# European Union Committee of Experts on Rare Diseases

# RARE2011 EUROPEAN DAY PROCEEDINGS



# A EUROBIOMED/EUCERD EVENT

# 4 NOVEMBER 2011, MONTPELLIER, FRANCE



20082291

# RARE2011 EUROPEAN DAY – 4 NOVEMBER 2011

# PROGRAMME

**Introduction and Welcome Message** - *Ségolène Aymé - Orphanet - Chair of the EUCERD*

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Co-Chairs: *Ségolène Aymé - Orphanet - Chair of the EUCERD & Andrew Devereau - National Genetic Reference Laboratory (NGRL)*

- Rare diseases in international nomenclatures - *Ségolène Aymé - Orphanet - Chair of the EUCERD*
- Data on rare diseases: which annotations to support R&D? - *Philippe Sanseau – GSK*
- Bioinformatics for rare diseases: Promises and challenges - *Peter Robinson - La Charité – Berlin*
- Roundtable of stakeholders and discussion

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    *Alain Garcia - IGAS – EUCERD*

    *Gábor Pogány - HUFERDIS – EUCERD*

## SESSION 2. PARTNERING TO OPTIMISE THE USE OF PATIENT DATA TO IMPROVE CLINICAL RESEARCH AND HEALTH CARE

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    - France : *Paul Landais - Assistance Publique/Hopitaux de Paris (AP/HP)*
    - Italy: *Paola Facchin - Veneto Region Rare Diseases Registry*

- Spain : *Manual Posada - Spanish registry of rare diseases, Instituto de Investigación de Enfermedades Raras*

- Patient data for the evaluation of the clinical-added value of orphan drugs: Possible mechanisms for collaboration at EU-level - *François Meyer - Haute Autorité de Santé*
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  *Domenica Taruscio - Centro Nazionale Malattie Rare – EUCERD*

  *Manuel Posada - Spanish registry of rare diseases, Instituto de Investigación de Enfermedades Raras*

  *Maria Madison – Shire*

## SESSION 3 : IMPROVING ACCESS TO EXPERTISE AND QUALITY CARE

Co-Chairs: *Helena Kääriäinen - National Institute for Health and Welfare Finland - Vice-Chair of the EUCERD & Odile Kremp – French Ministry of Health, EUCERD*

- Centres of expertise for rare diseases at Member State level: current situation in Europe and recommendations from the EUCERD - *Edmund Jessop - National Commissioning Group, NHS London – EUCERD*
- Networking between expert centres : Where do we stand ? The Cross-Border Health Care Directive and its implications for rare diseases - *Ségolène Aymé - Orphanet - Chair of the EUCERD*
- The testing landscape in Europe: Challenges and solutions - *Gert Matthijs - University Hospitals Leuven – EUCERD*
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  *Wills Hughes-Wilson - Genzyme – EUCERD*

  *Samantha Parker - Orphan Europe – EUCERD*

  *Christel Nourissier - EURORDIS – EUCERD*

## CLOSING REMARKS

# INTRODUCTION

On 4 November 2011, the European Committee of Experts on Rare Diseases (EUCERD www.eucerd.eu) organised, in collaboration with Eurobiomed, the first European day of the French 'Rare2011' conference in Montpellier, France. The day consisted of three sessions highlighting priority topics in the field of rare diseases which call for collaboration at European level: Ensuring Visibility of Rare Diseases in Health Information Systems, Partnering to Optimise the Use of Patient Data to Improve Clinical Research and Healthcare, and Improving Access to Expertise and Quality Care. A wide range of stakeholders including researchers, policy makers, members of the industry and patient representatives were present at this event, of which the proceedings are detailed in this present document.

This event was organised in the context of the EC Joint Action N°2008 22 91 to support the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases.

This document does not represent the official position of the EUCERD. The suggestions contained in this document do not prejudge the form and content of any future proposal by the EUCERD.

This event was also organised by Eurobiomed in the context of Rare2011[1]. Eurobiomed[2] is a non-for-profit organisation which has been accredited by the French government as a "competitiveness cluster". With more than 200 members, Eurobiomed develops and federates a network of healthcare stakeholders in order to boost the development of therapeutics, diagnostic tools, medical device and healthcare services. Rare diseases are one of the priority topics of Eurobiomed.

Eurobiomed federates healthcare stakeholders in both the "Provence-Alpes-Côte d'Azur" and "Languedoc-Roussillon" regions of Southern France. Eurobiomed's role is also to provide business development support, highlight the excellence of academic and industrial healthcare research, and foster the implementation of collaborative R&D projects.

To build on this success, Eurobiomed will organise the event again in 2013, as a reference event in the fight against rare diseases.

www.eurobiomed.org

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[1] http://www.rare2011.com/index_en.php
[2] http://www.eurobiomed.org/

# PROCEEDINGS OF THE DAY

## INTRODUCTION

### *Ségolène AYME (Orphanet and Chair of the EUCERD, Co-Chair of conference)*

We are very pleased to welcome you to the Rare 2011 conference, which is an event that happens every two years in France that is dedicated to rare diseases. For the first time, it has been decided to hold a European session and we thought that it would therefore be a good idea to have a joint event, with a workshop that was already happening and was being organised by the European Union Committee of Experts on Rare Diseases (EUCERD).

## SESSION I: ENSURING VISIBILITY OF RARE DISEASES IN HEALTH INFORMATION SYSTEMS

## Rare Diseases in International Nomenclature

### *Ségolène AYME*

### I.    The Revision of the WHO Classification

It is my pleasure to be able to tell you where we stand on the efforts that we started more than three years ago when we heard that the World Health Organisation (WHO) was starting the revision process for the international classification of diseases. We immediately saw that this was a major opportunity for us to introduce rare diseases into this major international nomenclature. We were lucky to be supported by the European Commission and received funding that allowed us to work on this in depth.

It is essential that rare diseases are part of all the nomenclatures. If they are not, they become totally invisible and many diseases are currently missing from some of the major nomenclatures. The four nomenclatures of the greatest interest are as follows: the International Classification of Diseases (ICD), which was established in the 19th Century and is used by many countries to code medical activity and mortality; the Medical Subject Headings (MeSH), which is used to classify articles published in the medical and scientific literature, and if a term is not included in MeSH, you will not find any articles on that disease; the Systematised Nomenclature of Medicine-Clinical Terms (SNOMED CT), which has been developed mainly in the Anglo-Saxon world and has some great things, but also some limitations, although it may be used more widely in the years ahead; and MedDRA, which is used to code the adverse effects of drugs and is mainly used by the pharmaceutical industry and drug agencies.

Our aim was to submit a proposal to the WHO for the International Classification of Diseases 2011 (ICD-11) to give visibility to these diseases for the new version scheduled for 2014. We wanted to ensure that the different coding systems were cross-referenced, which will of course provoke cooperation with the other nomenclatures and allow missing terms to be identified. In addition, we wanted to take a big step forward in having a better classification of rare diseases themselves regardless of which coding system was used.

The WHO process started in the 19th Century with 139 diseases, which was then the view of how many different conditions existed, and this has increased to 14,000 today. In the next edition, this may double because the view that we have in relation to diseases depends a lot on our knowledge of physiopathology and causes and, as we know, knowledge is currently expanding very quickly.

The revision goals for 2014 are to build a classification where all users can find what they need. This is very difficult to achieve because of the different things that people are interested in. People want to code mortality, but they are also interested in morbidity in major teaching hospitals, clinical care and private practice. Classification is also needed for research purposes and public health authorities have their own views on what they require. To reconcile all these views is therefore very difficult.

It is also important to have a classification that is consistent and interoperable. In addition, it needs to meet the expectations of countries that have different cultures, healthcare systems and interpretations of what a disease is. For example, people in Africa or China have a very different approach to disease classification and we even have to take into account the traditional medicine approach. We have to then ensure that it can be used for electronic health records, which will be the norm in all developed countries.

The revision process is carried out on a permanent, Internet-based platform that brings in a very large number of groups, being an international effort. The work of the working groups is then passed forward for expert opinion and a peer review will be carried out next year, with the public also being involved. It has been decided to have an electronic version of the classification, which will be a multi-hierarchy system, with each disease being classified in several chapters as appropriate. There will also be the traditional book and for the printed version there will be a need to identify the main chapter for each disease. In fact, it is not easy to do this for rare diseases as many of them are multi-systemic and almost impossible to classify in that way. The classification will be then tested by coding institutions to ensure that there are not too many changes, given that people do not like major changes, and that it is consistent with people's needs.

A large number of groups are involved in the process, of which rare diseases is just one, and each works independently. When you try to reconcile all these views, with no clear instructions on how the work should proceed, it can sometimes be surprising to see what has been achieved. We have set up an international committee for rare diseases and people are contacting experts in their own regions of the world to contribute to the revision of the chapters that we have prepared.

Only 240 rare diseases were in the current classification system with specific codes and it is therefore a big challenge to increase that number to 6,000.  There had been a total lack of a systematic approach previously because changes had been made without having any real thinking about the structure.  It was therefore impossible to understand the logic that had been employed, with some chapters being organised by clinical expression and others by etiology.  For instance, with metabolic diseases, metabolic is a mechanism and not a clinical approach.  There was also confusion between organs and systems, where, for example, for the digestive or respiratory system, some diseases are not in the lung but are outcomes of dysfunction.  In addition, all the genetic diseases had been placed in the malformation chapter, which is normally not *stricto sensu* malformation.  We therefore had to revise that concept in depth.

We have therefore suggested that there should be an extra multi-systemic chapter and that it should be arranged by system and not by organ, and this has more or less been accepted.  The malformation chapter is now also a system and in each chapter we have introduced a clear distinction between what is constitutional and what is acquired as a disease.  Some diseases can be classified in a number of chapters and it is essential that they are therefore assigned to the relevant chapters or subchapters.

We work on each chapter at Orphanet level and send it to the experts that we have identified.  Only about 25% of people reply but when they do they usually provide us with excellent comments and we then send a second version of the chapter back out to the experts.

The WHO also wanted each working group to complete a content model, as they were under the illusion that computers could classify diseases automatically.  We were therefore asked to fill in a form where we were to include the definition of the disease, its evolution, the system or organ involved, causal properties, severity, impact, treatment and so on.  This was a bit like having a complete encyclopaedia of all the world's diseases and was impossible to do – and with no budget for it either.  In the end, it was agreed that we would provide just a definition.

The two-draft process will end with the production of what is called the alpha draft, which is due in December 2011.  We will be ready, although I am not sure about the other groups, and in 2012 this will be made available to people for comment.  For rare diseases, we have revised totally a number of chapters.  In terms of structure, we were the first to work on these chapters and have therefore taken the lead, while for other chapters other groups took the lead and we had to work within their hierarchy.

We have basically revised all the chapters, which are available on the EUCERD website.  Everyone is welcome to comment on them because even if we release the alpha draft in December, major revisions can take place in 2012 and, in any case, we have not included the rarest diseases.  We did not want to put in too many new diseases because we saw that some people were very nervous about rare diseases becoming the most common diseases in the ICD.  We therefore have a total of about 4,000 diseases and the rarest will be added towards the end of the process.

People may be slightly puzzled by what they see because there are still a lot of unsolved issues.  However, this is because of a lack of decision-making by WHO, where, for example, they have not really made up their minds on laterality, when an event can occur on two sides, such as limb

defects, and whether there should be a different code for unilateral and bilateral, or for the range of severity, for instance.  As the organisation is very light, things can be difficult.

Rare diseases should therefore be included in the next edition.  We will be preparing the beta draft with all the experts and there will be cross-referencing with all the other terminologies.  This classification can also be found in Orphanet and you can see where a disease fits in the different classifications.  You can also download the data from the new website, www.orphadata.org, where all the classification systems can be accessed.  We have done our best to make this freely available and involve as many experts as possible.  I would encourage people to check that diseases have been classified correctly and to tell colleagues about it and then promote the use of the new nomenclature in health information systems.  The rare diseases found on Orphanet will correspond to an ICD-11 code in the future and using our classification will help when you need to move from ICD-10 to ICD-11.

# Questions and Answers

**From the floor**

With approximately 14,000 diseases indexed in ICD-10 at the moment plus the 4,000 rare diseases that you are going to add, do you expect there to be a total of about 20,000 diseases?

**Ségolène AYME**

It could be even more than that as diseases will be added in other chapters too.  Rare diseases will probably account for about 20% of all the diseases.

**From the floor**

Rare cancers is an area that is obviously being dealt with the oncology team, so how have issues of reconciliation worked there?

**Ségolène AYME**

This is an ongoing battle.  We see rare cancers as rare diseases and we therefore work on them.  In principle, when rare cancers are located in a specific organ, we assign them to the chapter of that organ system, which was not what was done in the past.  With multi-assignment, there is no limit.

# Data on Rare Diseases: Which Annotations to Support R&D?

*Philippe SANSEAU (GSK)*

## I.    The Use of Information on Rare Diseases in R&D

In trying to compare rare and common diseases, we used Orphanet to create two pools of publications from over the last five years, with one pool concentrating on common diseases and the other on rare diseases.  In each pool, we then looked at which MeSH terms were under-represented and over-represented, breaking this down into six broad categories.  For rare diseases, the over-represented terms were genetics, genomes and genetic technologies, which was probably not surprising because a lot of rare diseases have a genetic origin.  The healthcare category seemed to be over-represented for common diseases and there may be opportunities there to develop more of a healthcare infrastructure around rare diseases.  'Information science' was over-represented in common diseases, while 'information services' was over-represented in rare diseases, possibly because of the many active patient organisations in rare diseases that deliver information.  With information science, which is more about the technology required to process information, there may be some improvements that could be made on the rare diseases side.  Just by looking at the information, therefore, you can see some interesting trends.

We then tried to see what was driving research and development in rare diseases where we used information on clinical trials from clinicaltrials.gov and mapped this back to publications using Orphanet.  This was a challenge because the names of diseases used in clinical trials do not always match the names in Orphanet.  However, we managed to do this, mostly manually, for more than 400 rare diseases and it showed us that there was a positive relationship between the number of publications and the number of clinical trials. It was also more likely that there would be clinical trials if there was a patient organisation.  Additionally, we found that if there is a known gene for the disease, it is three times more likely that there will be a clinical trial.

## II.    Contextual Information

At GlaxoSmithKline (GSK), we have been working on rare diseases individually for many years and just over 18 months ago a specific unit on rare diseases was created.  The whole area of rare diseases is quite daunting, with more than 6,000 diseases, and it was interesting to look at the information on rare diseases and try to give a focus to our portfolio at GSK.

Using Orphanet and other data sources, we looked at whether we could prioritise diseases based on a number of criteria.  We built a computational pipeline and developed an algorithm and then looked at the information associated with each disease such as its prevalence, whether there was a patient organisation, if a gene was known, what the pathway looked like and what people were working on in both academia and industry.  This algorithm allows us to score in different ways and we established a list of approximately 200 priority diseases, which we divided into four therapeutic categories.  This simply serves as a guide and we will not work on all the diseases.  In fact, we have programmes that cover diseases that are not on the list.  Nevertheless, it has given us a focus and we can play with the different parameters as it is computational and

we have already ongoing clinical programmes for some of the prioritised diseases, such as Duchenne Muscular Dystrophy.

We played around with the parameters at least three times and we have seen that with genes, for example, it is important to add information quickly.  There is an explosion of information on causal genes. For example a paper published in *Nature* last month identified 50 novel genes for recessive cognitive disorders (**478**, 57-63, 2011). This is driven by technologies such as next generation sequencing (NGS) and exome sequencing and this will continue.  You therefore need to capture this information very quickly to assess new therapeutic opportunities.

When you work in drug discovery and development, you have to ask some basic questions, such as whether you can develop a compound against a certain gene (e.g. is the gene tractable by small molecules) or whether you should use a nucleic acid-base approach. It is therefore important to look at what the delivery mechanism might be for a drug.  It is also important to know whether the genetic cause is loss or gain of function. This will help to decide if you need to develop an agonist or an antagonist.  If the gene is not tractable, so you need to understand the pathways to identify better targets downstream or upstream of the disease causal gene. Information on genes is therefore very important.

## III.    Molecular Information

Moving more towards a molecular type of data now, we are very interested in networks, which are a good way of visualising information and this is very interesting for rare diseases due to the large number of conditions.  For example in the in the same paper in *Nature*, they described how they were able to build networks and identify relationships between the causal disease genes.  This kind of visualisation is very useful and is what we have been trying to do at both the molecular and the disease level.

We have developed a number of different methods over the years.  For example, we are very interested in building disease maps to look at the relationships between diseases and try to redefine diseases.  We published a couple of papers two or three years ago using information from publications that looked at how often terms were coming together and whether that was more by chance or not.  You can then expand that further so that the terms can be related to genes and the genes to pathways and map back these terms to the diseases.  It is therefore possible to start to build interesting networks very quickly and overlay additional information, such as compounds.  You then can have what I call 'mechanistic expansion', where, based on scientific evidence you can see whether you can expand disease indications and what might be a development plan for potential opportunities.  We tend to use this type of network views extensively.

The networks are composed of rare diseases and common diseases but you can focus on a limited number of diseases only (e.g. a subset of rare diseases).  Using a resource such as Orphanet and some additional databases we have on pathways, with genes we have been able to link pathways to diseases and we have also done some clustering there.  One network, for example, has thousands of rare diseases, but you can dive down and look at very specific information.   Again,

visualising the information, because of the large number of diseases, is very useful and once more we are able to overlay various types of data.

## IV.    Conclusion

I hope that I have shown how important information on rare diseases, provided by resources such as Orphanet, is to us.  We have been using it very actively and network visualisation is very useful because of the large number of diseases.  We believe that it is important to have some integration of the knowledge as it is a challenge for us having to move from one database to another.  For example, when we have to move from clinicaltrials.gov to map the names of the diseases back to Orphanet, we have to do a lot of manual work and more integration would be useful there.  Having common data exchange standards, ontologies and control vocabularies is also absolutely fundamental.

# Questions and Answers

**From the floor**

It seems to me that it is quite simple to build these kinds of networks, but ultimately most of this is based on mainly one or two studies that have not been proved.  Therefore, creating these kinds of issues is a good thing for business, but not for researchers.

**Philippe SANSEAU**

There are tools that can really help to mine these networks – and building the networks is not always as easy as it looks.  We have been using these kinds of network approaches for common diseases and have been able to add new disease indications to some of our assets.

**From the floor**

Do researchers have access to the networks that you are building?

**Philippe SANSEAU**

Yes, if they are networks that have been built on information that is in the public domain.  However, when we map back our compounds on the networks, that is proprietary information.

**Ségolène AYME**

Philippe Sanseau has shown that it is possible to link different databases and our job is to ensure that they can be linked easily.  We believe that this will be a key tool in the future.  We are only at the beginning now, but people are recognising that their data should be made available to others.

# Bioinformatics for Rare Diseases: Promises and Challenges

*Peter ROBINSON (La Charité Berlin)*

## I.    Exome Sequencing

I agree with Ségolène that we are at the beginning of a new era with rare diseases being the gateway to personalised medicine and understanding the human genome.  In bioinformatics for rare diseases and medicine, there are many promising possibilities for improving medical care for patients with rare diseases, and the technology that is really changing things is next generation sequencing, in particular exome sequencing in the area of diagnostics and rare diseases.  The word 'exome' refers to all the exons (ca. 250,000) of all of the protein-coding genes (ca. 24,000) in the genome; the great majority of mutations found in people with rare diseases affect this 1.5% of our genome.  It is cheaper to concentrate on this region of the genome and its interpretation is massively simpler.  A number of technologies have emerged that capture all these exons at once, and thereby allow them to be subjected to targeted analysis on next generation sequencing machines.  This is therefore massively accelerating the pace of research, and with the current generation we can sequence up to 600 Gb bases in a single run, which is about 50 patients.  However, the problem can be that just one of many variants may be responsible for a disease and we need ways of finding it.  That is where bioinformatics comes in.

Looking at a typical process of bioinformatics, after we do the sequencing, we obtain DNA sequence reads, which are approximately 150 nucleotides long, and they are mapped onto the genome.  We then get an alignment of the reads and use various programmes to identify variants of which there are typically 30,000 in an exome.  We then have to have some way of filtering down these variants to a short list of candidates that are examined in detail by a geneticist.

In one of our examples, we had about 22,000 variants and the first thing you can do here is to look for rare variants lead to a change, such as missense, nonsense or splicing mutations or small deletions or insertions, that is predicted to be pathogenic.  That will get rid of over 95% of the variants.   You do this with data from databases of common variants, such as the Single Nucleotide Polymorphism database (dbSNP) or 1000 Genomes. The assumption is that variants that are common in the population are probably not the cause of a rare disease and thus can be excluded from further analysis.  This typically leaves you with up to about a few hundred candidates and for these we need intelligent bioinformatics to get down to one, two, three or four.

The kinds of filters that are being used here include genetic linkage and de novo filters.  A powerful approach has been using the de novo intersection filter and we know that with every generation approximately 100 new de novo mutations occur and as our coding sequences make up about 1% of the genome, we expect there to be about one de novo mutation per generation.  Many of these will not change the amino acid or lead to a neutral change, but it means that we do not have to look through hundreds of candidate variations if we are searching for de novo mutations.  Many cases of mental retardation are de novo spontaneous mutations, as was shown by the work of Joris Veltman and Han Brunner.

Things are now starting to get more complicated and groups are developing more sophisticated bioinformatics algorithms to exploit the data more effectively to improve our ability to use exome sequencing. In our group, we looked at a family with an autosomal recessive mental retardation. After the above filtering steps had been taken, we were still left with about 16 candidates and did not know what to do next. However, we then developed a method using a hidden Markov model that performs a type of linkage analysis directly in the exome sequence data of the affected children and this got us down to the true disease gene. A lot of groups are developing very sophisticated algorithms to narrow down from 30,000 variants to one or two and they have been one of the reasons for the massively accelerating pace of discovery. The first use of this technology was in 2009/2010 and we are now just seeing more and more of it. There are currently about 4,000 named rare diseases that do not have a known disease gene but we should be able to find these genes in the next five years and provide comprehensive diagnostics for people with rare diseases by 2020.

## II. Ontologies and Standards

Another technology that is rapidly changing the playing field is ontologies and standards. In many databases, such as PubMed and the Online Mendelian Inheritance in Man (OMIM), different words are used to mean the same thing, so it is not surprising that you cannot get a comprehensive and accurate search result or generate an accurate network if things are not called by their proper name. That was one of the reasons why my group developed the Human Phenotype Ontology, which has about 10,000 terms for individual phenotypic abnormalities with the signs and symptoms of disease and, as is common in ontologies, the terms are related by sub-class relations.

For example, *atrial septal defect* is a sub-class of *abnormality of the atrial system* or *cardiac malformation* in the sense that a patient with an atrial septal defect can also be said to have a cardiac malformation. We currently have annotations for about 5,000 Mendelian diseases and are greatly indebted to OMIM and, increasingly, Orphanet. This ontology can be used to look at the phenome of humans in a holistic way.

A powerful approach for diagnostics is based on ontological similarity measures. People who are involved in genetic counselling will know that we often do not know the diagnosis and all that we can usually do is to enter the signs and symptoms into a computer programme. We therefore tried to develop a programme based on our ontology through what we call the *Phenomizer*. Here, you enter the signs and symptoms of a disease and get a ranked list of differential diagnoses. The programme, which was developed by the PhD student Sebastian Köhler, has already been used a lot and I was proud to see that it was featured in a medical textbook on genetics.

You can also use ontologies for research. One of the most important topics that researchers are currently involved in is the identification of the remaining human disease genes. If we look at mice and zebra fish, we can see that there is phenotypic information for over 5,000 genes in the model organisms for which no human disease is known. About 4,000 Mendelian diseases are known currently, corresponding to about 2,100 genes, so that more than twice as many genes have phenotypic information in model organisms.

We have been working with the a group of people involved in ontology and ophenotype research from the Gene Ontology Consortium, ZFIN, and the University of Cambridge to create logical definitions of ontology terms in which we define HPO terms based on terms from other ontologies. For example, we can say that 'short nose' is 'nose' from the anatomy ontology and 'short' is from an ontology for phenotypic qualities. If we know that 'snout' is analogous to 'nose' and that 'short' and 'hypoplastic' are close to one another in the ontology of phenotypic qualities, the system can recognise that *short nose* in humans and *hypoplastic snout* in mice are nearly equivalent.

The Rare Diseases (RD) classification developed by Orphanet will be one of the most important projects for the field of rare diseases, and for the first time it will give us a realistic view of how common, collectively, rare diseases are in our population. We have been correlating Orphanet's rare diseases classification with the phenotype data that we have been assembling. We can therefore take the classes from Orphanet and use our phenotype data and the phenotype data from Orphanet to perform computational clustering. Phenotypically, these diseases cluster together quite a lot and this shows that Orphanet's classification is of a very high quality. We have of course identified a few errors, which we have reported, so this can also be used for automatic quality control and we will be making a lot of suggestions in 2012. This is certainly a very powerful approach.

## III.    Future Developments

Finally, we want to use all this information for patients and a major difficulty to date has been that a genetic finding is not always good at predicting the phenotype – the disease course. Exome sequencing and genetic modifiers could be key in terms of how things might develop in the next five years. The big question in genetics is that while you have 10 people in a family, for instance, where although they all have the same mutation, some family members have severe clinical manifestations and others are mildly affected. If one identifies the mutation in a child, how can one tell whether the child will be severely affected or will lead a reasonably normal life?

We performed exome sequencing on samples from a large family with cardiomyopathy and found that while all patients had a single mutation in the same gene, only those severely affected had a second mutation in a different gene. Although this result will be useful in this family,  I think we will need to collect a lot of data from many patients and families with cardiomyopathy in order to be able to understand the role of genetic modifiers in this disease in a way that will allow us to improve clinical care of affected patients. It will be important to take advantages of data from healthcare systems and studies using ontologies and standards to be able to identify the phenotypic consequences of variation in genes. We also need to have a way of getting the information back to practitioners, who simply cannot integrate everything from across the Internet. We need to develop knowledge portals that take information from the databases that exist and the genomes that will be done for patients in hospitals over the next few years and provide practitioners with this information and so improve their decision-support systems.

# Questions and Answers

**From the floor**

By comparing the phenotypic expression of different genes in different species, you have a great tool for designing a candidate approach for identifying new genes.  Are you working on that?

**Peter ROBINSON**

In the next five years data will be available for all the mouse's genes and we will then be able to see what the phenotype might be that would correspond to humans.  This will work well, although not perfectly, on a genome-wide scale because there are a lot of genetically heterogeneous conditions where a large number of genes make a relatively similar phenotype.

# Roundtable of Stakeholders and Discussion

*David Whiteman (Shire HGT), Alain GARCIA (French Ministry of Health and EUCERD), Gábor POGANY (HUFERDIS and EUCERD)*

## I.    Relevance to Industry

**David WHITEMAN**

I found those presentations fascinating because trying to identify clusters in phenotypes to make a diagnosis rings true with someone like me who has spent their life trying to solve these problems for patients.  The systematic link to massive amounts of data that are now coming from genome analysis shows a glimpse of a systematic clinical solution now from the research that is currently being done.

**Ségolène AYME**

Is this approach of interest to a company like yours?

**David WHITEMAN**

It definitely is and it is also key in terms of drug discovery.  The same strategies have to be applied to networks of compounds and biologicals.  Many of the diseases that we have chosen as targets for drug development for very specific presentations are now turning out to be components of completely unrelated diseases or interesting modifiers for genes for other diseases and interactions with the environment.

**Ségolène AYME**

In the previous two days, we talked about databases and tools as pre-competitive resources that could be shared between the academic and pharmaceutical worlds. What do you think about that?

**David WHITEMAN**

When there is collaboration between industry and academia, there will always be concerns about proprietary information, but much of this current work is pre-competitive. In a sense, you cannot have effective competition afterwards without sharing this kind of ground knowledge and building up from there. Each time things are done better and more comprehensively with new technologies, that links into and enhances the discovery process.

## II.      Relevance to Research

**Alain GARCIA**

I'm a trained medical doctor. I have come to the field of rare diseases through my responsabilities at the Regional Health Agencies in France. The rare disease field is an extraordinary world where all stakeholders are highly implicated, from patient organisations to professionals, at clinical level as much as at the research level, which is extraordinary.

The second extraordinary thing to remark is the strong movement at European level, particular to the field of rare diseases. There is a real conjunction of efforts, implicating also the Industry. At yesterday's round table there were discussions of the cost and pricing of drugs, and I remarked the willingness of all stakeholders to make rare diseases a sort of clinical model, a scientific research model, and more generally a model for society, as behind all this is the question of people who suffer from these diseases. Rather than scientific or clinical approaches, we owe patients and their organisations social approaches.

## III.      Relevance to Patients

**Gábor POGANY**

An important part of all this is awareness and here the patient organisation has a very important role. The latest Eurobarometer results show that there is a relatively good knowledge of rare diseases in society, even within the new member states of the European Union. Nevertheless, the new member states have a lot of problems with healthcare, and because of the financial crisis, all member states are having problems. In addition, the new member states have a crisis in human resources and in terms of an inadequate healthcare structure. Healthcare systems are therefore unsustainable in their present form and coherent action is now required, which means that collaboration is essential. The ICD codes for rare diseases can help us in any reorganisations that may be made.

# IV. Summary

**David WHITEMAN**

I would like to comment on how we can make all this relevant to doctors. With the various genome education programmes that we have had to date, we have tried to teach genetics from our different perspectives to people in primary care and other disciplines. While this has not been a waste of time as such, the moment has now come when we have to present rare diseases as the common symptoms that doctors deal with and the ontological approaches will make that more feasible. This is a computational issue and we are now possibly entering the era of the smart hospital as opposed to the very smart individual doctor who is the diagnostician.

**Ségolène AYME**

I think that the people in charge of funding understand that this is an era in science now where we need fund bioinformatics and that we have to train young people in this area. In recent years, there has been too much of a focus on technology and, as Peter Robinson said, it is not enough to produce a lot of data; someone has to interpret it and without the right tools and databases, we will go nowhere.

**Andrew DEVEREAU, National Genetic Reference Laboratory**

I share your view. Research and education work on bioinformatics and the extension of bioinformatics to healthcare workers are themes that continuously come up today.

**Alain GARCIA**

All European countries have been hit by the recession. I speak in the name of the French ministries, and observe that France has been able to maintain her financial engagements towards rare diseases. We are in the important stage of building a national database for rare diseaes, led by Paul Landais, and the creation of the Rare Diseases Foundation, which will also include the National Database, as well as the creation and financing of RADICO (*RAre Disease COhorts*).

Yesterday, I was struck by the presentation of Prof. Mandel and the presentations made today on next generation sequencing. In the second French National Rare Disease Plan we have decided to finance 7 platforms and 8 next generation sequencing machines (CGH). We should continue to invest in this area so as to aide one another pursue theses discoveries and anticipate so that we are ahead of the current and therefore able to present patients with pallative solutions or cures for their rare disease.

# SESSION II - PARTNERING TO OPTIMISE THE USE OF PATIENT DATA TO IMPROVE CLINICAL RESEARCH AND HEALTHCARE

## State of the Art of Disease - Specific Registries in Europe: Successes and Challenges

*Stuart M TANNER (Sheffield Children's Hospital and EUCERD)*

### I.     Background

When we teach our medical students about a disease, we tell them about its clinical features, how to diagnose and treat the disease and the expected the outcome, which is very straightforward.  However, when we practice medicine, we find that patients vary a great deal in the features that they present, even for a common disease.  Diagnostic tests are not always diagnostic and we sometimes choose different treatments for different patients, and patients differ in terms of response, side effects and compliance.  Outcomes also vary hugely given severity, other pathology and the psychosocial coping mechanisms that influence welfare.  This is true of both common diseases and rare diseases and to help us understand the spectrum of disease pathology and outcome variability, we collect data from very large numbers of patients.  This is relatively easy for common diseases, but very difficult for rare diseases, hence the need for need for the collection of data on rare diseases.

Excellent disease-specific registries, for instance, have told us a great deal about variability of clinical features, diagnostic developments and difficulties, treatment variability and outcome.  They have also told us a great deal about the epidemiology of rare diseases and about quality in terms of collecting data and care, and this has been reflected in differential outcome measurements.  A rare diseases registry also raises the profile of a disease, attracts funding, is a powerful tool for advocacy within a healthcare system and promotes dialogue between professionals.  It creates a research environment with spin-offs and is a basis for the collection of data for trials.  There are therefore many benefits and successes in disease-specific registries.  As Peter Robinson said, it is essential that we have excellent phenotypic data to inform relevant genetic research.

Ségolène Aymé and her team have produced an excellent report that summarises the benefits and challenges in setting up a rare diseases registry and this draws attention to the 514 registries in the Orphanet database, which vary in terms of coverage and provenance.  There is therefore a great deal of activity going on, but we might wonder whether there is some duplication of effort.

### II.     Registries for Biliary Artesia and Bile Acid Synthetic Defects

There are seven registries for biliary artesia and six for bile acids, although only one of them is disease specific.  Biliary artesia is a developmental abnormality of the bile ducts which, without surgical     treatment,     is     fatal     within     two years     in     almost     all     cases.     The

European Biliary Artesia Registry (EBAR) reported in 2005 that it had only been able to capture 35% of expected patients in Europe. However, this showed a dismal figure for survival of 78%, which was actually 41% in the worst areas. This was therefore indicating a serious problem.

The results for biliary artesia survival this year in England and Wales for cases diagnosed between 1999 and 2009 show a survival rate of 94%. This outcome has resulted from a policy change where the treatment of biliary artesia was localised to three centres. The registry had therefore shown a bad situation and the Department of Health was required to act to achieve the necessary result. One of the challenges, therefore, is that a registry will give us the data, but unless the data informs what we do, the benefits will not feed through to patients.

The rare disorders of bile acid synthetic defects produce either liver disease in infancy or neurological disease in later childhood and adulthood. They are treatable in many cases with bile acid replacement therapy, which does not cost a lot. A retrospective study from two centres in London last year showed that of 18 children diagnosed with bile acid synthetic defect, three died at younger than five years because the diagnosis had come too late and they were untreated. However, of the 13 who were treated, 12 had an excellent outcome both in terms of liver and neurological progress.

This is a rare disease that is treatable. As a paediatrician, I would like there to be greater emphasis on the rare diseases that are treatable and if the treatment is cheap and therefore not likely to attract much industry interest, it is up to clinicians, patients and academia to become active.

## III.    The International Rare Disease Research Consortium

In three meetings over the last 18 months, the International Rare Disease Research Consortium (IRDiRC) has come up with a set of policy proposals on registries, biobanks and other areas of activity. However, that is the easy part; the hard part is to meet the challenges of rare diseases registries and that is now been addressed by a working party. What is needed are uniform policies, common data elements and standardised operating procedures so that databases can communicate. This then requires Open Source rather proprietary software and there need to be policies on data sharing and access to data, appropriate data collection, guarantees of privacy, feedback to those providing data and, perhaps most importantly, a sustainability plan. A large number of registries have done good work but they have then failed because the money has run out. In addition, we know that patients and their families are excellent at collecting data, particularly long-term data, and we have not enabled patients enough to contribute in this area. Finally, there also needs to be training and education.

Disease-specific registries are hugely valuable and produce wonderful data. There is sometimes a problem using that data and the challenge now is to ensure that this is done more efficiently in the future.

# Questions and Answers

**From the floor**

What are the strategies that registries can adopt for sustainability?

**Stuart TANNER**

Our Framework Programme 6 (FP6) project is sustained through a DG SANCO grant. I think that consideration should be given to whether something should be sustained for ever or whether there needs to be a cohort and where economies can be achieved. Applications for a registry programme should now cover what happens at the end of the project.

**From the floor**

As well as treatable cases, should we not also include preventable cases?

**Stuart TANNER**

I agree. This touches on the difficult area of neo-natal screening, but we would like to see greatly enhanced neo-natal across Europe. There also should be much more family screening.

**From the floor**

One of the goals of the network that I belong to on rare anaemias was to build a registry, but national regulations prevented us from doing this. We therefore need harmonisation in this area.

**Stuart TANNER**

I agree. The voice of the patient also needs to be heard more loudly.

**Domenica TARUSCIO, Coordinator of EPIRARE**

Harmonisation is very important and at EPIRARE we are collaborating on that.

# State of the Art of National Data Repositories

# The Experience in Spain

*Manuel POSADA (Institute of Health, Spain)*

## I. Background

In Spain, we started by creating a research network where we tried to identify what patient registries there were in the country to compare the specificity and utility of the registries with other kinds of information systems. In one of the Spanish regions, we then set up the population-based regional registry for rare diseases and at the same time other databases and registries were created. For example, the Spanish Network of Associations of Neurologists established databases on muscular diseases, Spain was represented on Alpha 1-Antitrypsin, a number of groups took part in the European Reference Networks and there was participation in networks sponsored by foundations, such as Huntington's Hereditary Disease Foundation.

## II. Defining the Context

We believed that conflicts of interest would arise in terms of different methodologies and ethical and legal areas and so on and decided to set up a project to deal with the issue. Accordingly, in 2005, we established a legal framework for our national registries and set up an Ethical Committee on rare diseases to establish guidelines. We also developed an operational definition of registries, which refers to a well organised information system, based on observational study from an epidemiological point of view, with the strategic collection of data, the evaluation and specification of outcomes, targeted at a well-defined population, with a prognosis that is judged from scientific policy activities. However, we could summarise our key objectives simply as promoting research into rare diseases and promoting and facilitating decisions in terms of health and social planning.

## III. The Registry Platform

On our website, users can check whether a disease is rare or not and find links to Orphanet. The main idea of the website is to provide a platform to provide access to different registries. The platform offers the possibility of creating population-based registries, where, on the one side, the regions can put on their databases and, on the other side, different research groups can allocate their patient registries and collaborate with different projects. In the middle of this is the patient and patients can also put on their own consent and personal and basic information. Patients can become involved in different ways in our central dataset, which is used as both a rare diseases registry and a patient registry. As well as the central information, they can also provide information on quality of life and medicines and so on and donate samples.

In terms a specific patient registry, after they sign an agreement with us as the central body with responsibility, researchers can add information and create their own databases and we are also collaborating with a number of groups to import their data into our system.

## IV.    Working with Stakeholders

We have linked up with a number of stakeholders to promote this platform, such as the Spanish Federation for Rare Diseases (FEDER), and have agreements with medical associations. We are also talking to industry about how we can collaborate and harmonise the various strategies that exist.  In addition, we of course work very closely with the Spanish regions.

For the population-based registry, we have a national strategy and the definition of the registry has now been formally accepted.  As well as the collaboration with the regions, we also collaborate with general practitioners.  With the patient registry, the idea is to facilitate collaboration by all interested groups.  We have created the platform and the rules on collaboration and we hope that this collaboration will expand in the future.

Our challenge is to identify and get hold of all sources of information from right across the board and make them available in the same place to cover our two strategies for a population registry and a patient registry.  While the two strategies are of course different in their own ways, in the end, they have to work together.  For me, the key to everything is the patient.

# Questions and Answers

**Ségolène AYME**

What kind of data are you actually storing?

**Manuel POSADA**

Previously, we were just making an analysis of the situation.  We are working on the coding and identification of specific patient registries before incorporating them into our platform.  Some patient registries are working with us with the intention of harmonising the data and collaborating on our platform.

# The Experience in France

## *Paul LANDAIS (Université Paris Descartes & Assistance Publique Hôpitaux de Paris)*

## I.    Background

Four major events took place in France in 2011.  Firstly, the Plan for Rare Diseases, which is the second of these plans and covers the next five years, stated that a rare diseases national

databank will be launched.  Secondly, in January, the Ministry of Research agreed to fund the development of cohorts for rare diseases for the next 10 years.  Thirdly, the biobanks network has also had funding committed for the next 10 years and, fourthly, we are hoping to see the creation of the Foundation for Rare Diseases at the end of the year.

At the heart of our concern are the patients and their families and in developing data repositories we need to understand all the difficulties that are involved, with the multiplicity of the disease, the complexity of the phenomes and genomes, the geographical distribution and the temporal evolution of these diseases.  This is a major challenge.

The clinical network required for these data repositories is based on 131 reference centres and 501 competence centres and the human network that the clinical data is based on is very important.  In total, we have 18 groups of rare diseases.

The ontological support is very important and the superb work of Orphanet has been very useful to us in building up our repositories.  We need to share vocabulary when exchanging information and the Orphanet database is important in terms of how diseases are described.  The need is to both draw in and spread out information and the *Orphanet Journal of Rare Diseases* is an important means of spreading information.

## II.    The French National Plan

The French national plan was launched in February 2011 and has three axes that relate to quality of care, research and European interconnection.  In terms of quality of patient care, the idea is to improve access to diagnosis and care for patients presenting a rare disease and link the rare diseases structure within a common information system.  Accordingly, the decision was taken to create  the  National Databank for Rare Diseases.   The  main  objective  of  this  data  repository relates to public health and the aim is to describe both the demand for care and the offer of care and to see whether the offer fits the demand.  It also aims to identify patients who would be eligible for clinical trials on a new drug or device.

The means of building up the data repository has been by defining a minimum common dataset established with the reference centres, INSERM and the Institut de Veille Sanitaire. It will share Orphanet's  common  nomenclature,  and  take  into  account  the  recommendations  of  the European Union  Committee of Experts on Rare Diseases,  as  well  as  the  work  of  the Office for Rare Diseases in North America and the National Institutes of Health (NIH).  In addition, it has been through defining a format for exchanging and exporting data into the national database and allowing the storage of the information in specific data repositories, and we have also taken into account the recommendations of DG SANCO's Rare Diseases Task Force.  We need to connect the different databases and centres and define policies on data collection with all those who work on rare diseases and it will also be necessary to develop a methodological structure  to  pilot  the  project  and  ensure  as  much  interoperability  as  possible  between information systems.

The second axis of the plan is aimed at the promotion of research on rare diseases, with the aim of creating a national structure that provides an interface between public and private actors and a foundation will be created by the Institute for Rare Diseases.

The main objective here is to structure and harmonise the actions contained with the overall plan and coordinate and articulate the missions of the GIS-Institute for Rare Diseases, the National Database for Rare Diseases and the cohorts, and work together with Orphanet. Other aims are to develop and federate databases oriented towards research and information and improve the biological resource centres and access to these resources. To this end, a biobank network will be established and more than 200 teams and 110 private partners will be part of the consortium on biobanks. Further aims are to foster access to national technological platforms and develop partnerships with industry on specific databases and encourage clinical trials and the work of Orphandev. The Institute for Rare Diseases, the National Databank and the rare diseases cohorts will be regrouped within the Rare Disease Foundation.

A funding has been obtained for the RADICO program (RAre dIsease COhorts), EUR10 million over the next 10 years, with the objective of looking for ways to provide better care for patients and families, based a better understanding of pathophysiology of the underlying mechanisms and a better exploration of the links between phenotypes and genotypes. The aim will also be to invest in the challenge of phenomics so as to be able to better characterise and annotate the phenotype. This program is under the aegis of the Ministry of Higher Education and Research.

The first set of the French databank has public health objectives based on a minimum dataset, with the aim of having complete cases. A budget of EUR500,000 per year has been obtained for the next 5 years. It will be managed by a dedicated project team under the aegis of the Ministry of Health. This program will be linked to the RADICO longitudinal project on the duration, based on the description on phenomics. Groups will have to prioritise the cohorts to be developed. This is led by INSERM and in the future it will be led by the Foundation for Rare Diseases.

The minimum dataset will be entered by the centres. There are other sources of data, such as the registries for rare diseases that already exist, the rare diseases mutation databases and other databases. They will have to exchange their data with the national databank in accordance with the minimum dataset. The interoperability of the information systems will be privileged.

The system works through a so called n-tier architecture where the first step is for the professionals to enter the data in a production database. The data is then validated and entered into a data warehouse. The professionals can direct queries to the data warehouse through a geographical information system that is able to provide results in the form of pie charts, tables, histograms or maps.

## III.  Conclusion

The French data repositories represent a new challenge that will address public health and research at the intersection of several fields. The repositories will be supported by information systems that allow professionals to promote the exchange of information and foster collaboration on research in rare diseases centres to produce and disseminate new knowledge that is dedicated to the better care of rare diseases patients.

# Questions and Answers

**Samantha PARKER, Orphan Europe and EUCERD**

Is it the case that clinicians would go through a core database and that the information would then be transferred to BAMARA?

**Paul LANDAIS**

It will be possible to enter the core dataset directly into the national database or to transfer the data of the core data set previously entered in a given database, towards the national data base. Both possibilities will be offered.

**Domenica TARUSCIO**

In Italy, we organised the national registry in the same way and we use a common dataset so that we have surveillance at the national level.

**Ségolène AYME**

The French concept is wonderful, but we did not hear much about the difficulties that can emerge. People only want to enter data on patients that the patient is happy with and there is an issue there with having a link to the information systems of hospitals. Very soon, we will also have personal medical files and it is important that all these initiatives are connected so that people do not have to keep re-entering their data.

**Paul LANDAIS**

We need to move forward step by step on this and our goal, of course, is to promote the interoperability of the information systems.

# The Experience of Italy

## *Paola FACCHIN (Veneto Region Rare Diseases Registry)*

### I. The Italian Rare Diseases Monitoring System

The Italian rare diseases monitoring system is, by law, a global system and population based. The system has two levels: the regional level and the national level. The regional level is responsible for collecting and providing information, and coordination. Coordination is done through an inter-regional board, which I currently supervise. Starting from regional registries, a synthetic data flow feeds the national registry. When this started in 2001, the regional registries differed in respect of their aims, the data they collected, operating definitions and their organisation. As a result, the national dataflow was incomplete and of poor quality. Over 10 years, the experiences

gained and strong pressure from patient associations has led to changes to objectives and to the homogeneity of regional data collection.  The national dataflow and thus the contents of the national registry have consequently changed in terms of quality and completeness.  From our initial experiences, we have progressively moved to a more synthetic minimum set of data collection and we now have an acceptable overall level of quality.

From 2001 to today, the regional population registries have been grouped in three typologies.  The first registry, which is shared by eight regions, monitors 24 million inhabitants, which is about 40% of Italy's population.  The second accounts for four regions and has three separate registries and monitors 18 million inhabitants, almost 30% of the population.  Globally, these two typologies are similar and focus on recording healthcare services and care provided to patients.  The remaining registries, which cover 30% of the population, are still being developed.

## II. The Value of Global Population Registries

The central question that I will look at today is whether the global population registries have a plus value compared with other disease registries in terms of public health and clinical research.  To answer this question, I will mainly use figures from Veneto, which has the most developed data and a higher coverage of population.

According to the rare diseases list that is required to be issued under Italian law, this registry for Veneto monitors about 3,000 disease entities, which represents 47% of the entities included in the Orphanet list.  Overall, the Italian list covers 58% of Orphanet entities as it does not include tumours and infectious diseases.  Of the 3,000 entities monitored in Veneto, only 1,163, about 40%, have at least one affected person.  Of the remaining 2,000 or so Orphanet entities, more than 60% have a frequency that is so low as to be unknown and only 10% are greater than one case per 1 million inhabitants.  Increasing the number of monitored diseases would therefore not correspond to a significant increase in the number of cases followed up.  The figures that I will present could therefore be affected by an underestimation rather than an overestimation.

The answer to my central question regarding value, we can consider things in terms of four categories: public health decision-makers; clinicians; patients and patient associations; and private companies.

Looking at public health decision-makers, the present population denominator allows the calculation of occurrence rates and this is essential for decision-makers in terms of resource allocation.  Utilising the years of life lost indicator, which is one of the indicators that is most used by international organisations, the percentage of years of life lost due to rare diseases (4.6%) is four times the value of infectious diseases (1.2%), twice that for diabetes (2.6%), a little bit lower than that for traffic injuries (5.7%), which is considered to be by far one of the most harmful aspects of community health in Western Europe, and half of years of life lost due to myocardial infarction and cardiovascular diseases, traditionally considered to be the main plague of Western Europe.  These figures can address the hesitation of decision-makers who are unsure of why they should allocate resources to rare diseases because they think that it will affect only a small portion of society.

Another key element in terms of public health is the availability of the prevalence and the incidence rates that can be used as a multiplier of actions and services. Data from our Registry show an overall raw prevalence of the monitored RD in the population under study of 3.53 per 1,000 inhabitants (C.I. 95% 3.47-3.58) and an overall raw annual incidence of RD of 3.87 per 10,000 inhabitants (C.I. 95% 3.69-4.05). Overall raw prevalence in the paediatric population is 5.1 per 1,000 inhabitants (C.I. 95% 4.94-5.25) and the overall annual incidence is 3.71 per 10,000 inhabitants (C.I. 95% 3.29-4.13).

The availability of epidemiological data is crucial not just for deciding how many centres of expertise to have but also for defining the resources that should be allocated to particular healthcare organisations, taking into account the specific problem of rare diseases.  For instance, in planning and organising the whole rehabilitation services in Veneto, we have to consider that 10% of users are rare diseases patients, who have special needs. Similarly, for establishing a network of paediatric palliative care, we have to consider that 30% are children with rare diseases, who have a completely different profile of health needs.

The third advantage of population registries is represented by expenditure control and the ability to predict costs for future provision of services.  For example, we can define how much it will cost if we provide certain treatments or devices free of charge, as, for example, eye gaze devices to amyotrophic lateral sclerosis patients,

With the assumption, therefore, that building a population-based registry for rare diseases constitutes value from a public health point of view, I think that there will also be a similar advantage for clinicians and clinical research.

One issue concerning clinical research relates to the definition and genotype/phenotype correlation within the same diseases and among related diseases.  Disease-specific registries have allowed there to be improvements in definition, but they are at risk of a bias that is not always possible to control.  Patients who are referred to centres of expertise and continue to be followed up by centres can differ by age, severity and evolution from other patients. For example, in Veneto, only 50% of Huntington Disease patients are followed up by the centres, while the other 50% are followed up at home or in first-level long-term care facilities, and it is a similar picture in other countries. In particular, HD patients who are not followed up by Centres are older, present higher psychiatric co-morbidity and have, in general, a different clinical and disability profile.

This selection bias also represents a serious limitation in terms of patient enrolment for clinical trials on the evaluation of treatment efficacy and safety.

What the disease registries collect is usually defined by clinicians working in the centres of expertise and this is therefore very rich in analytical detail and much less rich or even lacking for matters such as rehabilitation, autonomy, social inclusion and so on, which have an impact on services and institutions.  The incomplete knowledge on this side justifies the need for research.

If we look at issues addressed by articles on rare diseases over the last five years, we can see that the area of greatest interest was on diagnosis and etiological treatments, mainly regarding drugs and the area of least interest was on the aforementioned issues of rehabilitation and so on. Additionally, other matters, such as innovative processes and nanotechnology, which can have a high impact on patients' lives, have been neglected.

On the patient side, the balance in the description of the life/disease pathway that population-based registers provide can offer much relevant knowledge and information. This pathway, which is generally considered to be secondary to the pathways of diagnosis and treatment, involves the patient's entire family. A series of interviews that were carried out with a family with someone with a rare disease in Veneto demonstrated the huge burden that a family bears and the consequences on their lives and health. More than one-third of this family have split up, compared with the 7% that would normally be expected. Many of these families have greatly reduced incomes and are forced to drastically change their plans for the future. The relief of this enormous suffering and social burden requires better organisation of current healthcare provision, but it also needs a deeper involvement by research and innovation. In this sector, as well as in the biological area, patients affected by rare diseases can be considered as a paradigm for research and innovation.

As regards the benefit for companies, firstly, prevalence and incident rates frame the potential market. Clinical research on a new drug can be more easily oriented towards new diseases and this can make the development of new products more sustainable. The issue of sustainability is crucial for everyone involved in the development of drugs.

The high cost of new and orphan drugs in seriously impairing health systems and it will be critical to find a balance between the right level of profit for the company and the survival of the health system. Decision-makers must consider how long they can keep on spending so much money on just a few people. It is important to look at economic sustainability in the context of social sustainability and this differs among communities and also in the same communities at different times. It depends on the shared values that are found in communities and is based on knowledge and perception. For example, in 2010, the NIIH allocated almost $18 billion to research into infectious diseases, while only $1.5 billion was allocated to rare diseases, which is 13% versus 1%.

Figures show that rare diseases account for 4.6% of the total of years of life lost by the general population, compared with 1.2% due to infectious diseases; this imbalance demonstrates the distance that there is between real data and perceptions, and it is only global population-based figures that can fill this gap.

**Ségolène AYME**

You may be surprised to learn that registries in Italy can collect data on all patients with rare diseases, but that is because notification is mandatory when patients want to be reimbursed.

# Patient Data for the Evaluation of the Clinical Added Value of Orphan Drugs: Possible Mechanisms for Collaboration at EU Level

## *François MEYER (Haute Autorité de Santé)*

### I.    Background

At the outset, I would just like to say that I am not really able to address the subject of my talk as it was originally framed.  Instead, I will look more at data collection for the evaluation of health technologies across Europe and rather than consider possible mechanisms for collaboration, I will look at current collaboration and how that might be developed, given that some collaboration is already taking place.  I will then look at where patient data fits in and the place for orphan drugs.

### II.    Health Technology Assessment

Firstly, from the point of view of national Health Technology Assessment (HTA) bodies, health technology assessment, just like any other aspect of aspects of healthcare, comes under national authority.  There is no European Community competence in this area so each member state has the right to decide what happens in their own country.

When we assess a health technology in France, we start by bringing together all the available data and make a report.  A specialist committee, the Transparency Committee for Drugs, then presents conclusions that provide advice to the decision-makers at the Ministry of Health and the Economic Committee for Pricing.  In terms of European cooperation, this more or less takes place at the initial phase of collecting the data and producing the assessment report that is used in national and regional systems to help put together the appraisal documents that are then transmitted to the decision-makers.

There can often be uncertainty at the stage of the initial assessment and some additional data collection may be required.  However, requests for additional data are not always answered in an appropriate way and international cooperation would be highly desirable here, particularly in the field of diseases for technologies where the population is low, which is of course the case with orphan drugs.  For instance, in France, we wanted to cooperate with other bodies to collect additional data on cochlear implants.  This was a case of a medical device, but it would be just the same for an orphan drug.  We contacted two HTA bodies outside France.  The first organisation had not assessed cochlear implants and was unable to cooperate.  The second organisation had done an assessment of the implants and then given a positive opinion, but they had also made a request for additional data.  We were therefore able to cooperate with them and make use of a more meaningful set of data.  However, it then turned out that the collection of the additional data would be undertaken care by another body that was not an equivalent HTA body.  As a result, it was quite difficult trying to cooperate and generate data at an international level.

# III.    Collaboration

This real-life case therefore shows how important it is to be able to cooperate and move from trying to develop ways of working with others on a just-by-chance basis to a more organised way of cooperating.  To do that, we need to take advantage of what has already been developed, particularly in terms of networking, through developments such as EUnetHTA.  EUnetHTA has already developed some tools, such as the Planned and Ongoing Projects (POP) database that will allow participating HTAs to know which HTAs are working on the same technologies and enable to direct contact to be made.  EUnetHTA also has the EVIDENT database, which is a database on all planned additional data generation requests that will be made by the HTAs and this will allow information to be exchanged.  In the future, this could allow cooperation to take place on defining common research questions and developing appropriate ways of collecting information.  This goes much wider than patient registries, of course, and addresses much more than the question of rare diseases.  However, rare diseases patient registries and other relevant areas of information are part of the data that can be taken into account when cooperation takes place.

Possible future objectives could cover the duplication of work and so reduce the unjustifiable differences in the outcomes of the assessments.  There will always be differences in the outcomes and the assessment and appraisal of different countries of technologies because of national priorities and criteria, but it may not be possible to justify some of these differences simply because people do not have the same set of data or because the same methodological ways of assessing the technologies are not used.  A lot of work needs to be done on methodological guidance and on reducing uncertainty through data collection after the launch of a product and EUnetHTA has in fact developed a work package within on that.  We are also aware that there will be activity by the European Medicines Agency (EMA), who are the licensing body in Europe, and the EMA can now make requests not just on data relating to the safety of drugs but also on their efficacy.  It has also been shown that a number of bodies have collected data and we can take advantage of that.  This is an area that we are committed to working on.

Collaboration within EUnetHTA started in 2006 as an initiative by a number of HTA bodies across Europe and has more recently been discussions at the European level on the Directive on Cross-border Healthcare.  In 2009, the European Commission issued a call for joint action by all member states.  Joint action 1 agreed to keep the name EUnetHTA and has developed work packages to produce common information so as to allow HTA reports to be issued by each agency and to work on methodological guidance and develop pilots for common assessment documents for the pharmaceutical industry, including the clinical added value of relative effectiveness and the new technologies that I have already mentioned.

While it is necessary to work in a local context and produce local reports, there is also common evidence that can be shared and the concept of pulling the available information together in structured ways and defining core elements that are important to everyone is central.  All these elements are combined into the core HTA information and that information helps in the production of the local reports.

In terms of assessing the clinical added value of pharmaceuticals, which is something that came out of the pharmaceutical forum on relative effectiveness assessment, there are two types of action.  Firstly, we have methodological guidelines.  For instance, when you assess the clinical

added value, you have to select a comparator.  If you ask different bodies a question, you will get different answers and we are trying to work together to define common standards.  Secondly, there is the use of the HTA core model concept for the assessment of the relative effectiveness of drugs and a pilot is currently taking place that aims to produce common core HTA information on new drugs that will be disseminated to the various HTA bodies that can then use that information to develop their own HTA guidance.

In terms of additional evidence generation, the deliverables of the current joint action will be, firstly, to define the criteria for selecting technologies for which there is a need for additional data generation.  This is the EVIDENT database, which, rather than being a database for collecting the results of the data, is for putting together the list of technologies where there is a need for additional information as well as the type of questions that could be asked.  A further action relates to a registry of clinical studies and planned additional data collection.  In some countries, public institutions fund studies and there can be duplication at times.  We therefore try to point out where that duplication is.

The Directive on Cross-border Healthcare was adopted in 2011 and Article 15 establishes a permanent cooperation network for HTA.  This will be used to exchange scientific information and will operate on a voluntary basis.  The main objectives relate to international cooperation, taking into account the avoidance of duplication of assessment and the desire to share information and methods of operating so as to enhance the quality of assessments.

After the activity of joint action 1, there will be a second joint action that is due to start in 2012, which will last for three years.  This will be the final three-year period because at the end of the three years there will be a permanent network of HTA bodies.  This will established in 2013 and we are starting discussions on what the network should do.  A meeting will take place in Dansk in December to look at the results EUnetHTA's current joint action and the future of cooperation in Europe.

## IV.    Orphan drugs

The Clinical Added Value for Orphan Drugs (CAVOD) initiative was established in 2009 when no joint action was taking placing in the HTA field and, looking back, we can now see a lot of duplication between the two initiatives.  CAVOD talks about information exchange and a methodology toolkit and that is similar to a lot of what is taking place in EUnetHTA so the question now is to look at CAVOD in respect of how cooperation in the HTA field will develop. HTA cooperation has evolved considerably since the CAVOD concept was initiated and it is vital that there is an integrated and coordinated approach.  Action needs to take place quickly here as there will be a meeting on 15 November 2011 to decide what will be done under joint action 2. However, we have not yet been informed within EUnetHTA of the status of the CAVOD report. That should have happened by now because we really need to be able to discuss what we can do together to ensure that there is no overlap.

## V.    Patient Data

There are many questions that relate to the use of patient data.  Firstly, a major issue within the HTA bodies relates to what the appropriate outcomes should be.  We are not very happy with the

outcomes that are used for marketing authorisation and licensing but which are not very patient centred.   There is therefore a major methodological question relating to patient-centred outcomes and there are projects taking place in Europe and the US to define what information should be collected for assessing benefits to patients.  A great deal of coordination is required here so that we avoid duplication, and cooperation between everyone involved is key, although that will not be straightforward.   Nevertheless, there are areas here where we can make considerable progress in the future and I think that this is an area where we can be hopeful.

**Ségolène AYME**

At its latest meeting on 24-25 October 2011, the EUCERD was asked to recommend ways of harmonising the activities of EUnetHTA and CAVOD.

# Questions and Answers

**Wills HUGHES-WILSON, Genzyme and EUCERD**

EUCERD is delighted that there is an imperative from all the stakeholders to encourage collaboration between the CAVOD process and the new reality of the Directive on Cross-border Healthcare.

There has not been as much open and active collaboration between stakeholders, notably industry, and EUnetHTA as may have happened with orphan drugs and where patients, diseases and expertise are rare, we have to work together to be successful.  If there is going to be cooperation on the assessment of orphan drugs and this finds a home in EUnetHTA, how can we ensure that stakeholders are involved in a much more ongoing basis rather than just through the stakeholder consultation forum?  I would add that I see this as an opportunity.

**François MEYER**

We will definitely have to work together in the future when we will have to take into account two things.  Firstly, in the field of health technology assessment where we will have to advise decision-makers on how public money will be spent on one technology or another, the question of possible conflicts of interest is very acute and we need to be very clear about what we say there.  If we do not have that clarity, our conclusions will simply be rejected as being flawed.

However, that does not stop us working together on certain issues.  For instance, we have started to have what we refer to as early dialogue, where we bring together people from the EMA on the regulatory side and others from HTA bodies - and we could also involve academics and patient associations - to discuss the development plan for a new drug.  This began last year through pilots and I believe that it will be developed further in the future.

We would be delighted to receive comments from industry on the methodological guidelines that we will be issuing for public consultation next year.  We asked the EMA if they wanted to see the guidelines before the other stakeholders but they were happy simply to be part of the public

consultation.  You are therefore not last in line in terms of seeing things and I think that we will have many actions that we can work together on in the future.

**Christel NOURISSIER, EURORDIS and EUCERD**

We strongly welcome increased cooperation between the different agencies and are very happy to hear you talk about databases and additional evidence generation for new studies and the harmonisation of what is being asked for for each drug.  Nevertheless, we have some concerns and the concerns that I hear around Europe relate mainly to the tools that are currently used for HTA evaluation in some countries, such as the National Institute for Health and Clinical Excellence (NICE), where we believe that the tools are not adapted to the evaluation of orphan drugs.  Might we therefore hope that the cooperation will improve processes rather than just imposing ways of evaluation that may not be appropriate to orphan drugs?

A second concern relates to the involvement of patient representatives.  As we all know, most rare diseases are extremely rare and what we see at EURORDIS is that for very rare diseases it is difficult to involve patient representatives because either the patient organisations are very small and the people are not professionals or trained to talk at European Union (EU) level or there is simply no patient organisation.

**François MEYER**

The European Commission puts a lot of emphasis on the involvement of patient representatives in HTA and the question of training patients on the HTA process will be included in the projects that are coming up.  This is therefore of very high importance to DG SANCO.

As regards cooperation and the criteria and so on, this is not something that will be included in the network because we respect the choices that each country makes regarding how it organises its healthcare systems, including criteria for health technology assessment and appraisal.  However, that does not mean that we do not speak to each and we can observe what is going on.  To take the UK, for example, given that you mentioned NICE, there was the question of the so-called ultra-orphan drugs for very rare diseases.  My understanding now is that drugs can be assessed through the regular appraisal system, even if they are orphan drugs, but that there is a different approach for drugs for very rare diseases.  This is a very interesting approach because it integrates the assessment of the technology and the healthcare pathway and organisation and makes recommendations on both aspects.  As I understand it, therefore, drugs for very rare diseases are not prevented from reaching patients in the UK.

# Roundtable of Stakeholders and Discussion

*Domenica TARUSCIO (Centro Nazionale Malattie Rare and EUCERD) & Maria MADISON (Shire)*

## I.    EPIRARE

**Domenica TARUSCIO**

EPIRARE is a new project funded by DG SANCO which began in April 2011 and will conclude in 2013.  The main aim is to assess the needs and opportunities of the existing registries, and we saw this morning that there are more than 500 registries on Orphanet.  We have already launched a survey aimed at identifying needs and gaps and identifying ways in which we might cooperate.  We want to see if we can find ways of having common data elements and sharing policies and activities.  We are also interested in identifying legal constraints, where privacy is an area that is a big problem.  EPIRARE will therefore aim to find synergies among all the stakeholders for building a European platform for the sharing of data, where I think the need is great, and to produce new inputs and information from both the public health and the scientific research points of view.

## II.    Trust and Quality

**Maria MADISON**

I think that much of what has been talked about is exciting.  This is the future and it is the direction that we would all like to go in and the aim would be to look a little more closely at personalised medicine and the genotype/phenotype.  However, three things come to mind that have not yet been highlighted.  Firstly, as regards partnering, we would like to shore up trust across all the groups and having trust with investigators and patients is the first hurdle when encounter when we try to form partnerships.  It is then about trying to get a clear sense of the variables that are required in terms of both regulation and what would be most meaningful in furthering the understanding of rare diseases.  The registries are rich, but by partnering we are more likely to produce something of a higher quality as those participating are anxious to use the data to further understanding.  We therefore need to ensure that we select a critical path of data, identify questions and hypotheses from the outset and refine the database to get a higher level of quality.

In terms of what we can add to the process, an area of huge importance is patient-reported outcomes, where we can get quality of life data and real-time information.  The field of hereditary angiodema, for example, is poorly understood as regards number and types of attacks and health-seeking behaviours and that kind of information would move treatment guidelines forward dramatically.

**Ségolène AYME**

We said exactly the same thing at EUCERD's workshop in London in October 2011 where we saw the way forward as being partnering and having common tools so as to design the registries together.

Andrew Devereau told me this morning that a lot of genomics data is generated but that the clinical data to make sense of it all is missing. It is therefore extremely important that clinicians collect the appropriate data to feed into the research.

**Andrew DEVEREAU**

That is exactly right. This related in particular to next-generation sequencing and how the people who design the analysis lacked right from the start of patient contact the input from the clinicians in terms of the coding and description of the phenotypes and diseases. That data was therefore not being fed into the design and analysis, but it also meant that it was not possible to annotate the genomic datasets with the phenomic data. It is vital to bring the clinician into the pipeline.

**Ségolène AYME**

It would therefore be useful for both public health and research purposes.

## III.    The Privacy Directive

**Ségolène Aymé**

There are obviously huge opportunities for collaboration and sharing, but there are also some pieces of European legislation coming out where people working in rare diseases might need to be a little more vocal. In particular, there is the Privacy Directive, which deals with data transfers in Europe. I do not think that the legislation there has been drafted with medical research in mind and having worked on national statistics occasionally I feel that issues may arise in terms of genetic-linked information and it is of concern that people with rare diseases are likely to be able to be identified even if their data is anonymised. Some policymakers are not used to working in the medical field and are not aware of the voluntary participation of many rare diseases patients as regards the sharing of their information. There is therefore a risk that the legislation will make it difficult to transfer information because very specific consents will be needed from patients on how the information is used and it may necessary to get consent a second time from people who have already consented to participate in a registry. Therefore, amongst all the optimism, there are some things where we need to be vigilant to ensure that the benefits of sharing information come through. Otherwise some unintended consequences of regulation, aimed at areas such as information on credit cards, could impede medical progress.

# SESSION III - IMPROVING ACCESS TO EXPERTISE AND QUALITY CARE

## Centres of Expertise for Rare Diseases in Member States: Current Situation in Europe and Recommendations from EUCERD for the Implementation of Centres of Expertise

*Edmund JESSOP (National Commissioning Group, NHS London and EUCERD)*

### I.      The Current Situation

They key point about Europe is its variety and different member states are at different points of development in designating centres of expertise.  A small number of countries have officially selected their centres of expertise for rare diseases but these are for different sets and categories of disease and they have gone about things in different ways.  A slightly larger number of countries have some form of designation, although this has not been done on an official basis.  While that is acceptable, it would be preferable if this informal system was made more formal, although doing that would have a number of funding implications.  Quite a large number of countries are then developing their designation as part of their requirement to produce a plan for rare diseases.

The European Commission issued a Communication and the European Union Council of Ministers and Parliament issued a Recommendation a few years ago on rare diseases, a key part of which was that each member state should have a plan, strategy or framework for rare diseases by end of 2013.  Although the content was not specified in detail, it would have to be assumed that a central part of the plan would be to identify the hospitals that have the necessary expertise for treating a range of rare diseases.  This work is therefore going on in the context of developing those plans.

In general terms, coverage is quite good and we are optimistic that every country will have a system for identifying centres of expertise within a few years' time.  Absolutely fundamental for ensuring high-quality care is identifying where that care can be obtained and labelling it as such.

Looking at some examples of centres of expertise, Denmark has two centres, while France and Spain both have about 130.  However it is not of course the case that France and Spain are 70 times as big as Denmark so the concept of a rare diseases centre is different in those countries.  Italy has a kind of regional system, with 250 centres of expertise.  There is therefore no single concept as to what constitutes a centre of expertise.

There is also no uniformity on coverage.  For example, four or five countries have centres of expertise for dismorphology, but only one country has one for cri du chat or bladder exstrophy.  Quite a few countries have centres of expertise for the porphyrias, but only one has it for

phenylketonuria.  There is therefore a huge variety in what is happening around Europe.  That is not surprising, but it presents certain problems.

## II.    The Recommendations of the Committee of Experts on Rare Diseases

The EUCERD is a very large committee, containing representatives from all 27 member states and including clinical experts in rare diseases, patient organisations and representatives from the pharmaceutical industry.  At meetings like this, I am always reminded of the famous lament of President Charles de Gaulle regarding trying to rule just one country.  If you multiply that by 27, trying to get agreement on anything is a very long and slow process.  Nevertheless, agreement has happened.

The first set of recommendations from the committee came in a document entitled *Quality Criteria for Centres of Expertise for Rare Diseases in Member States* which was agreed at a meeting in October 2011.  The member states are formally represented on the committee and, in principle at least, each member states has signed up to the quality criteria.  As it was a long and detailed process, there has been a lot of expert input, including from clinicians, patient groups and industry and although the recommendations are not mandatory, they carry weight.

45 recommendations were made, grouped into the following categories: the mission and scope of the centres; the criteria for designation; the process by which designation is achieved; and the European dimension.  The document states explicitly that recommendations are not listed in any particular order of priority nor are they labelled as essential or desirable.  Some of them are obviously more important than others, but the prospect of trying to put them into some kind of order was just too daunting.  Bearing that in mind, the recommendations that I will focus on today are just a personal selection to give people a feel for the document.

Doctors are taught to focus entirely on the patient in front of them.  Their duty is to the patient and there is a one-to-one relationship with the patient.  That is admirable, but it has the unfortunate effect that doctors then feel no duty to patients elsewhere.  One of the key features of the recommendations on centres of expertise therefore is that they must look outward and not focus solely on their own particular patients.  The making available of expertise is hugely important and a number of the recommendations bring that out.

Firstly, centres of expertise must be concerned with what is happening in primary care.  There is no point in a family doctor making a diagnosis if they do not refer the patient to the centre of expertise and it is therefore one of the tasks of the centres of expertise to build a pathway that takes the patient from primary care to the centre of expertise.  The recommendations do not go into detail on how that should happen, but they make it clear that it is part of a centre's mission.

The movement of the patient to the centre of expertise will be necessary at times, particularly when a patient requires an operation or other kind of intervention.  However, the dominant ideology here is that the expertise should go to the patient.  Travel is burdensome, especially if you are suffering from a severe illness and it is therefore better for the expertise to travel rather than the patient.   That can take place through the centre of expertise developing and promulgating good practice guidelines, offering education and training to local healthcare staff, and making information widely available.   This is a great achievement and many of the

developments in improvement of care for patients with rare diseases have been spearheaded by France and Ségolène Aymé in particular.  The Orphanet database is an enormous resource of huge importance to the care of patients with rare diseases.

The second group of recommendations that I will look at is criteria for designation.  Although all 45 recommendations are equally important, my personal view is that more could have been done to emphasise the importance of experience in expertise.  In the UK, we think that it is very important for centres to deal with large volumes of patients because we believe that volume and experience bring expertise.  That concept is in fact included in the recommendations, although it is not easy to find.

The recommendations also see quality management systems as important, although the document does not specify what these should be.  We have talked at this conference about the quality management of laboratories and there has been concern about quality testing and external quality assurance as regards laboratory work.  However, this also applies to quality systems throughout clinical care.  In the UK, we tend to regard this as part of clinical audit, but the concept exists clearly in the recommendations.

Centres must also contribute to research.  If you do not contribute to research, you are probably not very interested in the disease and if you are not interested in the disease why would a centre claim to be an expert in it?

The actions outlined here need to be taken by member states and if the processes are run by the member states the hope is that there will be a reasonable amount of resources attached to them. In fact, it was felt necessary to include a recommendation to member states that if they designate centres of expertise, that implies an obligation to resource the centres to carry out their missions. The designation process needs to be transparent, as does its evaluation in due course, and this is particularly important in respect of patients moving from country to country.  When a member state is running its own process, patients from other member states who wish to go to that member state for treatment will want to know how that process is being run.

The recommendations also state that designation will not be in perpetuity but for a fixed period only.  They do not set out what the period is, but centres will need to be re-evaluated.

There are also recommendations at the European level.  Transparency requires member states to share experiences and that is a good thing because we can all learn from each other.  There is also the issue of networking and the document touches on the Directive on Cross-border Healthcare.  The Directive is legally binding and includes an article on rare diseases, although that article encourages cooperation and collaboration rather than compulsion.

## III.    Summary

We believe that the EUCERD is the only international committee focused solely on rare diseases. It is a large group, which means that things are done slowly, but that means that when we achieve consensus it should carry considerable weight.  The Committee's document will be made

publicly available and I hope that everyone will be able to make use of it to improve the care of patients with rare diseases.

# Questions and Answers

**Helena KAARAINEN, National Institute for Health and Welfare, Finland, Vice-Chair of EUCERD and Co-Chair of Conference**

What happens before a specific diagnosis of a rare disease is made?

**Edmund JESSOP**

Two aspects of the recommendations address this. Firstly, there is the importance of information, which needs to go both to patients and primary care doctors. Secondly, this goes to the point that the centres of expertise must build pathways from primary care and feel responsible for what is happening in primary care in their area of responsibility. One recommendation is for centres of expertise to have a defined catchment area and feel responsible for what is happening there. In fact, data has shown that the act of designation reduces delay in both time to diagnosis and time from diagnosis to effective therapy.

**From the floor**

We have had mandatory training in certain parts of France for medical students for six or seven years where they are encouraged to think, where they do not quite understand a particular disease, that it may be a rare disease.

**Edmund JESSOP**

The dominant philosophy for higher-level medical training in the UK currently is that curriculum time should be proportional to the commonality of the disease. However, there is also a very strong school of thought that that is the wrong way round.

# Networking Between Expert Centres: Where Do We Stand?

## *Ségolène AYME (Orphanet and Chair of the EUCERD)*

### I.      Defining What Should be Shared

With 27 different healthcare systems that have different priorities and centres of expertise that are at very different stages of development, it is very hard to talk about networking. Nevertheless, with the recommendations of EUCERD, we now have something that we can build on.

We agreed at the European level that networking is useful when the aim is to collaborate, and there are a number of areas where this could be relevant. Firstly, as experts will be familiar only with certain aspects of a disease, the sharing of wider expertise is important. In addition, if guidelines are to be produced, that needs to be done at an international level and if we want to make progress in the area, we need to have research teams with people from different fields.

There is also then issue of the sharing of tools. We need tools to enable us to consult colleagues, disseminate guidelines, identify where the expertise lies and show where the laboratories can be found and so on. There is also a need to establish databases of patients, cohorts and biobanks.

## II.     Developments in the Fields of Rare Diseases and Public Health

Over the past 10 years, the European Commission has funded several networks where people have shared data on patients, and as regards rare diseases the first step is to get together a sufficient amount of data that people can work on. Those who were interested in networks wanted to establish a repository of biological samples and share expertise on approaches to research problems. DG SANCO has also funded a number of public health networks for the sharing of clinical experience in relation to difficult cases and for producing guidelines and other information. The main thing that people requested funding for was to establish a database of patients. Therefore, although the aims of those two funding areas were different, the approach taken was virtually the same.

## III.     The European Reference Networks

The emergence of the concept of European reference networks came from the fact that patient organisations wanted to identify European centres of expertise for very rare diseases. We knew that it would not be possible to work directly on this because health is an area that is decided at the member state level and what we did therefore was to set up the Rare Diseases Task Force, which preceded EUCERD, to explore the relevant concepts. This culminated in a recommendation to develop national centres of expertise, which would be done at the member state level, and the idea then was to develop European networks as a second step. This was consistent with other work that had been done by the High Level Group for Healthcare Management and Medical Care, which defined the need for expert reference networks in Europe for other areas of medicine, but including rare diseases, and we have exchanged a lot of ideas with them. The need for European reference networks is also mentioned in the recommendations of the Council of Ministers of June 2009 and the Commission agreed to fund a small number of pilot networks.

The networks that have been funded to date cover a wide range of medical areas, although these have basically been public health networks and rather than linking expert centres, they have linked individual experts themselves. They have therefore been more about collaboration between people and establishing the use of tools for collaboration. We therefore cannot say that there are real examples of what we propose the European networks to be like in the future, but it is nevertheless interesting to take a look at them because you can always learn from experience.

Almost all these networks have established a common patient registry, which are either European or national according to the relevant national legislation. They also have usually established a process for submitting questions to experts and one project on cystic fibrosis has set up a system

for storing the questions and answers in a database with the aim of making this available to all patients and clinicians. This is still in the early stages of development, but the idea is excellent and is an example of what could be done in the future.

Of greater interest has been the development of a system for unsolved clinical cases where within two days of submitting a query to a network of experts professionals receive an analysis of their case and suggestions for further action. All these cases have been stored to create a database and it is quite likely that we will be able to refine this approach in the future. The network developed very well in its first three years but funding then stopped and they simply do what they can now.

Importantly, all the networks developed clinical guidelines.

Funding was a major issue for most of the networks and it is therefore not a good idea to start work on a network if the funding resources are not there. Collaboration therefore has a cost. A report produced by Orphanet lists all the centres of expertise for rare diseases at the national level and analyses the coverage of centres. A lot of our data is therefore available for people to access.

## IV.    Lessons Learned

The lessons that we have learned are, firstly, that you cannot have all the required expertise at the level of a single centre. Once a network is established and there is collaboration, it immediately begins providing data that improves people's knowledge of diseases and, as a consequence, diagnosis is improved and the data allows the development of guidelines. It also means that there is enough knowledge on patients should a clinical trial be started and this attracts the interest of industry. Suddenly, everything about a particular disease is more visible and patients end up getting better care.

The most successful networks have contributed to the pathophysiology and the possibility of there being trials as well as the delivery of therapy. Once you have the data, you have something that you can discuss with the regulatory bodies and the payers and you can demonstrate what the added value is. It is therefore a very positive loop and even if there is a cost, the benefits can be enormous.

Networks and registries are key success factors for the development of drugs and therapies and together with the patient organisations they are a key factor for success. We need to support both approaches. In addition, collaboration at European level can be very successful and easy to demonstrate.

## V.    Challenges

However, there are quite a number of challenges in front of us. Firstly, as already mentioned, most of the funding agencies provide funding for limited periods only, when the real value of a database can come after 10 years or so. We therefore need to find a mechanism to provide long-term funding to these types of initiatives, which must be seen as a shared facility. As resources are so scarce, it is vital that duplication is avoided. The data needs to be shared with

other researchers, industry and patient organisations and funding needs to be provided by all the interested parties. There also needs to be discussions with, for instance, the health technology assessment agencies and the public health authorities, as they need to contribute to the setting up and management of these registries.

In terms of next steps, the Commission will need to help these networks, but first of all the member states have to establish their centres of expertise and encourage them to connect to other centres of expertise, if that is relevant for the disease. We cannot of course force people to collaborate and this must be done voluntarily.

## VI.    The Directive on Cross-Border Healthcare

The work that we are doing on the European reference networks for rare diseases fits very will within the new Directive on Cross-border Healthcare that was adopted last year and will be implemented by the member states over the next two years. The aim of the directive is to help patients exercise their right to reimbursement for the cost of healthcare that they receive in other EU countries. This is quite a common issue today because people travel a lot and some surgical resources may only be available in another country. The directive also aims to ensure that the care provided is safe and of high quality and establishes formal cooperation between health systems.

Up to now, citizens have been able to receive financial support when receiving treatment in another country, but they had to apply for that support in advance and the country of origin was required to confirm that it was impossible to provide the care. With the directive, payment will have to be made upfront, with reimbursement taking place later in the patient's own country in line with the health insurance coverage of that country. For some countries, that means that the cost will of course not be fully covered. Essentially, therefore, this is not real progress for patients and I hope that the old system will also remain in place alongside the directive. As regards the European reference networks, cross-border healthcare will be justified per se in the few areas where these networks will exist and they will be for specific conditions. However, bilateral cooperation agreements between member states will of course remain in place and there are also agreements between payers, so a number of opportunities for cooperation exist.

Article 12 of the directive relates to the enhancement of cooperation between member states in the area of European reference networks where the main aim is to facilitate improvements in the diagnosis and treatment of certain diseases through the delivery of high-quality, effective and cost-effective healthcare for patients suffering from medical conditions that require a particular concentration of expertise or resources. The field of rare diseases therefore fits into the definition very well, although it was not defined specifically with rare diseases in mind. This is therefore about improving the diagnosis and the delivery of high-quality, accessible and cost-effective healthcare. Cost effectiveness relates to having these costly platforms concentrated in a small number of places and a small number of centres.

## VII.    Other EU Initiatives

The Directive on Cross-border Healthcare is not the only approach in Europe for improving collaboration. As we know, EUCERD looks after the field of rare diseases and there are also

initiatives in the area of electronic health, where I do not think that we have had enough of an interest. There, the member states are looking at how to exchange data in hospital files and I believe that opportunities exist there for us as well. In addition, some joint action is starting on patient registries in general and we should also be collaborating with that. Finally, there are initiatives on patient quality and safety. We are therefore just one element within a group of initiatives and we should take advantage of this where we can.

## VIII.  Criteria for the European Reference Networks

The areas that the European Commission has identified for future European reference networks currently are rare diseases, plastic and reconstructive surgery, ophthalmology, medical oncology, transplantation, traumatology, cardiology and heart surgery, neurology, neurophysiology and spinal chord injury. The assessment of areas is ongoing and we will continue to liaise with Commission on that. A number of diseases that are quite rare have already been listed, although the way the Commission has gone about this has been a little odd.

The Commission used a number of priority criteria to come up with their list. What they were interested in was the identification of diseases whose prevention, diagnosis and treatment could bring added value if a network existed. For these relatively rare diseases, the criteria relate to: where the diagnosis and treatment is complex and requires specific expertise; where there is a large amount of resources and advanced medical equipment involved; where there can be added value through improving the health outcomes and quality and safety of care; and where the cost effectiveness and sustainability of the European healthcare system could be improved.

There were also some other quite general criteria where they looked at issues such as the kind of organisation that can be put in place to ensure collaboration, the elements of an information system that are already in place, such as data protection, respect for patient rights and ethical issues, and clinical guidance. All these issues will apply to the European reference networks, but as these networks will be made up of expert centres there will be no need to look at the expertise of the centres again; what will be required instead will be to look at the quality of the networks and what they will add.

There will also be disease-specific criteria that will look at whether a particular disease will really benefit from having a network and again whether there is an appropriate information system in place, with the right human resources, equipment and so on. However, what is not clear to us is what the expected funding provisions are. It is obviously impossible to network without funding but we do not know where the funding of the networks will come from, although funding by DG Public Health is one possibility.

## IX.  Activity at European Level

We therefore need to liaise with the people who are developing the criteria for the Directive on Cross-border Healthcare to ensure that they take into account the specific features of rare diseases. In fact, they expect the Committee of Experts on Rare Diseases to help them with this because they believe that we have more experience in this area, although they are highly experienced in the field of transplantation, where there are very good networks. We

therefore propose that the member states designate their own centres because without the centres in the member states there will be no reference network.

At EUCERD level, we will work in the coming weeks on a recommendation on the quality criteria for European reference networks for rare diseases, in exactly the same way as we did for the centres of expertise at national level.  We will try to consult all the member states and other stakeholders and our hope is to have the recommendation adopted by June of next year.  I think that we can achieve this if we work hard and this will really assist the group working on the implementation of the Directive on Cross-border Healthcare.  All of this will be in our best interests and I hope that everyone will contribute to the effort and that we will be able to ensure that there will actually be European reference networks for rare diseases.

The establishment of the expert groups has to be completed in 2011.  There will then be the adoption of criteria and conditions for centres of expertise and European reference networks in 2013.  We already have our set of criteria for the centres of expertise and will provide another set for the European reference networks.  A committee will be established with the aim of publishing a directive or recommendations in 2013 and developing criteria for evaluating the European reference networks.  Everything should therefore be in place by 2013 and the first European reference network should be identified and financed between 2013 and 2015, after which there a permanent support mechanism needs to be put in place.  We therefore have to act quickly if we want to input into this process.

# Questions and Answers

**Samantha PARKER**

The European reference networks do not cover all 27 European member states but, in my area, where it has not been possible to identify an expert centre it is often because no expert centre exists.  What then happens is that a centre is identified that could be trained to take on the responsibility.

These networks certainly need funding to run, but there is a great deal of voluntary participation by the clinicians.  Additionally, having a good leader of the network is essential.

**Peter Robinson**

The different medical specialities that deal with rare diseases have very different perspectives and, as a medical geneticist, I feel that my perspective has not been adequately represented here.  The structures are great if you already have a diagnosis but people with rare diseases spend years looking for a diagnosis.  That is the responsibility of medical genetics and I can see that there are several unmet needs here.  Hospitals have nobody who knows how to interpret the new sequencing technologies and I therefore think that we need a new medical speciality, which would be called medical genomics, to deal with the interpretation of sequences and also, over time, more complicated genomics technologies.  There needs to be centres for making diagnosis and interpreting genome sequences to help with diagnosis.

**Ségolène AYME**

I see that as being a perfect example of a future European Reference Network.  However, first of all, the national centre of expertise needs to be established.  This could be a typical example of the network given that the technology is costly, there are few experts and interpretation is crucial.

**Christel NOURISSIER**

In France, we have designated centres for people with mental disabilities who are currently undiagnosed (about 50% of them) and in this field European cooperation is really mandatory.

# The Testing Landscape in Europe: Challenges and Solutions

### *Gert MATTHIJS (University Hospitals, Leuven and EUCERD)*

### I.       Genetic Testing

In terms of genetic testing, there are probably five areas of key interest at the European level. First, we have the question of the quality of test results. This will become an enormous challenge as soon as we start dealing with next-generation sequencing. Secondly, I am concerned about cost and reimbursement. There is a real need to change direction there.  The two other issues are slightly technical in nature. The Directive on In Vitro Diagnostic Medical Devices, which includes laboratory tests, is currently being revised and it is important to correctly introduce genetic testing into the directive. Finally, Direct to Consumer Testing results in the increasing and uncontrolled availability of genetic testing through the Internet.

Looking, firstly, at the quality of genetic testing, a report in 2003 revealed that there were more than 1,500 laboratories offering genetic testing. It showed that most activities take place in public hospitals. This report was the basis of the creation of EuroGentest, a network that brings together laboratories and genetic centres to try to deal with the issue of quality and harmonise activities. Errors are still being made in genetic testing and our aim is to raise the level of quality.  In terms of legislation, there is no need for new regulations in this area.  ISO 15189 exists to guarantee quality in the laboratories and at EuroGentest our standpoint is that accreditation will be the norm and patients can be confident about the quality that is being offered if laboratories are accredited.  It is therefore simply matter of putting the existing rules in place.

Accreditation is obligatory in only a few countries today.  In Belgium, for example, it will be conditional in terms of reimbursement once the Government signs a law which has prepared concerning this area.  This law requires all Belgian genetic laboratories to be accredited by 2014. A similar situation applies in France.  However, colleagues in France are extremely concerned: the deadline there is 2016 and the directors in the hospitals should work hard to make sure that the laboratories get the additional funding needed to reach this level because both money and time are required to prepare for accreditation.

In terms of compiling a list of accredited laboratories, EuroGentest joined forces with Orphanet. The quality indicators can be found there. In addition, we are currently undertaking a survey to see how many laboratories are accredited currently and our aim is to bring everyone up to the same level.

For quality assurance, we insist that there should be only one route between test development and the clinical use of the test, which would be through extensive validation. This is a step that many people tend to skip, although it is the most important step of all. Unfortunately, we are now seeing the opposite happen in the private laboratories as well as the public laboratories - people think that it is easy to offer genetic testing and as the market becomes increasingly competitive, validation is at risk of being skipped. EuroGentest is therefore setting down guidelines to instruct people on how to validate tests and guarantee sensitivity and specificity before anything is put into practice.

In terms of clinical service, it is true that clinicians are somewhat refractory to quality assessment, but this is not an impossible area. Again, EuroGentest is working hard here on guidelines on genetic counselling and practice. There are ways of assessing the quality of the clinical service in genetic centres. We are working hard on clinical utility gene cards: for each rare disease we try to have a very short 'gene dossier' that sets out what the state of the art is and what should be done both clinically and in laboratory terms. These cards will help in setting standards and making sure that quality of care is being guaranteed.

What about next-generation sequencing? There is a general belief that the next-generation sequencing will soon come of age and while I share that belief, I think that we need proceed with care.

Before looking at next-generation sequencing, I would like to set out what I understand to be genetic testing today. On the one hand, we have molecular tests, i.e. mutation analysis. This starts with one disease and one mutation, as in the case of Huntington's disease, where one simple test is sufficient. On the other hand, Down Syndrome is easily detected through a cytogenetic analysis, for example, and there is no need for a new technology there. However, in the middle you have cases where one disease may be linked to several genes and it is very hard to address those issues with current technologies. This is where new technologies will eventually be able to help us: to deal with heterogeneous conditions where it is not easy to pinpoint the mutation. Thus, these technologies can be used at different levels. They can be used to speed up current diagnostics, where, for instance, breast cancer genes can be sequenced much more quickly than with previous technologies. We can carry out targeted screening and sequence a number of genes at once. The next step is exome sequencing and we may eventually go as far as total genome sequencing.

Let's take the example of Charcot-Marie-Tooth Disease. It is very hard to distinguish on a clinical basis between the different types of the disease and some 36 different genes can cause the condition. At present, no single laboratory can test everything and when everything is tested, it becomes extremely expensive. This is where this technology can come in. Some laboratories, such as Nijmegen, are doing pilot work and offering exome sequencing in a diagnostic setting. However, I think that people should be very careful here because the issue of quality has still not been resolved.

There are 250,000 exons that need to be sequenced if we want to sequence the 'exome' of a patient. Imagine that you would have reliable data on 99% of them; you would still miss a lot of individual data points. The technology therefore needs first of all to be improved and validated. Nevertheless, it will be very helpful in those cases where we are dealing with difficult diagnosis.

Companies have been quick to jump on these new technologies and they are faster at investing than public laboratories. For instance, one company has announced that it is offering a next-generation application for sequencing all the mental retardation genes at once. While this sounds good, I would like to see the validation data behind this technology and I would like to ask them to provide details on sensitivity and specificity and how this is validated. We have to ask the question whether this is ready to be offered in a clinical service and, for me, the answer is not yet.

One of the key questions regarding next-generation technologies relates to who will actually be doing it, and it is clear that private companies are getting ready for this. In the United States, Illumina is setting up a diagnostic company where they are sequencing the genome. However, they are leaving it to the customers to analyse the data. So they are generating raw data and not providing diagnostics. As a community, we will therefore have to insist that there is a complete service before something is placed on the market. In Leuven, we are lucky to have a Genomic Core facility where we access the next generation sequencing technology. I am aware of the frustration that colleagues in France have, where they are not in a position to put this into operation in the public health service because they are lagging behind in acquiring these machines. However, my hope is that everyone will be able to be involved eventually, particularly as the technologies are getting cheaper day by day.

Another concern is about the interpretation of the sequencing results. I doubt that we are ready today to generate useful reports on a total exome or genome analysis at the clinical level.

Even today, we are not sure how genetic testing should be reimbursed. We know from Orphanet where to find a laboratory that offers tests for the rarest diseases. However, the cost of a single gene test is often EUR 1,500 or more. For most health care systems, this is not affordable certainly not if one needs to test several genes for a number of patients. This may work in a health system such as Germany's where there is apparently a lot of money available or in the US, where people can afford it, but it is not compatible generally with our public health services. With prices of exome and genome going down rapidly, we may eventually be able to solve the problem of paying for comprehensive genetic testing.

In terms of data on reimbursement, it does not appear that any kind of inventory has been put together on what the situation is in each country. I know that this is not well organised in France while in Germany prices are extremely high. In the Netherlands, everything falls within the public health service but laboratories there receive twice as much money per test as compared to Belgium. Thus, the whole situation does not appear to be sustainable. Recently, we have proposed a new reimbursement system in Belgium with the introduction of a stratified system where a small amount of reimbursement is provided for a simple test, while a complex test will be reimbursed more generously.

# Roundtable of Stakeholders and Discussion: How to Organise Healthcare at the European Level to Meet the Expectations of Patients

*Helena KÄÄRIÄINEN (National Institute for Health and Welfare Finland - Vice-Chair of EUCERD), Odile KREMP (French Ministry of Health, EUCERD), Wills HUGHES-WILSON (Genzyme, EUCERD), Samantha PARKER (Orphan Europe, EUCERD), Christel NOURISSIER (EURORDIS, EUCERD)*

## I.       Organising expert centre for rare diseases in Europe

### Helena Kääriäinen & Odile Kremp

All the member states believe that the way forward in organising healthcare for rare diseases at the European level is through the expert centres and European networks, but a number of conflicting issues have come up in recent discussions that I would like to highlight.  One of the more obvious of these has been that while patients want the best possible expertise available, they also want healthcare that is convenient.  Additionally, most healthcare practitioners feel that they lack expertise in rare diseases, while on the other hand they often view this as the most interesting and exciting part of their work.  They want to play a role in cases of rare disease and do not want their patients having to go to remote expert centres.  Another point that has been raised is that while most countries recognise that expert centres provide the most effective way of using healthcare resources, the centres do not always fit neatly into current systems.  In economic terms, rare diseases can require treatments that are very expensive and while patients for rare diseases are themselves quite rare, the unfortunate case with healthcare is that whenever money is being used for one thing it is always at the expense of some other healthcare or wider public sector need.  It would therefore be helpful to have some studies on how these expensive treatments are used, although there also needs to be an element of solidarity.  A third point that concerns the cost of usage relates to the provision of social services to patients with rare diseases.  All the member states agree that there should be ample provision, but in many countries there is not always an understanding of why services need to be different for rare diseases.

### Christel NOURISSIER

In the EUCERD Joint Action 2012- 2015, there will be a special work package where countries will share experiences on social policies and specialised social services for rare diseases.

## II.      European Reference Networks

### Samantha PARKER

A key added value of the European Reference Networks (ERNs) is the multidisciplinary approach, where patients will be seen by a range of specialists and clinicians.  In addition, the

multi-stakeholder governance of ERNs is a major contributor to success, where patient groups, clinicians, regulatory authorities and industry are involved in the strategy, decision making and dissemination. From personal experience, I see four principal areas of action. Firstly, there is the identification of expertise: many networks start from small groups of people with a common interest and their role is to identify where other centres exist and provide training facilities when required. Secondly, the sharing of expertise in patient management, particularly in terms of difficult cases, is a major strength of collaboration at European level. Thirdly, building standards of care and quality, in terms of laboratory quality assurance programmes and clinical care guideline development. Finally, it is vital that we improve clinical research and these networks are the hub of moving forward on trials and further research. There are between 5,000 and 7,000 rare diseases and we need to provide solutions such as the reference networks for all RD.

## III. Areas for Future Collaboration

### 1. Gathering Information

**Wills HUGHES-WILSON**

We have had the orphan drug regulation for 10 years now and while it has been very successful, we are now beginning to be frightened of the fruits of this work because of the cost of treating patients. However, we have to acknowledge that we live in a very different world today from the world in 1983 when Genzyme first started clinical trials in this area. For me, collaboration at the European level will therefore be the key going forward. Countries themselves are responsible for paying, which is absolutely right, but we also know that where patients and expertise is rare we need to avoid duplication and make the most of what we have. I would therefore suggest that the first area that we should collaborate on at the EU level is gathering the information on orphan drugs through the CAVOD process, which would be voluntary, bottom up and between countries and stakeholders.

### 2. Price and Reimbursement

A second area of collaboration could be price and reimbursement, and there is currently a project between EU member states that is focusing on creating a mechanism for coordinated access on price and reimbursement. The information here would come from CAVOD and we could then work together to figure out how price and reimbursement could be negotiated.

### 3. Early Dialogue

A third area that we need to focus on is having early dialogue. A lot of work has been done on what happens after a drug has been approved but I believe that that is probably a bit late in the day. If people invest a lot of time and money on something and then the decision is taken that society is not going to pay for it, it is a dreadful waste. Therefore, if something is going to be turned down, it needs to be done up front and we need to have an early dialogue to decide that. We also need to focus on the cost of not treating. We hear a lot about the cost of drugs and it is often felt that patients are either too expensive to treat or that companies are somehow wrong for having made the investment. We therefore need to think about not treating and a three-year

study has been commenced recently by the London School of Economics on the costs of not treating rare disease patients where the hope is that this will help decision-makers weigh up all the issues.

## IV.    Key Hopes and Expectations

**Christel NOURISSIER**

As we have been discussing, one of our key expectations is that no patient living with a rare disease should be denied access to diagnosis, information, an expert centre and adapted social care.  This is the big challenge that we have to meet currently and in the second French plan: we are trying to find a way of grouping diseases in a way where the maximum number can be covered, including the rarest diseases.  We therefore need to group diseases in comprehensive networks, which will be a complex task, and networks will need to have a very comprehensive coverage, ranging from diagnosis labs to medical and social care and responsibility for referral of biological samples and patients abroad, if necessary.  Additionally, we need to work at finding ways for expensive equipment to be shared between centres, although that is perhaps something of a dream at the moment.

A second key hope is that people will make the best use possible of biological and clinical data and it is important here for EUCERD to disseminate best practices for the collection of data: use of Orphanet nomenclature, ICD 11, minimum common data set, quality control, association of patients to the collection of data on quality of life.

Thirdly, there needs to be innovation.  We believe that the centres of expertise, regrouped in new advanced networks, will be the best incubators for research. This could be research on best clinical practices for care, for example, but there is an endless list of possibilities in the field of rare diseases. Centres of expertise should generate new data for innovative care practices, conduct strategy trials covering all aspects of patient care, beyond and in addition to drug treatment, and look at research into quality of life, social needs, living and working conditions and education.

Finally, something that we all agree on is the exchange of best practice throughout Europe in European reference networks, and we need to extend this to new areas.  It is very important that we find new models for linking high-level expertise at EU and national level to provision of care and disability policies at regional level.  For me, this is the biggest challenge and it is vital that we share experiences in the years to come.

I would like to end by thanking the Eurobiomed team, Ségolène and everyone for the energy that they have put into organising this event and I hope that we can meet again soon to carry on our work.

# END OF PROCEEDINGS