Programme of Community Action on Rare Diseases

Contract 2004105

RDTF Scientific Secretariat Second Annual Scientific Report

1 June 2006 to 31 May 2007
Project Leader: Dr Ségolène Aymé, INSERM, Paris, France
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SUMMARY

Objectives

To assist the European Commission services in implementing the Community Action Programme in the field of Public Health for all issues related to rare diseases (RD) and information a scientific secretariat for the Rare Disease Task Force (RDTF) was established in 2005. This scientific report describes the accomplishments of the RDTF during Year 2 (1 June 2006 – 31 May 2007) of the contract.

The RDTF provides a forum for discussion and exchange of views and experience on information and knowledge in the fields of Morbidity and Mortality of Rare Diseases at the national, sub-national and European Union level. The work is based on the agreed mandate of the Rare Disease Task Force.

The scientific secretariat of the RDTF works through: communication with EC services, ad hoc meetings with RDTF members, an electronic newsletter produced in close co-operation with the European Commission Services, and a website.

The deliverables during Year 2 include:

- Close and productive cooperation between the RDTF members and the EC services to guarantee that the RDTF provides all the necessary scientific support to the European Commission. Despite requests for face-to-face meeting of the project leader with the Public Health Executive Agency, no such meetings took place as the Public Health Executive Agency schedule was overbooked. Communication between these two parties continues through emails and telephone calls.

- Production of two reports “How Many Drugs for How Many Patients”, and “Centres of Reference for Rare Disease in Europe: State-of-the-art in 2006 and recommendations of the RDTF”

- A better cooperation between EC funded projects

- A wide dissemination of the available information to all stakeholders in order to encourage continuity of work and trans-national cooperation.

- A wide dissemination of the information produced by projects funded by DG Sanco, DG Research and EMEA

The RDTF results have been made available via several well established web portals: Orphanet, Eurordis, Eurocat. They are also posted on the RDTF website and disseminated via the OrphaNews newsletter currently distributed to more than 8,500 registered readers from 32 countries including professionals already listed in Orphanet, OrphaNews France readers, mailing lists on contracts from RDTF members and from EC services.
ACTIVITY REPORT

Work Package 1 – Coordination with EC Services

The RDTF mandate was established as follows:

The aims of the RDTF are to advise and assist the European Commission Public Health Directorate by promoting the optimal prevention, diagnosis and treatment of RD in Europe, in recognition of the unique added value gained for the RD community through European coordination. The specific objectives are:

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

1 – Communication on Rare Diseases


The Working Group on Reference Networks of the High Level Group on Health Services, Eurodis, EMEA-COMP, and Orphanet will also be consulted by DG SANCO for the Communication. The Communication will be accompanied with a Proposal for a Council Recommendation on rare diseases covering the areas of:

- Common definition of rare diseases in the EU.
- Necessity of national plans for rare diseases in the EU Member States
- European guidelines for the elaboration of the national plans for rare diseases
- Common databases and medical protocol for the identification of genetic rare diseases
Rare Diseases Task Force

- Common approach for a better codification and classification of rare diseases in the process of revision of the International Classification of Diseases
- Creation of the EU Forum on Rare Diseases
- The European Conference on Rare Diseases organised by the EU Forum on Rare Diseases with the specific budget be fixed in the EU Budget during the coming years for the activities of the EU Forum.
- Common approach to the support of patient's organisations
- Creation of the EU Rare Diseases Portal as a part of the EU Health Portal and as common tool for rare diseases identification
- Using e-health facilities for information and treatment
- Better integration of the EU rare diseases public health action with other rare diseases policies (research, orphan drugs, advanced therapies, etc)
- The participation in the COMP of all the EC DG's involved in the field of rare diseases as well as the most relevant NGO's
- A procedure for the creation and recognition of EU networks of reference for rare diseases. The EC will prioritise cooperation in sharing knowledge as the most efficient approach.
- EU identification and certification of laboratories worldwide that perform gene tests for rare genetic diseases, the methodology employed, and whether the tests they provide are in the investigational stage, or are being used for clinical diagnosis and decision making.
- Networking Bio Banks in the EU
- Data protection
- Training of rare diseases researchers and professionals
- Intensifying Therapeutic Research, toward a Public–Private Partnership
- A systematic report on the situation of rare diseases in the EU: The Commission should produce every three years a report on the situation of rare diseases in the EU. An Atlas of the epidemiology on rare diseases should be also produced on a five-year basis.
- A monitoring for the future: On the basis of the work of DG SANCO and the advice from the European Forum on Rare Diseases, the creation of a European Office on Rare Diseases could be considered as an appropriate way of action in the framework of the future EU Programme of Public Health (2014-2020).

2 – Bi-Annual Meetings of the RDTF

The RDTF had two meetings during the second year of the contract on 8 June, 2006 and 14 December, 2006 both of which included the attendance of DG SANCO representatives. The minutes for both meetings are annexed to this report (Annex 1a, 1b). Despite requests for face to face meetings of the project leader with the Public Health Executive Agency, no such meetings took place as the Public Health Executive Agency schedule was overbooked. Communication between these two parties continued through emails and telephone calls.
Work Package 2 – RDTF Scientific Secretariat

1 - Working Group on Standards of Care

A Working Group on Standards of Care was established in January 2004 and is chaired by Edmund Jessop (UK). This working group decided to start its activity by looking at the possible development of European Centres of Reference for RD. Its findings feed into the more general reflection on Centres of Reference undertaken by the European Commissions High Level Group on Health Services and Medical Care.

Two Working Group meetings took place during the second year. On 1 September, 2006 a meeting was dedicated to producing a second report on Centres of Reference in European countries. The report was issued according to schedule and provided to the Higher Learning Group on Health Services and Medical Care. It is available on the RDTF website, [www.rdtf.org](http://www.rdtf.org), and the European Commission Rare Disease website, [http://ec.europa.eu/health/ph_threats/non_com/rare_diseases_en.htm](http://ec.europa.eu/health/ph_threats/non_com/rare_diseases_en.htm).

A subgroup of this Working Group was created to focus on the assessment of rare disease prevalence and the future of orphan drugs. This expert group, which included representatives from the RDTF, patient organisations, Industry, and Orphanet, met in Paris on 30 of May, 2007. The report “How Many Drugs for How Many Patients” is annexed to this report (Annex 2a). The conclusions from this meeting will also serve as a basis of discussion for the 8th EPPOSI workshop on Partnering for Rare Disease Therapy Development.

2 - Working Group on Health Indicators

A Working Group on Health Indicators was established in January 2006. It is made up of RDTF members and invited experts and is chaired by Juliette Bloch (France). No meetings were organised by the group’s chair following the decision to postpone meetings until the completion of a survey investigating the visibility of using death certificates to monitor age at death for a few RD with specific ICD codes. The results of this investigation will be made available by the end of 2007 by the French Health Watch Institute (L’Institut de Veille Sanitaire).

3 - Working Group on Coding and Classification

A Working Group on Coding and Classification of RD was established in October 2006 and is chaired by Ségolène Aymé (France). Members of this group include RDTF members, RD experts directly involved in the classification effort, experts of coding in the field of genetic diseases, experts of coding for death certificates, and representatives of the WHO. The groups aims to tackle existing coding systems regarding RD (ICD, Snomed, MeSH, MedDRA), plans for contributing to improve these systems (especially to contribute to the revision of ICD10 in
The Working Group held two meetings during the second year. The first meeting took place in Paris on 11 October, 2006. The minutes of this meeting are annexed to this report (Annex 2b).

Following the launch of the WHO’s ICD revision process, this Working Group met to discuss its role in the activities of the Topic Advisory Group for Rare Disease chosen the WHO to be chaired by Ségolène Aymé to advise on the revision process of the classification of RD. The minutes of this meeting are annexed to this report (Annex 2b).

4 - Communication of RDTF activities

The leader of the RDTF, Ségolène Aymé was invited to give the following lectures on RDTF activities:


Aymé S. The European Rare Diseases Task Force International Conference on Rare Diseases and Orphan Drugs. Rome, Italy 18 September, 2006.


Aymé S. Concepts and facts about rare diseases and orphan drugs. Workshop on Orphan drugs in the EU: toward a common approach for a fair and sustainable patient access. Haute Autorité de Santé. Paris, France 10 November, 2006

Aymé S. Rare and orphan diseases. Journées pédiatriques Félix Guyon. St Denis de la Réunion, France 24 November, 2006

Aymé S. Information on Rare Diseases. Health Economics Seminar, l’Université Dauphine. Paris, France 6 December, 2006

Aymé S. National Plan for Rare Diseases, Federal Belgian Parliament Conference on Orphan Drugs. Brussels, Belgium 7 December, 2006


5 – Progress reports

Two progress reports were completed reporting on all activities during the second year in July 2006 and January 2007. They are included in the Annexes of this report (Annex 2c).
Work Package 3 – Newsletter

The RDTF Scientific Secretariat has continued the publication of the RDTF electronic newsletter, OrphaNews Europe. Currently distributed to more than 8,500 registered readers from 32 countries, subscribers are free to opt in or out of the service at any time. Since its creation in June 2005, 12 issues have been completed. In May 2006, a satisfaction survey reflected a high level of readership satisfaction and suggestions to expand topics covered in OrphaNews Europe to include more relevant issues on the political level and in research findings. To decrease the quantity of information in each newsletter, it was decided in January 2007 to publish a newsletter every two weeks when possible. All stakeholders including RDTF members are encouraged to send their contributions to orphanews@orpha.net.

Issues were published on:

<table>
<thead>
<tr>
<th>2007</th>
<th>2006</th>
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<tbody>
<tr>
<td>16 May 2007</td>
<td>21 December 2006</td>
</tr>
<tr>
<td>11 April 2007</td>
<td>20 November 2006</td>
</tr>
<tr>
<td>28 March 2007</td>
<td>10 October 2006</td>
</tr>
<tr>
<td>14 March 2007</td>
<td>8 September 2006</td>
</tr>
<tr>
<td>21 February 2007</td>
<td>10 July 2006</td>
</tr>
<tr>
<td>7 February 2007</td>
<td>5 June 2006</td>
</tr>
</tbody>
</table>

The archives are accessible at the following address: 
http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews

All deliverables for Year 2 were produced including the maintenance of the tool to produce the newsletter, maintenance of the tool to archive the newsletter on the website, maintenance of the tool to browse the newsletters, maintenance of the tool for registration, and the newsletters themselves.
Work Package 4 – RDTF Website

The RDTF website, including the public zone and zone reserved exclusively for RDTF members, was maintained during the second year.
### Work Package 5 – Administration

#### Table 1. Deliverables

<table>
<thead>
<tr>
<th>WP1</th>
<th>WP2</th>
<th>WP3</th>
<th>WP4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Electronic contacts with DG SANCO, PHEA, and RDTF members</td>
<td>• Production of report on European Networks of Centres of Reference</td>
<td>• Production of 12 newsletters</td>
<td>• Uploading of reports and Working Group meeting minutes</td>
</tr>
<tr>
<td>• Telephone calls with DG SANCO, PHEA, and RDTF members</td>
<td>• Production of “How many diseases for how many patients?” report</td>
<td>• Maintenance of tool to archive newsletters on the website</td>
<td>• Maintenance of website</td>
</tr>
<tr>
<td>• RDTF bi-annual meetings 8 June 2006 and 14 December 2006 and subsequent minutes</td>
<td>• Minutes of Working Group meetings</td>
<td>• Maintenance of tool to allow users to browse issues</td>
<td></td>
</tr>
<tr>
<td>• Development of Communication on Rare Diseases</td>
<td>• Progress reports every 6 months</td>
<td>• Maintenance of tool for subscription registration</td>
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</tbody>
</table>
ANNEXES

1. MINUTES OF FORMAL MEETINGS

   a. Sixth Meeting of the RDTF

Minutes
6th Meeting of the European Commission “Rare Disease Task Force”
Luxembourg, 14 December 2006

On 14 December 2006, the sixth meeting of the Rare Diseases Task Force (RDTF) included the attendance of:

**Rare Disease Task Force:**
- V. Anastasiadou
- S. Aymé
- S. Berrih-Aknin
- K. Beuzard-Edwards
- J. Donadieu
- L. Fregonese
- G. Gatta
- N. Kerlero de Rosbo
- E. Jessop
- Y. Kodra
- C. Nourissier
- M. Posada de le Paz
- A. Ramirez Vanegas
- C. Malattia
- J. Sandor
- R. Stefanov

**Observers:**
- R. Capocaccia
- A. Federico
- S. Giampaoli
- A. Phinikaridou
- M. Ratsep
- M. Carl
- F. Kendel

**European Commission:**
- C. Berens
- G. Margetidis
- A. Montserrat
- J. Ryan
- J. Waligora

A. Welcome and Approval of Agenda

No changes.

B. Presentation on the Disseminations of the European Community Health Indicators

Antoni Monserrat
European Commission
DG SANCO Health Information Unit

Current Work Plan
The DG SANCO’s Health Information Unit aims to produce an EU health information system with indicators on health-related behaviour, diseases, and health systems. The information system is being developed on the basis of several Public Health Programme (2003-2008) projects and other EU actions, in collaboration with Eurostat, the OECD and the WHO. It is available through the DG SANCO website and the internet-based EU Health Portal.

One such Public Health Programme project contributing to the health information system is the European Community Health Indicators (ECHI) project carried out in the framework of the previous Health Monitoring Programme (1997-2002) and the current Public Health Programme. The objectives of this project:

- measuring health status, its determinants, and trends within EU,
- simplifying planning, monitoring and evaluation of EC Programmes and actions,
- providing Member States (MS) with relevant health information for national health policy-making,

result in a list of “indicators” for the public health field arranged according to a conceptual view on health and health determinants.

The current Work Plans 2005, 2006, 2007 contain explicit mention to chronic, major and rare disease (RD) indicators, thus constituting the legal basis for the development of an EU health information system:

- pilot studies on health examination surveys as part of the feasibility study
- creation or improvement of morbidity registers covering all MS on all major and chronic diseases for which a solid indicators base definition exists and for those not yet covered by existing projects
- provision of evidence & reports on community policies on health, health and economic growth, and sustainable development
- support for disease knowledge projects relating to prevalence, treatments, risk factors, risk reduction strategies, cost of illness, and social support
- development of strategies and mechanisms for exchange of information among people affected by RD and promotion of better epidemiological studies, coding, classification, and definition
- support for European networks of Centres of Reference (CR) for RD to define guidelines for best practice in treatment, and knowledge sharing on these diseases, along with performance evaluation
- feasibility studies to develop mechanisms for data collection on the volume and impact of cross-border healthcare, integrated into existing data collection systems within MS avoiding undue additional administrative burden

**Seventh Framework Programme (FP7)**

The future legal basis for health indicator developments in EU Public Health Policy was presented:

In the 2007-2013 period a new Health & Consumer Protection Programme is expected to
replace the existing Public Health Programme (pending Council and Parliament approval). A new strand, “Generation of Knowledge” will be introduced, but there will be no “Diseases” strand.

The Draft Regulation from the Council and Parliament (developed by Eurostat) is creating a statistical framework for data collection on health and safety in the workplace in some areas and should be an “umbrella regulation” to be developed via Commission Regulations.

A direct contract agreement via Commission Decision with OECD has been signed for developments in several areas.

A. Montserrat announced the Commission must now make some clear action in the RD field. There has been a suggestion to expand the existing 3 strands to 6 in the future Public Health Programme. The proposal was not accepted. Contribution to FP7 constitutes one of the Commission’s priorities on RD.

A. Montserrat explained a new common approach between research activities and health information under the “Cooperation” specific programme of FP7. Emphasis will be put on translational research (translation of basic discoveries into clinical applications), the development and validation of new therapies, methods for health promotion and disease prevention, diagnostic tools and technologies, as well as sustainable and efficient health care systems. For RD specifically, the focus will be on pan-European studies of natural history, pathophysiology, and the development of preventative, diagnostic and therapeutic interventions. This sector will include rare Mendelian phenotypes of common diseases.

Under the “Ideas” specific programme of FP7, an entirely new approach will be taken. Unlike the approach under FP6 which does not fund activities that can be better conducted at a national or regional level, but focuses on topics of European or global significance, and supports projects involving cooperation between partners from several different European countries, the new approach will be an “investigator-driven” one, allowing researchers to propose their own topics. Grants will be provided for individual teams, allowing teams to be composed of any group of researchers required for the projects to achieve scientific excellence, rather than of members determined by administrative requirements.


Over 2007/2008 DG SANCO is to elaborate a proposal for a Commission Communication on the European Health Information and Knowledge System. This proposal includes:

- a summary of the principles of the EU Health Information and Knowledge System
- the responsibilities of different actors in the field of RD as well as the role of DG SANCO
- the national and EU responsibilities in the mechanisms for collecting health data
- the interoperability of different systems of health indicators and cooperation with other players such as Eurostat, ECDC, and OECD.
- the role of the consultative structures
- a code of good practices on health information
• the obligation of the European Commission to respect the individual decisions of MS in the field of health information.

This proposal should be discussed in all the existing DG SANCO advisory structures.

**A Council Recommendation**

It is hoped that this Communication will be followed by a Recommendation from the Council. A. Montserrat stipulated that these Recommendations are the only legislative tool provided for by Article 152 on public health (except for certain measures or incentive measures may be adopted (see Article 152.4)). Between 2008 and 2011, new Communications, public consultations or legal initiatives affecting health information issues, will be established. The consolidation of instruments to develop RD systems is considered very important.

A. Montserrat said it was important to remind members present of the significance of a Recommendation in the preparation of a Communication on RD. He pointed out that Recommendations do not have any legal status as such, but are negotiated and voted on according to the appropriate procedure. However, unlike Regulations, Directives and Decisions, Recommendations are not binding for MS. Despite their lack of legal impact, they do have a real political impact. So by definition, a Recommendation is an instrument of indirect action used in the preparation of legislation in MS, and differing from a Directive only by its absence of obligatory power. It is therefore appropriate and necessary to accompany the developing Communication with a Proposal for a Council Recommendation on RD.

A. Montserrat pointed out that the timetable for the elaboration of this Communication and Recommendation is already in the Annual Management Plan (AMP) 2007 in time to launch the Commission adoption by the end of 2007.

**New Health Strategy**

In 2007 the Commission plans to adopt a new Health Strategy aiming to

• set a clear, strategic framework covering mainly DG SANCO work with some new initiatives,
• define broad objectives within a 10-year timeframe with a 5-year mid-term review
• encourage close cooperation with MS to improve health in Europe over coming decade,
• focus on key health issues, on mainstreaming health in all policies and address key challenges on global health issues.

RDTF members and all stakeholders are actively encouraged to submit their own input via comments on a discussion document on operational aspects of the Health Strategy by 12 February 2007. It is expected that this new strategy will be adopted mid to late 2007, after which it will be discussed by the Council.

**Community Action on Health Services**

Before the Commission brings forward proposals for Community Action on Health Services, it consults all stakeholders involved in the health services sector, on the basis of a specific
Consultation document. This Consultation is already in place (available on the DG SANCO website) and responses to this document should be sent to the Commission by 31 January 2007.

Improving Health Indicators

To improve the mechanisms for health reporting common methodologies and systems of collection must be sustained and accepted by all the MS. To improve mechanisms of health reporting from a rare disease perspective the following actions are necessary:

- European Health Survey System (health interview survey (HIS) and health examination survey (HES) databases).
- revision of several international classifications. The European Commission is very involved in the revision process of the WHO ICD-10 with particular attention being paid to RD.
- development of the System of Health Accounts
- a common system of collection of information on hospital activities
- development of some disease registers
- collection of information on primary care
- sentinel networks

Health Reports Based on Indicators

The following series of significant Health Reports has been launched by DG SANCO as part of the 2006 Work Plan:

<table>
<thead>
<tr>
<th>Report Type</th>
<th>Date</th>
<th>Agencies/Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Communicable Diseases Reports</td>
<td>3rd Quarter, 2006</td>
<td>ECDC &amp; SANCO C-2 &amp; ESTAT</td>
</tr>
<tr>
<td>1st Chronic Diseases Report</td>
<td>1st Quarter, 2007</td>
<td>TF MCD</td>
</tr>
<tr>
<td>1st Global Report on Health in EU</td>
<td>End 2008</td>
<td>EUGLOREH Project (Italy)</td>
</tr>
<tr>
<td>2nd Report, European Conference on RDs</td>
<td>2008</td>
<td>RAPSODY Project (EURORDIS)</td>
</tr>
</tbody>
</table>

The 1st Global Report of Health in the EU will include a chapter on RD. A. Montserrat reminded members of the web address for the dissemination of indicators data, informing them that all MS languages will be available during 2007. The Report may be consulted at: http://ec.europa.eu/health-eu/index_en.htm.

Other DG SANCO Priorities on Rare Diseases

Projects

With regard to the evaluation of project proposals, DG SANCO’s priority criteria are: 1) projects that identify RD and assess prevalence, 2) projects supporting cooperation between rare disease organisations, 3) projects creating networks of action for RD. A. Montserrat reminded members of last year’s successful project applicants, listing each of them.

European Conferences on Rare Diseases
Centres of Reference for Rare Diseases

DG SANCO has established the High Level Group (HLG) on Health Services and Medical Care as a means of taking forward the recommendations made by the reflexion process on patient mobility. One of the Working Groups of this HLG refers to reference networks of centres of reference.

The RDTF Work Group on Centres of Reference (CR) has submitted a report “Contribution to policy shaping: For a European collaboration on health services and medical care in the field of RD” updating the information about CR in Europe. The report details the use of the concept of CR in Europe as well as the respective functions. A. Montserrat summarised the suggested criteria to be fulfilled by a European reference network.

The Orphan Regulation

A. Montserrat reminded members present of the importance of this Regulation (EC Regulation 141/2000) that was proposed to set up the criteria for orphan designation in the EU and describes the incentives (e.g. 10-year market exclusivity, protocol assistance, encouragement of R&D & marketing of RD medicines) to encourage research, development and marketing of medicines to treat, prevent, or diagnose RD, thus better serving patients. The incentive programme has resulted in 32 new orphan medicines with marketing authorisations, more than 450 applications for orphan designation, and 270 medicines already designated as orphan medicinal products, but still undergoing clinical evaluation.

Discussion

It was asked why so many projects were accepted by the Commission. With so many new projects accepted, existing ones experience 30-50% cut in funding while still having to meet the same objectives. Why not accept fewer outstanding projects with appropriate funding for each?

A. Montserrat explained that there was no official policy to reduce project budgets. There was competition between the projects involved and though this was not ideal, this was the system. He agreed that ideally the policy should be fewer projects and more funding for each.

It was asked why the evaluation of projects takes place in one week as it was felt that this time is too short. It was suggested that the Commission develop a 2-phase approach to the evaluation process with a pre-selection phase followed by a more in-depth evaluation.

A. Montserrat responded that unfortunately the current resources available to the Commission only allow for one week of evaluation.

Project budgeting was addressed as a real problem to researchers as the process has become more and more complicated. Several members identified with this struggle. Consultation with
others, and sharing of budget experiences and abilities was encouraged.

It was suggested and agreed upon that a smaller working group be assembled to prepare the Communication content in time for the next RDTF meeting in June 2007, but that all members of the task force would continue discussing topics together. Task force members interested in contributing to this work group included: **J. Llinares-Garcia, C. Berens, E. Jessop, D. Taruscio, C. Nourissier, L. Fregonese, and J. Sandor.**

### C. Presentation on Research on Rare Disease: Overview of FP6 activities

*Catherine Berens*

*European Commission*

**DG Research Health Directorate – Medical and Public Health Research Unit**

#### Fifth Framework Programme and Sixth Framework Programme

Under FP5 the RD budget was 64 million € which included 47 RD projects in research and development, infrastructure, and biotechnology.

Members were reminded that topics in FP6 relevant to RD were often found under other headings. To track current RD projects, members were encouraged to use the following website:

http://cordis.europa.eu/lifescihealth

→ Thematic Areas

→ Application-orientated genomic approaches to...
  → Combating cardiovascular disease, diabetes and RD
  → FP6 rare disease projects (http://cordis.europa.eu/lifescihealth/major/rare-disease-projects1.htm)

The global budget for RD under FP6 is ~230 million € with 59 projects selected for funding related to RD. Under Priority Thematic Area 1 of FP6 -Life Sciences, Genomics and Biotechnology for Health- there were four calls for proposals.

In addition to funding disease specific research projects, a transversal project was also funded, OrphanPlatform, aimed at developing a platform with information tools to address the set of factors that currently affect research on RD and its coordination by (1) developing an information service, freely accessible on Internet, dedicated to research activities in the field of RD and orphan medicinal products, including a database of research projects, funded at MS level and at the EU level, and a database of collections and research networks, (2) developing services aimed at speeding up the enrolment of patients in clinical research, (3) developing a database of research projects with development potential, to help scientists and Industry establish the necessary partnerships. This Platform is accessible at www.orpha.net and at www.orphanxchange.org.

C. Berens explained the need for dialogue between the scientific community and society at large. One such project, “Capacity-Building for Patient Organisations in Research Activities (CAPOIRA)” aims to equip rare disease patients and patient organisations with the
knowledge necessary to take action in research activities and policy. The project is built along two main activities:

1) “Understanding clinical trial protocols”: six training sessions in 3 MS
2) ‘Gaining Access to Rare Disease Research Resources’: a two day European workshop in Paris, 4-5 May 2007, to increase the capacities of patient representatives to understand the concepts, vocabulary, policies, and instruments of health research activities at the EU level.

C. Berens continued by highlighting the achievements of the FP6 Programme:

- mobilisation of top researchers, tackling fragmentation, production of new knowledge
- coordination of the field at EU level (e.g. OrphaPlatform and E-Rare)
- mobilisation of and dialogue with stakeholders (including patients)

And room for improvement remains in the following areas:

- clinical research
- focused topics
- emerging consortia/topics

**Seventh Framework Programme**

The first framework programme to run for seven years from 2007-2013, FP7 has a total budget of 50,521 million €. The “Cooperation” sector is the biggest at 32,413 million € of which Health takes up 6,050 million €. The “Cooperation” sector is comprised of ten themes of which Health is the first.

The Health objectives were outlined, covering improvement, global health issues and increasing competitiveness in related industries, and the rationales behind them were presented. Health is broken down into 3 “pillars”: 1) Biotechnology, generic tools & medical human health technologies; 2) Translating research for human health; 3) Optimising the delivery of healthcare to European citizens including better clinical practice and use of medicines, quality, efficiency & solidarity of health systems, and enhanced health promotion/disease prevention.

C. Berens then turned to Collaborative Research with explanations for the different funding schemes within the FP7:

- Small or medium-scale focused research actions (STREP)
- Large-scale Integrated Projects (IP)
- Networks of Excellence (NoE)
- Coordination actions (CA)
- Specific Support Actions (SSA)

An important scheme in funding is the continuation of Marie Curie Actions which include support for training and career development of researchers and are open to third country nationals.

C. Berens set out the principles of the FP7’s new European Research Council (ERC). She explained that the ERC will be the first pan-European funding agency for innovative projects. Investigators with a range of experience from across Europe will be able to compete for ERC
grants with scientific excellence as the only criterion for funding. Funding will be distributed via two schemes: 1) ERC Starting Grant and 2) Call Advanced Grant.

C. Berens introduced new support for existing and new research infrastructures of which 6 are relevant for health issues:

- **EATRIS** (European Advanced Translational Research Infrastructure in Medicine)
- European biobanking and biomolecular resources
- Mouse models for life sciences (INFRAFRONTIER)
- Infrastructures for clinical trials and biotherapy
- Integrated Structural Biology Infrastructure
- Upgrade of European Bioinformatics Infrastructure

Further information on these and other European research infrastructure projects can be found at http://cordis.europa.eu/esfri/home.html.

**Rules for participation, Funding Rates & Calls for Proposals**

C. Berens set out the rules for participation in these projects. Only electronic submissions will be considered for a minimum number of participants per country. Page limits will be set. Three independent legal entities will be set up in three different countries. Candidates will now be judged according to 3 evaluation criteria: scientific excellence, impact and implementation (including relevance to the work programme’s objectives). Funding rates were also presented, and the various funding percentages allowed to different types of applications were quoted.

Clause 2.4.4 of the Call for proposals covers RD. It includes trans-European natural history studies, pathophysiology, development of preventive, diagnostic & therapeutic interventions, and rare Mendelian phenotypes of common diseases.

For information sources, members were advised to use the following web addresses:

EU research:  http://ec.europa.eu/research/
FP7:  http://cordis.europa.eu/fp7/
Research programmes and projects:  http://cordis.europa.eu/
Latest info on ERC:  http://ec.europa.eu/erc/index_en.cfm

The Commission encourages all interested parties and RDTF members in particular to register as an expert via the following web address:  https://cordis.europa.eu/emmfp7/

Members were also strongly urged to get involved in the Rare Disease Research: Building on Success” Conference taking place in Brussels on 13 September 2007.

**Discussion**

A. Montserrat confirmed that it was possible to invite some project leaders from the FP6 to
consult with the RDTF and C. Berens emphasised how important it was that they contribute to the debate. It was now important that the appropriate people be selected to do this.

It was asked why only 6 areas for RD were taken into account, and these did not include dermatological diseases. C. Berens replied that the Commission had thought about this and decided it was impossible to cover all RD on a limited budget, so it preferred not to fund too many projects to avoid time-wasting. However, she stressed the importance of taking into account remarks received and confirmed that the Call criteria would be redefined, although the limited budget would unfortunately prove restrictive in this area.

A member asked about the objectives on the Conference on RD Research. C. Berens replied that the aims of the conference were to provide the RD community with a forum to express their needs in terms of research, to provide the Commission with a strong basis for FP7 calls for proposals, and increase the visibility of RD research and thus benefiting all of the RD community. The beginning of the FP7 coincides with the date of the RD Research Conference so it will attract a lot of attention.

Another member pointed out that one objective should be to try to simplify Call application forms to help scientists fill them in properly. C. Berens said the Commission was working hard to improve and simplify these forms. For example, repetition of questions would be avoided in the future to avoid wasting time for scientists having to re-write their proposal applications.

D. Presentation on the Community Public Health Programme 2008-2014
John Ryan
European Commission
DG SANCO Health Information Unit

J. Ryan stated that the Council agreed on the new Public Health Programme necessary for the coming 2008-2014 period, which would include 3 strands: Health information and knowledge, Health threats and Health determinants. Unfortunately, funding is limited and will be spread thinly over 7 years to 27 or 28 MS. This means that the same funding will be distributed to more MS for a longer duration (7 vs. 5 yrs). This meant it was essential to take a hard look at other means of resource, such as involving neighbouring countries. Nevertheless, the PH Programme will help RD to stay “on the radar screen”.

With regard to the Communication on RD, J. Ryan pointed out that the Luxembourg RD Conference in 2005 had constituted a major event that contributed to the recognition of RD on the policy level. More was required than projects alone so it was decided that a Communication was needed to look at health aspects. It was important to contact colleagues to contribute so that the Council Recommendation can be made. The RDTF should be mobilised to identify areas for recommendations.

Discussion

A discussion regarding the content of the Communication began. The following topics were discussed and proposed to be included:
European Approach to Genetic Testing (GT)

An OECD report shows a large flow of specimens across borders especially for RD. This now raises the issue of specimen mobility and all related aspects such as European-wide regulations harmonising quality control and ensuring confidentiality. Among the problems is the heavy cross boarder flow of specimens due to the lack of expertise at the MS level. The report of Institute for Prospective Technological Studies (IPTS) 2003 in Seville provided a clear analysis of GT development issues. Tests are usually available only when translation is available but the decision is left to RD researchers. It is an area in which the US has already taken initiative by developing a network of six laboratories providing testing for extremely RD at the lowest possible cost (February 2007).

J. Ryan agreed that the Commission was interested in developing cooperation with the US. The NIH’s Office of Rare Diseases was also keen to cooperate and was seeking to emulate Europe’s achievements in this field.

Patient Mobility

A public consultation is currently up and running on the DG SANCO website regarding patient mobility and the implications of this problem. One of the chief questions to address is the definition of reimbursement rights for patients. The deadline for consultation is 31 January 2007.

Regulation of Orphan Drugs

Harmonising the assessment of the clinical utility of orphan drugs across MS will speed up the time between market authorisation and availability, thus allowing patients to face shorter waiting periods for medicinal products to arrive on the market. It is suggested that this harmonisation can be achieved by conducting assessment at the European level with the possibility of one agency sharing the load of this work. J. Ryan added that there is an EU project funding the collaboration between Heath Technology Assessment (HTA) agencies in the MS, specifically for this purpose. It is coordinated by the Danish HTA agency.

Other topics

Other topics raised as needing to be included in the Communication include:

- Trans-Atlantic collaboration
- Pooling of resources -( i.e. establishment of a network of biobanks, European-wide registries of patients)
- Support of patient support groups at the European level
- Increased sharing of data at the European level (such as Orphanet)
- Establishment of good clinical practice guidelines
- Facilitating multicentric clinical trials
- Development of telemedicine

E. Presentation on Rare Disease Task Force Secretariat
Ségolène Aymé
The structure and functions of the RDTF and RDTF Secretariat are available on the RDTF website http://www.rdtf.org.

**Newsletter**

RDTF Secretariat has continued the publication of the RDTF electronic newsletter, OrphaNews Europe. Currently distributed to more than 7,000 registered readers from 28 countries, subscribers are free to opt in or out of the service at any time. Since its creation in June 2005, 16 issues have been completed. In May 2006 a satisfaction survey reflected a high level of readership satisfaction and suggestions to expand topics covered in OrphaNews Europe to include more relevant issues on the political level and in research findings. All stakeholders including RDTF members are encouraged to send their contributions.

**Working Groups**

**Working Group on Centres of Reference**

The Working Group on CR held its last meeting in September 2006. Several conclusions and recommendations resulted from this meeting and can be investigated in more depth in the publication “Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force” available on the DG SANCO website under RD. It was agreed that a common label was necessary for such centres as an indicator of quality for patients and health care providers (particularly with regard to reference networks already in place) The term ‘Centre of Reference’ was not currently used by many MS and definitions of them still differed. Thus far, CR for RD only exist in the following countries: Denmark, France, Italy and Sweden. Experts on RD are also not abundant and often only found on the international level, further implicating the importance of CR in Europe to make research most efficient. Coordination of clinical research relevant to RD was also identified as an obstacle. As such, the following recommendations were made to the Commission:

1) To fund reference networks of centres of expertise for RD
2) To open its call for proposals to the definition of a methodology to assess the benefit from such networks from the perspective of a range of stakeholders
3) To encourage of the development of electronic services in the RD field

The Working Group on CR is dedicated to reaching its goal as a step forward for the improvement of the delivery of care for RD patients. The achievements of this working group can serve as a model for other medical sectors such as severe chronic diseases. Members were invited to follow the developments of this working group via the RDTF website. A new report on methods assessing the added-value of CR and the added-value of reference networks will be published by the end of 2007.

**Working Group on Coding and Classification**
This working group held its first workshop on 11 October 2006. The objectives of this working group include the collaboration between organisations that code RD. Some contacts have already been established and an exchange of RD coding and classification tables will occur between Orphanet and these organisations to coordinate codes. The final aim is to improve existing coding systems regarding RD (ICD-10, Snomed, MeSH, MeDRA) to increase their visibility in information systems. The group will work on the establishment of a database of expert classifications of RD. This is currently being done by Orphanet and should be released by the end of 2007.

The members of this working group include RDTF members who have volunteered, experts of RD directly involved in the classification effort, coding experts in the field of genetic diseases, and coding experts for death certificates.

In April of 2007 the revision of the WHO’s ICD-10 to ICD-11 will officially be launched. The WHO is considering involving the RDTF Working Group on Coding and Classification in this process.

**Working Group on Indicators**

The first meeting of this working group took place in Paris on 30 Jan 2006. The following areas were identified as requiring action:

- Prioritisation of RD for surveillance
- Feasibility of using death certificates for RD
- List of macro-indicators
- Mapping of existing sources of epidemiological data

Members expressing interest in the participation of future workshops include: **J. Donadieu, M. Posada de la Paz, Claire Webb, and D. Taruscio**. The date and agenda for the 2007 meeting remain to be decided. It has been proposed that the next meeting will include a follow up on on-going projects and preparation of a report.

**Future Initiatives**

The future initiatives of the RDTF Secretariat include

- an updated version of the “Inventory of Community and national incentive measures to aid the research, marketing, development and availability of orphan medicinal products”
- the addition of a permanent section in OrphaNews Europe about genetic testing in collaboration with EuroGenTest (NoE)
- preparation of the RDTF work programme for 2008-2010.

**F. Presentation on the Eurordis Workshop on European Centres of Reference**

Christel Nourissier
Representing Eurordis

The RAPSODY (Rare Disease Patient Solidarity) Workshop, coordinated by EURORDIS, the
European umbrella organisation for patient groups aims at facilitating a discussion on CR for RD at the national level. National workshops will be organised to review current proposals for the creation and development of centres of reference in the national context. A set of recommendations and a synthesis will be developed during a European Workshop in Prague in July 2007.

There was concern that many of the national workshops had not yet occurred. It was assured that all speakers would be contacted on the national level by patient organisations as soon as possible.

There was a concern that not all MS could be included in this debate, but due to the limited funding of the project countries were chosen on a volunteer basis and not all MS volunteered.

C. Nourrissier reminded members of the upcoming European Conference on RD in 27-28 November next year in Lisbon, to be held as part of Portugal’s EU Presidency Programme (also part of the RAPSODY contract). This major event was designed to focus political attention on RD actions in Europe.

G. Conclusions

Final Thoughts

Members were encouraged to send their comments or further suggestions regarding the Communication. All topics suggested for inclusion in the Communication must now be presented in an Action Plan. The preparation of the document will start by January 2007. All suggestions should be included and any more suggestions should be forwarded to the Secretariat of the RDTF. Consultations will be advertised in OrphaNews and a member of the Communication editorial committee will soon be contacted.

Next Meeting

7th RDTF Meeting will be held 21 June 2007 and will coincide with meeting of the Major and Chronic Diseases Task Force.
Meeting Report
7th Meeting of the European Commission “Rare Disease Task Force”
Luxembourg, 20 June 2007

On 20 June 2007, the seventh meeting of the Rare Diseases Task Force (RDTF) included the attendance of:

**Rare Disease Task Force:**
S. Aymé  A. Kole  A. Trama
E. Daina  J. Linares Garcia  J. Vasquez
H. Dolk  C. Nourissier  J.L.Vives Corrons
J. Donadieu  M. Posada de le Paz  Y. Wagener
L. Fregonese  A. Ramirez Vanegas  S. Webb
G. Gatta  J. Sándor
HK Hartle  R. Stefanov

**Observers:**
R. Capocaccia
A. Federico
G. Filocamo
A. Fourcade
S. Giampaoli
O. Kremp
Y. Le Cam
A. Phinikaridou
B. Piantanida Pizzera
A. Ramirez Vanegas
M. Rätsep

**European Commission:**
K. Freese
A. Montserrat
A. Welcome and Approval of Agenda
No changes.

B. Presentation on the Commission Communication on a European Action in the Area of Rare Diseases (Including Genetic Diseases)
Antoni Montserrat
European Commission
DG SANCO Health Information Unit

The concept of “rare disease” (RD) emerged in 1978 with the publication of an article (Holzman NA. Rare diseases, common problems: recognition and management. Pediatrics, 1978; 62(6): 1056-1060) stating that rare diseases, though diverse, have common problems of being recognised by physicians and problems of being effectively managed as knowledge about each is very limited and little clinical research in the field exists. In the early 1980’s, rare diseases gained recognition as a political issue with the fight of patient advocacy groups to obtain a set of incentives for the development of therapeutic products in the USA. In the early 1990’s the debate centered around research challenges when rare diseases, which are mostly genetic, became instrumental for mapping human genes. More recently, the public health dimension of rare diseases has been recognised by the European Commission and by several individual countries and consequently specific action plans were developed.

A Community action programme on RD, including genetic diseases, was adopted for the period of 1 January 1999 to 31 December 2003 with the aim of ensuring a high level of health protection in relation to RD. As the first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases.

Rare diseases are now one of the priorities in the EU Public Health Programme 2003-2008. According to the DG SANCO Work Plans for the implementation of the Public Health Programme, the two main lines of action are the exchange of information via existing European information networks on rare diseases, and the development of strategies and mechanisms for information exchange and co-ordination at EU level to encourage continuity of work and trans-national co-operation.

For the period 2008-2013 a new Public Health Programme will replace the existing Public Health Programme (if approved by the Council and the Parliament). It will include a new strand ‘Generation of knowledge’ and no ‘Diseases’ strand.

In 2007, the Commission plans to adopt a new Health Strategy, which includes the need of a Commission Communication in the field of RD. During 2007 the Impact Assessment and Strategy White Paper will be developed and adoption of this strategy is expected mid to late 2007 at which point the European Council will discuss the strategy.

During 2007/2008, DG SANCO will elaborate a proposal for a Commission Communication on the European Health Information and Knowledge System:
• Summarising the principles basing the EU health information and knowledge system,
• The responsibilities of the different actors in this field, the role of DG SANCO,
• The national and EU responsibilities on the mechanisms for collecting data (health surveys, hospital information, etc.),
• The interoperability of different systems of health indicators, the cooperation with other actors (Eurostat, ECDC, OCDE),
• The role of the consultative structures
• A code of good practices on health information
• Obligations that the European Commission should assume respect to the Member States in the field of health information.

The proposal should be discussed in all the existing SANCO advisory structures. A Consultation regarding Community action on health services is in place. Before the Commission brings forward proposals for Community action on health services, all stakeholders involved in the health services sector are consulted, on the basis of a specific consultation document.

There is probably no other area in public health in which 27 national approaches could be considered to be as inefficient and ineffective as with rare diseases. The reduced number of patients for these diseases and the need to mobilise resources could be only efficient if done in a coordinated European way.

This initiative is one proposal in the Annual Management Plan 2007. Article 152 provides for the adoption by qualified majority by the Council of Recommendations, on the basis of Commission proposals, for the purposes set out in that article. These Recommendations are the only legislative tool provided for in Article 152 on public health except for the few areas where measures or incentive measures may be adopted (see Article 152.4). Recommendations are without legal force but are negotiated and voted on according to the appropriate procedure. Recommendations differ from regulations, directives and decisions, in that they are not binding for MS. Though without legal force, they do have a political weight. The Recommendation is an instrument of indirect action aiming at preparation of legislation in Member States, differing from the Directive only by the absence of obligatory power. In order to coordinate the position of the Member States in respect of this important field, it is considered that a Recommendation is the appropriate legal instrument. In the case of the proposed Communication on rare diseases, it is considered necessary to accompany that Communication with a Proposal for a Council Recommendation on rare diseases covering the areas of:

• Common definition of rare diseases in the EU.
• Necessity of national plans for rare diseases in the EU Member States
• European guidelines for the elaboration of the national plans for rare diseases
• Common databases and medical protocol for the identification of genetic rare diseases
• Common approach for a better codification and classification of rare diseases in the process of revision of the International Classification of Diseases
• Creation of the EU Forum on Rare Diseases
• The European Conference on Rare Diseases organised by the EU Forum on Rare Diseases with the specific budget be fixed in the EU Budget during the coming years for the activities of the EU Forum.
• Common approach to the support of patient's organisations
• Creation of the EU Rare Diseases Portal as a part of the EU Health Portal and as common tool for rare diseases identification
• Using e-health facilities for information and treatment
• Better integration of the EU rare diseases public health action with other rare diseases policies (research, orphan drugs, advanced therapies, etc)

• The participation in the COMP of all the EC DG's involved in the field of rare diseases as well as the most relevant NGO's
• A procedure for the creation and recognition of EU networks of reference for rare diseases. The EC will prioritise cooperation in sharing knowledge as the most efficient approach.
• EU identification and certification of laboratories worldwide that perform gene tests for rare genetic diseases, the methodology employed, and whether the tests they provide are in the investigational stage, or are being used for clinical diagnosis and decision making.
• Networking Bio Banks in the EU
• Data protection
• Training of rare diseases researchers and professionals
• Intensifying Therapeutic Research, toward a Public–Private Partnership
• A systematic report on the situation of rare diseases in the EU: The Commission should produce every three years a report on the situation of rare diseases in the EU. An Atlas of the epidemiology on rare diseases should be also produced on a five-year basis.
• A monitoring for the future: On the basis of the work of DG SANCO and the advice from the European Forum on Rare Diseases, the creation of a European Office on Rare Diseases could be considered as an appropriate way of action in the framework of the future EU Programme of Public Health (2014-2020).

A. Montserrat stated that the CR WG of the High Level Group, Eurordis, EMEA-COMP, and Orphanet are the preferable bodies consulted for the Communication. It is important to remember that after the finalisation of the Communication it is not known how it will be received by the Council.

Next Meeting of the Drafting Group
The next meeting of the Drafting Group will take place in Luxembourg on 18 July and will include S. Aymé, D. Taruscio, L. Fregonese, J. Llinares Garcia, A. Montserrat, M. Posada de le Paz, R. Stefanov, and C. Nourissier.

C. Commission Communication for a Community Action in the Area of Health Services and Activities Related to Rare Disease Reference Networks
Alexandra Fourcade
French Ministry for Health
Working Group on Reference Networks of the High Level Group on Health Services

The High Level Group (HLG) established in 2004 in response to the decision to address the issue of RD patient mobility. This HLG is made up of many Working Groups (WG), one of which is the WG on European Networks of Centres of Reference (ENCR). This WG aims to encourage a close link between research and health professionals and patients for very RD in
which healthcare professionals are rare as well. This WG seeks input from the RDTF on the definition of networks, from the HOPE project for a patient perspective, and from EURORDIS to help with the consensus of how to define a Centre of Reference at the European level. Eventually, it was agreed by the WG members that ENCR should comply with the following criteria:

- appropriate capacity to diagnose, to follow-up and manage patients with evidence of good outcomes when applicable
- sufficient capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control
- demonstration of a multi-disciplinary approach
- high level of expertise and experience documented through publications, grants or honorary positions, teaching and training activities
- strong contribution to research
- involvement in epidemiological surveillance, such as registries
- close links and collaboration with other expert centres at the national and international levels and a capacity to network
- close links and collaboration with patients associations where they exist.
- Although an ENCR should fulfil most of the above criteria, the comparative relevance of these various criteria will depend on the particular disease or group of diseases covered.

This definition is rather vague. As such, in 2004 a questionnaire was sent to many centres of expertise to assess the reality of such centres. The results indicated that the centres were very diverse in their characteristics. The first report from the RDTF assessing CR presented the status of centres at the country level. The second report included recommendations to the HLG.

The WG on ENCR began its discussions around the criteria required to label a centre a CR. As the work of the WG progressed the discussion moved towards that of networks of CR. It was agreed by the WG that

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

Heavy emphasis is place on the links of a CR with patient groups. After the establishment of such suggested criteria, 5 pilot projects were launched to test the criteria at the EU level. It has been clear from the activities of these 5 CR that there is much diversity among the way these criteria are interpreted. Another concern included the sustainability of these centres; what happens after their funding runs out?

The WG on ENCR of the HLG include is eager to be consulted on this topic for the Commission Communication. The outcome of the European Workshop on Centres of Reference for Rare Diseases in Prague sponsored by EURORDIS will also serve as very valuable feedback for the WG.
**Discussion**

One RDTF member was particularly impressed by the emphasis placed on collaboration between public health agencies, research professionals, and patients. Previously, research was very much on one “track” while the public health and patient agendas were on another.

It was agreed that the outcomes of the Prague workshop will be important to assess appropriation and evaluation of the WG. When asked how flexible the WG was on its CR criteria as it is already clear from the national workshops (preparatory workshops for Prague) that the outcomes of the Prague workshop will require the CR criteria to be refined, A. Fourcade responded that indeed the WG must be very flexible in its CR criteria as even with only 5 pilot projects there is great diversity. It is certain that certain criteria will remain, such as epidemiological surveillance, research development, access to diagnosis and links with patient groups. The details of these criteria, however, must certainly be flexible and ideally not too exhaustive. Most importantly the criteria that are agreed upon must be agreed upon at the EU level.

It was suggested that when presenting the idea of ENCR one must be clear in specifying that funding will not come from a common “pot” but will remain up to CR at the MS level.

A. Fourcade continued by explaining that the very idea of pilot projects is to highlight unexpected findings. As such, it will be important for the WG on ENCR to follow up on them in a few years to see what kind of concrete impact they have had (ex. has diagnosis improved as a result?).

A. Montserrat added that indeed the experience of all five projects has been very different. For each project, the idea of ENCR was interpreted in different ways. They differed, for example, in the transportation of patients or in the use of e-health.

One member disagreed with the approach and suggested that the five pilot projects should be seen more as case studies. As the CR were built on very vague criteria it is no surprise that they function so differently depending on the disease area. It would be better to look at each project’s achievements and then apply the lessons to an *a priori* set of criteria.

It was also expressed that there has been much confusion during this and previous discussions between CR and ENCR. One must be very careful that when assessing ENCR to limit the discussion to the added value of such linkages. Only when assessing individual CR can the previously described criteria be applied. It is imperative to separate the two.

Finally, RDTF members were reminded that underlying this work is the goal of improving access for patients though it is not explicitly stated anywhere. It seems necessary to demonstrate that patients, the end-users, are benefiting from these networks.

**D. Progress Report on the Rapsody Project**

Yann Le Cam  
EURORDIS

Y. Le Cam presented progress on the Rare Disease Patient Solidarity project funded by DG SANCO including patient surveys providing information on patient satisfaction with the provision of healthcare for rare diseases and national workshops organised to initiate the
debate on centres of reference for rare diseases at the national level.

Surveys were sent across Europe to patient organisations covering 16 rare diseases representing a diversity of prevalence, age of onset, clinical manifestations, handicap generated, and availability of treatments. Surveys have been completed in France, Hungary, and Spain and are in progress in the remaining 23 countries. These surveys have proved to be a complicated process as many questions must be catered to each disease and the surveys have been translated into 16 languages.

The number of surveys sent to each patient organisation varies depending on the prevalence of the disease but also the number of members of an organisation. A preliminary analysis of the responses (focus on questions common to all surveys) is underway.

On 11 June 2007, the Advisory Group met to discuss the results of the 11 completed national workshops (Luxembourg has not yet turned in its report). The synthesis of the 10 completed national reports will be structured around the three following Questions:

- Q1: Needs and expectations for national Centres of Reference/Expertise
- Q2: Proposals for the evaluation of national Centres of Reference in the country
- Q3: Cooperation with other countries and recommendations for European Reference Networks

The European Workshop in Prague will indeed give good insight on the expectations of the patients. It is important to emphasize that these are opinions of patients in each Member State and not the official expectations of the MS. It is already clear from national reports that the added value of European Reference Networks is real and impressive. The national workshop participants include patients as well as other stakeholders that are consulted.

Y. Le Cam continued by presenting the Draft Agenda of the European Workshop in Prague.

**European Workshop in Prague – Day 1**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>11.00 to 12.00 am</td>
<td><strong>Introduction</strong></td>
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<tr>
<td>5 min</td>
<td>Co-chairs: Birthe Holm (Rare Disorders Denmark), Martin Benes (SUKL director)</td>
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<tr>
<td>5 min</td>
<td>Welcome speech</td>
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<td>20 min</td>
<td>Czech patient representative</td>
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<td>20 min</td>
<td>Workshop objectives</td>
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<td>10 min</td>
<td>François Houyez EUORDIS, EU</td>
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<td>10 min</td>
<td>Presentation of the proposals of the High Level Group on Health Services and Medical Care</td>
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<td>10 min</td>
<td>Aude Marlier Sutter, Ministry of Health, France</td>
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<tr>
<td>10 min</td>
<td>Discussion</td>
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<tr>
<td>12.00 – 1.00 pm</td>
<td><strong>Presentation of selected European networks</strong></td>
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<tr>
<td>10 min</td>
<td>Co-chairs: Birthe Holm (Rare Disorders Denmark) Martin Benes (SUKL director)</td>
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<tr>
<td>10 min</td>
<td>Establishing the six first European Reference Networks: practical experience</td>
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<tr>
<td>10 min</td>
<td>Prof Lara Fragonese, Rare Bleeding Disorders Network, Netherlands</td>
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<tr>
<td>10 min</td>
<td>Cystic fibrosis, a European Reference Network supported by DG SanCo</td>
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<td>Prof Thomas Wagner, ECORN-CF, Germany</td>
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<tr>
<td>10 min</td>
<td>EuroAtaxia, a European Network of Centre of Expertise supported by DG. Research</td>
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### European Workshop in Prague - Day 2

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<tr>
<th>Time</th>
<th>Activity</th>
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<tr>
<td>10 min</td>
<td>Synthesis of national workshops 9.30 am – 1.00 pm</td>
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<tr>
<td></td>
<td>Chair person: Terkel Andersen (EURORDIS), Maryna Krenkova (SUKL, Czech Republic)</td>
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<tr>
<td>10 min</td>
<td>Synthesis of responses to question 1 by Christel Nourissier, EURORDIS, EU</td>
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<tr>
<td>30 min</td>
<td>Discussion</td>
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<tr>
<td>10 min</td>
<td>Responses to question 2 by Simona Bellagambi, UNIAMO, Italy</td>
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<tr>
<td>30 min</td>
<td>Discussion</td>
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<tr>
<td>11.00 am</td>
<td>Coffee break 11.00 am to 11.20 am</td>
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<tr>
<td>10 min</td>
<td>Proposed priority of criteria and their content for European Reference Networks</td>
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<tr>
<td>30 min</td>
<td>Discussion</td>
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<tr>
<td>12.00 am</td>
<td>Lunch 1.00 pm to 2.30 pm</td>
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<tr>
<td>20 min</td>
<td>Methodology to assess the outcomes of European Reference Networks, 2.30 to 4.00 pm</td>
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<td>Chair person: Prof Birgitta Strandvik, Sweden and Prof Olaf Riess, Germany</td>
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<tr>
<td>20 min</td>
<td>Discussion based on DG SanCo RDTF meeting June 2007</td>
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<td>Dr Edmund Jessop, Ministry of Health, UK</td>
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<td>30 min</td>
<td>Description of the evaluation plan as proposed by the French policy on centres of expertise</td>
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<td>HAS representative (France)</td>
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<tr>
<td>15 min</td>
<td>Closing remarks 3.45 to 4.00 pm</td>
</tr>
<tr>
<td></td>
<td>The way forward form the Commission’s perspective</td>
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<tr>
<td></td>
<td>Toni Montserrat, DG SanCo, EU (tbc)</td>
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<td></td>
<td>Ends at 4.00 pm</td>
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</tbody>
</table>

A report of the outcomes of the European Workshop will be distributed to all national and European Workshop participants along with a CD including all presentations and national workshop reports.

### E. Presentation on RDTF WG on Coding and Classification of RD

Ségolène Aymé  
Orphanet  
INSERM-SC11

On 2 May 2007 a meeting of the WG on Coding and Classification occurred in Paris just after
WHO’s launch the ICD revision.

Orphanet has recently added a lot of relevant information to its database. Currently, MESH terms, MIM codes, proteins (via SwissProt collaboration), and genes are linked to 2,000 diseases in the database. The prevalence, age of onset and other text is also associated with almost all of the diseases in the database.

The goal of the WG on Coding and Classification is to make RD traceable in terms of morbidity and mortality by defining one group of the “main” rare diseases which must have a specific ICD code and organising the remaining “ultra-rare” diseases under “other RD” subcategories of the more general codes.

The steps in this process include:
1. making a list of the diseases deserving a specific code
2. Analysing the current ICD coding system and identifying problems by cross-referencing many coding lists (with the cooperation of other coding bodies)
3. Contributing to ICD-10plus, a tool provided by the WHO to communicate suggestions to the current ICD version

These steps will require a significant amount of technical work and thus we will apply for support from DG SANCO.

The revision process will be led by a Revision Steering Committee under which several Topical Advisory Groups (TAG) will represent a particular field. The rare disease TAG represents Europe and several other countries have been approached for a truly international contribution. Steve Groft of the Office of Rare Diseases at the National Institute of Health in and Roberta Pagon of GeneTests have joined the effort from the US. Colleagues from South America are currently being approached.

Currently there are 384 specific codes for RD so a lot of work remains. Simple coding mistakes in the ICD-10 will be easy to correct, however, many codes will be the source of difficult debate and will require face to face discussions. As such, the next WG on Coding and Classification workshop is scheduled 13 November in Luxembourg.

S. Aymé continued by sharing Robert Jakob’s (of the WHO) presentation on the organisation of this revision process. The next meeting of the TAG will be in Trieste this year. The next meeting of the WG on Coding and Classification will be in Washington DC.

A. Montserrat stated that this activity of the RDTF is very important. In 2008 DG SANCO can help increase the number of meetings for the activity. As for further funding for the work DG SANCO is investigating the possibilities. DG SANCO has approached the WHO to establish an agreement for funding but the WHO has not responded with any interest yet. A. Montserrat clarified that funding must be sent to an identifiable body (i.e. institute, laboratory, etc.). The identification of the body responsible for revision of RD alone is not obvious. The use of the EMEA database of experts in this endeavour was fully supported.

Though the ICD-11 revision will truly be an ambitious process reviewing RD codes “from scratch”, the TAG is aware that drastic changes are not seen as favourable and the role of the Revision Steering Committee is to make sure that changes are only dramatic when necessary.
It was suggested that it may be important to include an explanation of why such a revision process is necessary and helpful in the Communication.

DG SANCO agreed to participate in the revision process by sending a representative to workshop meetings. J. Vasquez stated he would also like to contribute to the process.

F. Presentation on Other Activities of the Rare Disease Task Force
Ségolène Aymé
Orphanet
INSERM-SC11

Communication

RDTF Secretariat has continued the publication of the RDTF electronic newsletter, OrphaNews Europe. Currently distributed to more than 8,500 registered readers from 32 countries, subscribers are free to opt in or out of the service at any time. Since its creation in June 2005, 16 issues have been completed. In May 2006, a satisfaction survey reflected a high level of readership satisfaction and suggestions to expand topics covered in OrphaNews Europe to include more relevant issues on the political level and in research findings. To decrease the quantity of information in each newsletter, it has been decided to publish a newsletter every two weeks. All stakeholders including RDTF members are encouraged to send their contributions to orphanews@orpha.net.

S. Aymé added that she and several other RDTF members presented at the first Canadian Conference for Rare Disorders and Orphan Products Policy. She is also participating in the 3rd International Conference on Rare Diseases and Orphan Drugs (ICORD). The conference is organised by the NIH in the US and the Karolinska Institute in Sweden. S. Aymé also visited the Minister of Health in Hungary who said she will consider proposals in RD very favourably.

It was suggested that the RDTF Secretariat prepare a basic RDTF presentation for members to be able to use in presenting the RDTF activities to others.

Workshop on Orphan Drugs

On 30 May 2007, in Paris, a workshop was organised for a subgroup of the WG on Standards of Care on the subject of the future of orphan drugs. This topic was selected because the discussion of the proponents of Orphan Drug Acts as being victims of their own success is becoming more and more common. Many fear that innovation will lead to an orphan drug (OD) for each rare disease and no healthcare system will be able to support it. At the moment, no one has data to show otherwise. The workshop in Paris facilitated a discussion on identifying the number of treatable RD and forecast the number of OD expected in the next ten years using the US experience and a model constructed by François Faurisson of EURORDIS. Using this information it looks as the ~200 new OD will appear on the market in the next 10 years.

The communication of this message will be difficult. It is a sensitive subject as on the one
hand patients may be very discouraged if a number of OD is defined and does not include treatment for their disease. Several participants were wary of providing any exact figures during the communication of this discussion.

It should be kept in mind that off-label drugs are used very often and truly help the quality of life of patients. It is clear that industry is not ready to coordinate clinical trials to show this but it could be helpful to mention in communicating the forecast of OD without discouraging patients. This information is available on Orphanet. It is known that ~500 RD are treated by drugs with other indications. Not only the ~200 OD but also the number of drugs in clinical trial could be reported in this forecast.

There continues to be a great need for better collaboration between industry and Public Health professionals as there is always a critical phase of drug development after the basic research phase and before clinical trials. The success rate of development is approximately 15%.

It was agreed during the Paris workshop that one must always present this dilemma in terms of solidarity and equity (as opposed to cost effectiveness).

S. Aymé stated that she felt it was a very productive meeting and that she hopes the RDTF will be able to have more such meetings, perhaps in conjunction with EMEA.

**Workshop on the Future Needs of the Rare Disease Community**

S. Aymé announced her participation in this expert workshop along with several other RDTF members. The Workshop included presentations of RD activities supported by DG Research and DG SANCO, and a discussion of research needs of the rare disease community. The next step in the discussion of RD research needs is the ‘Rare Diseases Research: Building on Success’ conference on 13 September 2007 in Brussels. Members are encouraged to get involved in this conference which provides the rare disease community with the opportunity to express their needs in terms of research. The conclusions from this conference will be presented at the European Conference on Rare Diseases in Lisbon in November 2007 (ECRD Lisbon 2007).

**G. Presentation on the European Conference on Rare Diseases (Lisbon, 27-28 November 2007)**

Yann Le Cam

EURORDIS

Y. Le Cam presented the European Conference on Rare Diseases sponsored by EURORDIS in Lisbon. Registration and all relevant information is available on the website www.rare-disease.eu which will progressively be updated. The conference is organised by a program committee of 14 members with two chairs, T. Andersen, President of EURORDIS and Professor Josep Torrent i Farnell, former chairman of the COMP. The local organising committee is the Directorate General of Health in Portugal and 10 patient organisations. It is very important that this conference takes place in conjunction with the new presidency as it will place RD on the national agenda.

Several pre-meeting workshops will take place the day before the official start of the
Workshop on help-lines for rare diseases
- Thalassemia International Federation and PBSA annual meeting
- Orphanet network meeting
- Council of National Alliances meeting
- Drug Information, Transparency and Access Task Force meeting

The official meeting will include 11 session spanning two days. Participants will be able to choose among several coinciding sessions on day 2. A fee reduction is available for those who register before the end of July and there is room for only 400 participants so early registration is encouraged. The deadline for submission of abstracts has also been extended to the end of July. Organisations that would like to pass out fliers during the conference should contact the Secretariat of the conference.

H. RDTF Future Initiatives
Ségolène Aymé
INSERM SC11 – Orphanet

European Networks of Centres of Reference

The third technical and scientific report on ENCR will be published as promised. This report will include a discussion on the added value of ENCR and more specifically on the methods used to assess this added value. A workshop, in collaboration with Eurordis and the High Level Group on Health Services and Medical Care, will be organised to produce this report. If desired by RDTF members, this can be the topic of the second semester RDTF meeting.

Emergency Guidelines/Emergency Cards

An initiative to provide patients and health professionals with concise information on emergency guidelines for rare diseases has begun in France. A pilot study, producing such guidelines for several rare diseases is already underway, thanks to the funding of the French National Plan of Rare Diseases. This type of effort could be valuable at the EU level. The question remains at what point guidelines should be managed at the national level due to the diversity of traditions in disease management and existing laws.

Essential Tests

Based on the concept of “Essential Medicines” designated by the WHO, the rare disease community could profit from a list of “essential diagnostic tests”. It was mentioned that the Council of Europe has a WG on this topic that could be consulted.

National Plans on RD

National Plans on RD were suggested as a future topic for the RDTF including the creation of best practice guidelines that can be implemented at the MS level. As such, there would be some guidance or steering of the evolution of National Plans on Rare Diseases.
All additional suggestion for future RDTF initiatives are welcome and should be emailed to the RDTF Secretariat.

Next Meetings

The drafting group for the Communication will meet July 18th. The following members voiced their interest in participating: S. Aymé, D. Taruscio, L. Fregonese, J. Llinares Garcia, A. Montserrat, M. Posada de le Paz, R. Stefanov, and C. Nourissier.

8th RDTF Meeting will be held 23 October 2007 in Luxembourg.

The next WG on Coding and Classification will take place on 13 November in Luxembourg.
2. SCIENTIFIC SECRETARIAT REPORTS AND WORKING GROUP MEETINGS
   a. Standards of Care

How Many Drugs for How Many Patients?

Recommendations of the Rare Diseases Task Force

July 2007
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ANNEX 1 – Orphan Drug Designations by Medical Designation and Product Type .... 7
Introduction

Rare diseases (RD) and orphan drugs (OD) represent an important discussion at the Public Health level. Orphan drug regulations have proven to be effective in boosting the development of therapeutic solutions that are otherwise expensive to produce and, by definition, benefit a small number of patients. Previously, healthcare systems could cover the costs of expensive OD because the treatments were rare enough that the effect on healthcare services and costs was minimal. As the number of drugs for RD grows, increased costs are straining healthcare budgets. The RD community has somewhat become the victim of its own success. Many health professionals have begun to fear that there may be a day when every RD could be treated with an OD and an endless increase of innovative therapies will cause an increased financial strain. The RD community is somewhat a victim of its own success.

In order to provide a sound framework for policy makers to discuss the forecast of OD in Europe, the Rare Disease Task Force (RDTF) organised a workshop on 30 June 2007 with participants from the RDTF, the European Commission, EMEA, Orphanet, and industry professionals of companies who already have a market authorised (MA) OD in Europe.

The specific aim of this workshop was to assess the number of treatable RD and estimate the proportion of patients eligible for treatment to serve as a basis for recommendations in the Communication on Rare Diseases to the European Commission. This workshop also serves as a preparatory meeting to ensure an effective debate during the Session of Epidemiology of Orphan Drugs “How Many Drugs for How Many Patients?” during the 8th European Platform for Patients’ Organisations Science and Industry (EPPOSI) Workshop on Partnering for Rare Diseases Therapy Development.

Analysis and Recommendations

Methods

This report has been prepared by an expert group from the Rare Disease Task Force (RDTF). The RDTF was set up in January 2004 by the European Commission’s Public Health Directorate. It is led by Ségolène Aymé, a medical geneticist and Director of the Orphanet, a database of rare diseases. The deputy leader of the RDTF is Helen Dolk, Director of the Eurocat Programme on Congenital Disorders. The aims of the RDTF are to advise and assist the European Commission Public Health Directorate in promoting the optimal prevention and case management of rare diseases in Europe, recognizing the unique added value to be gained for rare diseases through European co-ordination.

Three Working Groups (WG) have been established within the RDTF to focus on the following topics: Coding and Classification, Public Health Indicators, and Standards of Care. This last WG has been divided into two sub-working groups, the sub-WG on European Networks if Centres of Reference and the sub-WG on OD, established to contribute to knowledge about expectations in the field in the next 10 years. Members of this expert group included representatives of the RDTF, the European Commission, EMEA, Orphanet, and
industry professionals of companies who already have a market authorised (MA) OD in Europe. RDTF members are current and former project leaders of European funded initiatives related to rare diseases, member state experts and representatives from relevant international organisations, including patient groups.

Results

Prevalence of RD Patients

A bibliographic report published on the Orphanet website assesses the prevalence of rare diseases (http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases.pdf). This information in the Orphanet database can help predict the future of OD and patients eligible for treatment in Europe.

Meeting participants agreed on the following concerns in estimating the prevalence of rare diseases and the proportion of treatable rare disease patients:

- Estimates can be made using information from all European Economic Area (EEA) countries with developed healthcare systems capable of providing useful estimates. Barriers in countries whose healthcare systems do not allow for patient estimates include: no centres of expertise, thus no place for evaluation; distance (due to scare centres of expertise), lack of awareness on government level; lack of awareness on patient and health provider level; and cost.

- The rarer the disease, the greater the deviation of the estimate from true prevalence.

- The phenotype of many of these RD is heterogeneous even if the genotype is simple. In addition, as a result of predominantly being genetic and X-linked many RD are racially or regionally concentrated. As a result, many epidemiological investigations occur at the local level and prevalence appears high. With new born screening a much more accurate prevalence is obtained, which is often times much rarer than what was initially concluded with a local study.

- In many prevalence studies, only the most severely affected patients are documented. Under diagnosis, however, is a problem common to rare and major diseases.

Future of OD

A model to forecast OD Development in Europe using US and EU experiences was proposed by Eurordis and endorsed by the members of the group. This model, describing the kinetics of development from OD designation to market authorisation (MA) in the US, was created using data collected (since the implementation of the 1983 Orphan Drug Act) on three kinetics parameters: designation rate, marketing half-life (the time between designation and marketing authorisation), and the MA rate. Analysis of EU data, since the implementation of the Regulation on Orphan Medicinal Products, shows that the development of OD in Europe follows that same pattern. As such, the proposed model can be applied in Europe where it is estimated that the designation rate is 80 designations/year, the half-time of development of an OD in Europe is 3 years (50% are developed in 3 years and 75% in 7 years), and the rate of MA is 15%. This robust model brings into consideration withdrawn products and variability.
of types of OD (i.e. biological, chemical, for oncology) and predicts ~200 new OD in the market in the next ten years.

Meeting participants agreed on the following questions for consideration in using this model to predict the number of market authorised drugs in Europe:

- It was suggested that there be two models, one for early designation OD and one for later designation.
- The model would be even more valuable if compared to a similar model for non-orphan drugs.
- How does the model allow for a cumulative effect of new drugs entering the market and replacing older drugs?
- Is this model sensitive to a change in designation criteria?
- The model could be compared to other similar drug categories in order to compare MA half-life of OD to other drugs.
- How does the difference of OD designation criteria in US affect the use of the model in Europe?

The Orphanet database also serves as a valuable tool in predicting the number of OD on the European market in the next decade. The Orphanet OD database aims to centralise information on current OD and currently, OD in Europe can be searched by disease, laboratory, active substance or brand name, stage of development and designation. All non-orphan drugs with RD indication are also included in the database and searchable with similar criteria. Currently this database includes 449 OD designations with the following breakdown of product types: 58% chemical, 30% biotechnology, 3% cellular therapy, 3% natural, 3% oligonucleotides, 2% gene therapy (Annex 1).

The group agreed on the following predictions:

- Biotechnological products will increase
- Cellular therapy products will only increase a bit. As there are few such products today, the % increase will be large but the number of products will remain small.
- Chemical therapies will decrease
- Gene therapy will increase; vectors will be used and designated as orphan products; the application of these therapies will be different than most drugs as they will most likely be administered in one dose in a hospital setting or a kit and not regularly consumed.
- Oligonucleotide therapy will greatly increase

It was also suggested that including all drugs with rare disease indications in this type of analysis would be persuasive as would the presentation of paediatric and non-paediatric data separately.

**Conclusion**
The 1983 American Orphan Drug Act has been an unbelievable booster for innovation. Orphan drug regulations in Europe and other parts of the world have since proven to be effective in boosting the development of rare disease therapeutic solutions that were previously considered to expensive to produce for too few beneficiaries. Considering the novelty of this legislation in Europe, it is not obvious what the future of OD holds. Similarly, the true prevalence of rare disease patients is also an area that requires more investigation. The exact prevalence rate of each rare disease is difficult to assess from the available data sources. There is a low level of consistency between studies, a poor documentation of methods used, confusion between incidence and prevalence, and/or confusion between incidence at birth and life-long incidence. In addition, it is likely that there is an overestimation for most diseases as the few published prevalence surveys are usually done in regions of higher prevalence and are usually based on hospital data. As such, it can be concluded that the number of rare disease patients is lower than often reported. Furthermore, although many rare disease patients benefit from off-label drugs, surgeries, and other therapies, of the total of rare disease patients only a fraction is eligible for treatment with OD. Investigation into the true prevalence of rare disease patients and the forecast of OD will allow policy makers to make sound decisions regarding legislation on orphan drugs and for rare diseases patients.
## Annex 1

Orphan Drug Designations by Medical Designation and Product Type - Orphanet

### Orphan Drug Designations (449)

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MINUTES OF THE FIRST MEETING OF THE
RARE DISEASE TASK FORCE
CODING & CLASSIFICATION WORKING GROUP
Luxembourg, 11 October 2006
10:00 – 16:00

Present:

RDTF members: S. Aymé, H. Dolk, G. Gatta, D. Taruscio

From the Commission: A. Montserrat, (DG SANCO Unit Health Information)


Introduction by A. Montserrat, DG SANCO

A. Montserrat welcomed the members of the Task Force Coding & Classification Working Group to their first meeting. He began by reminding members of the Task Force’s background, its mission and future. The first wave of the health programme (2003-2008) is now making way for the second wave (2008-2013) currently under revision. The enlargement of the EU presents new needs including the necessity of adapting objectives to this new period. This has been under discussion for 1 year already. Theoretically, financing should be covered for this period but in practice, it has dropped by 30% compared with previous years.

He noted the importance of achieving better networking between RD players, creating synergies between professionals, patients and other members of the medical community concerned. A more-in-depth elaboration of policy needs must be made. Only a very few Member States have national RD health plans; 27 plans must be aimed for. Better classification is essential to improve the quality and quantity of registering in national health care systems. Reference networks of centres of expertise are essential to improve the quality of health care delivery in Europe. Two documents by the RDTF are targeted, with a report from the High Level Group expected by the end of this year. In addition, pilot projects have been set up.

Three major events were presented for 2007:

1. A workshop on Centres of reference in Europe in Prague, 12-13 July: This major workshop, organised by Eurordis in the context of the Rapsody project, is produced by 11 consultations by Member States in discussion aimed at producing recommendations on the way health services must be organised to serve the needs of the patients in the context of the Directive for free circulation in Europe.
2. European Conference on Research in the field of rare diseases, organised in Brussels on 14 September by DG Research: This event is designed to give better visibility to projects taking place in the RD field and to discuss future research trends.

3. 4th European Conference on Rare Diseases organised by Eurordis in Lisbon on 27-28 November. This major event is designed to focus political attention on RD actions in Europe.

S. Aymé added that a series of ten workshops by Rapsody would be taking place on the national level, and that the RDTF must be present at all of them. Members will be officially invited to the workshops.

**Presentation of Coding & Classification aims & achievements to date by S. Aymé**

S. Aymé gave a brief outline of the history, objectives, duration and composition of the RDTF for the benefit of new members present. The Group is made up of 35 members, of which 25 (previously 20) are now expenses-covered. Issues to be tackled by the Coding & Classification (C & C) Working Group (WG) were:

- A state-of-art of the existing C&C systems
- Plans for contributing to improve them
- Creation of a database of expert RD classifications

S. Aymé presented an update of Orphanet’s contribution to C&C issues currently being developed, including a database consisting of 4,300 rare phenotypes, with an average 200 new phenotypes being added each year. Of the total rare phenotypes, approximately 1,200 concerned most patients. Orphanet’s Encyclopedia of peer-reviewed short articles now includes a total of 1,713, with 420 new review articles out this year. S. Aymé briefly presented Orphanet’s definition of diseases, conceding that the definition is open to discussion and presented an outline of various classifications already collected. The different codes attributed to each disease by Orphanet include the ICD 10 codes, the attribution of MeSH terms and Pubmed auto-search facility, and the OMIM code.

Next, Orphanet’s forthcoming update, “V4”, was discussed. This new version will be more user-friendly, easier to understand and will include new features such as the classification of RD search facility by different basic criteria.

**Presentation of RD Coding Initiatives from 4 countries**

A. Devereau, UK

A. Devereau from the UK’s National Genetics Reference Library in Manchester, made a presentation co-written with S. McKee, also present at the meeting, from Northern Ireland Regional Genetics Service, dealing with a variety of UK coding initiatives. The first, a major NHS project, “Connecting for Health” (NHS CfH) showed a system adapted to the recent devolution events taking place in the UK, making it important to deal with four separate countries as different entities each with its own system. It aims to deliver a comprehensive health IT infrastructure project for England, including physical networks, electronic patient records, requesting and reporting. The extremely large scale of this
The “Do Once and Share” (DOAS) project involves clinicians in a consultation and sharing of expertise for specific clinical specialities to provide requirements for NHS Connecting for Health services on the national level. The Clinical Genetics DOAS concluded that there existed no universal disease coding used in genetics clinics and since current systems couldn’t deliver, (SNOMED CT/Read codes do not yet include many rare genetic diseases and ICD codes fail to meet needs), a single national coding system was needed to link services. A White Paper issued by the Dept. of Health insisted on the need for genetics services to integrate with NHS Connecting for Health systems. This has led to data standards being set for genetics. Chief sources used were the NHS Data Dictionary and the Government Data Standards Catalogue.

A. Devereau moved on to the SNOMED CT system which comprises a bi-national development of SNOMED RT (College of American Pathologists, USA) and Read codes (or Clinical Terms, NHS, UK), which is becoming the mandated terminology standard for the NHS in England. He noted that the ICD-10 and OPSC4 codes are used as classification standards. There is a Clinical Genomics working group being formed under the SNOMED International Editorial Board which is being led by Yves Lussier in the US who is keen to work with genetics groups in the UK.

Next, he presented HL7 (Health Level 7, a US health messaging standard now in its V3). It is specialised for each country (HL7 international standards are specialised for national affiliates such as HL7 UK) and then for each application. It is mandated for NHS CfH systems. There is an HL7 Special Interest Group (SIG) for Clinical Genomics being led by Amnon Shavo from IBM Haifa.

Among the UK genetics initiatives indicated were the further development of data standards following from the initial data standards development and DOAS project, and following up from a UK Genetics Testing Network project which cross-referenced ICD-10 codes to its list of UK genetic testing services. A UK working group has been proposed to coordinate and interact with SNOMED/HL7 working groups, seeding solutions for UK genetics service.

Comments on the UK initiatives came from R. Jacob who noted that despite its strong central national health system, the UK has not pursued harmonization actively enough. There is a real need for compatible systems. He pointed out that the E.U. has been carrying out research and setting standards which have not been taken up by the UK. He felt SNOMED should go further towards internationalising its system since it was in danger of becoming too closed.

**P. Facchin, Italy**

P. Facchin from the University of Padua, Italy, presented the Italian RD C&C experience through the Veneto regional registry of rare disorders. She traced the history of the 2001 Law in Italy which led to listing RD. Patients have to register if they want to have their expenses covered. The diseases are coded with ICD 10.
The comparison between the RD register and the hospital discharge register showed that 70% of patients registered with the RD register were found in Hospital discharge register as well.

ICD-based current statistics were useful for a rough estimation of the number affected which is 1/200 for this Italian region.

P. Facchin discussed the limits of the ICD which has no specific code for most diseases. Next came a presentation by A. Sollie from Netherlands' Department of Human Genetics and the VSKG, the Dutch umbrella association for clinical genetic centres, who presented a Central Information System for Hereditary Diseases and Synonyms – CINEAS. She explained that the system was developed both for and by clinical geneticists to determine diagnoses for patients, based exclusively on Mendelian inheritable diseases. It has been noted that there is a need for a more centralised listing of diseases on the international level. The system has been used by all of the Dutch clinical genetic centres as well as the NKI (Dutch Cancer Institute).

The database and website in English use no hierarchical classification system which gives them the advantage of having “no limits”. Each entry is cross-matched with a disease name, a (unique number) disease code and synonyms. All entries are cross-matched with ICD-9 (or +10) codes, plus an OMIM code if possible. The system grows through utilisation: between its conception in 1992 and now, it has grown to accommodate a total of 5,000 diseases. New editions are available online and are compatible with other systems for uploading.

Questions and comments came from R. Jakob, who suggested a comparison of the Orphanet and CINEAS databases could throw some interesting light on the subject. H. Dolk found the system tricky to use in terms of finding the right codes when going back in time (e.g. checking classification details during the 1990’s) with regard to new information updates. She suggested this could be shown by using code suspension and by creating new, clearly indicated codes.

A. Sollie, Netherlands

Next came a presentation by A. Sollie from the VSKG, the Dutch umbrella association for clinical genetic centres, who presented a Central Information System for Hereditary Diseases and Synonyms – CINEAS. She explained that the system was developed both for and by clinical geneticists with the main purpose being to allocate diagnoses to patients, The system is used by all of the Dutch clinical genetic centres as well as the NKI (Dutch Cancer Institute).

The database and website in English use no hierarchical classification system which gives them the advantage of having “no limits”. Each entry has a disease name, a (unique number) disease code and synonyms. All entries are cross-matched with ICD-9 and ICD-10 codes, plus an OMIM code if possible. The system grows through utilisation: between its conception in 1992 and now, it has grown to accommodate a total of 5,000 diseases. Physicians using the CINEAS system can request new codes online. These requests are evaluated by a coordinator and an expert group. In this way the system is kept up-to-date at all times. New editions are made once a month and are available online. These editions are compatible with other systems for uploading.
Questions and comments came from R. Jakob, who suggested a comparison of the Orphanet and CINEAS databases could throw some interesting light on the subject. H. Dolk found the system tricky to use in terms of finding the right codes when going back in time (e.g., checking classification details during the 1990’s) with regard to new information updates. A. Sollie replied that in the database disease codes are never deleted, they can however become “suspended”. Users can still track patients using these suspended codes, but are advised online to use newer codes now available. A. Devereau asked if the rapid growth could be problematic for the overall system. A. Sollie replied that it did not in as much as the information was contained by a system capable of adapting and expanding.

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U. Vogel, Germany

U. Vogel began his presentation by informing members about what DIMDI represents. It is an Institute that is part of the German Federal Ministry of Health with a collection of databases that cover a wide medical spectrum. DIMDI issues an official German version of classifications and nomenclatures. In the area of rare diseases, the Federal Ministry of Education and Research has been funding 10 disease-specific networks for RD’s since 2003.

In Germany the ICD-10-WHO is used for mortality coding while the ICD-10 GM (German modification) is used for morbidity coding. Research and clinical trials are reliant on the ICD-10-GM and WHO systems. Given the complexity and wide variety of different clinical syndromes covered, there are problems associated with describing groups of similar expenses for diagnostics, treatment and care.

With regard to German coding RD initiatives, there is currently no specific involvement by DIMDI. Reimbursement is recognized as a major issue. There is an annual maintenance process to adapt the system to the German health care system. Justification for each new category required for inclusion in classification is needed. Efforts directed at a new, adapted system mean that each new classification must be adapted and assimilated.

A brief summary of the C&C situation in Spain was given by O. Zurriaga. He confirmed that the ICD-9 system is used in Spain for morbidity registrations. His team has been using ICD-9 to work on a recently published “National-Provincial Atlas of Rare Diseases (1999-2003)”, a major source of epidemiological information from across the regions of Spain.

H. Dolk explained that EUROCAT uses ICD-10 coding format, but with a BPA (British Paediatric Association) extension. A 1-digit extension needs to be taken into account for ICD-10. She noted that there have been some clashes between ICD-10 and BPA systems and that BPA classification is not maintained anymore. This issue should be tackled. EUROCAT has its own guides to syndromes and has dropped efforts to adopt Euro coding, since it is impossible to adapt and incorporate. Containing and updating also pose
Presentation of the WHO’s plans for ICD Revision by Robert Jakob

R. Jakob, a medical officer at the WHO, presented the WHO’s family of classifications and its extensive revision plans. He described the need to identify a way of merging and linking activities with three major classifications: Related – Reference – Derived. The aim is to avoid overlap and data merging in a worldwide, growing network of registries. He noted that cancer registries use ICD/ICD-0. WHO is placing its classifications in HIS and IT. Terminologies to health record systems are being developed along with mappings (using ICD, ICF and ICHI classifications) in a pragmatic approach. He described the requirements to achieve ICD revisions involving code changes. Key drivers WHA and EB are mandated. The main objective is to reply to consumer requirements while updating to new scientific knowledge compatible with WHO-FIC members. This should help achieve a better implementation with health information systems (HIS).

R. Jakob presented colour-coded slides to give a graphic representation of ICD renal diseases. The clinical dimension is given and a need for definitions is clear. National perceptions regarding universal codes mean diverse interpretations can be made. How can different perceptions and definitions be avoided? ICD revision work streams were presented: scientific stream, clinical stream and public health stream. A knowledge portal, a web for ICD revision operates for evidence-based systematic reviews and knowledge sharing of all ICD chapters, structured discussion forums, field trials (including global practice networks) and classifications (online journal).

Core classification issues were outlined to summarise best practice regarding limits, validity, reliability, clinical utility, cultural perception differences, clustering and links, etc. An involvement strategy has been developed by the WHO between different countries, languages and health care systems. This takes in different clinical specialties and other professionals, in addition to different health sector aspects such as surveillance (injuries, etc), prevention programmes, different types of care and consumer demand from different sectors.

As part of the ICD Knowledge Portal, three main applications will be included: 1) ICD-10+ application, 2) ICD-11 draft creation and 3) ICD-terminology / ontology tools. For 1), a designated scientific group review will provide systematic reviews, scientific, clinical and public health streams as well as taxonomic rules and definitions. It will also invite open comments and suggestions from a periodic, continuous structured peer review. This will be accessible to all users. With regard to 2), Codes, definition of the entity (including type of disease, level of use, glossary description and taxonomic ontology status) and diagnostic criteria for the entity will all be taken into consideration. A series of screenshots was used to demonstrate these ICD-11 draft points. For 3), R. Jakob described a joint-authoring tool with a Wiki-like structure called “Hi-Ki”, designed by the WHO. Selected expert groups will draft portions of ICD-11 with each group placing their draft to the WHO web portal using this tool. Following a taxonomic review, this will be posted and clarified by WHO experts as required. Finally, the WHO will carry out a structured scientific peer review before the product is posted for public review.

R. Jakob went on to outline the process of rewriting ICD using Snomed, using clear and
varied cases to illustrate his point. He described the “big picture” with the use of a flowchart and a “tree” structure graphic integrating the three applications mentioned above to show the different stages of the updating procedure. The selection criteria for WG members were outlined. It was noted that one of the most important criteria not to be forgotten was that of age since candidates must be young enough not to have left the project (or deceased) before the revision process was completed. This could easily take more than 20 years! So the timescale is extremely important when examining this time scenario.

Carefully controlled field trials including e-questionnaires within a global practice network are an important stage in the revision process. Finally, a tentative timeline is programmed. 2006 sees the international consultations for starting multiple streams of the workplan. 2008 is expected to see the Alpha version (ICD 10+ \(\rightarrow\) ICD 11 draft). Next, in 2009 the Beat version and the field trials version should see the light of day. In 2012 a final version for public viewing is expected to be ready with the WHO approval scheduled for 2015 and implementation scheduled for 2015+, if all goes to plan.

The end result, as described by R. Jakob, should be easy to use and implement and reflect a spectrum of needs from multiple cultures, levels of development, user groups and various utilisations. It is expected to be compatible with existing classifications and will have statistical continuity. It will be fully interoperable in its classifications and terminologies, with a system of one classification for multiple projections. The resulting system will place rare diseases in WHO classifications thus guaranteeing a complete integration of rare diseases.

**Discussion on the way forward with the WHO**

The suitability of the system with regard to rare diseases was questioned by H. Dolk. R. Jakob claimed that the use of taxonomic structure generated statistics comparable to ICD statistics. It was important to determine the impact of classification features before adapting the code.

U. Vogel asked what could be expected from new codes for RDs in ICD 10 (or ICD-11 in the future): what and where were the needs? In the ICD-10 to ICD-11 process, the revision would not be put together “from scratch” but modifications would only need to be made in specific areas.

U. Vogel claimed that classifying RDs in ICD-10 (or ICD-11 in the future) means assigning diseases to categories as ICD is not a list of diseases, but primarily a list of categories. Accordingly, a better representation of RDs in ICD (especially for ICD-11) would benefit from mapping RDs categories (which still may have to be developed/modified in some areas) to the categories of ICD classification. It was generally agreed that the new code would improve the situation of RDs on the international as well as on the local level, and would greatly improve the visibility of rare diseases.

S. Aymé concluded that this discussion more than proved the necessity of having a C&C Working Group. Whilst divergence surrounding some of the codes evoked was to be expected, a real step towards world harmonization of coding in RDs was being achieved.
General Discussion (Incorporating the MeSH, Snomed & MedDRA Systems)

D. Taruscio announced that coding updates had already been carried out in a region of Italy, however they still needed to verify the system properly.
E. Garne felt it was important only to have a low number of non-specified codes.
S. McKee stated that a degree of non-specificity should be retained for patients, e.g. diagnosis should not necessarily be given or arrived at. R. Jakob replied to this that he predicted changes which should be taken into account.
J. Donadieu from InVS in France claimed that coding is only part of the problem in epidemiology since it is easy to use a coordinated database using a code. Many other ways exist associated with the doctors involved. The new French mortality system has links between the text and code.

Definition of Action & Planning Needed:

S. Aymé suggested on a general agreement of members present to work on RD coding with ICD 10 and compare the EUROCAT, CINEAS, University of Padua and DIMDI systems.

With regard to WHO revision activities, R. Jakob explained that strictly speaking, it was not possible for the Working Group to become an “Expert Group” but in practice, it would be possible to make the system work.
He was looking into the possibility of integrating a “Coordinating Group for Rare Diseases” for which a Correlating Centre should also be set up. It was generally felt that no hierarchical approval was necessary to establish such a group, so plans were embarked upon immediately.
Firstly, it was suggested that a work plan be drawn up to harmonise work carried out in common. The group should not constitute a “body”. R. Jakob said he would further examine how the group should proceed.
S. Aymé said she needed to receive confirmation that all resulting work would actually be used.
WG members were curious to know if they would be able to use the WHO’s “Hi-Ki” tool.
R. Jakob answered that the WHO would need to adapt the necessary software. He added that proposals could be given visibility on the WHO system. The system was on the web already. He therefore suggested that members register themselves individually to enter the system.

For the C&C WG schedule, a meeting was planned for 2007, the date of which will be confirmed.

S. Aymé said that MeDRA coding system had already been selected by the EMEA for orphan drugs. Therefore Orphanet should be brought in to work on coding rare diseases with this system. ICD, MEDra and MeSH should be the main coding systems available on the Orphanet website, in addition to OMIM..

A. Devereau asked what should now be done with the SNO code used in the UK’s system. Should feedback on this be passed on to the Group?
S. Aymé commented that Orphanet currently had good relations with the Office of Rare
Diseases at the National Institute of Health (ORD NIH), and that Orphanet’s US contacts there think that Europe is ahead of the States with regard to C&C. They want to learn from the European experience.

A. Montserrat said it was acceptable to collaborate with non-EU countries and that DG Sanco was in its mission when supporting financially the activity of the current working group. S. Aymé added that the NIH may cover mission expenses.

Finally, S. Aymé concluded, saying she had invited some new members along to the meeting but they had been unable to show up. They should, however, be taken into account for further activities and the next WG meeting in 2007.

R. Jakob thanked the group of experts present and S. Aymé thanked A. Montserrat in particular for accommodating this additional meeting, which had not originally been planned as part of the WG schedule.
Minutes
Meeting of the Rare Disease Task Force
Coding and Classification Working Group
Paris, 2 May 2007

On 2 May 2007, the meeting of the Rare Diseases Task Force (RDTF) Working Group (WG) on Coding and Classification included the attendance of:

S. Aymé  J. Huizer  A. Rath
C. Barrère  R. Jakob  A. Sollie
L. Ciccolaloi  Y. Kodra  D. Taruscio
E. Daina  A. Kole  A. Trama
A. Devereau  O. Kremp  M. Vihinen
P. Facchin  M. Lévi-Strauss  U. Vogel
S. Groft  P. Lunt  O. Zurriaga
E. Garne  C. Martos-Jimenez

A. Welcome and Approval of Agenda

Apologies from T. Monserrat, who has now been promoted as acting Director of the Informatics Unit at DG, and J. Donadieu. No changes to agenda.

Introduction to the Meeting
Ségolène Aymé
Orphanet (INSERM SC11)
Chair of RDTF

The RDTF WG on Coding and Classification was established in 2004 to assist the European Commission (EC) in promoting the optimal prevention, diagnosis and treatment of rare diseases (RD) in Europe, providing a forum for discussion and exchange of views and experience on all issues related to rare diseases in recognition of the unique added value gained for RD through European coordination.

At the time of creation it was said that this WG will promote the development of a coding and classification system of RD supplementing the World Health Organization’s (WHO) International Classification of Diseases (ICD)-10. It is more appropriate to say that the WG will assist in the modification of the ICD-10. During the last meeting for the WG on Coding and Classification (11 Oct 06) it was discussed what work was already in place for this endeavour, what countries were missing in terms of participation and R. Jakob of the WHO mentioned that RD would be a priority on the agenda of the ICD-10 revision. Today we see that it is.

Previously, it was decided that the WG to focus on the ICD revision should be composed of those deeply involved in coding (e.g. those managing registries). The end result is a group with a great range of expertise. This group has begun to tackle a comparison of coding and classification systems such as the ICD, SnoMed, MedRA (used by FDA and EMEA), and
MeSH. This data must continue to be homogenised through the exchange of data. Today we must set up the exact composition of the group and mandates of this activity as well as any funding we may be able to receive to support it.

B. Presentation on Feedback of the Revision Steering Group for the Launch of the Revision Process April 2007, Japan

Robert Jakob
WHO
Medical Officer Responsible for ICD update

The meeting in Japan began with a press conference, followed by the introduction to leaders of many Japanese Scientific Societies. Japan is very eager to participate and the first country to offer funds for the revision process. For this reason the launch was held in Japan to show that the WHO greatly appreciates their contribution.

The first official day of the meeting included a presentation on review process overall, very much like the presentation given at the last WG meeting 11 Oct 2006. There were a few notable differences:

- The technical platform was presented
- The Topical Advisory Groups (TAG) were presented

The members of the Revision Steering Group are as follows:

**Chair of the RSG**
Christopher Chute
Mayo Clinic
Rochester, USA

**Rare Diseases**
Chair: Ségolène Aymé
Orphanet
Rare Diseases Platform
Broussais Hospital, Paris, France

**Injury and External Causes of Injury**
Chair: James Harrison
AIHW National Injury Surveillance Unit
Flinders Univ., Adelaide, South Australia

**Mental Health**
Chair: Steven Hyman
Provost
Harvard University, Boston, USA

**Internal Medicine**
Chair: Kentaro Sugano
Department of Internal Medicine
Jichi Medical University, Japan

**AND**
WHO Dept. of:
- Violence and Injury Prevention
- Drug safety
- Occupational Health

**AND**
WHO Dept Non-Communicable Diseases
The following are not chairs of TAG but trans-group members:

**Marjorie S. Greenberg**  
Chair of the Planning Committee, WHO-FIC

**Martti Virtanen**  
Chair of the Terminology Reference Group, WHO-FIC

**Richard Madden**  
Chair of the Family Development Committee, WHO-FIC

**Mea M. C. Renahan**  
Chair of the Update and Revision Committee, WHO-FIC

RD is one of the top groups in terms of preparation.

As Cancer did not have a TAG chair, R. Jakob volunteered. With collaboration with the International Agency for Research on Cancer (IARC) and the WHO team for Cancer Surveillance the goals are to realign cancer codes with ICD-O. The structure of classification remains to be decided. Do we want to have cancer classified and coded by anatomy or by stages?

Other fields will also soon be involved in the revision process: maternal, neonatal, and child health, infections diseases, neurology, eye, otorhinolaryngoiatrics, skin, female/Male genital diseases, urology, congenital malformations, deformations and chromosomal abnormalities.

S. Aymé mentioned that congenital malformations, deformations and chromosomal abnormalities will be dealt with by the RD WG.

The structure of the organization of the ICD-10 revision:
The number of WG is not at all proportional to each topic. These will vary.
Although all can see the suggestions for revision not all can contribute. The hierarchy of Hi-Ki submission is:

1. Revision Steering Committee
2. Revision Domain/Topic Working Groups
3. Accredited Experts (Designated by Working Group Members)
4. Accredited Persons (Designated by Experts)
5. Registered Interested Persons (Public)

Registration for the public will include the reading several pages of introduction to guarantee an understanding of the ICD structure.

The next meeting will be in Trieste, Italy to discuss progress and set up Work Programmes until 2010.

Examples of potential ICD revisions were presented (i.e. breast cancer, diabetes mellitus). The anticipated timeline includes implementation for all revisions by 2015 and use in all countries by 2020.

**Discussion**

E. Garne commented that children do not fit into ICD-10 though they make up 25% of people in the world. Children are not small adults, and currently there is no way to show that a patient is a child in the system except for with age.

R. Jakob responded that it has been acknowledged that children do not fit. And that an overall paediatric WG may be added or a smaller paediatric WG within in topic. Adding an age criteria is also being discussed.

S. Aymé asked if ICD-11 will be “flat” as before, will it be able to be published in a hard-copy format?

R. Jakob responded that it will be a multidimensional product but what the user will see will be “flat”. It will still be printable.

M. Vihinen proposed adding a query system to the model.

R. Jakob responded that with the new ontology base you will be able to have different perspectives (by age, by anatomy, etc. while still avoiding overlap). You will also be able to merge ICD-O.

S. Groft asked about linkages.

R. Jakob responded that there will be linkages to MeSH and the National Institutes of Health (NIH) Library. He added that as the actual implementation of ICD-11 is so far away (~2020) and so much work will have been put into that the next revision will not be done for a long time, so
this revision must be very carefully planned anticipating the types of tools used in the future.

C. Presentation on the methodology used to revise RD Coding and Classification

Ségolène Aymé

RD specialists must be approached carefully as many times their way of classifying may be very different from the structure of the ICD. The revision WG must be composed of coding and classification experts as well as international experts as the ICD is of course an international coding system. Thus far we have participants from: France (Orphanet, Ségolène Aymé and Ana Rath), CINEAS, UKGTN, Italian regional registries, EUROCAT, USA (Office of RD, Steve Groft), Korea (GH Lee), and Australia (Agnes Bankier).

No other organisations in Europe were identified that the group felt should be approached. As for Japan, S. Aymé has already asked WHO to identify a representative. She asked how important it was to include someone from South America.

R. Jakob responded that it is important to include representation from each continent. E. Garne agreed to identify such potential representatives through EUROCAT’s network of collaborators. S. Groft agreed to identify someone through the Library of Medicine and to fill in the gaps for specialists serving as peer review from NIH.

S. Aymé felt it was more efficient to have fewer TAG members and more peer reviewers. The approach was agreed on.

TAG Tools

TAG tools include the WHO platform, the OrphanetPlatform, the TAG platform, and meetings. A mini website and newsletter was proposed and agreed on for this project. Meetings were identified as crucial to resolving coding and classification discrepancies.

The following principles were presented as guiding the revision group’s actions:

- Rare Diseases should be traceable in mortality and morbidity information systems
- There are two categories of RD
  - The recurrent RD (approx. 1,500 to 2,000)
    - should have a specific code in ICD11
  - The ultra rare (approx. 4,000)
    - should be coded as “other specific RD” within relevant subcategories, but indexed nevertheless

R. Jakob added that how you classify the diseases depends very much on what you would like to do with them afterward. This is why the way Orphanet organizes diseases is a good example.

The following steps were proposed:
Step 1: Establish the priority list of RD which require a specific code in ICD-11. To be established at Orphanet.

Step 2: Analyse ICD-10 to identity mistakes and gaps by cross referencing with others (i.e. CINEAS, UKGTN, Italian registries). This serves as an excelled quality control system for Orphanet.

Step 3: Start contribution to ICD10+

Step 4: Collect other classification systems

Discussion

When discrepancies are encountered first ask for justification. If no agreement can be made a list will be forwarded by S. Aymé, A. Sollie (CINEAS), Italian registries, and A. Devereau (UKGTN) to R. Jakob to distribute to mortality/morbidity reference groups at WHO.

E. Garne added that she worried if there were enough 3-digit codes available within ICD-10 and asked if the 4th place should also be a number or if could be a letter. R. Jakob suggested staying with numbers only.

S. Aymé asked members not yet mentioned to describe the contributions they would be able to make to the project.

D. Taruscio informed that they have 770 classified diseases some of which are not included in the ICD. Some are very specific. Others, approximately 40, have a heavy social burden. She offered to present the “big picture” for RD in Italy and cross reference her data with other registries.

P. Facchin informed she had a registry of approximately 2100 diseases with a specific code (mandatory for patients since 2001) and genetic registry.

U. Vogel from the German Institute of Medical Documentation and Information (DIMDI) informed that he does not have many resources but a lot of knowledge to contribute. R. Jakob agreed that DIMDI will be crucial in verifying the classifications. U. Vogel agreed to act as an advisor to the group.

S. Groft informed that there are many partners to “tap into” such as patient groups, etc. In the next few months he will approach these partners. He suggested that S. Aymé make a list of explicit needs and he will look for resources. He will even consider approaching industry though usually this is avoided.

O. Zurriaga and C. Martos added that they could contribute mortality data from Spain.

The following activities were identified as needing funding.
Preparatory work for experts including the creation of a list of priority diseases, the preparation of RD with ICD10 codes, matching of existing tables, and a list of problems and possible solutions.

- A validation process by TAG members through in-person meetings and by external experts.
- ICD10+ contribution, contribution to proposals, and moderation
- Coding of RD with other coding systems

S. Aymé will finalise an FP7 application to provide 60% of the funding.

**D. Conclusions**

A list of future activities was made:

- Cross-reference with UKGTN and CINEAS by the end of 2007. The end product will be a list of diseases with a code.
- Start comments in ICD10+
- Create tools for WG: website and newsletter
- Look for funds from NIH
- Liaise with colleagues world-wide (S. Groft)
- S. Aymé will contact colleagues from Brazil
- Send a letter to all WHO sub-groups to ask if they know of any RD registries in their respective countries.

**Next Meeting**

The next RDTF Coding and Classification WG Meeting will be held Tuesday 13 November 2007 in Luxembourg. The exact location of the meeting is yet to be decided.
c. Progress Reports

PLEASE EMAIL THE COMPLETED FORM A.S.A.P. TO:

<table>
<thead>
<tr>
<th>NIVEL Scientific Assistance Office of the NCA and NWPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email: <a href="mailto:NCA.NWPLSecr@nivel.nl">NCA.NWPLSecr@nivel.nl</a></td>
</tr>
<tr>
<td>Fax. nr: 0031 - 30- 27 29 729.</td>
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</tbody>
</table>

Task Force on Rare Diseases
Task Force Leader: Ségolène Ayme

(You may enlarge the boxes if needed).

This form was completed by: Ségolène Aymé

Date: 23 June 06

What were the main activities* that have been carried out by your Task Force since February 2006?

1. Meeting of the Task Force in Luxembourg on 6 June 06

2. Meeting of the working group on Indicators for rare diseases in Paris on 30 January 06 to prepare a work plan and initiate the preparation of several application for the call for proposals

3. Meeting with the High Level Group of Health services and Medical Care in Brussels on 22 March 06 to discuss a new work plan on European Centres of Reference.

What were the main objectives* for the period February 2006 – June 2006, and to what extent have these objectives been achieved?

<table>
<thead>
<tr>
<th>Objectives February 2006 – June 2006</th>
<th>Has this objective been achieved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To launch the activity of the working group on health indicators</td>
<td>Yes</td>
</tr>
<tr>
<td>2. To decide on the next step of our action in the field of European Centres of Reference</td>
<td>Yes</td>
</tr>
<tr>
<td>3. To publish 6 issues of our newsletter and to do a satisfaction survey of our readers</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Please describe the progress which has been made by your Task Force since February 2006.

1. We have published 6 new issues of our electronic newsletter for which we have 6,700 registered readers. An on-line survey has collected comments from 488 readers from 28 countries. The most important groups are (1) researchers, (2) health professionals, (3) patients organisations, (4) governmental bodies. Their satisfaction is high both in terms of content and layout. For them the most interesting section is on research developments, followed by news on orphan drugs, then national and international political news.

2. We have had an important workshop on health indicators for rare diseases. The main conclusions were that we should work on the priorisation of rare diseases for surveillance, on the feasibility of using death certificates for assessing life expectancy for some selected diseases, on establishing a list of macro-indicators using ECHI as a source, on mapping of existing data sources (registries, cohorts, databases, other resources), on the feasibility and interest of registering patients with rare diseases in a geographically defined area. Each of this item was taken on board by one of the participants for further action. A new workshop is planned in January 07.

3. We have further worked on the concept of European centres of Reference and proposed to the High Level Group on Health Services and Medical Care to issue a new report covering the situation in all members states and providing more detailed recommendations for further action. This report is due by September 06.

Are there issues concerning the progress of your Task Force that should be raised at the NWPL meeting in July 2006? If so, please explain. We wonder whether it would be possible for the working parties and task forces to comment in more details on the content of funded projects, their direction and methods (advisory only). An annual workshop of project leaders presenting their progresses and plans would be very useful.

What are the main objectives for the period of July 2006 – December 2006?

1. Issue 6 newsletters and re-design the RDTF website

2. Launch the activity of the working group on coding and classification

3. Issue a report on European Centres of reference

Do you foresee any problems in achieving these objectives? If so, please explain. NO

Does the Task Force have a Workplan? Yes

What is the date of the next meeting of the 14 December 06
Please provide a summary of the projects that are were finalised in the previous period and their major findings.

We have established contacts with WHO to participate in the revision of the International Classification of Diseases.
We have also established contacts with the Office of Rare Diseases at the NIH.

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS.

PLEASE EMAIL THE COMPLETED FORM A.S.A.P. TO THE NIVEL SCIENTIFIC ASSISTANCE OFFICE OF THE NCA AND NWPL: NCA.NWPLSecr@nivel.nl
PLEASE EMAIL THE COMPLETED FORM A.S.A.P. TO:

NIVEL Scientific Assistance Office of the NCA and NWPL
Email: NCA.NWPLSecr@nivel.nl
Fax. nr: 0031 - 30- 27 29 729.

Task Force on Rare Diseases
Task Force Leader: Ségolène Ayme

(You may enlarge the boxes if needed).

This form was completed by: Ségolène Aymé
Date: 12 January 07

What were the main activities* that have been carried out by your Task Force since July 2006?

1. Meeting of the Task Force in Luxembourg on 14 December 06

2. Meeting of the Working Group on Centres of Reference for rare diseases in Europe, on 1 September 2006 in Paris. The purpose of this meeting was to prepare a report for the High Level Group on Health Services and Medical Care, describing the current situation and proposing recommendations for action at EU level and at Member States level.

3. Meeting of the working group on coding and classification of rare diseases, on 11 October 06 in Luxembourg. The purpose was to discuss a possible collaboration between institutions having to code rare diseases for their information system in order to reach an agreement on coding with ICD and proposing an evolution of ICD 10 to prepare ICD 11.

What were the main objectives* for the period July 2006 – December 2006, and to what extent have these objectives been achieved?

<table>
<thead>
<tr>
<th>Objectives July 2006 – December 2006</th>
<th>Has this objective been achieved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To launch the activity of the working group on coding and classification</td>
<td>Yes</td>
</tr>
<tr>
<td>2. To decide on the next step of action in the field of Centres of Reference in Europe and to publish a report for the High Level Group of Health services and Medical Care</td>
<td>Yes</td>
</tr>
<tr>
<td>3. To publish 5 issues of our newsletter</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Please describe the progress which has been made by your Task Force since February 2006.

1. We have published 5 new issues of our electronic newsletter for which we have 6,700 registered readers. To follow on the satisfaction survey done during the first semester of 06, we have modified the content of the newsletter to give more attention to scientific news and we have established a section on job opportunities.

2. We have had an important workshop on Centres of Reference in Europe which was followed by the publication of a report to the High Level Group on Health Services and Medical Care. The main recommendations are:
   - The RDTF recommends exploring all possible forms of cooperation between Member States in the field of health services and medical care for rare diseases.
   - The wording "centre of reference" should not be used in the future when referring to the nodes of a network to be established or when discussing a possible cooperation between member states in the field of health services and medical care for rare diseases. The preferred wording is “centre of expertise”. Centres of expertise exist everywhere, whereas centres of reference are confined to a few countries.
   - Countries having a policy for establishing national or regional centres of reference for rare diseases should agree as much as possible on an operational definition of what is a CR and on how to designate them. Countries with established centres of reference should be encouraged to share their experience and the results of their outcome measures.
   - Countries not having a policy regarding the establishment of centres of reference for rare diseases, should find an appropriate way to organise their health care system to serve the needs of patients, either through the establishment of CR or through contracting with other CR or centres of expertise abroad (not too distant if possible), and developing electronic communication between local clinics and centres of expertise from all over Europe.
   - The European Commission should play an important role in supporting the identification of centres of expertise and in the diffusion of the information about them.
   - Networks of centres of expertise identified and funded at European level would be better called "European Networks of centres of expertise".
   - The European Commission should continue its financial support to networks of centres of expertise in the field of rare diseases until an evaluation of the output of the networking process demonstrates that it is not cost-effective (which is extremely unlikely). It should open its call for proposals to the definition of a methodology to assess the benefit of such networks from the perspective of the different stakeholders. It should encourage, by all possible means, the development of electronic tools necessary for the development of telemedicine in the field of rare diseases.
   - The member states should contribute to the identification of their expert centres and support them financially as much as possible and organise healthcare pathways for their patients through the establishment of cooperation with all necessary expert centres from within the country and from abroad when necessary.
3. We have had another important workshop on coding and classification where representatives of major institutions from Germany, The Netherlands, France, Italy and UK and from WHO agreed on:
- working together on the coding of rare diseases with ICD 10 and releasing the information for further use by information systems
- establishing a group of experts to contribute to the revision of ICD 10 in partnership with WHO.

Are there issues concerning the progress of your Task Force that should be raised at the NWPL meeting in July 2006? If so, please explain.

We wonder whether it would be possible for the working parties and task forces to comment in more details on the content of funded projects, their direction and methods (advisory only). An annual workshop of project leaders presenting their progresses and plans would be very useful.

What are the main objectives for the period of January 2007 – June 2007?

1. Issue 6 newsletters and re-design the RDTF website

2. Prepare a workshop on centres of reference to produce a new report on possible methods to assess the added-value of these centres and the added-value of European networks of centres of expertise. Th workshop would be held in September 07

3. Establish the group of experts to revise the coding and classification of rare diseases and Organise a workshop on coding and classification to launch the revision of ICD 10 in the field of rare diseases

Do you foresee any problems in achieving these objectives? If so, please explain.

NO

Does the Task Force have a Workplan? Yes

What is the date of the next meeting of the Task Force? 21 June 07

Please provide a summary of the projects that were finalised in the previous period and their major findings.

We have issued an important report on centres of reference in Europe and we have been selected by WHO to act as an expert group to revise the International Classification of Diseases

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS.

PLEASE EMAIL THE COMPLETED FORM A.S.A.P. TO THE NIVEL SCIENTIFIC ASSISTANCE OFFICE OF THE NCA AND NWPL: NCA.NWPLSeer@nivel.nl
3. SAMPLE NEWSLETTER

Editorial

- The expanding universe of orphan drug regulation: transatlantic collaboration now in place

The European Medicines Agency (EMEA) announced it has just passed a milestone with the recent recommendation of marketing authorisation for its 40th orphan medicinal product. Things are truly moving forward in the field of rare disease medicinal products and collaboration is a part of this forward motion. The US Food and Drug Administration (FDA), the European Commission, and the EMEA have decided to expand many of their cooperative activities - including the area of medicinal products for rare diseases - in order to better protect public health, reduce regulatory burden and costs, and bring "innovative products to patients in a timely manner".

The call for further collaboration also extends to paediatric medicines, working within the framework of the recently-implemented Paediatric Regulation in the EU. It has been estimated that up to 80% of rare diseases affect children. The EMEA and the FDA are committed to developing a foundation to facilitate the regular exchange of information on scientific and ethical issues to minimise the exposure of children to unnecessary trials. The Principles of Interactions document has been created to achieve this goal and to better coordinate paediatric medicinal product development on both sides of the Atlantic. The document delineates several goals, including the development of global scientific paediatric plans compatible to both agencies. Information to be shared includes material referring to trial design issues, draft guidance documents, and safety issues such as adverse drug reaction reporting and database statistics. The two groups will be granted observer status for each others' Paediatric Committee meetings to be better kept abreast of "optimal mechanism and timing of exchanges". Monthly conferences and listings of applications and decisions are also proposed. A secure link, such as EudraLink, will be employed for the exchange of information.

It was in September 2003 that Confidentiality Arrangements between the EU and the FDA were reached in the context of regulatory cooperation and transparency, establishing a framework for "upstream regulatory cooperation including the possible exchange of information on advance drafts of legislation and regulatory guidance documents as well as non-public information" relating to the assurance of "quality, safety and efficacy of medicinal products - including orphan medicinal products authorised or under review both in the USA and the EU." To facilitate this exchange of documents and information, an Implementation Plan describing the processes of information and document exchange was finalised in September 2004. A year later, a five-year extension of the plan was signed into effect. Within this plan, article 2.1.4 calls for a regular exchange of information in the area of orphan medicines, among others, on topics including marketing authorisation applications, extensions of indications, and risk management plans.
A Transatlantic Workshop on Administrative Simplification in Medicines Regulation is being planned for late November in Brussels, Belgium.

The extension of existing collaboration can only mean good news for orphan drug development, often hindered by small clinical trial sizes and limited potential customer bases, resulting in lengthy delays and high costs. Rare disease patients, their families and stakeholders on both sides of the pond have reason to celebrate with the deepening of international collaboration.

**Task Force Update**

- Seventh RDTF meeting discusses an array of issues

The Rare Diseases Task Force held its 7th Meeting on 20 June 2007 in Luxembourg. Presentations included an update on the scoping paper of the Commission Communication on a European action in the area of Rare Diseases (RD). The completion of a first draft of this Communication is scheduled for September 2007 after a meeting of a Communication Drafting group on 18 July. A final draft will be made available for public consultation in November 2007.

Other activities of the RDTF included designation of Ségolène Aymé, chair of the RDTF, as chair of the Topical Advisory Group for the World Health Organisation ICD revision process followed by a meeting of the WG on Coding and Classification in Paris on 2 May to establish a strategy for the revision process. On 30 May 2007, a workshop on the future of orphan drugs served as a platform for WG members to contribute recommendations in this area to the Commission Communication. The outcomes of this workshop will also serve as the framework for a discussion on rare disease prevalence during the 8th EPPOSI Workshop on Partnering for Rare Disease Therapy Development taking place in Copenhagen on 18-19 October. Progress of the DG SANCO supported RAPSODY project was also presented. Currently, preliminary analysis of a patient satisfaction survey of the provision of health care for RD is underway. A synthesis of the outcomes of 11 national workshops on European Networks of Centres of Reference (ENCR) is also underway and recommendations resulting from this process will be presented at a workshop on ENCR in Prague on 12-13 July. The programme for the upcoming Rare Diseases Research: Building on Success conference (13 September 2007 in Brussels) was briefly summarised by RDTF members. The conclusions from the conference will be presented at the European Conference on Rare Diseases in Lisbon in November 2007, for which all RDTF member are encouraged to register. The next meeting of the RDTF is scheduled for 23 October 2007 in Luxembourg and will be dedicated to discussing the first draft of the Commission Communication.

**EU Policy News**

- Physicians and Industry form cooperation

Two non-profit international associations, the Standing Committee of European Doctors (CPME), representing the 2 million medical doctors in the EU in the promotion of the highest
standards of medical training and practice, and the European Medical Technology Industry Association (Eucomed), an organisation representing some 4500 designers, manufacturers and suppliers of medical technology for the diagnosis, prevention, treatment and amelioration of disease and disability, dedicated to improving patient and clinician access to innovative and reliable technology, have forged a cooperative agreement. The "Joint Declaration on the Cooperation between the Medical Profession and the Medical Technology Industry" stresses the importance of compliance between doctors and medical technology companies at all stages of development and use of medical technology. This cooperation aims to ensure the safety of patients and the efficacy of diagnosis and therapy. The two groups consider it essential to establish jointly accepted guidelines that can serve as a framework at both European and national levels. Each interest has already adopted ethical principles to govern the conduct of their activities, which are confirmed in the joint statement.

- DG Research

Simpler payment scheme adopted for non-EU FP7 participants

The European Commission has implemented a lump-sum payment option for Seventh Framework Programme non-EU participating countries. It is hoped that the flat-rate lump-sum amounts, which can be incorporated in grant agreements, will simplify the grant-agreement process as well as project administration and will ultimately facilitate the participation of International Cooperation Partner Countries. For more information.

- EMEA

Orphan drugs and rare diseases at a glance

The EMEA has put a new document online: Orphan drugs and rare diseases at a glance provides definitions of orphan medicinal products and lists the incentives manufacturers have to invest in orphan drug production. The document also provides information on the definition of a rare disease and provides useful links.

EMEA publishes advice document for orphan drug applicants

The European Medicines Agency (EMEA) has released a new document: Practical Information for Sponsors during the Early Phase of an Orphan Drug Application, an informal set of recommendations designed for orphan drug applicants to help the application process go smoother but that does not replace the legal requirements laid out in the EU Directives nor the guidelines available on the EMEA website. This list instead addresses issues that typically arise during the early phases of the application process, including the pre-submission meetings that are strongly encouraged and can take place via teleconference to save travel expenses; the format of the final application at the time of submission; and various items of general advice.

EMEA issues Paediatric Regulation documents, revamps website

The EMEA has issued several documents pertaining to the implementation of the Paediatric Regulation that came into effect in January of this year, including templates to use for various application requests, information concerning practical issues relating to the application
procedures, calendars and timelines, and a template for letters of intent. Furthermore, the Medicines for Children section of the EMEA website has been redesigned and updated to accommodate the new Paediatric Regulation. Finally, the EMEA is establishing a new Paediatric Committee due to come into effect by 26 July 2007. The Paediatric Working Group that prepared the groundwork for the implementation of the new regulation over six years has ceased its activities. The EC has launched a Call for Expressions of Interest in becoming Commission appointees to the Paediatric Committee as representatives of healthcare professionals or patient associations, to be sent electronically to Peter Arlett at the European Commission by 31 August 2007. Further details, including the criteria for selection, can be found in the European Commission's call for expressions of interest.

EMEA welcomes new leaders

The EMEA Committee for Medicinal Products for Human Use (CHMP) has elected Dr. Eric Abadie (France) as new chair and Dr. Tomas Salmonson (Sweden) as new vice-chair for three-year mandates beginning 18 June 2007. Dr. Abadie previously was a member of the Committee for Orphan Medicinal products. The EMEA Management Board also has a new chair and vice-chair. Pat O'Mahony and Lisette Tiddens-Engwirda will serve three-year mandates as chair and vice-chair, respectively. The Management Board has requested a staff increase in anticipation of an increase in applications following the implementation of the new EU paediatric regulation.

First-in-man clinical trials guideline workshop debates high-risk definition

Following the 12 June 2007 workshop held as part of the public consultation of the draft guideline of recommendations for first-in-man clinical trials for potential high-risk medicinal products, participants were able to reach a consensus on certain points and move toward finalisation of the guideline. The draft guideline was released for a two-month public consultation period that ended in May. The workshop focused on specific points, including "how to define high risk medicinal products", and "elements of design of first-in-man clinical trials". The EMEA defines a community guideline as a document designed to provide advice on the best way to fulfil an obligation set forth by EC pharmaceutical legislation. In this case, the guideline provides counsel on managing the transition from non-clinical studies to tests in humans. Concerning the concept of the classification of high-risk, proposals were made to replace it with a risk management and mitigation approach "based on the concept of risk as a continuum for all medicinal products". Considering the particular concerns and often small number of subjects in rare disease product clinical trials, guidelines such as these will be important for orphan drug sponsors.

Gene Therapy Working Party calls for comments on genetic-based medicine documents


The second document is titled, The Development of a Guideline on Clinical Monitoring and Follow-up of Patients exposed to Gene Therapy/Gene Transfer Medicinal Products. Interested
parties, including members of the pharmaceutical industry, academic networks and learned societies within the EU, may send comments electronically using the templates provided. The consultation period will finish in November for the first document and July for the second.

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**National & International Policy Developments**

- Spanish geneticists campaign for official recognition

*Feliciano J. Ramos, MD PhD, President of the Asociación Española de Genética Humana (AEGH), describes for OrphaNews Europe the efforts underway in Spain to have the field of Clinical Genetics officially recognised:*

Spain is one of the few EU countries that does not officially recognise genetics as an independent specialty. Spanish geneticists of different backgrounds, most represented by the Asociación Española de Genética Humana (AEGH), have been struggling with government authorities for more than three decades to obtain this recognition. Many attempts to create the specialty have been undertaken. In recent years these efforts, most of which are lead and coordinated by the AEGH, have been intensifying and producing some headway. Two advancements have occurred within the last few months. In May, a no-law proposition was presented to the Spanish Senate by Socialist party deputy and pediatrician-geneticist Joaquín Bellón, requesting the government create a "Specialty in Genetics" in Spain. The proposition was passed with the approval of all political parties represented in the Senate. Some 20 members of the AEGH, including members of its directive committee, witnessed *in situ* this unprecedented event. Moreover, in March, after attending a workshop on Spain's new "Biomedical Research Law", ERC political party deputy Rosa Maria Bonás presented a no-law proposition to the Spanish Congress requesting the Government create a working group to study the programs and competences that would form the bases of the future Genetics Specialty in Spain. It is hoped that these two steps forward are the beginning of the final stage of our seemingly never ending journey to establish a specialty for Clinical Genetics in Spain. It is about time...

- Spanish Parliament authorises therapeutic cloning

On 14 June, Spanish deputies adopted a law authorising biomedical cloning strictly for therapeutic purposes. An ethics committee will be established to ensure research follows legal and ethical guidelines as well as a commission charged with regulating the donation and usage of human cells and tissues.

- Italy extends umbilical cord stem cell storage and use

The Italian Health Ministry has issued a decree consenting blood conservation intended for neonatal use or the benefit of a consanguineous person affected by a disease (either genetic or acquired) at the time of collection, for which the use of umbilical cord blood-derived stem cells is scientifically established and clinically appropriate by presentation of acceptable clinical documentation. The Lazio Region in Italy has proposed an autonomous law concerning the "Regional interventions to promote the use of hemopoietic stem cells derivated from cordonal and placental blood for therapeutic, clinical and research purposes". In families at high risk for
genetically determined diseases, the charges for autologous cordal and placental blood for the infant or a related person would have to be paid by the regional sanitary system. A 28 June disposition taken by the Lombardy Region, following a decree of 4 May 2007 issued by the Italian Health Ministry, will allow, for the first time in Italy, the free conservation of umbilical cord stem cells for private use. Requests, spontaneously made by the parents, will be approved only in the presence of a genetic disease in the family and/or of a disorder already diagnosed at the time of delivery in the neonate or a relative.

Two Italian non-profit associations, the Associazione Donatrici Italiane Sangue del Cordone Ombelicale and the Associazione M3V ONLUS are promoting umbilical cord blood donation throughout the entire nation. In addition, they are collecting money for the research of umbilical cord blood in transplants and for the creation and development of a network of umbilical cord blood banks at the national level. At a round table discussion that took place in June, geneticist and Orphanet partner Bruno Dallapiccola discussed the use of these cells as a tool for treating rare diseases. Data was presented concerning the activities of the 15 public Italian banks, where more than 22,000 cord samples have been stored and more than 600 samples used for transplants, including over 300 donations to foreign countries.

- Other European news

A national British network for stem cell research

The United Kingdom National Stem Cell Network (UKNSCN) officially launched in April of this year as a direct result of a recommendation contained in a report presenting a “ten-year vision for UK stem cell research” commissioned by then-Chancellor of the Exchequer Gordon Brown in 2005. This nationally-funded network was established to “improve the coordination of stem cell research and the dissemination of research results, in addition to providing a focal point for communication with overseas researchers, the media and the general public”. The network is intended to “maximise the cross-fertilisation between those involved in the sub-disciplines of UK stem cell research” and has as its central mission the “promotion of research activities and events at the national level which help to speed the translation of basic stem cell research into therapeutic applications in the control of degenerative diseases…” Huntington disease and amyotrophic lateral sclerosis (ALS) syndrome are just two examples of rare degenerative diseases. The UKNSCN does not fund research and does not replace already existing regional stem cell networks in the UK. The UKNSCN is attributed with playing a key role in attracting the International Society for Stem Cell Research’s annual science conference for 2009 to London, the first time this conference will be held in Europe.

- Other International News

Ten new rare disease genetic tests available in the US

In the United States, the Collaboration Education and Test Translation Program (CETT), a pilot program developed by the National Institutes of Health Office of Rare Diseases, endeavours to facilitate the availability of genetic tests for rare diseases. Ten such new rare disease genetic tests thus became available to the US public in the past year: Joubert syndrome (Prevention Genetics), Cornelia de Lange syndrome (University of Chicago), cherubism (Hospital for Sick Children
Toronto), X-linked chondrodysplasia punctata (University of Chicago), Kallman syndrome (GeneDx), progressive familial intrahepatic cholestasis (Baylor College of Medicine), Russell Silver syndrome (Emory University) mucopolysaccharidosis type VI (Emory University), Niemann Pick disease type A/B (Emory University) and X-linked periventricular nodular heterotopia (Harvard University). Fortunately, Orphanet confirms that all of these tests are also available in Europe.

Orphanet News

- Updated Orphanet Reports Series available online

The following Orphanet Reports Series have been updated: The prevalence of rare diseases: A bibliographic study April 2007 - Issue 4 and List of marketing authorised orphan drugs in Europe May 2007

- New Research Projects open for Recruitment

A Phase I-II Study: Infusion of Donor Lymphocytes Transduced With the Suicide Gene HSV TK, After Transplantation of Allogeneic T-Depleted Stem Cells From a Haploidentical Donor in Patients With Haematological Malignancies

Above multicentre trial in Germany
Above multicentre trial in Italy

New Syndromes

- A new genetic disorder in mitochondrial fatty acid beta-oxidation: ACAD9 deficiency

The acyl-CoA dehydrogenases are mitochondrial enzymes that act in fatty acid beta-oxidation and amino acid catabolism. To date, nine members of this group of proteins have been identified and seven different genetic anomalies have been described. In this study, the authors describe three patients with ACAD9 deficiency. The first, a 14-year-old boy, died following an acute hepatic insufficiency episode reminiscent of Reye syndrome along with a cerebral stroke. The second patient, a 10-year-old girl, has presented acute hepatic insufficiency and hypoglycemia since 4 months of age. The third patient, a girl aged four and a half years, died of cardiomyopathy. Despite the variable phenotypes, the spectrum of clinical manifestations is the same as those observed in other ACAD deficits.

Read the Pubmed abstract
Am J Hum Genet ; 87-103 ; July 2007

New Genes

- FGD4 gene mutations are responsible for the 4H form of Charcot-Marie-Tooth neuropathy
Charcot-Marie-Tooth (CMT) diseases are a heterogeneous group of hereditary motor and sensory neuropathies characterised by muscular weakness and wasting and feet and hand deformities. The 4H subtype is an autosomal recessive demyelinating form that was recently linked to 12p11.21-q13.11 chromosome region. Two articles describe the identification of \textit{FGD4} gene mutations in several families. \textit{FGD4} codes Frabin, a GDP/GTP nucleotide exchange factor specific to Rho GTPase Cdc42.

\textit{Read the Pubmed abstract of the first article}  
\textit{Read the Pubmed abstract of the second article}

The American Journal of Human Genetics ; 1-16 ; July 2007  
The American Journal of Human Genetics ; 158-164 ; July 2007

- A gene linked to Joubert syndrome now involved in Meckel syndrome

Meckel syndrome (MKS) is a rare autosomal recessive lethal condition characterised by central nervous system malformations, polydactyly, multicystic kidney dysplasia, and ductal changes of the liver. Three loci have been linked to the disease and mutations in two genes situated in the MKS1 and MKS3 loci have been identified. Through a linkage analysis performed in eight families, a French research team identified a new locus, MKS4, carrying mutations in \textit{CEP290} gene in four families. This gene was recently identified as causative of Joubert syndrome (JS) and isolated Leber congenital amaurosis. This study confirms that Joubert and Meckel syndromes could have a common origin despite their variable symptomatology (MKS3 mutations have already been linked to the two syndromes).

\textit{Read the Pubmed abstract}

The American Journal of Human Genetics ; 170-9 ; July 2007

- Gene \textit{MFSD8} is mutated in late-infantile forms of the neuronal ceroid lipofuscinoses (NCLs)

Late infantile forms of neuronal ceroid lipofuscinoses (NCLs) are a genetically heterogeneous group of diseases characterised by epileptic seizures, psychomotor decline, myoclonus, vision loss and premature death. Through a genomewide scan and homozygosity mapping, the Finnish authors identified six different mutations in \textit{MFSD8} gene, which codes a membrane protein principally located in the lysosomes and of which the function is still unknown. Furthermore, analysis of the data from other families revealed a link with three other loci, confirming the heterogeneity of the late infantile forms of the disease.

\textit{Read the Pubmed abstract}

The American Journal of Human Genetics ; 136-146 ; July 2007

- PLEKHG5 and NFk-B pathway are suspected in an autosomal recessive form of lower motor neuron disease

In 2006, the authors described an African family presenting an autosomic recessive form of lower motor neuron disease characterised by childhood onset, generalised muscle involvement, and severe outcome. They linked the phenotype to chromosomal region 1p36. In this study, the authors have identified a homozygous missense mutation in \textit{PLEKHG5}, provoking protein aggregation and disturbing NFk-B pathway signalisation. Both these phenomena probably contribute to the neuronal toxicity observed.
• NR2E3 is mutated in an autosomal dominant form of retinitis pigmentosa

"Autosomal dominant retinitis pigmentosa" refers to a genetically heterogeneous group of retinal dystrophies, of which 54% of all cases can be attributed to 17 disease loci. The Belgian authors have identified mutations in NR2E3 gene in four families afflicted with autosomal dominant retinitis pigmentosa. NR2E3 codes a nuclear receptor expressed in the retina and has already been linked to Goldmann-Favre syndrome, an autosomal recessive retinopathy.

Research in Action

• Fundamental Research

The genes implicated in Bardet-Biedl syndrome code a protein complex needed for ciliogenesis

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder caused by primary cilium dysfunction. Symptoms include obesity, retinal degeneration, and nephropathy. Although mutations in 12 BBS genes have been identified, their cellular function remains unknown. The authors have identified a complex composed of seven highly conserved BBS proteins localised to the centriolar satellites and membrane of the cilium and required for ciliogenesis. Its function appears to be dependent on the Rab8 GDP/GTP exchange factor, already known to be involved in ciliary function. The authors propose that the mutations responsible for Bardet-Biedl syndrome may cause defects in vesicular transport to the cilium.

• Clinical Research

Perforin implicated in aplastic anemia

Aplastic anemia is characterised by hematopoietic stem cell destruction by activated T cells and Th1 cytokines. The authors have identified mutations in the gene coding perforin in five patients with acquired aplastic anemia, all of whom presented an abnormally low level of the protein. Normally, perforin is expressed principally in the T cytotoxic lymphocytes and natural killer cells, two cell types known to be implicated in auto-immunity. The perforin mutations may thus contribute to the development of aplastic anemia.
Gaucher disease and increased risk for non-Hodgkin lymphoma, pancreatic cancer or malignant melanoma

Gaucher disease is a lysosomal surcharge illness caused by a deficiency in glucocerebrosidase (also referred to as glucosylceramidase or acid beta-glucosidase) or, in rare cases, by a deficiency in the activator protein saposin C. The disease is characterised by the presence of glucosylceramide (or glucocerebroside) deposits in the reticuloendothelial cells of the liver, spleen and bone marrow. In this study, the authors identified 1525 Gaucher disease patients using data from US Veterans Affairs hospitals. Besides yielding a large patient population, the data source allowed for follow-up for as long as 27 years. A two-to-three time elevated risk of developing non-Hodgkin lymphoma, pancreatic cancer or malignant melanoma was discovered. Read the Pubmed abstract
Arch Intern Med ; 1189-1194 ; June 2007

- Stem Cells

Human embryonic stem cells differentiate in cardiac cells in rats

_In vitro_, human embryonic stem cells can give rise to cardiomyocytes. To test_ in vivo_ their regenerative capacity, the French researchers injected embryonic stem cells in rat myocardium that had undergone coronary artery ligation two weeks prior. Two months after the injection, the human cells had differentiated into cardiac cells. This ability of cardiac-specified HES cells to differentiate along the cardiomyogenic pathway following transplantation into infarcted myocardium raises the hope that these cells might become effective candidates for myocardial regeneration. Read the Pubmed abstract
Stem Cells ; Epub ahead of print ; 31 May 2007

- Gene Therapy

Gene therapy suppression and replacement to circumvent mutation heterogeneity in retinitis pigmentosa

Autosomal dominant forms of retinitis pigmentosa can be attributed to mutations in the gene coding rhodopsin. More than 100 mutations in this gene have been described. The Irish research team developed a new genetic therapy approach in mice to avoid developing a specific treatment for each mutation. They injected retinitis pigmentosa mouse models with a virus delivering interfering RNA that suppressed the expression of both the normal and mutated allele of the gene coding rhodopsin. At the same time, a virus delivering a normally functioning gene coding rhodopsin, but resistant to the RNA interference was injected. This suppression and replacement strategy improved the condition of the mice treated, confirming that this approach presents a potential solution for circumventing mutational heterogeneity. Read the Pubmed abstract
The American Journal of Human Genetics ; July 2007 ; 127-135
Therapeutic Approaches

Parathyroid hormone improves bone growth in embryos of achondroplasia mouse models

Achondroplasia is characterised by short height and short members. It is caused by activating point mutations in \textit{FGFR3}. Various studies suggest a deregulation in the proliferation and differentiation of the chondrocytes (the cells that participate in the synthesis and maintenance of the cartilage tissue) as the origin of the disease. The Japanese authors tested \textit{in vitro} the effect of parathyroid hormone on growth of femurs from mouse disease model embryos. In four days the hormone reduced the differentiation and cell death of chondrocytes and improved bone growth. Thus parathyroid hormone is a potential treatment for achondroplasia. Read the Pubmed abstract
Bone ; 13-18 ; July 2007

Calcineurin as a possible therapeutic target for T-cell acute lymphoblastic leukaemia

Acute lymphoblastic leukemia (ALL) is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation and accounts for three-fourths of all cases of childhood leukemia. Calcineurin is a phosphatase enzyme implicated in T-cell differentiation. The French research team tested \textit{in vivo} the effect of calcineurin inhibitors on two murine models with T-cell lymphoblastic leukaemia. They observed a rapid regression of tumours and a prolonged duration of life. Moreover, one of these inhibitors induced the death of human lymphoma and leukemia cell lines. Thus calcineurin and the cellular pathway that depends upon it, represent a new therapeutic target. Read the Pubmed abstract
Nature Medicine ; 736-741 ; June 2007

The combination of two antibodies induce complete remission in mice with pancreatic carcinoma

Pancreatic carcinoma has a five-year survival rate of less than 20\%, due in part to extreme tumour resistance to treatment. The French research team injected mice with these tumours with anti-EGFR and anti-HER2, either alone or together. Combined, these antibodies have a synergistic effect leading in some cases to complete remission. These results bring a new therapeutic hope to patients with pancreatic carcinoma. Read the Pubmed abstract
Clin Cancer Res ; 3356-3362 ; June 2007

Orphan Drugs

- Ten EMEA orphan designations for June 2007

The COMP (Committee for Orphan Medicinal Products) adopted the following 10 positive opinions on orphan medicinal product designation at its \textit{June meeting} for the treatment of:
- acute myeloid leukaemia
- cystic fibrosis
- malaria
- ligneous conjunctivitis
- idiopathic thrombocytopenic purpura
- orthostatic hypotension in patients with multiple system atrophy
- orthostatic hypotension in patients with pure autonomic failure
- cutaneous T-Cell Lymphoma
- cardiogenic shock
- idiopathic thrombocytopenic purpura

Consult the European Registry for Orphan designations
Consult the Orphanet list of orphan drugs authorised for marketing in Europe

- Marketing authorisation recommended for orphan drugs Atriance® and Gliolan®

The CHMP has recommended marketing authorisation for Atriance® (nelarabine), produced by Glaxo Group Ltd., for the treatment of T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic leukaemia (T-LBL) of patients in second relapse. Atriance is the 40th orphan medicinal product to receive a positive opinion. EMEA review began on 21 June 2006 with an active review time of 203 days. Atriance® is the first medicinal product for which an application was submitted using the Product Information Management (PIM) system. PIM enables the electronic exchange of the product information part of a marketing authorisation application in the European Union. Its aim is to increase efficiency of the management and exchange of the product information and to improve the quality and consistency of the published product information.

The CHMP has also recommended marketing authorisation for Gliolan® (5-aminolevulinic hydrochloride), produced by Medac, for the visualisation of malignant tissue during surgery for malignant glioma in adult patients. Gliolan is the 41st orphan medicinal product to receive a positive opinion. EMEA review began on 24 May 2006 with an active review time of 199 days.

- FDA approves Letairis™ for pulmonary arterial hypertension

The US Food and Drug Administration has approved marketing for Letairis™ (ambrisentan), manufactured by Gilead Sciences, Inc. for the treatment of pulmonary arterial hypertension, a rare condition. Letairis was granted a priority review designation intended for products that address unmet medical needs. Because of the risks of liver injury and birth defects, the product will be available through the Letairis Education and Access Program (LEAP), a restricted distribution program designed to help patients learn about the potential risks of the product. Gilead Sciences has also designed a set of programs to assist patients with various reimbursement issues for Letairis™ in order to enhance patient access to the product.

News from the Patients' Associations
The Croatian Society of Patients with Rare Diseases is a non-profit organisation which was renamed in November of last year, continuing the work of the Croatian Society for Inherited Metabolic Diseases, which itself was renamed in 2003, succeeding the Croatian Society for Mucopolysaccharidoses and similar diseases. This process of changing names illustrates the necessity to expand the scope of our work from one specific rare disease to all inherited metabolic diseases and, finally, to all rare diseases.

Members of our organisation include other groups that are at work solving the particular problems of those affected by rare diseases. The following organisations have joined our Society: the Croatian Organization for Osteogenesis Imperfecta, the Croatian Organization for Cystic Fibrosis, and the Association for Persons with PWS Croatia and DEBRA Croatia.

While these organisations have worked for years on finding solutions for patients with specific rare diseases, now that we are working together as one network for rare diseases, we can achieve much more. It became essential to strengthen the cooperation of non-governmental organisations, because the difficulties of living with a rare disease are many and complex. The situation in our country is such that many medical products for rare diseases are still not registered, despite their usage in the European Union.

Our main goal is improving the quality of life for patients suffering from rare diseases as well as their families and our main activities include:

- Supporting patients and their families in their efforts to solve their problems.
- Organising gatherings for patients, their families and others interested in exchanging experiences and organising problem-solving efforts in relation to rare diseases.
- Cooperating with health organisations and other relevant stakeholders in order to solve the particular issues that patients face.
- Organising lectures and public gatherings through which foreign and domestic health experts can provide information and education, especially in terms of new developments in the treatment of rare diseases.
- Making a centre for receiving and distributing rare disease data, using telephone technology and flyers.
- Publishing material concerning rare diseases and the activities of our organisation.

We have specific targeted activities for 2007: the organisation’s office in the centre of Zagreb has been equipped and is accessible to people with disabilities. We are working on a Croatian rare disease website for our organisation, patients and their problems, which will provide essential information concerning these themes. We are also organising the first Congress on Rare Diseases.

We are planning to publish written material on rare diseases flyers and educational brochures, which we consider to be a good way of reaching people with rare diseases, many of whom are disabled. Many of our activities, such as public lectures and discussions, are directed to the general public, an effort we consider relevant to improving the quality of life for rare disease patients. Because rare disease patients are a minority in our society, it is necessary to diminish prejudices concerning rare diseases and make public the challenges those afflicted face in their every day life.

For more information, contact the group president Vesna Skulic or Ana Stavljenic-Rukavina.

First Person Plural!

With the EMEA and the EC including patient groups more and more in the legislative processes for rare diseases and orphan drugs, these layled organisations are becoming more active in lobbying for recognition. They are also working together more to meet their own needs and share information. Below, British Fibrous Dysplasia patient Ann Underhill provides OrphaNews Europe with the unique opportunity to learn how a patient organisation comes into being. Here is the path she took to create the recently formed Fibrous Dysplasia Support Society:

I have Fibrous Dysplasia (FD). In September 2006 I became the UK Liaison for the Fibrous Dysplasia Foundation, an American charity set up in 2003. Initially, I simply intended to arrange a get-together for FD patients in the UK. Using the email addresses of UK residents registered on the American website, I sent out an introductory letter to gauge the level of interest. The replies to that letter left me no doubt of the urgent need for information on how to treat FD and where to access treatment.

In November 2006, I contacted Dr Edmund Jessop (National Specialist Commissioning Advisory Group member and leader of the Rare Diseases Task Force working group on Standards of Care) at the Department of Health. He put me in contact with Professor John Wass, Chair of Endocrinology at the OCDEM, Churchill Hospital, Oxford, and the Nuffield Orthopaedic Centre, Oxford. I met with Professor Wass in December. Our conversation focused on defining the needs of FD patients and how best to meet them.

It was agreed that I would organise a meeting for patients with FD and their carers. This meeting, held on the 24th of March 2007 with Professor Wass in the chair, presented the first opportunity that most present had ever had to meet anyone else with the condition. Professor Wass gave a presentation on FD, which generated many questions. It was during the course of this meeting that we decided to set up the Fibrous Dysplasia Support Society. Officers were elected and a
patient volunteered to create the website. Still under construction, this tool will provide a brief description of FD, an outline of possible treatments with a protocol for the medical follow up of patients, a list of UK specialists experienced in treating the condition, contact numbers and email addresses, an events diary (we are planning a second meeting on the 13th of October 2007), and any other information which would be useful to patients or the medical profession. Pr. Wass generously offered to produce a pamphlet to be used by patients and physicians containing information on FD and protocols for the long-term monitoring of the condition. A set of DVDs, recorded at the FD Foundation convention in Santa Monica, California in August 2006, and containing medical presentations given to patients, including an overview of FD/McCune-Albright Syndrome, craniofacial issues, paediatric orthopaedics, endocrine issues and drug treatments, pain and quality of life studies, and adult orthopaedic issues will be available to interested professionals.

For further information on the Fibrous Dysplasia Support Society, please email Ann Underhill.

Courses & Educational Initiatives

European School of Genetic Medicine: 1st Course in Clinical Dysmorphology

Focusing on the development of advanced counselling skills for use in a genetic health care setting and offering an introduction into spectrum, evaluation techniques, and character and etiology of dysmorphism and dysmorphic patterns in order to enable clinical geneticists to better evaluate and interpret as well as distinguish between inborn and acquired congenital developmental defects; tracing the origin back to a given prenatal period; pattern recognition and syndrome delineation. The course is a post-graduate level program directed to clinicians, either geneticists or pediatricians or neonatologists.

Date: 9-12 September 2007
Venue: Bologna, Italy
Further details and to register

What's on Where?

1-day Conference: Clinical Research for Rare Diseases: Opportunities, Challenges and Solutions
Date: 5 September 2007
Venue: Washington, DC, USA
More details

Rare Diseases Research: Building on Success - a European Conference
Date: 13 September 2007
Venue: Charlemagne Building- Brussels, Belgium
This EC conference will focus on increasing the visibility of rare diseases research and raising awareness within the 27 EU Member States and the European Parliament on the research needs in this area, providing the rare diseases community with the opportunity to express their needs in terms of research and the EC with input for future FP7 calls for research proposals.
For more information
To register
4th Stem Cell Gene Therapy Conference  
Date: 13-17 September 2007  
Venue: Halkidiki, Thessaloniki, Greece  
More details  

EuroGentest Workshop on internal auditing for genetic testing laboratories  
Date: 20-21 September 2007  
Venue: Leuven, Belgium  
Registration is open for this EuroGentest workshop on internal audit for genetic testing laboratories that will feature presentations, role play, video fragments and group discussions on how to prepare, execute and report internal audits. Registration deadline: 15 July 2007  
More details and to register now  

EFGCP Children’s Medicines Working Party 3rd Annual Conference on EU Paediatric Regulation  
Date: 9 October 2007  
Venue: Brussels, Belgium  

First European Experiences & Strategic Outlook  
With a pre-conference workshop on 8 October on the background of off-label drug use in children, US and EU paediatric legislations, and the basics of child physiology and paediatric clinical trials.  
More details on the conference and workshop.  

8th EPPOSI Partnering Workshop on Orphan Drugs  
Date: 18-19 October 2007  
Venue: Copenhagen  
This year's workshop is dedicated to exploring the topic The Reality of Orphan Medicines and will provide a platform for consensus building and the cultivation of partnerships between patients, academia, and industry as well as European and member state authorities in order to convert policy issues and scientific developments into therapies for rare diseases.  
More details and to register now  

3rd International Meeting on Congenital Disorders of Glycosylation  
Date: 18-19 October 2007  
Venue: Paris  
This international meeting on CDG is preceeded by the 3rd Orphan Focus Course on "Protein Glycosylation in Health and Disease" on Oct 16-17.  
For more details on the course  
More details on the conference  

Biology and clinical applications of cord blood cells  
Date: 19-21 October 2007  
Venue: Paris, France  
More details
4th European Conference on Rare Diseases (ECRD 2007)
Date: 27-28 November 2007
Venue: Lisbon, Portugal
This important rare disease conference will be held in English and simultaneously translated into French, German, Portuguese and Spanish.
NB: Registration is open. Deadline for abstract submission: 31 July 2007
More details

15th Annual Meeting, Int'l ALS/MND Associations Alliance & 18th ALS/MND Int'l Symposium
Date: 1-3 December 2007
Venue: Toronto, Canada
More details

Press & Publications

- Genetics, Health Care and Public Policy: An Introduction to Public Health Genetics
  Setting out the basic principles of public health genetics, including basic concepts, technology, epidemiology, genetics in medicine and health services, ethical, legal and social implications, and public health policy.
  Authors: Alison Stewart, Philippa Brice, Ron Zimmern, Hilary Burton, Simon Sanderson, Paul Pharoah
  Publisher: Cambridge University Press, May 2007

- Pediatric Hematopoietic Stem Cell Transplantation
  Recognised experts provide detailed discussions of the unique issues encountered during hematopoietic stem-cell transplantation in the treatment of various disorders, including metabolic diseases and other rare disorders, and consider some of the challenges unique to treating paediatric patients.
  Author: Ronald M. Kline –Ed.
  Publisher: Informa Healthcare, 2006

- Myeloproliferative Disorders
  Providing a thorough summary of the topic with contributions from internationally recognised experts in one or more of the myeloproliferative diseases.
  Authors: Junia V. Melo and John M. Goldman –Eds.
  Publisher: Springer, January 2007

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