should be the rules of referral for patients to a European Centre of Reference? Should doctors be able to refer a patient directly or should there be, at national level, a mechanism for granting authorisations (gatekeeper)?

There was a difference of opinion on whether or not national authorities should first evaluate applications and only forward approved applications – broadly, ministries would like to be able to control the applications process, but other participants did not consider that this would be appropriate and feared that national gatekeeping might hinder research. In any event, it is important to recognise that being considered a European centre would have consequences at a national level that should be taken into account. For example, the designation of an ECR would attract more patients and therefore place more financial burden on national bodies, unless sufficient EC funding is available to cover this. A suggestion was made that a national commission could make a decision at Member State level.

9. Would you support the idea that Centres of Reference could take different forms? (not only as a centre, but also, for example, a network, a specialised department in a centre, a virtual network, a mobile team...)

ECRs could take different forms such as:

- a centre/unit specialised in one specific pathology
- a network of centres geographically separated but developing joint expertise
- a mobile team who could provide care in different places
- a virtual network (telemedicine)

10. How to ensure adequate (additional?) capacities for European Centres of Reference, which at the moment only treat national patients? Should extra funding be granted (for example at EU level)? How do you see the payment / compensation rules between member states when their patients are treated in a centre of reference located in another member state?

There would need to be an element of core infrastructure funding in order to build up relevant structures and networks though some funding would come through providing services. Regarding whether a guarantee of patient flow could replace the need for infrastructure funding, this was considered unrealistic; the number of likely cases could be predicted, but there could be no compulsion to use one particular centre.

The 2007-2013 Public Health and Consumer Protection Programme has provision for 20-30 million euros for all cooperation in health issues. Network activities could be funded from this budget but not infrastructure. Consequently, it seems that there will not be large sums of money available to fund the activities of ECRs. DG Research will have some funds available for research-related activities. The structural funds might also be able to fund investment in centres as part of national priorities for investment in health infrastructure, although this possibility is not yet widely used.

11. For which duration should centres of reference be appointed? How should they be evaluated?

European centres of reference should show added value in comparison to non-specialist care when evaluated, though in practice such evaluations are very difficult to do. On duration of labelling, five years would be appropriate, but with intermediate evaluation. One of the criteria for evaluation should be cost-effectiveness/cost utility. However, European support should not necessarily stop after 5 years; services should be sustainable over the medium term.

12. How to ensure the dissemination of information on the centres of reference for citizens and the professionals? (website, database...)

Dissemination activities could include training and diffusion of information through a website. The Orphanet website already fulfils this role for existing centres.

13. If more than one Centre of Reference is appointed for a specific type of pathology, at EU level, do you consider that a network should be set up, with one of the centres appointed as a co-ordinator of the network?

Where there is more than one centre on a particular area, all centres must be networked.

Next steps

The conclusions of this expert group will be presented to the High Level Group at their

next meeting in Brussels on 16 June 2005. The expert group may be associated with the call for proposals stage at the end of 2005 or early 2006.

ANNEXE 1: List of participants

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ANNEXE 2: Questions to the experts on the concept and implementation of European Centres of Reference

- 1. What would be the added value, at European level, of the concept of European Centres of Reference for Rare Diseases?**
Improve access / Pool resources / Share expertise / spread best practices / provision of services to citizens from small countries
- 2. What defines a European Centre of Reference compared to a national one?**
Services not possible at national level/ Innovative technologies / very expensive equipment / very few experts
- 3. What kind of services / tasks should be provided?**
Expert advice/ Second opinion/ clinical research / diagnosis / care / information / training /
- 4. How to prioritise needs? For which categories of diseases should such centres be set up first?**
Most common rare diseases / very high level of expertise / expensive equipment / expensive treatment / cancer prone diseases / prognosis depending on treatment
- 5. Which criteria should be used to select European Centres of Reference?**
Volumes of activity, and patients from other Member States / track record of research / added value of the organisation and technical platform / national reference centre
- 6. The concept of Centre of Reference for Rare Diseases already exists at national level in some countries? Should there exist any link between the concept of centre of reference at national and European levels? If yes, what about countries without national centres?**
- 7. What should be the process for selection of Centres of Reference at European level ? Should all centres which fulfil the criteria be appointed, or should there be some kind of co-ordination at EU level (for example a selection committee at EU level, a co-decision between the Commission and the Member States...)?
Would you agree with the idea of a European "Quality label" for Centres of Reference?**
- 8. What should be the rules of referral for patients to a European Centre of Reference? Should doctors be able to refer a patient directly or should there be, at national level, a mechanism for granting authorisations (gatekeeper)?**
- 9. Would you support the idea that Centres of Reference could take different forms? (not only as a centre, but also, for example, a network, a specialised department in a centre, a virtual network, a mobile team...)**
- 10. How to ensure adequate (additional?) capacities for European Centres of Reference, which at the moment only treat national patients? Should extra funding be granted (for example at EU level) ? How do you see the payment / compensation rules between member states when their patients are treated in a centre of reference located in another member state ?**
- 11. For which duration should centres of reference be appointed ? How should they be evaluated?**

- 12. How to ensure the dissemination of information on the centres of reference for citizens and professionals? (website, database...)**
- 13. If more than one Centre of Reference is appointed for a specific type of pathology, at EU level, do you consider that a network should be set up, with one of the centres appointed as a co-ordinator of the network ?**