Programme of Community Action on Rare Diseases

Contract 2004105

RDTF Scientific Secretariat
Third Annual Scientific Report

1 June 2007 to 31 May 2008
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 3 (1 June 2007 – 31 May 2008) 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 3 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.

- Organisation of 4 Working Group Workshops

- Production of three reports, “European Reference Networks in the Field of Rare Diseases: state of the art and future directions”, “Health Indicators for Rare Diseases”, and “Patient Registries and Databases in the Field of Rare Diseases: technical, legal, and ethical issues”.

- 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 10,700 registered readers including
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

An RDTF Communication Drafting Group met in Luxembourg on 13 February, 2008 and included the attendance of S. Aymé, L. Fregonese, J. Llinares Garcia, A. Montserrat, C. Nourissier, R. Stefanov, and D. Taruscio.

The High Level Group on Health Services and Medical Care, Eurordis, EMEA-COMP, and Orphanet were also 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
• 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 public consultation regarding a European Action in the Field of Rare Diseases resulted in over 400 responses, subsequently introduced into the text of the Communication.

2 – Bi-Annual Meetings of the RDTF

The RDTF had two meetings during the third year of the contract on 23 October, 2007 and 28 February, 2008 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 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. In 2007, a Topic Advisory Group was created by the WHO to advise the revision process of the classification of RD. Ségolène Aymé will chair this group.

The Working Group held one meeting during the third year on 6 February, 2008 to discuss a preliminary list of coded and classified RD proposed by Orphanet. The minutes of this meeting are annexed to this report (Annex 2a).

2 - 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.

One Working Group meeting took place during the third year on 11 March, 2008. The meeting was dedicated discussing networking among Centres of Expertise and producing the report, “European Reference Networks in the Field of Rare Diseases: state of the art and future directions”. The report 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). Minutes from the meeting are also available on the RDTF website as well as Annex 2b.

3 - 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 officially chaired by Juliette Bloch (France) though no meetings were organised by the group’s chair in the last two years. As such, two Working Group meetings were organised in Paris. The first was led by Laura Fregonese on 12 March, 2008. The discussion during this workshops centred around the finalisation of the report “Health Indicators for Rare Diseases” 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). Minutes from the meeting are also available on the RDTF website as well as Annex 2c.
A second Workshop on Patient Registries and Databases took place on 13 March, 2008. The goal of this workshop was the creation of a document providing guidance on the establishment and management of patient registries in the field of rare diseases, “Patient Registries and Databases in the Field of Rare Diseases: technical, legal, and ethical issues”. The report is available on the RDTF website, www.rdtf.org, and the European Commission Rare Disease website, http://ec.europa.eu/health/ph_threats/non_com/rare_diseases_en.htm. Minutes from the meeting are also available on the RDTF website as well as Annex 2d.

4 – Communication of RDTF activities

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

S. Aymé: “European programmes in support of rare diseases and orphan drugs”. 3rd International Symposium on Genetic and Rare diseases. Seoul, Korea, 31 August 2007


S. Aymé: “L’information des professionnels de santé et des maladies” Premier forum régional Maladies Rares des Pays de la Loire. Angers, 11 October 2007

S. Aymé: “Assessing Treatable Rare Diseases And The Proportion of Patients Eligible For Treatment: Epidemiology and Literature Systematic review”. EPPOSI partnering workshop. Copenhagen, Denmark, 19 October 2007


S. Aymé: “The revision of the International Classification of Diseases: an opportunity for rare diseases coding and classification”. International Conference on Rare Diseases and Orphan Drugs, Rome, Italy, 5 November 2007

S. Aymé: “L’information des professionnels de santé et des malades” Forum régional Maladies Rares. Nice, 8 November 2007

5 – Progress reports

Two progress reports were completed reporting on all activities during the third year in May 2007 and January 2008. They are included in the Annexes of this report (Annex 2h).
Work Package 3 – Newsletter

The RDTF Scientific Secretariat has continued the publication of the RDTF electronic newsletter, OrphaNews Europe. Currently distributed to more than 10,700 readers, subscribers are free to opt in or out of the service at any time. Since its creation in June 2005, 41 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.

During the third year issues were published on:

<table>
<thead>
<tr>
<th>2008</th>
<th>2007</th>
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<tbody>
<tr>
<td>28 May 2008</td>
<td>19 December 2007</td>
</tr>
<tr>
<td>17 May 2008</td>
<td>5 December 2007</td>
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<td>30 April 2008</td>
<td>21 November 2007</td>
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<td>16 April 2008</td>
<td>30 October 2007</td>
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<td>2 April 2008</td>
<td>10 October 2007</td>
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<td>19 April 2008</td>
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<td>17 August 2007</td>
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<td>12 July 2007</td>
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<td></td>
<td>28 June 2007</td>
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<td></td>
<td>14 June 2007</td>
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Archives are accessible via the following address:
http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews

All deliverables for Year 3 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 was maintained during the third year. Minutes from all Plenary Meetings and Working Group Workshops, along with links to the Public Health Executive Agency and other relevant events and documents were uploaded, bringing the website up to date.

About the Rare Diseases Task Force

Rare diseases are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. As a guide, low prevalence is taken as prevalence of less than 5 per 10,000 in the community.

The Rare Diseases Task Force (RDTF) was set up in January 2004 by the European Commission's Public Health Directorate. Its aims are:

- to advise and assist the European Commission Public Health Directorate in promoting the optimal prevention, diagnosis and treatment of rare diseases in Europe, in recognition of the unique added value to be gained for rare diseases through European co-operation.
- to provide a forum for discussion and exchange of views and experience on all issues related to rare diseases.

The Task Force is led by Dr Sépulchre Armeo, a medical geneticist and director of the Orphanet database of rare diseases. The Deputy Leader is Professor Helen Dolk, director of the Eurocat programme on congenital disorders.

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

Read the mandate of the Rare Diseases Task Force
### Work Package 5 – Administration

#### Table 1. Deliverables

<table>
<thead>
<tr>
<th>WP1</th>
<th>WP2</th>
<th>WP3</th>
<th>WP4</th>
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</thead>
<tbody>
<tr>
<td>• Electronic contacts with DG SANCO, PHEA, and RDTF members</td>
<td>• Production of report on European Reference Networks</td>
<td>• Production of 20 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 report on Health Indicators</td>
<td>• Maintenance of tool to archive newsletters on the website</td>
<td>• Maintenance of website</td>
</tr>
<tr>
<td>• RDTF bi-annual meetings 23 October 2007 and 28 February 2008 and subsequent minutes</td>
<td>• Production of report on Patient Registries and Databases</td>
<td>• Maintenance of tool to allow users to browse issues</td>
<td></td>
</tr>
<tr>
<td>• Continued development of Communication on Rare Diseases</td>
<td>• Minutes of Working Group meetings and progress reports every 6 months</td>
<td>• Maintenance of tool for subscription registration</td>
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1. MINUTES OF FORMAL MEETINGS

a. Eight Meeting of the RDTF

Meeting Report
8th Meeting of the European Commission “Rare Disease Task Force”
Luxembourg, 23 October 2007

On 23 October 2007, the eighth meeting of the Rare Diseases Task Force (RDTF) included the attendance of:

**Rare Disease Task Force:**

- S. Aymé
- H. Dolk
- G. Gatta
- A. Kole
- J. Llinares Garcia
- M. Jespersen
- E. Jessop
- C. Nourissier
- M. Posada de le Paz
- A. Ramirez Vanegas
- J. Sándor
- A. Schieppati
- H. Segura
- D. Sheppard
- R. Stefanov
- D. Taruscio
- S. Tanner
- J. Torrent Farneli
- A. Trama
- G. Zambruno

**Observers:**

- R. Capocaccia
- H. Jensen
- O. Kremp
- M. Rätsep

**DG SANCO:**

- K. Freese
- A. Montserrat

**Public Health Executive Agency:**

- G. Margetidis

A. Welcome and Approval of Agenda

S. Aymé welcomed new members and suggested that the composition and organisation of the RDTF be presented to these new members.

A. Montserrat listed the composition of the group to include representatives of Member States (MS) chosen by MS health authorities, project leaders of on-going or past Rare Disease (RD) projects, NGO and patient organisation representatives, leaders from FP7 RD projects funded by DG Research, representatives of relevant bodies and institutions such as the EMEA and the High Level Group on Health Services and Medical Care, and other observers invited for their expertise in the field. The RDTF is assisted by a Scientific Secretariat supporting communication and administration of RDTF meetings and tasks.

S. Aymé asked to add the discussion of RD in the Programme of Community Action in the Field.
A. Montserrat stated that the explicit mention of RD in the Health Strategy and the Public Health Program shows the Commission commitment to RD as a priority.

B. Public Consultation on the Commission Communication on a European Action in the Area of Rare Diseases

Antoni Montserrat
European Commission
DG SANCO Health Information Unit

1. Producing the Communication Document

A Communication Drafting Group was composed to create the 1st Draft of the Public Consultation of the Communication on European Action in the Area of Rare Diseases. A. Montserrat clarified that before any Communication or Recommendation to the council a public consultation is required to allow all EU citizens to have input on the document. The Public Consultation will eventually be translated into 21 languages. Although the document will be available in some languages earlier than other, all translations of the document will be allotted a minimum of 8 weeks for public consultation. The English version of the text will be presented and distributed during the 2007 European Conference on Rare Disease (ECRD) in Lisbon, Portugal on November 27-28.

Today the 3rd Draft of the document will be approved and it will be the last opportunity to input on its content before its presentation for public consultation. Eventually, this document will be accompanied by an Impact Assessment which includes statistics, background documents, etc. supporting the content in the Communication. These documents are then presented to the Impact Assessment Committee after which they are passed to the Council and the Parliament.

It was asked who makes changes to the document after public consultation. A. Montserrat replied that in February 2008, the Drafting Group, perhaps an enlarged version, will propose how to incorporate the comments from the public.

A. Montserrat went on to explain that the Drafting Group made the 1st draft. This draft was sent to the following specialised bodies: Rare Disease Task Force, the Higher Level Group, EMEA Committee for Orphan Medicinal Products, and Eurordis. On 15 October the Drafting Group met to incorporate the contributions of these bodies and finalised a 2nd draft. It was explained that although there are no limitations in length of the document, we must remember that it is best to keep it as short as possible with respect to translation into 21 languages. The accompanying Health Impact Assessment is certainly unlimited in length.

2. Section by Section Discussion of the Communication Document

A. Montserrat explained that the word “Action” was specifically included in the title as the role of the Council is to approve actions. He stated it was important to retain the definition of RD to
show that although they are very diverse, they can still be defined. The term ‘ultra-rare diseases’ was removed at the request of the EMEA-COMP as it introduces an unnecessary additional category. RDTF members agreed on the following modifications to the text (Draft dating from October 23, 2007 Communication from the Commission: Public Consultation regarding European Action in the Field of Rare Diseases).

Section 1
- It should be stressed that RD are complex as this is a major argument for why collaboration at the EU level is imperative.
- The definition of RD prevalence does not apply to rare cancers. As such incidence, which is more appropriate, should be included in the Health Impact Assessment.

Section 2
- The objective of this section is to explain in reference to RD, an EU level approach will be efficient where Member States will be less efficient.
- Text describing a RD’s patients right to equal treatment should be adopted from the text of the Orphan Drug Regulation.
- The descriptions of “very” rare diseases and “small” countries should be removed.
- Using the phrase “biological test” may not be clear and it should be monitored to see if this misunderstanding comes out during the public consultation.

Section 3
- Rearrange main lines of DG SANCO action so that DG SANCO’s priority of networks of RD is mentioned first

Section 4
- In every public consultation, the inclusion of questions is obligatory.

4.1
- Keep the common definition of RD in the EU as less than 5 per 10,000 and perhaps include an excerpt of the Orphan Drug Regulation.
- Include other disease classification systems
- Add why it is so important to sustain financial support of coding and classification activities and emphasize that the Commission has already supported so much activity in this area it would be a waste to discontinue it.

4.2
- Change the title of the section to include prevention
- Remove redundant text at the end of Question 2.
- Change wording to “online tools and electronic records” in Question 3
- “Biological tests” should be changed to “diagnostic tests” in Question 4
- Change wording about laboratories.
- Wording about population screening should be changed to emphasize that it should be done consistently across EU even if it is not for the same diseases in each MS.
Population screening seen as a controversy. Notion of ‘recommendations’ should be changed to ‘assessment’. (Question 5)

Sentence referring to improved clinical training in MS where it is not sufficient should be re-included as it was removed from a previous draft. (Question 6)

Cost of registration should be removed and comments from EPPOSI discussion should be included: OD administered in hospitals should be administrated at a level higher than the local hospital.

Omit sentence concerning the question whether RD patients “deserve” payment of drugs. (Question 8)

Article 83 includes a provision of compassionate use and should be included as a footnote. (Question 8)

No reference to home-care and should be included. (Question 8)

Health Economic Evaluation should be changed to Health Technology Assessment

4.3

Clarify that EMEA does not “approve” the use of biomarkers as efficacy endpoints in clinical trials.

Text referring to registries should be moved to the previous section.

Remove “Therapeutic” from bullet title Intensifying Therapeutic Research

Mention that the Clinical Research Directive has been shown to deter clinical trials occurring in Europe because of cost.

Add that clinical trials should be supported at national level using example of Italy, France, Spain.

4.4

Agreement

Questions for Consultation will be changed to the following:

All agreed that S. Aymé and A. Montserrat will incorporate all suggestions. A. Montserrat will finalise the test tomorrow and shortly disseminate the timeline for translations. All responses to the public consultation will be visible. The Drafting Committee will meet around the end of January and the next RDTF meeting will follow (a bit earlier than usual in terms of interval). All members of the RDTF will receive the 3rd Draft

C. Calls for Proposals

G. Margetidis
Public Health Executive Agency

By the beginning of December the results of the evaluation will be made public. Previously there were 8-9 RD proposals most related to disease-specific networks (building up of reference networks), but what it now more important will be an emphasis on a more horizontal, transversal approach.

The RDTF Secretariat has not been supported in this call justified by the opinion that its activities
were redundant. The Commission responds with the following proposals:

1. To give the task of Orphanews Europe and the Coding and Classification WG to another project. (This proposal was subsequently rejected by the “other project”)
2. Call for tender: different non-competitive process
3. Joint project: submit another proposal limited in scope.

Both the Commission and the Public Health Executive Agency ensured that a solution will be identified to prevent a gap in the funding of the newsletter and activity related to coding and classification.

The Public Health Programme for Action next year includes a budget of ~40 million/year and has just been officially adopted. The first two years of the 2008-2014 funding period will include the implementation of financial tools per activity/project. Pilot Reference Networks will not be included as priorities.

The results of the European Health Info Survey will be included in the 1st quarter of the 2008 period.

It was asked what happened to the role of the RDTF in contributing to the Work Plan? G. Margetidis said the RDTF would be solicited for a written consultation.

D. Presentation on RDTF Upcoming Initiatives

Ségalène Aymé
Leader of Rare Disease Task Force
Director of Orphnet

Achievements of the Coding and Classification Working Group

The previous meetings were held on 11 October, 2006 and 2 May, 2007. The WG on Coding and Classification is involved in tackling the following issues:

- Comparing and correcting state-of-the-art coding systems
- Contributing to the WHO ICD-revision process
- Establishing a database of expert classifications of RD

Part of Orphanet mission is already to collect this information including MESH terms, MIM codes, proteins (via SwissProt collaboration), and genes which 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. It is for this reason that S. Aymé has been selected as leader of the Rare Disease Topical Advisory Group.

RD can be made more traceable in mortality and morbidity information systems 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) which will be discussed at the next WG meeting as ~1200 disease have been crossed thus far.
3. Contributing to ICD-10plus, a tool provided by the WHO to communicate suggestions to the current ICD version

Cross-referencing data sets will allow the identification of mistakes in respective data sets, improve coding sets, and identify problems in ICD10 such as need for category rearrangement and need for more specific categories which reflect homogeneous groups of RD.

Consequent activities include:

- Continued matching of lists of codes
- Release of the new version of Orphanet with the classifications: Dec 2007
- Organisation of Coding and Classification WG meeting
  - Priority list
  - Mismatches
- Apply for funding

**Additional RDTF Initiatives in 2008**

The proposed topic for the next Standards of Care WG workshop is the evaluation of the added value of European networks of Centres of Expertise. During this discussion the current networks scheme, the evaluation process used in France, and a proposal for a framework guiding an evaluation of the European added value will be analysed.

The proposed topics for a Health Indicators WG workshop is the indicators used to monitor RD and RD policy in Europe. More specifically, existing indicators, implementation of new indicators, and the areas of demography, epidemiology, health status, socioeconomic factors, health services, R&D outcomes, and policies will be reviewed.

A second workshop of the Health Indicators WG is proposed regarding RD registries. During this workshop existing registries, optimisation/exploitation of data, and the production of recommendations on ways to establish a registry, rules for accessing data, and prioritisation can be discussed.

The outcomes of these workshops will include a report on the methods used to assess the European added value of Networks of Centres of Expertise, a report on the indicators used to monitor the impact of the implementation of the Communication, as well as guidelines created to establish and exploit RD registries.

The activity of the Scientific Secretariat of the Rare Disease Task Force will unfortunately end on May 30, 2008.

**Next Meetings**
The drafting group for the Communication will meet February 13th in Brussels.

The 9th RDTF Meeting will be held 28 February, 2008 in Luxembourg.

The following WG workshops will be taking place in Paris:
Coding and Classification: February 6, 2008
European Networks of Centres of Expertise: March 11, 2008
Health Indicators: March 12, 2008
Health Registries: March 13, 2008
Meeting Report
9th Meeting of the European Commission “Rare Disease Task Force”
Luxembourg, 28 February 2008

On 28 February 2008, the ninth meeting of the Rare Diseases Task Force (RDTF) included the attendance of:

RDTF Members and Observers:

V. Anastasiadou  A. Kent  J. Sándor
S. Aymé      N. Kerlero de Rosbo  A. Schieppati
R. Capocaccia  A. Kole  S. Rumenov
H. Dolk       O. Kremp  J. Torrent Farneli
A. Fourcade   J. Llianes-Garcia  A. Vegnente
L. Fregonese  S. Lynn  G. Zambruno
G. Gatta      C. Nourissier
M. Gattorno   B. Pizzera Piantanida
E. Jessop     M. Posada de la Paz

DG SANCO: A. Montserrat

DG Recherche: C. Berens

PHEA: G. Dargent

Welcome and Discussion of Agenda
Ségolène Aymé
Leader of the Rare Disease Task Force
Director of Orphanet

S. Aymé opened the meeting by stressing the importance of the day’s agenda as it most importantly includes a discussion on the public consultations of the Communication.

The minutes of the 8th RDTF meeting have not yet been distributed as they have not been approved by the Commission. They will be distributed shortly.

S. Aymé welcomed new participants:
- Stephen Lynn of the TREAT-NMD Network
- A. Vegnente, member of the EuroWilson project
- M. Datorno, member of the PRINTO network.
It was asked of the Commission if the leaders of newly funded RD projects have been invited to join the RDTF.

A. Monsterrat replied that they will be officially invited for the next RDTF meeting.

No requests were made to change the agenda.

Public Consultation Regarding European Action in the Field of Rare Diseases
Antoni Montserrat
DG SANCO

The Communication Process

A. Montserrat prefaced his presentation of the public consultation asking members to remember that we are in a transitional stage of the process in which the content of any documents may change very quickly. As such, no electronic copies of the documents under discussion were distributed. Nor were any slides used.

In 2008 the European Commission (EC) accepted a Communication in the field of RD addressed to the Council, the Parliament, and the Committee of Regions. The Committee of the Regions has explicitly asked to see the document. Although this is not an obligatory step in the process, it will give good political weight to the initiative and thus a positive aspect.

We have now completed the first step of the Communication process – the public consultation. The public has consulted on a document finalized by the following voluntary RDTF members for whom we thank for their hard work: Rumen Stefanov, Jordi Llinares Garcia, Domenica Taruscio, Laura Fregonese, Cathrine Berens, Manuel Posada, Segolene Ayme and Christel Nourissier. They produced a document for consultation making as acceptable as possible for the EC, for the Parliament, and for the Member States (MS) – not an easy task. The most complicated task will follow with the incorporation of the responses of the public.

The Communication for public consultation was first presented at the European Conference of Rare Diseases (ECRD). The document was presented in 22 languages with the deadline of consultation on February 14, 2008. The authorities of several MS such as the United Kingdom, Germany, Spain, Denmark, and France have requested additional time. The EC will of course accept these any other late coming responses to the Communication, but will firmly close the invitation once all the contributions are published on the EC website (to be expected on Monday, March 3, 2008).

Over 600 contributions were sent to the EC regarding this communication. Many were simply confirmations of the document or congratulations on the work. Of these, 488 had significant content and will be posted on the EC website. This quantity of contributions the most successful in the area of health in the EC and is an enormous success in relation to other public consultations. For example, 200 contributions were sent for the consultation on a Communication regarding cross-border care and 60 contributions were received for a Communication on bio-
Of the 488 public contributions:

- 25 came from the pharmaceutical industry (a very large and useful contribution)
- 46 came from international patient organisations
- several international orgs (who, etc)
- 26 from authorities of MS (this does not mean responses from 26 MS as some MS sent responses from several authorities)
- national orgs of patients
- 52 from patients themselves
- 12 came from reference networks
- 16 came from local authorities
- 4 came from research centres
- 40 came from universities
- 47 came from other parties

The next step entailed the analysis of contributions to arrive at the Staff Working Document accompanying the White Paper on Rare Diseases received today. In the Commission procedures a Staff Working Document is an annex to a Communication. Its presence is not obligatory, but it permits an extension of the (15 page) Communication another maximum of 40 pages (39 in this case). The boxes in this text summarize the actions that can be done. It becomes a sort of intermediate document between the Communication and the Impact Assessment. RDTF members have not received it electronically as it is only a draft, and will change according to the discussion.

After the completion of this annex the Impact Assessment will be drafted and presented to a tribunal where the added-value of the actions is assessed. This is currently scheduled for April 16. If the impact assessment is judged as contributing a significant added-value the document is presented to the Inter-Service Group on Health. After this passage the documents will be presented to the EC Inter-Service Group on Rare Diseases.

The impact assessment will be presented to the Commissioners sometime between July and September 2008. At this moment the Communication becomes a White Paper and will be presented to the Parliament if the rapporteur agrees. It is known that several people are fighting for position as rapporteur – which is a ‘good’ sign.

The following step is a process in the Council which includes a discussion with the Member States. This is a very frustrating experience as all must agree. The presence of the French presidency and the favourable attitudes of the Health Commissioner and the President of the Council are all good signs.

Discussion

S. Aymé asked a question about timing of this process: if the Parliament only receives the White
Paper in September can they have enough time to review it?

A. Montserrat responded that although there is no specific health group in the Parliament and time must be shared with all other social issues presented, it is possible to complete the review in 2 months.

A. Fourcade confirmed that the French Presidency supporting all actions and that they will do their best for it to be done by the end of 2008.

H. Dolk suggested that a list of those who responded to the Public Consultation favourably (even if without content) be created and added to the publication of responses. C. Nourissier agreed that it is very important to acknowledge all contributions even if they are not unique.

A. Montserrat presented a rough presentation of the list of contributions as a table which included the person or institution responding, the language, and a link to the response. From the 488 responses, 300 were in English, 150 in French, 70 in Polish, and the fourth largest groups in German and Spanish.

S. Aymé mentioned that it was unfortunate that there is not more time to review the responses in more depth as they are very valuable. She suggests that the RDTF publish a report of this analysis in the future. C. Nourissier stated that Eurordis will also be doing a more in-depth analysis. A. Montserrat agreed that this sort of exercise is relevant material for many EU groups such as the COMP, Eurordis, and Orphanet.

H. Dolk expressed concern about contributions in foreign languages that were not translated. She suggested asking contributors to be made aware that if they would like their contribution to be distributed widely, to translate into English.

A. Montserrat responded that the Commission is not allowed to request for contributions in English as MS have the right to contribute in their native language. Unfortunately, the Commission does not have the resources to translate every contribution.

**The Content of the Staff Working Document**

A. Montserrat introduced the Staff Working Document as having a similar structure to the Communication in that each section is concluded with a summary of defined actions. In Section 1 very few modifications are made in relation to the Communication. There are, however, a few changes in the RD provided as examples. Section 2 is an explanation of the political context of the Communication.

Section 5 is where differences between the content of the Communication and comments become more significant. The previously presented aims are proposed to be reached by 11 objectives and actions: 11 objectives detailed one by one.

1. To improve information, identification and knowledge on rare diseases
2. To improve prevention, diagnosis and care of patients with Rare Diseases
3. To develop national/regional centres of reference and establish EU reference networks
4. To ensure equal access to all EU patients to orphan drugs and compassionate use
5. To develop specialised and adapted social services for rare diseases patients
6. To gather at European level the limited and scattered expertise on rare diseases
7. To accelerate research and developments in the field of Rare Diseases and Orphan Drugs
8. To empower patients with Rare Diseases at individual and collective level
9. To support implementation of National Plans for Rare Diseases
10. To develop the international cooperation on rare diseases
11. To coordinate the policies and initiatives at EU level

Participants of the meeting agreed on the following conclusions for each objective:

**Objective 1 – To improve information, identification and knowledge on RD**

**Actions:**

- The EU definition of rare disease based on a prevalence of less than 5 per 10,000 is maintained (Commission, EMEA)
- An EU or an international project exploring an incidence based definition of rare diseases will be launched (Commission)
- The EU will contribute to the ongoing process of revision of the ICD (International Classification of Diseases) in order to ensure appropriate codification and classification of rare diseases in the future ICD-11. A working group will be supported for all the period of this revision (Commission, WHO)
- The EU will establish since 2009 an Inventory of Rare Diseases to be periodically updated (Commission)
- The database Orphanet will be supported using appropriate financial instruments from the Health Programme or the FP7 (Commission)
- The support to the disease information networks through the Health Programme and the FP7 should be pursued (Commission)

The fact that there is no intention to change or discuss the threshold of a RD as it applies to the Orphan Drug regulation should be emphasized. It should rather be stated that both indicators – prevalence and incidence- have different values and should be used in different contexts. Using the EMEA text on the use of these two indicators should be used to find correct language. An EU or international project should collect incidence data as well and a purpose-oriented approach should be employed when using these indicators. If RD are classified by prevalence as well, the classification of rare and ultra-rare will be implied.

**Objective 2 – To improve prevention, diagnosis and care of patients with RD**

**Actions:**


Development of e-Health in the field of RD using on-line and electronic tools (Commission)

To create a help line unique EU-wide number for information and social services on rare diseases a 116 number (Commission)

An evaluation of population screening (including neonatal screening and Preimplantational Genetic Diagnosis) strategies for Rare Diseases in the Member States will be launched (Commission, Member States)

To launch a European series Patient Leaflets on some rare diseases in all the EU languages (Commission, Member States)

It must be clarified that the 116 help-line involves the establishment of national helplines that will all use the same number.

Currently, an evaluation of population screening strategies in the field of RD should be launched at the EU level as there is a need for a combined European effort. It is premature to give recommendations on how MS should implement policies on population screening, but it must be emphasized that the decision is ultimately up to the MS. Screening and diagnosis should be separated as concepts and although the discussion of Preimplantational Genetic Diagnosis should remain in the preceding text (as it was frequently expressed in Communication responses), it should not be included in the action points.

E-Health is mentioned as a highly supported development at the European Commission. The field of RD can greatly benefit from online and electronic tools created at the European level. It is perhaps one of the fields in health that can most greatly benefit from such tools.

**Objective 3 – To develop national/regional CE and establish ERN**

**Actions**

- To repertory in an EU list the existing Centres of Expertise identified throughout the Member States by the end of 2010 (Commission)

- To establish by Commission Decision a procedure for designation and accreditation methodology of EU Reference Networks for Rare Diseases (Commission)

- To provide adequate, long-term public funding to Centres of Expertise in order to ensure their sustainability and continuity of care for patients (Commission, Member States);

- To recommend inclusion in the National Plan for Rare Diseases provisions on the creation of Centres of Reference and their participation in European Reference Networks (Commission, Member States)

Orphanet currently maintains a list of existing Centres of Expertise (CE) throughout Europe. It
must be decided how this effort will be supported and sustained by the EC.

The accreditation of CE should only be at the national level. It is questionable how and why ERN should be evaluated at the EU level, though it is clear that such a surveillance could ensure that such networks benefit countries which do not have adequate resource to serve RD patients and support RD research on their own. The next RDTF A procedure for the creation, selection, evaluation, etc. of European Reference Network (ERN) must be established. This will be the centre of the discussion during the next RDTF Standards of Care Working Group meeting.

The definition and responsibilities of a CE and a ERN must be more correctly and precisely defined. A significant number of hospital representatives responded that they do not have adequate resources to support CE (in most cases hospitals) activities as described in the Communication.

In the third action point ‘Centres of Expertise’ should be replaced by ‘European Reference Networks’. Despite this clarification in vocabulary, the difficulty in guaranteeing long-term funding for ERN remains. Currently participating institutions of any networks in the field of RD are funded by DG research. DG Research funding competitive and renewable by nature (and is unknown after the end of and thus, long-term funding is problematic. In addition, it is unknown what will happen at the end of the Programme of Community Action in Public Health in 2013.

Several RDTF member expressed reservations in the official designation of ERN as doing so would mean the exclusion of networks that although are not official are equally if not more effective. The scope of these networks also remains unclear. Nevertheless, RDTF members expressed the opinion that ERN should focus on actions not manageable at the MS level (e.g. databases and registries, outreach to MS in need).

Objective 4 – To ensure equal access to OD and compassionate use

**Actions**

- To explore additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State familiarity with these products (Commission, EMEA)

- To establish of a European Committee to evaluate the appropriateness of compassionate use (Commission, EMEA)

- A European guideline should be developed clarifying responsibilities in a Compassionate Use situation (Commission, EMEA)

- A European Guideline should be developed clarifying requirements for import licenses and labelling (Commission, EMEA)
The Commission should present, a report to the Council and the Parliament identifying bottlenecks on orphan drugs access (delays, marketing, access, reimbursement, prices, etc.) every two years, proposing the necessary legislative modifications in order to guarantee equal access to orphan drugs throughout the EU on the basis of a COMP/EUACRD European collaborative scientific assessment (Commission, EMEA)

An EMEA Committee for the assessment of the Therapeutic Added Value of Orphan Drugs should perform a common scientific assessment of the TAV for each Orphan Drug and deliver an opinion document (Commission, EMEA)

A feasibility study should be launched to explore incentives for industry in the field of medical devices and diagnostics for RD (Commission)

Significant contributions were received concerning this objective, namely from the COMP, Eurordis, and the pharmaceutical industry. One simple observation in the contributions is that big pharmaceutical companies were largely in favour of the OD section of the Communication whereas smaller companies were not.

Activities described in Action point 1 currently exist for drugs in general; the specification for these activities for OD may be unrealistic. It was suggested that ‘medical devices’ be added to Action point 1.

Many contributions reflected the opinion that RD patients are ‘used as guinea pigs’ in the compassionate use program. It was agreed that it should simply be stated that compassionate use is an issue, without specifying the proposal of a committee dedicated to the topic as compassionate use should be regarded as part of a national health plan.

Guidelines clarifying responsibilities in a Compassionate Use situation are homogenous in many MS and even non-existent in others. As such it could be beneficial to provide such guidelines at the EU level.

The discussion of reimbursement and pricing posed difficulty as reimbursement is done at the MS level and pricing is determined by pharmaceutical companies with an attempt to keep them the same across Europe. RDTF members agreed that the pharmaceutical industry should be more transparent in how they arrive at a price.

The therapeutic added-value of orphan drugs is linked to reimbursement and pricing. As some MS would welcome this assessment at the European level, others reject it. It was suggested that Action point 6 should be made more general.

A European approach assessing the use medical devices is not agreed upon by all stakeholders. Therefore, at this time, the action point should either be removed or softened.

Objective 5 – To develop specialised and adapted social services for RD patients
The development of social services is a national competence. The Commission can only recommend that the development of such services be included in national initiatives and provide financial support through the support of networks in general and not specific activities such as recreational programs.

Objective 6 – To gather limited and scattered expertise on RD at the EU level

Actions:

- The Health Programme and the FP7 will continue to support, in a coordinated way, registries, databases and biobanks on rare diseases with appropriate financial tools for a sustainable funding (Commission)

- The Commission will establish, by Commission Decision, a publicly accessible EU Register of Rare Diseases patient registers databases and biobanks defining criteria for register accreditation and qualification and the access to samples. EU registering will become mandatory for publicly funded or co-funded repositories under the Health Programme and the FP7 (Commission)

- Specific support to further research into biomarkers should also be given to encourage long-term follow-up, and the acquisition of robust evidence on clinical effectiveness (Commission)

The second action point is included to control the inappropriate nomination of a EU registry, database, etc. This will simply include the documentation (not accreditation) of patient registries, databases, biobanks, etc.

C. Berens suggested moving the third action point under Objective 7 as it relates more to RD research. She strongly urges finding an appropriate solution for long-term funding of such registries because it will not come from DG Research.

Objective 7 – To accelerate research and developments in the field of RD and OD

Actions
The EU Advisory Committee on RD and the Committee for Orphan Medicinal Products (COMP) in the EMEA (European Medicines Agency) will address to the FP7 biannual recommendation on research priorities on RD (Commission, EMEA)

To create an adequate EU mechanism through the FP7 to specifically support the clinical research development of designated orphan medicinal products up to the end of phase II and the specific Genetic and molecular characterisation for the more than 4 000 diseases for which it remains to be done (Commission)

To launch the creation of a public-private foundation for RD, the European Research Foundation for Rare Diseases (Commission, Member States, private sector)

Though research priorities cannot be established in this document, a procedure of how to communicate biannual recommendations on research priorities in RD can be established.

The second action point was proposed by several pharmaceutical companies in their response to the Communication as a development that can benefit both the industry and patients.

The role of the proposed public-private foundation for RD should be better defined. A feasibility study on its function was proposed.

**Objective 8 - To empower RD patients at individual and collective level**

**Actions**

- The Health Programme will continue to integrate the support to the patient’s organisations as a priority for action (Commission, Member States)

As the goal of support for patient organizations is to create equity, patient organization representatives should receive support to make sure that they are not disadvantaged by their voluntary participation in RD work (meetings, committees, etc.)

**Objective 9 – To support implementation of National Plans for Rare Diseases**

**Actions**

- The Member States are invited to establish national or regional action plans for RD in order to implement the actions suggested in the Commission Communication and the Council Recommendation before 2010 (Member States)

- The Commission will provide European guidelines for the elaboration of these action plans for RD. Appropriate international conferences will be organised (Commission)

Instead of enforcing a precise deadline (which introduces a risk of MS not meeting the deadline) MS should be required to submit yearly reports on their progress towards establishing a national plan on RD.
This objective should be introduced earlier in the document.

**Objective 10 – To develop international cooperation on RD**

**Actions**
- An international cooperation framework on rare diseases with other countries (e.g. US, Canada, Japan, Singapore, Australia,...) will be adopted (Commission)
- A proposal of resolution on an international action in the field of rare diseases will be submitted by the European Commission to the World Health Assembly (Commission)

This objective was missing from the Communication, but appeared in many contributions and was welcomed by RDTF members. It was suggested that this could be an appropriate Objective under which the cooperation with the WHO on the Coding and Classification of RD can be reaffirmed.

**Objective 11 – To coordinate the policies and initiatives at EU level**

**Actions**
- An EU Advisory Committee on Rare Disease (EUACRD) will be created, by Commission Decision, in order to advice the European Commission. A specific budget for this Committee will be allocated in a sustainable basis in the EU budget (Commission)
- The European Conferences on Rare Diseases will be organised every two or three years. Funds will be provided by the Health Programme (Commission).
- A Rare Diseases Fund will be included in the Financial Perspectives (2014-2020) (Commission).
- A feasibility study for the creation of a European Agency on Rare Diseases will be launched in 2009 by the Health Programme (Commission).
- Every two years the Commission should produce an Implementation report on the Commission Communication and Council Recommendation addressed to the Council, the Parliament, the Social and Economic Committee and the Committee of the Regions (Commission)

The EU Advisory Committee on Rare Disease (EUACRD) is not a new title for the RDTF, but the creation of a new structure. The members of this committee will include a representative from each of the 27 MS (more if it is decided to include candidate or neighbouring countries). This framework of an advisory committee will result in a loss of intimacy but a gain in legitimacy in relation to the current structure of the RDTF. Current RDTF members expressed concern regarding the expertise of each designated MS representative, the flexibility in the agenda, and the possibility of inviting other experts as needed. The EUACRD will be supported until 2013 after which its support will have to be reassessed.
Among contributions to the public consultation of the Communication most patient organisations were in favour of the creation of a European Agency on RD, most pharmaceutical companies were not, and MS health authorities were divided. It is proposed that a study should be launched to investigate the relevance and feasibility of such a structure.

**European Conference on Rare Diseases 2007**

**Christel Nourissier**

**Eurordis**

This year’s European Conference on Rare Diseases was organized in Lisbon, Portugal under the Portuguese presidency and its partners. It was attended by participants from 35 countries by a good balance of stakeholders. The conference received good media coverage which was encouraging as one goal of the conference was to raise awareness of RD in Portugal. This was a crucial moment and Portugal is currently working on a National Plan of Rare Diseases.

The main outcome of the conference was the successful launch of the Communication as we see from the large amount of responses received. This meeting also served as a platform for the first presentation of the outcomes of the RAPSODY project.

The next ECRD is scheduled in Poland under the DG SANCO funded POLKA project. This conference will be much larger with more satellite meetings, more patient representatives and more of an opportunity for communication with neighbouring countries. The conference is proposed to take place in Poland in May 2009 though this has not yet been confirmed.

S. Aymé congratulated Eurordis on their previous ECRD meetings. She stated that as the RDTF was not very involved in the previous meetings, it would be nice to work more together on future conferences.

**Workshops of the Task Force**

**Ségolène Aymé**

**Leader of the Rare Disease Task Force**

**Director of Orphanet**

Four workshops have been planned this spring. The outcomes of the first – Workshop on Coding and Classification – took place on February 6, 2008. Outcomes of this workshop will be presented soon. The Coding and Classification Working Group has already met several times. It has agreed on several principles of action:

1) Rare Diseases should be traceable in mortality and morbidity information systems
2) There are two categories of RD:
   • The recurrent RD (~1,500 to 2,000) should have a specific code in ICD-11
The ultra-rare (~4,000) should be coded as “other specific RD” within relevant subcategory but indexed nevertheless.

The Working Group has also agreed on the following criteria for assigning RD with a specific code in ICD-11:
- Any disease coded in a registry of patients or an information system
- Any disease covered by a support group
- Any disease with a clinical test

Using these criteria, Orphanet has identified almost 900 diseases of which 400 do not have a specific code in the ICD-10 and must assigned a code. In the next three years these suggestions will reviewed by experts and presented for comments using the WHO’s technology platform for the ICD revision process.

The WHO is fully open in its organisation of RD in ICD-11 is fully open in its organization. For RD a clinical approach based on medical specialties is most appropriate where some classifications are by etiology and others by anatomy. All RDTF member will have an opportunity to comment on the organisation via WHO technological platform.

The Workshop on Assessing the Added-Value of Centres of Expertise (CE) and European Reference Networks (ERN) in RD will take place on March 11, 2008 in Paris. Participants will be provided with a workshop working document which will serve as a working document. Following discussion with workshop participants, and consultation with other experts, a new draft of the document will be published as an RDTF Scoping Paper on the topic by June 2008.

The Workshop on Health Indicators (HI) will take place on March 12, 2008 in Paris. The working document for this workshop is prepared by L. Fregonese and the RDTF Secretariat and will include the following topics of discussion:
- Discussion of HI in the Communication
- Definition, objectives, and legal basis for HI
- Past and ongoing projects on HI
- Potential Sources of Data
- Criteria of Selection of appropriate HI for RD

The ultimate goal is to create a list of feasible HI for RD.

The last workshop on Health Registries and Databases will take place on March 13, 2008 in Paris. The aim of this workshop is to produce recommendations and guidelines for:
- requirements in maintaining and maximising the use of registries
- obtaining funding to support tools and resources shared by rare disease registries on a European level;
- creating a repository of data in the event of a termination of registry funding.

In the next coming years the RDTF will have to identify new working groups addressing new pressing issues. Suggestions are welcome.
New projects selected for funding in 2007
Gemma Gatta
RARECARE
Fondazione IRCCS Istituto Nazionale dei Tumori

The project began in April 2007 and is funded for three years. The aims of the project are:

- To provide an operational definition of “rare cancers”, and a list of cancers that meet this definition
- To estimate the burden of rare cancers in Europe
- To improve the quality of data on rare cancers
- To develop strategies and mechanisms for the diffusion of information among all the key players involved in Europe-wide surveillance on and treatment of rare cancers

The proposed actions of the project include:

- Estimation of incidence, survival, prevalence and mortality for all rare cancers
- Analysis of data quality for a subset of cancers, by confirming the diagnostic data and, if possible, analysis additional data on stage and treatment
- A web-site on rare cancers will be designed to disseminate the results of the project, and in particular, to inform clinicians, patients and health planners

The major aim of year one is to agree on an international level on a list of rare cancers. To attain this goal, periodic meetings of clinicians, advocacy groups, epidemiologists, etc. have been organized. During the most recent meetings, the topography and morphology of approximately 400 entities was presented and incidence and prevalence was calculated. Using the threshold of 3 per 100,000, a list of rare cancers was defined. Four additional meetings of this nature are planned.

J. Llinares-Garcia asked why the threshold of 3 per 100,000 was chosen. He also requested if the EMEA could be provided with this data as a large portion of applications concern rare cancers.

G. Gatta replied that the threshold of 3 per 100,000 was chosen because with this threshold 55% of all patients are included. She also responded that an EMEA representative was invited to the meeting, but responded that they could not participate because the RARECARE project measured incidence and not prevalence.

S. Aymé stated that she did not agree with some of the approaches. She felt that the threshold is not relevant, and that it should not matter the percent of patients included as long as it reflects reality. She stated that in her opinion experts who specialized in one area (such as cancer) lose perspective on what cases are rare because they see them relatively often. Oftentimes this is not the reality and their work loses credibility if a solid foundation for choosing a threshold is not established.
A. Montserrat concluded this presentation by stating that purpose of any project is that it proves useful for the European Commission. Consequently, the results should have utility, continuity, etc.

**New projects selected in 2007 for future funding**  
Antoni Montserrat  
DG SANCO

- European Haemophilia Safety Surveillance System (EUHASS)  
- Patients’ Consensus on Preferred Policy Scenarios for Rare Diseases (POLKA)  
- European network of paediatric Hodgkin’s lymphoma – European-wide organisation of quality controlled treatment (Paediatric Hodgkin Network)  
- The PRES Network for Autoinflammatory Diseases in childhood (EuroFever)  
- European Network of Reference for Rare Paediatric Neurological Diseases (nEUroped)  
- European Project for Rare Diseases National Plans Development (EUROPLAN)  
- A reference network for Langerhans cell histiocytosis and associated syndrome in EU (EURO-HISTIO-NET 2008)

**Next call for proposals**  
Antoni Montserrat  
DG SANCO

The next Call for Proposals is being launched tomorrow. The deadline for this call is **23 May 2008**.

In the call several new important themes can be observed:
- Co-financing of projects intended to achieve a Programme objective (call for project proposals)  
- Co-financing of the operating costs of non-governmental organisations or specialised networks (operating grants) – intended for projects requiring stability such as registries.  
- Co-financing of conferences intended to achieve a Programme objective (call for conference proposals) – intended for small conferences and small working groups  
- Joint actions by the Community and Member States as well as other (third) countries participating in the Programme – A joint action exist between (at least five) MS and the Commission. This instrument will allow for faster turn-around. This instrument will be used to fund the activities of the RDTF.  
- Tendering of actions to achieve a Programme objective – This instrument will not affect RD.

On March 12, an Info day on calls for proposals is scheduled but unfortunately it is already full. A few additional more information days in other MS are being organized as the Luxembourg Info Day is full.
Future Actions of the Rare Disease Task Force
Ségolène Aymé
Leader of the Rare Disease Task Force
Director of Orphanet

S. Aymé emphasized that input of RDTF member is very important as we will have to apply for funding together under the new instruments of funding. She herself has listed several possible topics and welcomes any others: indicators, population screening for RD, principles guiding compassionate use.

N. Kerlero de Rosbo proposed a workshop on ethics in the context of trans-European RD projects, networks, data sharing, etc.

A. Montserrat responded that a subgroup of the Network of Competent Authorities is already working on this but that a discussion specifically about RD could be useful.

Cornelia suggested work on prenatal diagnosis.
The group agreed that this was not a topic for the RDTF.

L. Fregonese suggested a workshop on the sharing of health indicators. So many projects are funded to collect health indicator data and the results could be consolidated to try and make the most of the results of past and ongoing data collection projects in the field of RD.

Several RDTF members agreed and A. Montserrat agreed to propose it to the PHEA.

Presentation of the 3rd Eastern European Conference on Rare Diseases and Orphan Drugs
Ruman Stefanov
ICRORD

This conference takes place in Plovdiv, Bulgaria beginning on March 1st, 2008. The Bulgarian vice Minister of Health will open the conference and 200 participants are anticipated. Twenty-five participants will attend a satellite workshop on the Marketing of Orphanet drugs. The results of this conference will be presented to RDTF members.

S. Stefanov added that he just received news of the resignation of Commissioner Markos Kyprianou and asked how this will affect the work on RD.

A. Montserrat responded that indeed Commissioner Markos Kyprianou has resigned and that he will most likely be replaced by Commissioner Maglena Kuneva to allow for a smooth transition.

Rare Disease Meetings of the French Presidency
Ségolène Aymé
Leader of the Rare Disease Task Force
Director of Orphanet

On November 18, 2008 a conference on National Health Plans will take place in Paris. Please note the change in date. On October 13 or 14 (to be confirmed) another a session on RD will take place as part of a larger conference at the Ministry of Health.

Though not an official event sponsored by the French presidency, the next EPPOSI meeting (European Platform for Patients’ Organisations, Science and Industry) will also take place in Paris (date to be decided).

Next Meeting of the RDTF

July 3rd, 2008
2. SCIENTIFIC SECRETARIAT REPORTS AND WORKING GROUP MEETINGS
   
a. Coding and Classification

Meeting Minutes

Meeting of the Rare Disease Task Force
Coding and Classification Working Group
Paris – February 6, 2008

On 6 February 2008, the meeting of the Rare Diseases Task Force (RDTF) Working Group (WG) on Coding and Classification included the attendance of (see Annex 1):

S. Aymé
C. Celik
E. Daina
A. Devereau
P. Facchin
G. Gatta
E. Garne
M. Georget
S. Groft
R. Jakob
A. Kole
C. Martos-Jimenez
S. McKee
A. Montserrat
A. Rath
A. Sollie
D. Taruscio
B. Ustun
M. Vihinen
U. Vogel
O. Zurriaga

A. Welcome and Approval of Agenda
No significant modifications.

B. Introduction to the Meeting
Robert Jakob
WHO

R. Jakob presented an overview of the revision process describing the aims, plan of activities, organisational structure, and technological platform used as the point of access for the update and revision process (Knowledge Management and Sharing (KMS) portal). (See presentation and Production of ICD-11: The overall revision process)

This web-based platform is a new approach to the ICD revision process, which previously included closed meetings of experts every 10 years. The new approach will allow for a considerably more comprehensive (allowing commentary from all users) and dynamic process.

ICD revision will instead be coordinated by WHO Headquarters in consultation with the WHO member states, the WHO Family of International Classifications, and other professional institutions forming Topical Advisory Groups (TAG). Ségolène Aymé has been selected as the leader of the TAG for rare diseases (RD) for her expertise in the field and previous work on Coding and Classification of RD at Orphanet. The WHO’s goal is to produce an open formal definition of RD and to present them in an unambiguous way with links to different ontologies.
such as genes, phenotype, SNOMED terms, etc. New additions to the structure of the revision process include several new TAG: Maternal and Neonatal TAG, Ophthalmological TAG, and Information Technology TAG. The IT TAG will be chaired by Dr. Marc Musen from the National Centre for Biomedical Ontology at Stanford University in the United States.

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

Ségolène Aymé
Orphanet (INSERM SC11)
Chair of RDTF

S. Aymé presented Coding and Classification work done at Orphanet. Using previously agreed upon guiding principles (see presentation RDTF Coding and Classification WG meeting May 2, 2007) a list of RD requiring new or modified ICD codes was created. As there are too many RD to allow a specific code for each, a portion of them have been designated as diseases that should at least be coded as an “other RD”. Of the most comprehensive list possible of RD, approximately 900 are frequent and severe enough that they must be traceable with ICD codes. In the newest version of the Orphanet database RD are linked to MIM number, gene, proteins, ICD-10 code, MeSH terms, Orphanet number, age of onset, age of death (all of which will be summarized on an RD identity card). The most recent related publications and relevant websites are also linked to many of the diseases in the database.

Next S. Ayme described the cross referencing exercise carried out with Orphanet’s RD database and other was crossed with other data sets of RD linked to ICD codes. This exercise facilitated the identification of coding mistakes and discrepancies. In addition, RD were organised according to their medical specialty using criteria from RD Centres of Reference (also known as Centres of Expertise). The result of this exercise is open for validation (see Coding and Classification of Rare Diseases at Orphanet and Comparisons with other data sets: Diseases of the priority list which ICD-10 codes do not match). The agenda is to define a process of how to review this list and corresponding timetable.

Discussion

E. Garne asked how to agree on a WHO definition of a rare disease to have a threshold of defining a disease as rare in the context of creating a list of disease which necessitate a new or modified ICD code. If prevalence is used as a measure, the threshold will differ considerably from disease area to disease area.

S. Aymé responded that it is not necessary to consider the threshold of what defines a RD as our primary goal is to ensure that disease not yet coded in ICD are coded. Those RD that are less rare (near a questionable threshold) are already coded in ICD.

S. Aymé proposed a discussion of the validation process. She began by recognising that this will be a very sensitive process as patients and their representative groups of diseases not selected as a RD receiving an ICD code may not agree.
S. Groft added that the Office of RD at the NIH in the United States had a similar problem when deciding what RD to define and list on its website. He suggested that the following questions should be considered:

- How can the assigning of ICD codes to RD be a dynamic process?
- How much work will it take to assign additional codes to newly introduced diseases?

S. Groft also mentioned the importance of emphasising the fact that all RD (even those that are ultra-rare) will be at least coded with a non-specific RD code.

B. Ustun stated that the TAG will have to act as a “scientific referee” for all stakeholders involved with a concrete criteria used to communicate. He reminded participants that all stakeholders will have the chance to input their comments on the preliminary decisions made by the TAGs.

S. Aymé concluded the discussion with the agreement that the list of diseases to receive an ICD code will be dynamic and that the list proposed today should not be called a “priority” list but rather a “starting” list.

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

Ana Rath
Orphanet (INSERM SC11)

As agreed upon during the last Coding and Classification WG meeting on May 2, 2007 the following criteria of selection were employed:

- Diseases listed in a rare disease patient registry
- Diseases having a diagnostic test
- Diseases having a dedicated patient organisation
- Diseases included in the priority list of the Orphanet Emergency guidelines project
- Diseases having an orphan designation/drug

These diseases were then crossed with:

- Veneto registry of rare diseases
- 1348 Orphanet disease entries with a diagnostic test
- 2751 Orphanet disease entries with a patient organisation
- 114 priority diseases with emergency guidelines
- 217 diseases linked to an orphan designation /drug (excluding infectious diseases)
- 1706 diseases with prevalence data

The result was the classification of 921 diseases designated as requiring an ICD code. Of these diseases 400 currently have no specific ICD code, 259 are listed under an existing ICD code (non-specific) and 262 have a specific ICD code. A. Rath questioned who should validate the selection process and proposed:
• Orphanet Scientific Advisory Board?
• Learned societies?
• WHO collaborating centre?
• Patient organisations?
• Network of EU competent authorities?
• Other?

A. Rath continued by presenting examples of RD with no ICD code, with a correct specific ICD code, and with an incorrect specific ICD-10 code (see presentation).

Discussion

R. Jakob announced that the effectiveness of this exercise is recognized by the WHO and it will recommend it to be repeated by the Morbidity Group. He recapped the presentation with the following summary:

- Some corrections in codes will be easy to fix
- Some corrections will require proposal, discussion, and consensus
- Some will include political obstacles

One major obstacle noted was the fact that the ICD-10 does not include the definition of a disease.

G. Gatta stated that regarding rare tumours the RARECARE project defines rare cancers and has produced a list of coded diseases. In a few months this list will be available and will include frequency (incidence and prevalence) and outcome (survival). As all of this work is based on population-based registries, G. Gatta, stated that she was confused about the list of RD provided in the document “Comparisons with other data sets: Diseases of the priority list which ICD-10 codes do not match”. For example, in her opinion gastric tumours were not rare.

S. Aymé and A. Rath disagreed.

G. Gatta concluded that there is obviously disagreement between the lists, but that collaboration with the RARECARE project should be considered.

E. Presentations of Coding and Classification work done in Finland and UK
Mauno Vihinen
Institute of Medical Technology - Bioinformatics Group

The ImmunoDeficiencyResource (IDR) is a Web accessible compendium of information on the immunodeficiencies. This resource includes IDbases – locus-specific databases for immunodeficiency-causing mutations with the aim of establishing databases for every immunodeficiency or providing links to those maintained elsewhere.

In addition to gene mutation, IDbases contains information about clinical presentation and links
to several disease classification systems including IUIS, WHO, ESID, and IDR. A crossing of these sources produced an unbiased computer output of disease classifications. Though the selection of the direct parameters is still under discussion, new diseases are easily introduced.

See websites of IDR (http://bioinf.uta.fi/idr/index.shtml) and IDbases (http://bioinf.uta.fi/base_root/).

F. Presentations of Coding and Classification work done in the UK

Andrew Devereau
United Kingdom Genetics

The UKGTN has completed the exercise of coding the diseases in their directory with ICD-10 and shared this information with the Orphanet. It was decided that the UKGTN will partner with Orphanet (and others) to apply for EU funding in order to continue work on coding rare diseases at an international level after May 2008. As Manchester University agreed to be the named applicant on behalf of UKGTN and Andrew Devereau will co-ordinate the projects in his capacity as a member of the Systems and Communication working group and for the Manchester National Genetics Reference Laboratory he expressed his eagerness in receiving funding to continue this work.

A. Devereau reported that the organisation of his working group is much like that of the TAG of the ICD-10 revision process. For organisational reasons, a ‘genetics’ subgroup was not formed in time and thus all work on genetic diseases will be placed as part of the ‘paediatrics’ group.

A. Devereau and his group will proceed with indexing RD with SNOMED terms.

G. Contributions of DG SANCO

Antoni Montserrat
European Commission
DG SANCO Health Information Unit

Two main political goals of the European Commission, as expressed in the Communication on a European Action in the Field of Rare Diseases, are

1. an inventory of RD. This is a right of all Member States (MS). And for this Orphanet will be encouraged and welcomed to provide this.
2. Coding and Classification. As a consequence of the recognition of a disease is the subsequent coding and classification of it.

A. Montserrat added that he suggests not using the title “Priority list”. The Commission would rather title these list by the year during which they were established allowing for and update of the list each year as new rare diseases are discovered (ie. RD with specific code 2007, RD with Specific code 2008, etc.)

The Commission also strongly recognises that the importance of correct coding and classification lies heavily in its users, for example EUROSTAT.
As for the financial support of these activities, DG SANCO proposes the funding of these actions as a Joint Action. This funding scheme invites the collaboration of several MS on the project. This proposal will be made public 29 February and INSERM will, of course, be encouraged to collaborate. Objective parameters will be used to choose among all applications.

A. Montserrat concluded that the way in which the Commission can directly contribute to the WHO’s ICD-10 revision activities remains to be discussed and decided.

Discussion

B. Ustun responded that the WHO looks favourably on the Commission’s contribution and welcome any collaboration. In March 2008 the Revision Steering Group is meeting with the NIH in the US to discuss collaboration and would gladly do the same with the appropriate Commission representatives.

B. Ustun continued by emphasizing that the entire ICD-10 revision approach (not just in the field of RD but in all Topic Advisory Groups (TAG)) is based on the organisation and work of Orphanet regarding the coding and classification of RD and thus it encourages the Commission to continue funding this activity until the end of the revision process.

S. Aymé asked A. Montserrat for clarification and elaboration on the Joint Action funding scheme for Coding and Classification activities.

A. Montserrat responded with the following statements:

1. The Commission is proposing to fund Coding and Classification activities through a Joint Action (as opposed to other funding schemes). In this scheme, the Commission provides participants with 50% of the funding and MS are asked to provide the other 50% in kind. This proposal marks the first use of the Joint Action funding scheme at DG SANCO.
2. As the current RDTF Secretariat contract is not being renewed and money accounted from the Joint Action will not appear immediately after its end, the Commission is looking for a solution for the gap in funding for the few months between contracts.
3. Money can (and possibly must) be used for face to face topical meetings (i.e. metabolics)

H. Discussion of work plan for coming years

S. Aymé reiterated the fact that the list of RD lacking more specific or correct codes in ICD-11 should not be referred to as a “Priority list” but rather a list-in-progress identifying RD code specifications and corrections.

S. Aymé asked WHO representatives whether the Coding and Classification WG should start by contributing to ICD10+ and then move to the revision of ICD-11 or do both at once?
B. Ustun responded that for all “under-lapping” diseases and “wrinkles” identified by the cross referencing of Orphanet codes with other coding sets should be reported using the ICD-10+ tool. At the same time the entire knowledge base (final suggestions for revision of RD ICD codes) can be imported (perhaps section by section; i.e. immunology, then gastroenterology, etc.) could be transferred to the Revision Steering Committee as an alpha-version of ICD-11. An exchange between the TAG’s and the Revision Steering Committee can continue until an ultimate list of new RD ICD codes is created by October 2008.

D. Wellesley and E. Garne commented to the ICD10+ website tool that it may be difficult for clinicians to use and B. Ustun promised to take a further look at the website tool to make is more user-friendly. WHO may also make it visible at the website that proposals are submitted from organisations as Ophanet and EUROCAT and not only from individual experts.

Participants ended the meeting by summarising their contribution:
UKGTN – multilingual test of SNOMED via triangular exercise
EUROCAT – contribute to the internal revision process of the WHO Rare Disease List to end up with ultimate list by October 2008 before sending the list out for external review
Italian Registries – provide validation through field testing by crossing the “ultimate list” with registry lists
NIH – Contact Library of Medicine and leaders of other RD organisations to contribute financially and to revision in ICD10+. After the March 6, 7 meeting between WHO and NIH the NIH’s contribution will be finalised.
DIMDI – make steps toward formalising the relationship between Orphanet Germany and DIMDI to allow collaboration.
CINEAS – participate and contribute to the revision process by continuing comparing data sets with Orphanet, and provide updated and revised list of metabolic diseases and rare cancers
Surveillance of Rare Cancers in Europe – cross EU rare cancer database with others to see if classifications are similar
Orphanet – preliminary list of RD needing specification or correction in ICD-10

The remaining representatives (those contacted for international representation but not present at the workshop) will act as advisors to the TAG. The structure of the TAG should be that of an editorial panel with approximately 15 members acting as spoke persons. The number of “reviewers” who act as advisors is endless. S. Aymé should act as the ultimate spokesperson for the panel.

B. Ustun stated that the full field testing of the revised ICD codes is projected to occur in 2012 and will be organised by the WHO. He suggested that the WG create user names to represent groups (i.e. ORPHANET, EUROCAT, etc.) for in the ICD10+ and Hi-Ki revision applications. S. Aymé can then provide a list of all the major groups that will contribute.

Next Meeting
The RSG will be meeting in Geneva between 7-11 April. This could provide an opportunity for S. Aymé to meet with the RSG as the leader of the RD TAG. No plan for an upcoming meeting of the RDTF WG was planned as it depends on EC funding which is not yet obtained.
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Minutes
Meeting of the Rare Disease Task Force
Standards of Care Working Group
Workshop on Assessing the Added-value of European Reference Networks
Paris – March 11, 2008

On 11 March 2008, the meeting of the Rare Diseases Task Force (RDTF) Working Group (WG) on Standard of Care included the attendance of:

A. Ambrosini  F. Houyez  M. Posada
S. Aymé  M. Jespersen  A. Schieppati
J. Dart  E. Jessop  R. Stefanov
A. Fourcade  A. Kole  V. Straub
M. Gattorno  A. Marlier-Sutter  D. Taruscio
P. Griffiths  A. Montserrat  L. Warren
E. Hampel  C. Nourissier

A. Welcome and Introduction
The objective of this meeting was to continue to clarify the definition of Centres of Expertise (CE) and European Reference Networks (ERN) and consolidate all work of groups working on this and to discuss the foundations of ERN, though it is too early to recommend a specific infrastructure with precise responsibilities or process of selection of CE as members. Through additional such workshops, an added value of ERN at the European level can be assessed.

Why Centres of Expertise at the Member State level is not enough
The capacity of these CE varies from MS to MS and in a time of increased patient mobility CE are experiencing strains in accommodating the patient load. Given the variable size of MS, some CE are able to provide more for their citizens. In the field of RD, where knowledge and resources are limited, the sharing of information and tools is crucial (compilation of data is imperative for clinical research – a topic that will be investigated in more depth during another workshop: RDTF workshop on Registries and Databases.)

RDTF agreed that patients should not have to travel because of negative affects of language, cost, burden of travel) although they should be allowed to if necessary. In addition local hospitals (CE) do not have the capacity to systematically accept patients from other MS.

The RDTF conclusions on the unmet needs surrounding CE are the following:

• There is a European added value of having CE
• Their experience must be shared at the European level
• The existence of CE in all MS should be identified and made aware by the EC.
• Definition of what is a CE. List of criteria has been agreed upon by HLG, by RDTF, and many health authorities at MS level. This is not to say that it has been agreed upon by all MS by all Ministries of Health or other relevant health authorities.
• It has been agreed that, in general, networking between CE is beneficial, though it has not been agreed on what exactly these networks are able to share (topic for today). We know that often CE are more specialised in one aspect of a RD and other CE are more specialised in another. So there is an obvious benefit to their collaboration.

Several years ago the concept of CE regulated at the European level was introduced by the HLG, though it has since been agreed that this is not possible. The initiative then evolved to the idea of ERN. Since then there has been a struggle to define their exact mission.

**Topics of Concern**
Official CE will be beneficial because it will be clear and know where the expertise exists, which can lead to the drawing of more research and expertise to these centres. It is recognised that by flagging these CE patients are pushed to these centres which causes overload, and a possible loss of trust in local services by the patients as well as a lack of interest of health professional at the local level as attitudes shift to feeling of being no longer required to care for the a disease when a CE cover it.

There are several types of possible CE. They can cover a single disease, a group of diseases, a technology or social support. It is rare for a CE to cover all these aspects. As such it is difficult to specify the characteristics of a CE.

It has been agreed that the existence and location of CE should be made available, but in order to publicize their existence and location, it must be decided who will designate them (ie decided what is a CE and what is not). It is agreed that this should not be decided at the European level. The coverage of CE has also been discussed at length. It is agreed that this coverage should certainly not be at the European level, but whether the coverage is regional or national is up to each MS.

ERN were proposed for:
• Sharing of expertise
• To be involved in introducing guidelines for clinical research
• Communication on the RD they work on
• Some have suggested that these ERN act as CE on an international level, but S. Aymé does not agree with this option

It was decided by RDTF that all these concepts must be communicated. This was successfully done by the Eurordis Workshop in Prague in July 2007. This has allowed patient organisations to become familiar with the concepts.

As most MS do not officially recognise CE within their healthcare systems, it is not yet possible to fully evaluate the varying experiences at the MS level. It should be decided how this analysis will be done once enough MS have had sufficient experience with this structure of care.

As a result of EC funding of 5 pilot network projects provide possible models of what will be
defined as ERN by the EC and serve as starting points for precisely defining ERN.

**RDTF 2006 Report on Centres of Expertise**
The RDTF previously reported that this area was very complex as the definition of many terms is very variable across MS:

- Definition of RD
- Definition of task of CE differs
- Definition of diseases covered differs

The RDTF recommended in their report for MS to explore all forms of cooperation as enforced by statements in the Communication.

The RDTF recommended that CE be created and recognised. Creating the concept of ERN will encourage MS to create them by proposing financial incentives. The RDTF also recommended that outcome measures be put in place in MS in which CE exist. This remains to be done.

For MS with no CE it was recommended to establish them, or at least to identify CE in other countries available (for example Luxembourg is too small to have its own CE). It was also recommended to establish electronic communication between centres.

RDTF also recognised the need to identify healthcare pathways, but that the needs of patients are sometimes contradictory. Patients want the best care, but also want this to be close to home. Often both are not possible.

RDTF recognises that in order to be identified, CE must receive additional funding as it is agreed that the designation as a CE requires additional work. Simply identifying CE is not enough.

RDTF recommendations to Commission were well accepted:
- Avoid wording Centre of Reference rather CE (applied).
- Support making information on CE available (as available on Orphanet).
- Fund pilot networks (has been done now for two calls)

Although the discussion on the elaboration of these concepts will continue, they require an enormous amount of dedication and should rather take the form of a EU funded project spanning several years. Encouraging the development of electronic tools necessary for the development of telemedicine in the field of RD is also an action that remains to be addressed.

- During the last meeting on CE it was agreed to make the topic of today:
  - Methods to assess the added-value of Centres of expertise
  - Reference networks of centres of expertise

**Discussion**
A. Fourcade described the designation and assessment process of CE in France. She encouraged that this process could be applied at the European level as many of the definitions used in France can be applied universally. She recognises that making strict definitions and criteria of ERN is probably not possible at European level, although at the least a consensus of the desired outcomes
of having ERN can be made if not an exact structure just yet.

A. Montserrat. The discussion of CE and ERN has been conducted by many groups:
- RDTF (distinction of EC role)
- HLG (mobility of patients)
- Eurordis (patients)
- 5 pilot projects (focused on their own research)
- Development of CE in MS (MS perspective)

All the discussions in the area that are not completely streamlined must be coordinated for addition into the Communication:
- Discussion of CE cannot be in the Communication
- All agree that European Commission:
  - Provides financing
  - Facilitates coordination
  - Recognises definition of ERN as flexible but structured
  - And supports the Advisory Committee (ie. group of experts similar to RDTF) as those who should be responsible for identifying ERN.

It is agreed by all that it is too soon to define this structure. Unfortunately, the opportunity of expressing this request in the Communication is immediate. It is not necessary to precisely define that structure but to open the discussion and cautiously define the method for the coming years. For example, the funding of a project to continue this discussion (in the style of EUROPLAN) could be suggested.

The Implementation Report accompanying the Communication in spring 2010 will be a place to re-evaluate the initially decided plan.

S. Aymé stated that the RDTF should publish a report on these concepts as up to now it has not been clear in any previously published documents.

E. Jessop agreed with this necessity and added that the confusion between CE and ERN occurs due to the fact that CE must be described in order to describe ERN. Additional overlap in the discussion between CE and ERN occurs because it must decide how membership of an ERN occur. Do we decide that anything that is recognised as a CE at the MS level can be a member of a network? Or do we introduce our own criteria? Do we use political criteria or scientific standards? It is already clear that assessing the value of networking is very difficult, although we all agree it is valuable, documenting it is very hard.

C. Nourissier stressed the fact that the Eurordis’ position on the added-value of ERN is to lessen the differences between CE at the national level.

M. Jespersen stated that ERN should not be too strictly defined. Who is to decide membership of ERN? It will not be easy to judge whether a CE is or is not good enough to join a network when public money will be used to pay for the networks.

V. Straub specified that it is important to distinguish between the establishment of a network and
what it will do when it is in place

M. Gattorno was surprised that there was no link between international learned societies and official ERN as learned societies are already established networks. He suggests that they be supported to continue the networking activities they already participate in, in a more official way.

L. Warren and L. Fregonese both asserted their opinion that we have the tools (over 200 EU level networks in place, several supporting documents) to create a background document that can guide MS to take action as they are eagerly awaiting these guidelines.

S. Aymé reminded members that based on the existence of previously established EU funded networks and other independently established networks, researchers and health professionals have not waiting for the RDTF’s guidelines to create networks. The applications for funding of these networks reflect the needs of their members: identifying the location of expertise, meeting and discussion to improve exchange of information for making guidelines and recommendations, establishing common databases or biobanks, etc. Some networks have even developed tools for submission of difficult cases, but no network of care centres exists for the cross border referral of patients. As such, the Commission should not force the creation of such a network?

E. Jessop agreed it is unclear why a few official ERN should be selected for funding by public funds when many professional networks already exist and function with their own support.

C. Nourrissier clarified that what distinguishes RD networks from other research networks is that RD networks must include social aspects. These aspects cannot be provided by research networks that, indeed, are working very well.

M. Jespersen questioned whether the creation of ERN would provide a solution to the lack of social assistance at the MS level. For example, in Denmark social care is provided to all patients (regardless of disease) based on need. This is a responsibility of the MS, not something that can be coordinated at the EU level.

D. Taruscio expressed the need to clarify the activities of CE into two categories (clinical care and research). By using the example of Italy, she described that patients are forced to attend certain clinics as they are the ones designated for free care (region by region). If we begin introducing the networking of these CE at the European level in terms of provision of care, we will run into trouble, as Italy and other MS are not going to restructure their reimbursement systems. The Commission must recognise the structure of the healthcare systems in MS already in place.

C. Nourrissier fully agreed that compensation of disabilities occurs at the local level. But what can be discussed at the European level is the knowledge available to all MS about the impact and complexity of the disease in the life of a patient. This knowledge will require the higher expertise at the EU level. The compensation for such impact will, indeed, be decided at the MS level.

V. Straub stated that the needs of RD patients (improved access to treatment, best standards of care) can only be met through multinational trials for which you need common assessment criteria, common standards of care, common standardized diagnosis. The “building blocks” of the
ERN are Standard Operating Procedures for diagnosis, assessment, definition of a database. These tools can be created by networks as they exist today. However, once these tools have been established the sustainability of these structures remains questionable. It is this level of funding that should be considered as a responsibility of the EC.

E. Jessop clarified that the discussion of research networking is a topic for DG Research. The discussion among RDTF members should focus on how the knowledge produced from such research can adequately implemented and equally available to professionals at the MS level with the support of DG SANCO.

F. Houyez clarified that RD patients do not ask for treatment on the EU level. Rather they ask that CE are required to include an element of social care so that standard of care is more harmonised from MS to MS (ie. a school doctor and teachers require some advice on how to take care of their RD students). Another request is the sustainability of CE and the lack of CE in each MS.

A. Montserrat clarified the fact that the title of Centre of Excellence and Networks of Excellence is reserved for research purposes funded by DG Research through the Framework Programmes, and should not enter the discussion. The focus of this discussion should be standards of care. Even if agreement on the criteria, selection, designation, etc. of CE and ERN is reached, there is no adequate budget to sustain such structures. The Communication provides and opportunity to demand such sustainable funding and he strongly advises that the recommendations brought forth by the RDTF in the Communication are not limited to scientific logic, patient needs, etc. Of course we should be cautious in the goals but to be more political and demand a long term calendar for such funding, i.e. continue funding of pilot projects, define needs in terms of sustainability, introduce a new structure of funding in 2014, etc.

E. Jessop suggested revisiting the rational for formalising the networking of CE. In most MS physicians are funded to care for their own patients and network with other national care centres to exchange expertise. A problem is introduced when the time spent networking is used to provide expertise mostly to other MS. It seems that these MS should be somewhat responsible for these services, and this is where the discussion should occur at the EU level.

S. Aymé agreed that the formalisation of networking is exactly the dilemma: do we really want to formalise this process or do we want to simply encourage the creation of guidelines that are then implemented at the MS level.

C. Nourissier feels that if the networks already, why not support for activities they are not able to accomplish.

It was agreed that support must address:
- Compensation for extra time spend by clinicians with foreign patients
- Additional training in MS to avoid the burden on clinicians to spend so much time with foreign patients.

**B. Draft Question of the High Level Group for Pilot ERN**
The Draft Questions prepared by the HLG for Pilot Networks were explored. Representatives of Pilot projects present at the meeting addressed the first questions concerning the establishment and development of their network. The specific questions included:

- How were partners of the network identified in the initial stage and how was the network formally established? Were the principles and criteria developed by the High Level Group so far taken into account?
- Is the network open for new partners and how are the potential new partners being identified or selected?
- What are the criteria to become a partner in the network?
- How is a centre and its capacity to become a partner in the network being assessed?
- How does the information about the network get to the potential partners, to the patients and other stakeholders (health professionals, patient associations, health authorities)?
- How is patient participation being ensured in the process of establishing and running the network?
- Can the network easily be expanded/transferred to other diseases?

**DYSCERN Network**
- Began as an informal network of clinicians in the field of dysmorphology already collaborating. When the call for proposal for such a network came along, the lead clinician, Jill Clayton Smith easily organised the formal network of clinicians for the DYSCERN project.
- The coordinating centre is in Manchester, with 5 other main partners. These 6 centres comprised the main coordinating bodies. They then met together to create an expert panel which included experts from CE to choose additional partners. Experts were invited representing each EU country through a peer-identification process (identification of partners with which they previously worked well)
- As the world of dysmorphology is so small, all the member experts have been collaborating for many years. Many good CE that were not chosen as part of the network because of a lack of previous communication. The network recognises that this may not be the best process by which to choose CE for a network. The coordinating team of the network believes that this system facilitates sustainability of a network, but that a lack of systematically using medical criteria to choose centres can result in the exclusion of some very good CE.
- Initial hierarchy was created in which there is a coordinating centre and five main partners. An expert panel evaluates the membership of additional centres which contribute their individual cases.
- A system of virtual diagnosis has been established in which patients are seen by their physicians in the centres, the cases are forwarded to the network and then an expert opinion is return to the primary physician to communicate to the patient.
- Is considering additional sources of funding as a contract of three years is insufficient to establish or sustain the network.

**Stichting Alpha 1 International Registry**
- The provision of care is left to a single centre.
- To enter the network, centres are required to have minimal standards, such as the ability to perform lung function and lung fusion capacity, but much of the networking has occurred as a result of previous collaborations in the field.
A Scientific Committee is established to evaluate based on minimum criteria, though no centres have been refused. Though a hierarchy (coordinator, treasurer, council, etc) exists, all decisions are made together and evaluation occurs informally during meetings which usually occur in conjunction with another larger conference. Only when new partners want to join the network do discussions of criteria arise. No formal quality management (three existing genetic labs that accomplish quality management with external funding) Receives some private funding for trials. Includes patient involvement, though it is too early to assess patient empowerment.

Treat NMD Neuromuscular Network
- Is somewhat different as it is an official network of excellence supported by RD research.
- Participating centres face challenges of language barriers and internet access
- Attempt to establish standards of care for as many neuromuscular diseases as possible so that patients have tool with which they can go to their primary practitioners or health care authorities and demand care.
- Consider becoming a legal entity (as opposed to a consortium with legal agreement) to more easily receive funding.

DebRA (National Charity for Epidermolysis Bullosa Patients)
- informal European network
- consists of professionals that have a longstanding history of working together in the field
- Despite the small size and informal nature of this group, some hierarchy exists.
- No exclusion of participating centres occurs as there is such a great need. Some centres certainly contribute more than others.

PRINTO Network
- Stems from Scientific Society for Paediatric Rheumatology. Criteria were used such as the number of patients, impact factor, to assess partners
- A steering committee supervises the proposal of new members
- Pharmaceutical companies provide the Society with funding, and the Society distributes this funding to centres

Prader-Willi Network
- is a network make up of parent and professional delegate in each EU country. Many of the professionals that are gathered would never have occasions to meet as they come from very diverse disciplines.

C. Financial Instrument for Funding ERN
The EU budget is defined by financial perspectives. No modifications to the Second Programme of Community Action in the Field of Health 2008-2013 are going to be made, although the creation of Operation Grants was intended to address the need for sustainability of previously establish networks. As such, goals must be established in the Communication (approved by the Parliament and Council) that will push the EC in 2013 to invest more funding for ERN and networking activities in general.
Workshop participants agreed that although quantitative data to support the beneficial affect of networking activities are not available, narrative examples can be included in the Communication (or as a separate report) to illustrate these benefits.

Workshop participants contributed their opinions on what specific activities should be funded in the scope of ERN:
S. Ayme – establishing electronic tools for sharing diagnosis and treatment options; meeting for consensus of best practice guidelines
C. Nourissier – disseminations of knowledge through conferences, for which patient organisations are a very good tool for such dissemination; creation of database and subsequent support
P. Griffiths – employment of a reliable coordinator and sufficient funding good quality applicants
L. Fregonese – databases must be sustained and further developed; training

D. Legal Issues
Workshop participants questioned whether these issues should be addressed by the Commission or left the responsibility of each individual network. As many of the legal issues that arise are not specific to RD, it seems as though the responsibility should rest with the Commission. The RDTF plans to assist the Commission in the production of such a document.

E. Conclusions
The input of all workshop participants and additional experts will be incorporated into a final report. The report will be presented to the HLG Working Group on ERN in July.
European Reference Networks in the Field of Rare Diseases:
State of the Art and Future Directions

Third Report

July 2008
I. Introduction

Due to the large number of rare diseases (RD), to their low individual prevalence, their severity, and to the scarcity of the information about each of them, the field of RD is one in which health needs faced by patients and their family is most acute. As such, it is also the field for which benefits of collaboration of expertise and maximisation of limited resources are most obvious.

As for all patients, the availability of expert local care for RD patients is ideal, but not always possible. The structure of such facilities implies a proximity to patients, limitation in patient capacity, and location in an area dependant on the patients’ health care system for reimbursement purposes, or in a more distant area but within the framework of an agreement between centres for healthcare delivery. The complexity and chronic nature of RD requires multidisciplinary care and expertise that is often not available at the local level. But having to attend a clinic located in a foreign country can create several negative outcomes. Travelling to distant clinics requires patients to face an additional financial burden, obliging them to travel mostly at their own expense. Psychological burdens due to consultation in a foreign language and the lack of support when far way from family and community are possibly introduced. The cost of care may not be covered at all by health insurances from the country of origin. The global cost of care may be much greater than it would be in a local clinic, without significant benefit for the patient.

As such some Member States (MS) have identified hospitals throughout their respective countries that serve as physical expert structures for the management and care of RD patients at the national level; tackle rare diseases or other conditions requiring specialised care; serve as research and knowledge centres; update and contribute to the latest scientific knowledge; and treat patients mostly in a local catchment area, but also patients seeking care from other regions of the country. In some cases these centres are officially recognised as such and called centres of reference, centres of expertise, reference centres, expert centres, centres of excellence, etc. For the purposes of this and all future discussions they will be referred to as Centres of Expertise (CE).

The establishment of a CE for each rare disease in each MS is an unrealistic concept and the scarcity in the scientific community’s knowledge of RD and the inadequate attention given to them by national competent authorities only further limits the abundance of such centres. As such, further collaboration at the European level in RD patient care is necessary.

The European Union is charged with responsibility of complementing, supporting, and adding value to the policies of the MS with the goal of encouraging healthcare systems based on solidarity, equality and accessibility and contributing to increased prosperity in the European Union by protecting and promoting human health and safety and by improving public health. Respecting the principle of subsidiarity and the responsibility of MS for the organisation and management of their health care systems, the creation of European Reference Networks (ERN) – physical or virtual networking of knowledge and expertise – can provide a high added-value for RD given the limited number of patients and scarcity of expertise at the national level despite the existence of CE.

Due to the varying definition of RD from MS to MS, differing healthcare structures, and different definitions of what constitutes a centre as a CE, a ERN consisting of individual CE will also reflect
this variability\textsuperscript{1}. Variability will additionally result from differences among the diseases in question, the experts involved (their expertise and interests) and the needs expressed by patient, researchers, and healthcare professionals. It is, therefore, very challenging to establish a common definition of an ERN and furthermore difficult to establish criteria of how to carefully select, create or assess ERN in a field where resources are limited.

In 2004, DG SANCO established the High Level Group on Health Services and Medical Care as a means of taking forward the recommendations made in the reflection process on patient mobility. One of the working groups of this High Level Group (HLG) is focussed on European Reference Networks (ERN)\textsuperscript{2} and is chaired by the French Ministry of Health. This HLG Working Group on ERN has solicited contributions from Rare Disease Task Force (RDTF) regarding the discussion of ERN.

The RDTF published already two reports, in September 2005 and in March 2007, which can be retrieved for the RDTF website. These reports were used by the HLG to define its own analysis of the current situation and its proposition for the future. They were also instrumental in designing the call for proposals for pilot ERN.

The RDTF working group on Standards of care decided to continue exploring this issue as many concepts are still not stabilised. The current report is the result of the work done since the second report published in March 2007.

A preliminary Working Document was drafted by the scientific secretariat of the RDTF and served as a basis of discussion for the 5\textsuperscript{th} Workshop on Centres of Expertise of the Standards of Care RDTF Working Group held in Paris in March 2008. This workshop served as an appropriate forum to discuss the definition, identification and assessment of ERN as all affected stakeholders are present (Annex 1). Conclusions of the discussion were incorporated into the preliminary report and validated by workshop participants. Finally, the report was sent to RDTF members and to coordinators of all EU funded networks in the field of rare diseases (Annex 2) for their contribution. Ultimately the recommendations in this document can serve to guide the actions concerning ERN at the Commission level.

\section*{II. Centres of Expertise}

RD are severe, chronic, incapacitating diseases and require specialised, significant, and prolonged treatment. A CE for a rare disease or a group of rare diseases brings together a group of multidisciplinary hospital-based competences, organised around highly specialised medical teams.

The DG SANCO funded Rare Disease Task Force (RDTF) was charged with providing a report\textsuperscript{3} on the current situation of CE in Europe to the High Level Group on Health Services and Medical Care Working Group on European Reference Networks. Their work revealed the following analysis.

\begin{itemize}
\item \textsuperscript{1}Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force <http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf>
\item \textsuperscript{3}Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force <http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf>
\end{itemize}
a. Definition of a Centre of Expertise in European countries

There is no common definition of what a CE is among MS which have established such centres. Even among countries with official CE, the definition of a rare disease varies between CE. The UK uses 1 in 50,000, Sweden and Denmark use 1 in 10,000 whereas France, Italy and Spain use the European orphan drugs regulation definition of 1 in 2,000. Regardless of the definition used, a large prevalence of diseases qualifying as rare exists in Europe.

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

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

The CE differ in form from one country to another:

- in form (reflecting the heterogeneity of national health systems)
- in focus (some CE specialise in one RD, some in several RD with similar needs, some on technologies shared across several RD)
- in the process used to identify, select and designate them (some have a specific policy regarding RD and have established CE in this framework (Bulgaria, Denmark, France, Italy, Sweden); some have established CE but not specifically for rare diseases (Belgium, Croatia, Czech Republic, Finland, Greece, Ireland, Portugal, Spain, UK); and some have no centres with these denominations, although they have centres with all characteristics of a CE (Austria, Cyprus, Estonia, Germany, Hungary, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Serbia, Slovakia, Slovenia, Switzerland, Turkey).

b. Suggested Criteria Used to define a centre as Centre of Expertise

As agreed upon by HLG and the RDTF, the following criteria should define CE:

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

Additional publications on CE are listed in Annex 3.

c. The Added-value of Centres of Expertise

The reason for designating CE differs from one country to another. In principle, there are two main purposes for officially identifying specific resource centres. The first is to provide a rating scheme that enables consumers to identify the appropriate healthcare resource for their case. The overall objective of a rating scheme is to guide consumers to trustworthy health information and empower them to select high-quality services for referral. It is recommended that the same rating scheme be used in all MS.

The second purpose of designating CE is to enable healthcare managers to identify where best to allocate specific financial resources in order to support the additional activities linked to the duties of these centres. This is because designated centres have both rights and duties that require additional staff and resources. It is well established that the designation of a centre as a CE increases its referral rate and the number of requests for expert opinions. In addition, CE must be actively involved in clinical research, issue best practice guidelines and produce information leaflets for patients; all these activities require additional resources that can only be allocated by national authorities at the MS level.

d. Assessing Centres of Expertise

As most MS do not officially recognise CE within their healthcare systems, it is not yet possible to fully evaluate the varying experiences at the MS level. However, several MS recognising CE have established measures to assess the added-value of CE and their findings should be noted.

Denmark established two designated centres for rare diseases at the university hospital level in addition to 100 specialised clinics. The final selection is done by the National Board of Health after consultation of the learned societies, the administrations and patient organisations. In 2003, Rare Disorders Denmark, the Danish national rare disease alliance, carried out a survey among 900 people suffering from rare disorders to investigate the scope of health care offered to patients with rare disorders and their overall satisfaction with their course of treatment in CE. Although only 33% of RD patients reported being treated at a CE, those receiving care at a CE were more satisfied with their treatment and individual actions plans were a significant factor.

Within the English National Health System, there are two tiers of commissioning (planning, funding and monitoring) for specialised services. The determining factor is the specialist skills required rather than the rarity of the disease. The lower tier of specialised commissioning is determined by a definition set of specialised services available on the National Health System website. These services are commissioned by 10 bodies in England (the specialized commissioning groups) each responsible for a population of about 5 million people. The higher tier of national services is commissioned by the National Commissioning Group. This tier includes procedures, medical and mental health services, and diagnostic services. The threshold for national commissioning is fewer than 1000 patients in England - equivalent to 0.2 per 10,000 population. Great emphasis is placed on monitoring clinical
outcomes in the nationally commissioned services. Outcomes of surgery (for example portoenterostomy for biliary atresia) and other interventions (for example interventional radiology for malformation of the Vein of Galen, or gene therapy for immunodeficiency disorder) are monitored for all patients treated – a 100% consecutive case series. There is however difficulty in defining appropriate outcomes for some rare and untreatable disorders (for example epidermolysis bullosa and Alström syndrome). For the diagnostic services (for example primary ciliary dyskinesia) emphasis is placed on external inspection and accreditation (CPA) and external quality assurance systems (EQAS). There are separate health systems in Scotland, Wales and Northern Ireland.

France is the only MS to recognise CE within the framework of a national plan on RD. In France, CE apply annually through a competitive call for proposals. As of 2008, 132 CE have been established. Each centre is designated for five years, with a mid-term self evaluation after three years and an external evaluation after five years by one RD expert and one representative of the French National Authority for Health to determine renewal of funding.

As has been the experience in France, the success of such assessment strategies is contingent on the fact that it be disease-specific, centre-specific, and above all, specific to the healthcare system in question.

**e. Recommendations**

Given the variability of CE across Europe, networking activities and cooperation are one solution in the provision of the highest quality of services for the widest audience. As such, the RDTF Working Group on Standards of Care recommended in their report ⁴ that:

- MS having a policy for establishing national or regional CE for RD agree as much as possible on an operational definition of what is a CE and on how to designate them.
- MS with established CE should be encouraged to share their experience and the results of their outcome measures.
- MS not having a policy regarding the establishment of CE for rare diseases, find an appropriate way to organise their health care system to serve the needs of patients, either through the establishment of CE or through contracting with other CE abroad (not too distant if possible), and developing electronic communication between local clinics and CE from all over Europe.
- MS contribute to the identification of their expert centres and support them financially as much as possible.
- MS 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.

The RDTF Working Group on Standards of Care also recommended in their report that:

- the European Commission play an important role in promoting the identification of centres of expertise and in the diffusion of the information about them.

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These recommendations were agreed upon by all Workshop Participants (Annex 1).

### III. European Reference Networks

The creation of European Reference Networks (ERN) – physical or virtual networking of knowledge and expertise – can provide a high added-value for RD given the limited number of patients and scarcity of expertise at the national level despite the existence of CE. Developing European collaboration for the delivery of health care and medical services in the field of RD has major potential in bringing benefits to European citizens by:

- overcoming the limited experience of professionals confronted with very rare conditions (including improved diagnosis, care, clinical research, and knowledge)
- improving access for EU citizens to treatment requiring a particular concentration/pooling of resources (infrastructure and knowledge) or expertise,
- offering patients the highest possible chance of success through sharing of expertise and resources,
- maximising cost-effective use of resources by concentrating them where appropriate,
- helping to share knowledge and provide training for health professionals,
- acting as benchmarks to help develop and spread best practice throughout Europe,
- providing to small countries with insufficient resources from their health care sector, a full range of highly specialised services of the highest quality.

Due to the varying definition of RD from MS to MS, differing healthcare structures, and different definitions of what constitutes a centre as a CE, ERN consisting of individual CE will also reflect this variability.

Variability will additionally result from differences among the diseases in question, the experts involved (their expertise and interests) and the needs expressed by patient, researchers, and healthcare professionals. It is, therefore, very challenging to establish a common definition of an ERN and furthermore difficult to establish criteria of how to carefully select, create or assess ERN in a field where resources are limited. It is possible, however, to distinguish in general between two possible types of networking activities: those that concern research and those that concern public health issues. In addition, funding for research and for public health policy making comes from different sources (DG Research and DG SANCO respectively). It is, therefore, logical to discuss these two types of networks separately with regards to their specific objectives, despite the fact that the CE are always mixed structure.

#### a. Structure of a European Reference Network

Whether it be for research or public health issues, on an abstract level, a network consists of nodes plus links between the nodes. A network is a European network when its nodes (CE) are located in more than one European country, though not necessarily every European country. The network encompasses the whole of Europe, because patients in every European country can benefit from the network. The CE are the nodes, and the links between them are communications. Thus, a network of CE is characterised by communication between the CE in the network. These communications may be electronic or face-to-face (at a meeting or conference). Communication in the network will
normally be from any node to all other nodes *i.e.* from one CE to all of the other CE. Occasionally communication may be private, from one centre to a subset of the other centres, but this will not be the norm. Communication may be needed to develop a consensus and CE are members of the network because they communicate in this way. CE which do not share ideas and opinions are not active members of the network. It is the sharing of expert opinion and ideas which provides the key benefit of the network. Within the network the nodes are equal; there is no hierarchy between CE, although one of them acts as coordinator on behalf of the others.

In summary, following characteristics of the ERN were agreed upon as guiding the discussion of ERN:

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

**b. Defining the Objectives: two types of networks**

In reality, however, the structure of a ERN is not so simple. Networking in any field is the result of a voluntary collaboration of professional, each with different needs, preferences, expertise, and experience. Their partnership is an evolving process; the result of a history of successful cooperation and mutual understanding of future progress.

**Research Networks**

In the field of RD research, groups of professionals spanning several European MS agree to collaborate, and most apply for competitive funding through the Framework Programmes of DG Research⁵.

An ERN focusing on research may:

- share data through the systematic collection of patient data
- establish repositories of biological samples
- share expertise for research purposes

Several projects funded under the DG Research Seventh Framework Programme illustrate such research networking activities.

The European Integrated Project on Spinocerebellar Ataxias (EUROSCA)⁶ aims to develop an international standard on the clinical evaluation based on clinical rating scales, structural imaging, and electrophysiology. The creation of the European SCA Registry (EUROSCA-R) will ensure standardized data acquisition and facilitate continuous recruitment of SCA patients throughout Europe for linkage analysis, identification of novel ataxia genes, natural history studies, and eventually genotype-phenotype correlations. This search for genetic modifier factors in SCA will allow a better comprehension of factors accounting for wide clinical variability with application for

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⁵ A collection of existing RD networks funded by the EC has been created by Orphanet.

prognosis and to identify new potential targets (modifier genes) for delaying the age at onset or disease progression. EUROSCA will also implement strong research projects to generate and characterize cellular and transgenic models, which will allow a more defined study of the pathogenesis and will serve as a tool for first therapeutic studies. Training programs will complement research efforts and clinical work.

European Research Network for Alternating Hemiplegia (ENRAH)\(^7\) aims to coordinate, support and promote educational and research activities in Alternating Hemiplegia in Childhood (AHC) by establishing a European multidisciplinary research network, setting up a web-based registry of AHC cases in Europe, identifying relevant SMEs and integrating them into the network’s activities, and collecting project ideas and research profiles of SMEs working in AHC.

The Prader-Willi Syndrome: gene expression, obesity and mental health Specific Targeted Research Project\(^8\) aims to integrate molecular biological studies and establish the basis for an EU wide clinical study of PWS. By establishing a standardised database, specifically designed for PWS, it will enable the collection of clinical data across the EU in a manner that will allow, in the future, the investigation of genetic and other influences on the development of people with PWS across all ages, thereby complementing the molecular biological studies that will identify the neurobiological mechanisms and signalling pathways that mediate between genotype and phenotype. The project will contribute to the understanding of early development and increase the comprehension of basic mechanisms responsible for obesity and severe psychotic illness in the general population. Given the high morbidity and mortality rate associated with having PWS, the project will provide the basis for clinical studies that will then establish a benchmark for early diagnosis as well as for best practice in the health and social care of people living with PWS. These findings will be disseminated through scientific and practice-based journals and in collaboration with the EU National PWS Associations who are partners in this study. Ultimately a model for the multidisciplinary investigation of other rare disorders in the EU may be developed.

**Public Health Networks**

Health care professionals spanning several MS may also collaborate to:
- share clinical experience to sort out difficult individual cases
- produce clinical guidelines based on their shared clinical experience
- produce information for patients or professionals in the form of a library of answers to frequent queries

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

The European Network of Centres of Expertise for Dysmorphology (DYSCERNE)\(^9\) aims to raise standards for the diagnosis and best practices for care of dysmorphic syndromes through the creation of the Dysmorphology Diagnostic System. This system will enable clinicians in the network to

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\(^7\) European Association for Research and Alternating Hemiplegia. <http://www.enrah.net>
electronically submit cases for diagnosis by uploading photographic images and results of investigations including imaging studies to a secure, searchable archive. Recommendations and opinions from the expert diagnostic panel will be collated and sent back to the referring clinician.

For other RD such as Cystic Fibrosis, considerable information about the disease exists, though not equally for all health professionals and patients all MS. In the framework of the European Centres of Reference Network for Cystic Fibrosis (ECORN-CF) project, collaborating partner-countries provide expert advice to their patients and care team members in their mother language on a local website. After translation of questions and answers in English they are published on a central website with open access for everybody who is interested in the topic. Thus, a transfer of knowledge and expertise throughout Europe will guarantee the same level of expert advice in all partner countries and avoid long travel to distant Cystic Fibrosis CE.

Still other networks focus on the establishment of standards of care and promote earlier diagnosis. To this end, the Patient Associations and Alpha1 International Registry (PAAIR) members collect and store cross sectional, prospective data on general health and disease-related items in an existing online database. The idea is to analyse the network’s impact on the disorder’s morbidity and mortality and early diagnosis. This will be achieved by comparing the standards of the centres already in the AIR network and the centres identified in the new EU countries with the requirements established by the HLG. The group will set up interaction between national patient and doctor/scientist bodies (AIR), to generate a model of doctor-patient interaction in three EU countries (the Netherlands, Italy and Germany).

As illustrated by the examples above, separate networks for specific RD or conditions (or groups of RD) ensure optimal focus of expertise as opposed to single networks for all RD or rare conditions.

If, indeed, a legal instrument is established to provide continuous support to ERN they can realistically be expected to:

- allow multi-centre clinical studies as well as partnership with pharmaceutical companies;
- provide shared research resources: databases, biological resources (DNA, RNA, tissues, cells), registries (harmonisation of standard operating procedures), international epidemiological surveillance and pharmacovigilance;
- be instrumental in promoting education and training activities. In partnership with patient organisation, they will provide information and communication outreach activities towards the public, but also the primary health care professionals in order to improve referrals and follow up. Training activities for health professionals includes staff exchanges, meetings and conferences to exchange best practices, harmonise processes and disseminate standards and guidelines;
- cooperate closely with patient organisations who should be actively involved in the management and evaluation of both CE and ERN as experts for the production of information documents, guidelines for diagnostic and care, the choice of the research tools and clinical trials to be performed within the networks.

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

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

c. Selection for funding of ERN and Assessment of ERN

Criteria for selecting ERN are set out above. Their application to specific situations, however, requires significant expertise and knowledge of the current international situation. The HLG and the RDTF each propose different schemes for such evaluations.

The HLG Working Group on ERN has also produced a Draft Procedure for the Identification and Development of ERN. The draft procedure describes three proposals for the identification and development of ERN. The document proposed the modification of the current system of selection and describes two top down approaches in which a Committee of the MS on ERN (i.e. the current HLG Working Group on ERN) in close collaboration with the EC and competent national authorities, identifies ERN to be continuously supported by the EC.

The RDTF bases its proposal of selection and of evaluation on the reality of the previously funded pilot ERN and DG SANCO funded research networks. In this framework collaborations occur because of voluntary application. Although their application for funding occurs in a competitive way, it does not guarantee that the most appropriate CE are initially selected to join the network. These decisions occur between researchers because of acquaintance, similarity in needs and interests, and a history of working well together. Respecting the principle of subsidiarity and taking into account the reality of networking in the field of RD it seems that guaranteeing the best CE to network and apply for funding at the EC level will be difficult. Continued compliance with the selection criteria can also only be ensured of funding for such networking remains competitive.

IV. Conclusion

Given the variability of health systems in each country involved, differing definitions of RD in each MS, and varying focuses of CE as a result of expertise of coordinators and needs of patients, it is difficult to suggest a unique structure for all possible ERN.

The DG SANCO-funded European Reference Network Pilot Projects provide an opportunity to assess the relevance of the procedures and criteria proposed by the HLG Working Group on ERN and

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12 Draft Procedure for the Identification and Development of ERN.
the RDTF. The HLG Working Group on ERN has produced Draft questions\textsuperscript{13} for each project leader of the pilot ERN projects. Analysis using these questions is anticipated to be carried out in two steps in which project leaders first provide provisional answers to questions concerning the preliminary stages of the establishment of their networks and then complete answers once the projects were complete or sufficiently progressed that practical experience was gained. Until a more thorough analysis of the experience of the Pilot Networks is possible, questions that remain include:

- How can the ERN of highest quality be selected?
- How will CE be selected as members of the ERN?
- Will the designation of a few ERN introduce a limitation when other successful networks also exist?
- How can a new instrument to ensure long-term funding be agreed upon while keeping the spirit of high quality research through a competitive application process?
- How do we ensure that selected networks truly comply with agreed criteria on a long-term basis?
- Who will address new questions and obstacles that arise from such pan-European collaborations such as the question of medical liability in virtual clinics?

Finally, direct indicators to measure the European added-value of ERN must be specifically identified for each type of network. It should be recognized that these indicators may change according to the experience of the DG SANCO pilot projects and other existing networks in the field of RD and could be different for each ERN.

The current recommendations of the RDTF for the European Commission include that it:

- continues its financial support networking of centres of expertise in the field of RD until an evaluation of the output of the networking process demonstrates that it is not cost-effective (which is extremely unlikely)
- opens its call for proposals to the definition of a methodology to assess the benefit of such networks from the perspective of the different stakeholders
- encourages, by all possible means, the development of electronic tools necessary for the development of telemedicine in the field of rare diseases.
- encourages the production of legal and ethical guidelines for participants of any European network involving patients
- with the cooperation of clinicians, patients, network coordinators, MS health authorities reconsiders the assessment of the added-value of ERN after:
  - Additional findings from the experience of the pilot projects\textsuperscript{14}
  - Learning from the experience of existing collaborations in the field of RD (Annex 2)
  - Continued identification of CE across Europe

\textsuperscript{13} HLG/COR/2007/5 REV1 Draft set of questions for each project leader of the pilot projects on European reference networks

\textsuperscript{14} DG SANCO – Public Health, European Reference Network pilot projects.


<http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm#4>
Annex 1
Participants
RDTF Workshop: Assessing the Added-Value of European Reference Networks
March 11, 2008 - Paris, France

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Annex 2

Existing Networks in the Field of Rare Diseases

- Curing autoimmune disease; a translational approach to autoimmune diseases in the post-genomic era using inflammatory arthritis and myositis as prototypes and learning examples (AUTOCURE)
- Paraneoplastic Neurological Syndromes (PNS) strengthening the European network (PNS-EURONET2)
- European Renal Genome Project (EUREGENE)
- Using European and international populations to identify autism susceptibility loci (AUTISM MOLGEN)
- Control of Intracellular Calcium in Arrhythmias (CONTICA)
- European Coordination Action for Research in Cystic Fibrosis (EUROCARECF)
- Integrated project to decipher the biological function of peroxisomes in health and disease (PEROXISOMES)
- Congenital disorders of glycosylation: a European network for the advancement of research, diagnosis and treatment of a growing group of rare disorders (EUROGLYCANET)
- Neuroprotective strategies for multiple sclerosis (NEUROPROMISE)
- Functional genomics of the retina in health and disease (EVI-GENORET)
- Adult mesenchymal stem cells engineering for connective tissue disorders. From the bench to the bed side (GENOSTEM)
- Rational Treatment Strategies Combating Mitochondrial Oxidative Phosphorylation (OXPHOS) Disorders (EUMITOCOMBAT)
- NOVEL APPROACHES TO PATHOGENESIS, DIAGNOSIS AND TREATMENT OF AUTOIMMUNE DISEASES BASED ON NEW INSIGHTS INTO THYMUS-DEPENDENT SELF-TOLERANCE (EURO-THYMAIDE)
- Genetics of coenzyme Q deficiency in humans (UBIGENES)
- Improved precision of nucleic acid based therapy of cystic fibrosis (IMPROVED PRECISION)
- Concerted Safety & Efficiency Evaluation of Retroviral Transgenesis in Gene Therapy of Inherited Diseases (CONSER)
- An integrated immunological and cellular strategy for sensitive TSE diagnosis and strain discrimination (TSEUR)
- Pulmonary Hypertension: Functional Genomics and Therapy of Lung Vascular Remodelling (PULMOTENSION)
- Neutralizing antibodies on Interferon beta in Multiple Sclerosis (NABINMS)
- Development and application of transposons and site-specific integration technologies as non-viral gene delivery methods for ex vivo gene-based therapies (INTHER)
- From molecules to networks: understanding synaptic physiology and pathology of the brain through mouse models (EUSYNAPSE)
- Nuclear Envelope-linked Rare Human Diseases: From Molecular Pathophysiology towards Clinical Applications (EURO-LAMINOPATHIES)
- Ex vivo gene delivery for stem cells of clinical interests using synthetic processes of cellular and nuclear import and targeted chromosomal integration (SYNTHEGENEDELIVERY)
- Prevention, diagnosis and molecular characterisation of mismatch repair defect-related hereditary cancers of the digestive system (MMR-RELATED CANCER)
- Normal and abnormal cardiac excitation: generation, propagation, and coupling to contraction (NORMACOR)
- European network to promote research into uncommon cancers in adults and children: Pathology, Biology and Genetics of Bone Tumours (EUROBONET)
- Combined isolation and stable non-viral transfection of hematopoietic cells- a novel platform technology for ex vivo hematopoietic stem cell gene therapy (MAGESELECTOFECTION)
- Biocompatible non-viral polymeric gene delivery systems for the ex vivo treatment of ocular and cardiovascular diseases with high unmet medical need (POLEXGENE)
- Mitochondrial diseases: From bedside to genome to bedside (MITOCIRCLE)
- Autoimmune polyendocrine syndrome type I - a rare disorder of childhood as a model for autoimmunity (EURAPS)
- CONnective Tissue Cancer NETwork to integrate European Experience in Adults and Children (CONTICANET)
- Insights into novel therapeutic strategies for a nuclear inclusion disease caused by polyalanine expansion (POLYALDA)
- Ovarian Cancer - Diagnosing a Silent Killer (OVCAD)
- PROgnosis and THERapeutic targets in the "Ewing" family of Tumours (PROTHETS)
• Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe (EUROPEAN LEUKEMIANET)
• Special Non-Invasive Advances in Foetal and Neonatal Evaluation Network (SAFE)
• European integrated project on spinocerebellar ataxias: Pathogenesis, genetics, animal models and therapy (EUROSCA)
• Wilson Disease: Creating a European Clinical Database and designing multicentre randomised controlled clinical trials (EUROWILSON (EUROCOPPER))
• CELLS INTO ORGANS: FUNCTIONAL GENOMICS FOR DEVELOPMENT AND DISEASE OF MESODERMAL ORGAN SYSTEMS (CELLS INTO ORGANS)
• European Consortium for Stem Cell Research (EUROSTEMCELL)
• Episomal vectors as gene delivery systems for therapeutic application (EPI-VECTOR)
• Molecular optimization of laser/electrotransfer DNA administration into muscle and skin for gene therapy (MOLEDA)
• Genetic testing in Europe - network for test development harmonization, validation and standardization of services (EUROGENTEST)
• Development of new methodologies for low abundance proteomics: application to cystic fibrosis (NEUPROCF)
• Ex vivo gene therapy for recessive dystrophic epidermolysis bullosa: pre-clinical and clinical studies (THERAPEUSKIN)
• Gene therapy for Epidermolysis Bullosa: a model system for treatment of inherited skin diseases (SKINTherAPy)
• Rare genetic skin disease: advancing diagnosis, management and awareness through a European network (GENESkin)
• DNA electrotransfer of plasmids coding for antiangiogenic factors as a proof of principle of non-viral gene therapy for the treatment of skin disease (ANGIOSKIN)
• Prader-Willi syndrome: a model linking gene expression, obesity and mental health (PWS)
• From stem cell technology to functional restoration after spinal cord injury (RESCUE)
• Multi-organismic approach to study normal and aberrant muscle development, function and repair (MYORES)
• Molecular mechanisms of neuronal degeneration: from cell biology to the clinic (NEURONE)
• Advances in hearing science: from functional genomics to therapies (EUROHEAR)
• ERA-Net for research programmes on rare diseases (E-Rare)
• RDTF - Scientific secretariat of the Rare Disease Task Force (RDTF)
• European Network For Rare And Congenital Anaemias (ENERCA)
• European Myasthenia Gravis Network (EUROMYASTHENIA)
• European Autism Information System (EAIS)
• Rare Disease Patient Solidarity RAPsody
• Towards the development of an effective enzyme replacement therapy for human alpha- mannosidosis (HUE-MAN)
• Novel molecular diagnostic tools for the prevention and diagnosis of pancreatic cancer (MOLDIAG-PACA)
• Development of a pre-clinical blood test for prion diseases (ANTEPRION)
• Translational research in Europe - Assessment and treatment of neuromuscular diseases (TREAT-NMD)
• Genetic control of the pathogenesis of diseases based on iron accumulation (EUROIRON1)
• Embryonic stem cells for therapy and exploration of mechanisms in Huntington disease (STEM-HD)
• Chimaeric T-cells for the treatment of paediatric cancers (CHILDHOPE)
• Selecting and validating drug targets from the human kinome for high risk pediatric cancers (KIDSCANCERKinome)
• Soft tissue engineering for congenital birth defects in children: new treatment modalities for spina bifida, urogenital and abdominal wall defects (EUROSTEC)
• Amplification of human myogenic stem cells in clinical conditions (MYOAMP)
• Systemic Amyloidoses in Europe (EURAMY)
• Development of models to improve management of Myasthenia Gravis: From basic knowledge to clinical application (MYASTAID)
• Small ligands to interfere with Thymidylate synthase dimer formation as new tools for development of anticancer agents against ovarian carcinoma (LIGHTS)
• Development of novel management strategies for invasive aspergillosis (MANASp)
• Identification of early disease markers, novel pharmacologically tractable targets and small molecule phenotypic modulators in Huntington's Disease' (TAMAHUD)
• Pathophysiology of the cartilage growth plate (EUROGROW)
• Diamond to retina artificial micro-interface structures (DREAMS)
Annex 3

Publications about Centres of Expertise and European Reference Networks

European Organisation for Rare Centres of Expertise and European Reference Networks for Rare Diseases. Eurordis Specific Contribution to the Public Consultation: "Rare Diseases: Europe's Challenges". February, 2008


Rare Disease Task Force. Overview of Current Centres of Reference on Rare Diseases in the EU. September, 2005
d. Health Indicators Working Group Meeting Minutes

Minutes

Meeting of the Rare Disease Task Force
Health Indicators Working Group
Workshop on Health Indicators for Rare Diseases
Paris – March 12, 2008

On 12 March 2008, the meeting of the Rare Diseases Task Force (RDTF) Working Group (WG) on Health Indicators included the attendance of:

S. Aymé  M. Mazzacuto  S. Tanner
J. Donadieu  A. Montserrat  A. Trama
L. Fregonese  M. Posada  H. Trang
G. Gatta  J. Sándor
A. Kole  A. Schieppati
O. Kremp  D. Schönfeld
Y. Le Cam  S. Simpson

A. Welcome and Introduction

The meeting was opened with an introduction of the context of the discussion. A collaborative European effort is always needed in the field of rare diseases (RD), and in particular for health indicators (HI) of RD as their impact on public health is unclear due to the lack of visibility in monitoring systems. The Communication on a European Action in the Field of Rare Diseases pays significant attention to the visibility of RD encouraging the compilation of existing sources as well as the definition of a realistic and meaningful set of indicators in the areas of orphan drug availability and accessibility, centres of expertise, and RD policy initiatives at the MS level.

Additional indicators of special interest to the field of RD include mortality age, survival rate from diagnosis, duration from first symptoms to diagnosis, related morbidity, and health expectancies. The following past and ongoing EU-funded projects were presented as contributing to the monitoring of RD HI:

- ECHI and ECHIM: European Community Health Indicators (Monitoring) projects
- ICHI: International Compendium of Health Indicators
- ISARE: Health Indicators in the European Regions
- EUPHIX: European Public Health Information, Knowledge and Data Management System
- EUROTHINE: Tackling Health Inequalities in Europe
- EHEMU: European Health Expectancy Monitoring Unit

Additional potential sources of data include:

- Registries
- Death certificates
B. Selection Process

As “classical” indicators do not apply in the field of RD due to inadequate coding of RD, the categories of HI for RD would ideally include:
- contribution of RD to morbidity and mortality
- socio-economic impact
- availability of appropriate Health Services
- state of the art in information, research, technology development
- monitoring of geographical differences in Europe
- enabling surveillance of status and trends over time

It was proposed that a pilot list of RD is chosen to begin this collection of data.

European Commission

The action of the EC in the field of HI in the coming years includes two main actions
- the EC, Council and Parliament to have a stable set of HI (for all diseases) standardized at the EU level
- collection of HI data should be an EU action in the field of RD.

In this pursuit, a Working Group on HI was established and is supported by a secretariat, European Community Health Indicators Monitoring (ECHIM). This group has established a list of 40 HI for which all MS are in consensus and are obligated to report on.

Such standardization among MS will not be possible in the field of RD, however, the EC supports this action in the field of RD despite this limitation.

Discussion

Participants discussed specific indicators within each category of HI listed above. Conclusions of this discussion were incorporated into the updated version of the report, Health Indicators for Rare Diseases: Working Document for the Rare Disease Task for Health Indicators Workshop - March 12, 2008.

Contribution to Morbidity and Mortality
1. Prevalence: measured by Orphanet by phenotype
2. Incidence: should be documented in addition to prevalence but for different applications
3. Mortality: as illustrated in feasibility study by INVS (O. Kremp) death certificates are not accurate sources of this data. But as they are a source that exists, they should be used with
caution. EUROSTAT will be asked to analyse the quality of this data source through another feasibility study.

4. Hospital admissions: not currently collected by EUROSTAT but collections could be appropriate for pilot study.

**Socioeconomic Impact**

1. Contribution to consanguinity: genetic services may be a source; the action would be educate populations in which this is frequent and present available services
2. Impact on families (economic, social, psychological): helplines may be a possible source (Eurordis)
3. Annual budget to cover orphan drugs: Eurordis is currently monitoring this

**Availability of Appropriate Health Services**

1. Genetic tests: certified labs, accredited labs, and availability of genetic counselling clinics could be measured. This would be a good way to encourage all MS to recognise genetic counselling as a medical speciality.
2. Number of diseases for which there is a biological test: measured by Orphanet
3. Impact of prenatal diagnosis on birth prevalence: measured by EUROCAT
4. Identify expert clinics: difficult to define expert clinic therefore too difficult to measure for the moment
5. Age at diagnosis: use biological tests as proxy and focus only on RD for which delay at diagnosis is deleterious.
6. Proportion of patients at home or in institutions: to difficult to measure
7. Availability of orphan drugs among those with EMEA approval: currently monitored by Eurordis
8. Number of Patients’ organizations and of diseases covered: Eurordis
9. Availability of Helplines for RD: lack of agreement on quality of data and whether the use of helplines should also be monitored

**Availability of Appropriate Health Services**

1. Number of RD with a specific code in ICD: will be published but not any time soon
2. New Orphan products approved by the EMEA
3. Call for proposals for research into RD: possible on EU level but not on MS level
4. RD for which good practice guidelines are available
5. RD for which there is a registry, geographical coverage
6. RD for which there are on-going clinical trials: EC will be asked for this information

**Equity, regional differences, EU initiatives**

1. Countries with specific funding processes and Plans for RD: in the field of research, in the field of information, in the field of clinical care (CE, orphan drugs), in the field of testing
2. European reference networks for RD
3. European registries
4. EU Funding programs for research and public health in RD
5. Courses, meetings, and seminars in RD

These indicators may be monitored for information, but not many conclusions can be made.
**Surveillance of Status and Trends**
1. RD for which a diagnostic test exists (genetic, biochemical, other)
2. Laboratories accredited for genetic testing
3. Neonatal screenings
4. Prenatal diagnosis
5. Diagnosis delay
6. Perceived health (QoL)
7. People at home or in institutions
8. New Orphan products approved by EMEA
9. Percent of marketed drugs among those with EMEA approval
10. Mortality, prevalence, incidence, were suggested as being added to the list.

**Contributions**

Participants closed the workshop by presenting data they would be able to provide from their respective institutions:

- G. Gatta (RARECARE) – incidence, survival, prevalence, mortality, and stage at diagnosis of rare cancers
- J. Donadieu (EURO HISTIO NET) – most previously mentioned indicators for LCH
- H. Trang (Centre of Reference for Ondine Syndrome) – majority of HI for Ondine Syndrome
- S. Simpson (European Huntington’s Disease Network) – 3,000 individual entries providing data on more than 12 HI.
- J. Sandor (Hungarian National Centre For Healthcare Audit and Improvement) – data from national database for hospital admission records and national registries for congenital anomalies.
- L. Fregonese (Stichting Alpha1 International Registry) – prevalence, age of diagnosis, mortality, epidemiological data, genetic labs
- M. Mazzacuto (Veneto Regional Registry of RD) – several HI from regional registry
- A. Trama (Italian Center of Rare Diseases and EUROPLAN) – onset, date of diagnosis, place of diagnosis (national registries) and identification of important indicators in terms of intervention (EUROPLAN).
- A. Schieppati (Clinical Research Center for Rare Diseases) – national registry data
- M. Posada (Spanish Rare Disease Research Institute) – all relevant indicators available from general patient registries
- A. Montserrat (Commission) – data from the following four sources: Programme of Community
Action in the Field of Health 2008-2013, 7\textsuperscript{th} Research Framework Programme, EMEA, and EUROSTAT

D. Schönfeld (German National Fabry Registry) – will provide all available data

Y. Le Cam (EURORDIS) – monitoring of socioeconomic impact

All EC-funded RD networks will be officially contacted to ask for their potential contributions and a resulting report will be published by June 2008.
HEALTH INDICATORS FOR RARE DISEASES:
State of the Art and Future Directions

First Report

June 2008
Introduction

In the framework of the Health Monitoring Programme and the Community Public Health Programme 2003-2008 the EU began an integrated approach to establish European Community Health Indicators (ECHI). Several projects, described in section 3, participate in this initiative. A list of ECHI indicators is regularly updated, following the needs of healthcare provision emerging in the EU. As a member of the general EU Working party on health indicators, the RDTF is called to identify indicators that can be used for rare diseases.

There is an unmet need of RD-specific health indicators as many ‘traditional’ indicators are not applicable to the field of RD (due to the low number of patients/disease and the lack of visibility in monitoring systems). The development of relevant indicators is crucial for the monitoring of rare disease health policy and knowledge progression at the European and single member state/region levels. A collaborative European effort is always needed in the field of RD, and in particular, for health indicators (HI).

Possible actions toward the development of health indicators in this field are:

- Creation of a list of indicators relevant to the field of RD;
- Assessment of applicability of these indicators (at national/regional and EU levels);
- Selection of some specific indicators for which sources of information are already operational, to test in a pilot study;
- Publication of the information generated by the first three actions, together with:
  - Recommendations over data collection methodologies and tools;
  - Health policy recommendations based on the collected indicators;

The present report describes the political context in which indicators are being developed in the EU, the purposes of collecting indicators for RD and the legitimacy of this collection. Past and ongoing activities in the field of health indicators are also reviewed, and a list of possible RD indicators provided. Finally, information sources and data collection methodology for RD indicators are discussed.

This document was elaborated by the RDTF Working Group on Health Indicators composed by members of the RDTF and invited experts. A working document was elaborated by the scientific secretariat of the RDTF in collaboration with the University of where. This document was discussed at a workshop held in Paris on 12 March 2008. Contributions from the participants were incorporated to the working document to constitute the present report.

1. The political context: Rare Diseases in the EU

Rare diseases (RD) are life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Most of them are of genetic origin; others include rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases. A Community action programme for RD was adopted by the EU for the period 1999 -2003. This programme
defined a disease as rare when it affects less than 5 persons per 10 000. On the basis of the present scientific knowledge, between 5 000 and 8 000 RD affect 3-6% of the total EU population at one point in life. This translates into approximately an average of 246 000 patients per disease in the EU with 27 Member States (MS).

RD is heterogeneous in terms of prevalence, age of onset, clinical severity, and outcome. These, all together account for a big part of the early-life deaths and life-long disabilities in the European population. RD share issues of invisibility with respect to most health care policies, and the healthcare provision for these diseases differs significantly in EU member states/regions with respect to its availability and quality. RD call for special and combined efforts to prevent significant morbidity and premature mortality, improve quality of life and socio-economic potential of affected persons, and solve regional inequalities in provision of care.

In January 2008, the Second Program of ‘Community Action in the Field of Health’ 2008-2013 of the European Commission has come into force. The Programme aims to: 1) Improve citizens' health security; 2) Promote health, including the reduction of health inequalities; 3) Generate and disseminate health information and knowledge.

The third strand includes:

- Action on health indicators and ways of disseminating information to citizens;
- Focus on Community-added-value action to exchange knowledge in areas such as gender issues, children's health or rare diseases (RD).

Information in healthcare is a main objective of the EU policy for the coming years, and indicators are the necessary information tools to guide and evaluate health policies interventions, particularly in those fields where these policies are missing or are inadequate, and where important European values such as equity and fight against discrimination are to be fulfilled, such as in the field of rare diseases.

More information on the Health Strategy and Program are available at: http://ec.europa.eu/health/ph_overview/strategy/health_strategy_en.htm

In the framework of the New Health Strategy, the Commission decided to develop a specific action on RD, which resulted in a Public Consultation: ‘Rare Diseases: Europe’s challenge’. The text of the public consultation was drafted by an expert panel composed of RDTF members and members of the Commission; the EC is planning to publish a ‘Commission Communication on a European Action in the Field of Rare Diseases’ in the second half of 2008. The Communication constitutes an important legal basis for RD initiatives at EU level, setting the main priorities in this field. The most important objectives in the European Action on RD are:

- Strengthening cooperation between EU programs;
- Encouraging EU Member States in developing national RD health policies
- Ensuring that common quality standards are developed and shared everywhere in Europe

The need of **health indicators for rare diseases** is crucial for the assessment of the present situation of RD and the monitoring of health policies in this field. Furthermore, the Communication pays significant attention to the visibility of RD also through the use of indicators, encouraging the compilation of existing sources as well ‘as the definition of a realistic and meaningful set of indicators in the areas of orphan drug availability and accessibility,
2. Definition and Objectives of Health Indicators for Rare Diseases

Indicators are parameters, or a set of parameters, to evaluate the health status of a population and the impact of health policies on this status. Indicators should be informative over the health status and sensitive to changes over time. The development of valid and relevant information is a prerequisite for planning efficient health interventions, health services, and allocation of resources.

In the field of RD, information tools have to be tailored to the specific needs and problems of this field. Due to the heterogeneity of RD, the low number of patients/disease and the geographical spread, many indicators used for more common diseases are not applicable. In the RD field, coordination and pooling of resources are the necessary basis to generate indicators.

As a general rule, indicators should be:
- **Relevant** to the question that is being posed
- **Reliable**: giving the same value if the measurement is to be repeated in the same manner on the same population
- **Useful**: providing information that is useful to decision-makers and can be acted at several levels (local/national/international)
- **Valid**: effectively measuring what they are meant to measure
- **Applicable** to the existing reality (to data collection tools and health policies)
- **Feasible** on an as-large-as possible geographical scale

Main purposes of health indicators for RD are to:

a) **Measure RD globally and individually as a public health issue**
   - For visibility/advocacy
   - To identify targets of interventions
   - To allocate appropriate resources

b) **Enable surveillance of status and trends to**
   - Measure the impact of prevention, diagnosis/screening and care
   - Identify etiological and modifying factors
   - Analyze geographical differences and changes over time
   - Document influence of health policy measures
   - Guide of new research initiatives

c) **Provide efficient and consistent reporting mechanisms**

The first purpose, ‘Measuring RD as a public health issue’, is almost unique to the situation of RD and it speaks of the situation of invisibility that characterizes them. When diseases are invisible in classification systems, hospital charts, death certificates, or are misdiagnosed, these diseases are invisible also for the healthcare systems. In the RD field, collection of data finalized
to epidemiological indicators, e.g. incidence, prevalence, and contribution to premature mortality and to morbidity, also respond to the aim of unrevealing the burden of disease and advocating the need for intervention.

The second and third purposes deal with the comparability of data and sensitivity of the indicators. In the event that data on RD are available, there is often discrepancy between countries/regions in the kind of data and the manner in which they are collected (e.g. data of incidence, prevalence and mortality for public health purposes are not always consistent with data collected for clinical and etiological studies). Comparability of data is an issue even more important for RD than as for common diseases, therefore the risk of losing signals of efficacy of healthcare interventions is higher in RD than as in more common diseases. A collaborative European approach toward common data collection methodologies is required.

The field of RD needs indicators that are particularly sensitive. An indicator is as sensitive as its ability of revealing changes in the issue/factor of interest. For example, indicators such as mortality rates can have low sensitivity to change in very rare diseases, due to the small numbers involved. However, the same indicators can become more sensitive in the presence of e.g. a very effective treatment or prevention action.

In the past years, the RDTF and related projects have undertaken several initiatives to improve data collection. In particular, efforts have been aimed to the creation of a better classification system for RD, which can unmask the presence of RD in hospital discharge charts and death certificates. To this aim, the RDTF working group ‘Coding and Classification of RD’ is currently acting as Advisory Group to the WHO in the ICD (International Classification of Diseases) revision process, from ICD10 to ICD 11. Specific initiatives toward a better classification in the field of rare tumours have been carried on by the projects EuroCare and RARECARE, among others.

Part of the work of the RDTF has been directed towards contributing to the creation and establishment of quality standards of databases and registries, so as to facilitate comparability of data for epidemiological and public health purposes.

3. Legal basis of Health Indicators for RD

One of the major aims of the EC is to produce comparable information on the health status of populations and health systems. This information must be based on common indicators agreed upon across Europe. Legal basis for health indicators is provided by several actions of the past Program of Community Action in the Field of Public Health 2003-2008 and in the New Health Strategy 2008-2013.

In particular, looking at the New Strategy, the ‘Health information and Generation of Knowledge’ strand states that attention is to be paid to ‘develop a sustainable health monitoring system with mechanisms for collection of comparable data and information, with appropriate indicators; ensure appropriate coordination and follow-up to Community initiatives regarding registries…..; collect data on health status and policies; develop, with the Community Statistical program, the statistical element of this system’. These points are identified as strategic directions.
and as areas to be supported with specific initiatives by the FP7 Program.

Other current and future actions legitimating the development of indicators include:

- A Regulation from the Council and the Parliament, to create (Eurostat) a statistical framework for data collection on health and safety at work in some areas;
- A contract agreement between the EC and OECD for the development of indicators in several areas, including indicators on Health Care Quality (report dated 30 Oct 2007);
- The development and maintenance of a System of Community Health Indicators (the ECHI project and projects under the umbrella of the Working Party on Health Indicators)
- The elaboration, in 2009, of a proposal for a ‘Commission Communication on the European Health Information, Knowledge and e-Health System’ with indication of the national and EU responsibility on data collection, the interoperability of different health indicators systems, and a code of good practices on health information.

**Legal basis for the development of health indicators in the field of RD** is provided by the New Strategy through the already mentioned third strand: ‘Action on health indicators and ways of disseminating information to citizens; Focus on Community added-value action to exchange knowledge in areas such as gender issues, children's health or rare diseases’. The implementation of the Strategy realized through the EU Public Health Work Plan 2008 acknowledges these bases; initiatives to be supported include ‘Building capacity for development and implementation of effective public health policies particularly in areas of high need’, such as the area of RD. The necessary basis for health policy development and implementation is the availability of effective health indicators.

As described in section 1 of this paper, in 2007, the EC initiated the a public consultation that will lead to a final ‘Commission Communication on a European Action in the Field of Rare Diseases’, to express the needs of the RD community. A Community action in the RD field is legitimated by the principle of subsidiarity (in which the Union does not take action —except in the areas which fall within its exclusive competence— unless it is more effective than action taken at national, regional or local level) and the legal basis for EU action in the Area of Public Health (art. 152).

As previously mentioned, the need for meaningful and realistic health indicators in RD is indicated in a specific paragraph of the Communication. Once finalized, the RD Communication shall be one of the most important legal bases for all European initiatives in the field of RD.

### 4. European Health Indicators Projects

Under the current and the incoming public health program, the work to develop European Common Indicators (ECHI) is being conducted through **Working Parties and Task Forces** that create a prototype for the future health monitoring system, coordinated under the ECHIM umbrella. Each working party/task force contributes in developing indicators in their own areas of expertise. Activities toward the development of indicators cover five phases: analysis of data needs in their respective area; definition of indicators and quality assurance; technical support for national efforts; data collection at EU level; reporting and analysis; and promotion of the results.
5. Health Indicators for Rare Diseases

Categories of health indicators for RD, based on specific purposes, should include:

a) Contribution of RD to morbidity and mortality
b) Socio-economic impact
c) Availability of appropriate Health Services
d) Information, research, technology development
e) Monitoring of geographical differences in Europe
f) Surveillance of status/trends over time

A list of RD health indicator classes and of potential relevant indicators in each class was discussed during the Paris workshop, in terms of their relevance and availability, and appropriateness of data sources. The following emerged as the most valid candidates for starting studies on feasibility and comparability of data:

a) Contribution of RD to morbidity/mortality
   - Prevalence, per disease and global
   - Incidence, per disease and global
   - Death rates (Mortality)
   - Hospital admissions
   - Contribution to mental/physical/neuro-sensory disabilities
   - Contribution to transplantation

b) Socio-economic impact
   - Impact on families (economic, social, psychological)
   - Annual budget to cover orphan drugs
   - Contribution of consanguinity

c) (Availability of appropriate) Health Services
   - Genetic testing: Laboratories certified/accredited
   - Availability of genetic counselling
   - Number of diseases for which there is biological testing
   - Prenatal diagnosis (impact on RD prevalence)
   - Neonatal screenings
   - Age at diagnosis (diagnosis delay)
   - New orphan products approved by EMEA
   - Availability/accessibility of orphan drugs with EMEA approval
   - Number of Patients’ Organizations and number of diseases covered

d) Information, research, technology development
   - Number of RD with an ICD code
- RD for which good practice guidelines are available
- Registries and databases for RD, geographical coverage
- Number of ongoing clinical trials for RD

e) Equity, EU initiatives
- Countries with specific funding processes and Plans for RD
- European reference networks for RD
- European registries
- EU Funding programs for RD (research, public health)
- Courses, congresses and seminars on RD

Some of the proposed indicators are particularly important for **surveillance of status and trends:**

- Prevalence, incidence, mortality
- Laboratories accredited for genetic testing
- RD for which a diagnostic testing exists (e.g. genetic, biochemical)
- Neonatal screening in place
- Impact of prenatal diagnosis
- Diagnosis delay
- New Orphan products approved by EMEA
- % of marketed drugs among those with EMEA approval
- Perceived health (quality of life – QoL)

6. Methodology for RD indicators

Due to the invisibility of RD in classification and health information systems, data collection is a critical limiting factor in the development of health indicators for RD. Therefore it is important to check the comparability and “fitness for use” of the data that are already being collected in this field. Furthermore, efforts have to be made in identifying new relevant indicators for which data are not being collected yet but whose collection appears to be feasible at the European level. As RD is very heterogeneous, it is impossible to think of generating specific indicators for each of them. It can be useful to select a limited number of diseases/groups of diseases to be used in pilot feasibility studies regarding RD health indicators.

a) Selection of “pilot” RD to monitor with specific indicators

Possible selection criteria:
- RD that are relatively “frequent” (and with an ICD-specific code);
- Groups of RD with similar characteristics (e.g. similar age of onset/survival/level of disability);
- Availability of screening measures of known risk factors and/or of effective treatments;
- Relevance of the disease (e.g. highly invalidating, fatal, rapidly progressing, high impact on families and the society);
- Data already being collected on a systematic basis;
Possible selection method:
The RDTF Working Group on Health Indicators (WGHI) agrees on the selection criteria and proposes a list of pilot diseases; from among these, the diseases to monitor will be chosen on the basis of a written enquiry (members of the WGHI and to other relevant experts/stakeholders in the field) using a consensus method (see Annex 1). In alternative, a consensus meeting with relevant experts will be organized.

b) Selection of indicators to be monitored in the pilot RD
For each pilot disease, the already existing sources of data will be revised.

Possible general selection criteria:
- Indicator is relevant; data are already being collected in a large geographic area of the EU in a common somewhat standardized manner;
- Indicator is relevant; data are being collected in a large geographic area of the EU in different ways but the data can be considered comparable;
- Indicator is relevant; data are not being collected or only partially collected at present but could be easily implemented in large areas of the EU.

Possible selection method:
As for the selection of pilot RD, possible indicators will be proposed by the WPHI and a list will be circulated among experts in the field/relevant stakeholders, with final consensus on the list. In alternative, a consensus meeting with relevant experts will be organized. Once selected, feasibility study of the indicators will be carried on with different sources and methodology according to the type of indicator and the type of disease.

Other issues relevant for the selection of RD HI:

Data comparability issues are present in any action aimed at the development of indicators. Some issues were presented in the last OECD report, having to do with use of data that are non-nationally representative, administrative vs. survey data, and harmonization of data-recall periods for cancer survival. In defining health indicators for RD, a tailored consensus should be found on the requirements of data in terms of comparability at the beginning of the selection. For this reason, an inventory of the available sources for each indicator will be performed prior to the choice of the indicators to monitor in the pilot RD. Besides comparability of data, relevance, reliability, sensitivity, usefulness, and validity of the indicators will be taken into account in the selection procedure.

Relevance of the indicators will be based on the following: a) it must be a tool for health policy; b) it must be related to a priority health problem; c) it must allow comparisons across regions/countries over time; d) data should be/become readily available; e) the choice of a set of indicators must be integrated into a more global perspective of the health information system.

As a result of the selection it should be possible to create e.g. a Minimum set of indicators that can be collected on a large geographical basis plus another small group of indicators with narrower geographical coverage but high relevance and reliable sources of data.
7. Data sources for Rare Diseases Indicators

Currently available sources of indicators include:

- **Death certificates**
- **Hospital charts**
- **Registries**: National/regional, international
- **Scientific/Clinical databases**
- **Dedicated web portals**
- **Patients’ Organizations**
- **Ad hoc clinical studies / Ad hoc surveys**
- **Surveillance systems**
- **Literature**

**Death certificates**: A source that contains mortality data and might be used for assessment over time and between countries. Demographic data such as age, gender, place of residence, marital status and occupation are also recorded. Data which are national are available and they are usually verified by national statistic institutes. Comparability of death certificate data is difficult, depending on the accuracy of the local registration system, the coding of the disease, and the type of professional who codes. Several initiatives toward uniform death certificate records across Europe are ongoing (Eurostat). Electronic death registration is also taken into account and being implemented in some countries (e.g. in France). To use them as source of prevalence data for RD, attention has to be paid to avoid overlap with hospital admission charts.

**Hospital charts**: hospital admission or discharge data are increasingly available in Europe, and several EU countries are keeping national databases of hospital admissions. However, most hospitals are still using ICD 9 and several RD are not coded, thus they can be misclassified on hospital charts. The WGHI thinks that for a certain number of well-known (well-coded) RD, hospital charts represent a valid tool to monitor indicators (e.g. prevalence, morbidity); for these diseases, a collection of hospital chart data could be asked to Eurostat. Hospital access/discharge data to be used for indicators such as prevalence should be based on person, not on episode, to avoid data duplication.

**Registries**: Registry of all RD are not available in any country. Italy has a systematic registration system of a large subset of RD in a few regions. International registries/networks of registries are important sources of information for specific diseases, for which they can provide additional data (e.g. diagnosis delay and quality of life). Registries of patients treated with orphan drugs allow gathering evidence on effectiveness of treatments. Handicap and rehabilitation registries, if available, may provide useful complementary information.

**Scientific/clinical database networks**: can contain genetic, epidemiological, clinical, and biochemical data. Provided that data are of adequate quality, they can generate information over prevalence/incidence and mortality, and several additional data (e.g. quality of life, diagnosis delay) on the specific disease. In most cases, databases are non-population-based, and further work on converting databases data into population-based data may be necessary to achieve adequate representation of the population affected.
**Dedicated web portals:** Orphanet is a source of epidemiological data and information over health services and orphan drugs. The Orphanet database for RD provides information for approximately 6,000 diseases. It provides a comprehensive encyclopaedia of RD; a directory of professional services in 36 countries; a directory of expert clinics, medical laboratories, research projects, registries and patients’ organizations in the field of RD; a database of orphan drugs with their stage of development and availability in EU countries; and a range of other services for specific categories of stakeholders.

**Patients’ Associations and Organizations:** are sources of information. Eurordis, the largest European patients’ umbrella association, publishes regular reports with information on orphan drug availability, pricing and marketing. Projects collecting health status and socio-economic status data (e.g. education and employment) for some RD are ongoing, using survey methods.

**Ad hoc clinical studies:** clinical studies can be used to investigate parameters such as prevalence, incidence and mortality in selected populations with a specific RD. Cohort studies (prospective/retrospective) might be appropriate study designs to monitor indicators in RD populations (e.g. cohorts of newborns with a certain genetic defect, or patients in a European database) since the low numbers of affected patients can render the conclusions of these studies generalizable to all patients with that specific RD. Cross-sectional studies on sufficiently representative populations might be useful to investigate how different indicators are associated with a certain disease/group of diseases.

**Ad hoc surveys:** survey data (household surveys, sample surveys, ad hoc surveys) are commonly used tools for monitoring health indicators. Available literature reports suggest possible discrepancies between data generated by administrative records and surveys; however the last OECD report (30 Oct 2007) on healthcare quality indicators shows that, with an improvement of data collection, there is no systematic difference anymore between the two methods. Surveys are the target of standardization processes at the European level (European Health Survey and Interview System). With some limitations, survey can be an interesting tool for specific RD indicators.

**Surveillance systems:** surveillance systems are in place in a very few settings and for certain conditions (e.g. British Pediatric Surveillance Unit: a card is sent to pediatricians each month to ask for any newly diagnosed cases of a few selected conditions; each condition runs for a few years and is then replaced by other priority conditions). Surveillance systems are very interesting tools of information and allow data collection of sentinel diseases and specific questions; applicability of such systems is limited to those healthcare systems in which the surveillance system is in place/can be implemented.

**Literature:** literature is a source of information accounting for e.g. diseases that are not classified, misclassified, or for extremely rare diseases, for which no system of data collection exists. Published case series, clinical trials, meta-analysis studies could be in certain cases the only available source of indicators of e.g. the effectiveness of a treatment/interventions toward patients’ survival.

**8. Conclusion**
As a result of the Paris Workshop of 12 March, the WGHI proposed to investigate with Eurostat the feasibility of collecting mortality (death certificates) and hospital admission (hospital charts) data for some well defined RD. It is the opinion of the WGHI that the quality of RD indicator data can improve (at the national and European levels) if they will be used on a more regular basis. Due to the readily mentioned classification problems, an approach toward the use of multiple sources of data is recommended (e.g. estimation of the prevalence of a RD using death certificates, registry and hospital charts). Concerning other indicators, an inventory of available data sources will be performed through use of different methods. One of the first initiatives will be a questionnaire directed to all known European scientific/clinical networks, to investigate which data, among those that are collected on a regular basis. This information could be useful in the development of RD indicators.

References


ISARE Indicateurs de Santé des Régions Européennes. www.isare.org


Rare Diseases Task Force, Working Group on Public Health Indicators, minutes meeting January 2006.


Van Teijlingen E, Pitchforth E, Bishop C, Russell E. Delphi method and nominal group techniques in family planning and reproductive health research


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ANNEX 1
List of European projects in the field of indicators

ECHI-European Community Health Indicators project (2001-2003): with the aim to provide common indicators for the European health information system, and give their operational definitions. A comprehensive list of around 400 indicators (long list) was produced throughout ECHI and ECHI-2. From this list of indicators, a so-called "shortlist" (approximately 80 indicators) was selected for priority implementation. Indicators are divided in classes/areas and classes/areas per disease, covering the most common diseases in the EU (http://www.echim.org).

ECHIM (2003-2008): this project continues the work of ECHI and ECHI-2. ECHIM acts as the scientific secretariat of the Working Party Indicators, comprising members from all Member States, leaders of five other Working Parties, project leaders of health indicator-relevant projects, and representatives from Eurostat, OECD and WHO. This should ensure that indicator development is in line with the needs of the European health information and knowledge system and that prerequisite for indicator implementation is created. Specific projects under the ECHIM umbrella develop indicators for: Mental health (MINDFUL and WP on Mental Health); Cancer (Eurochip and CAMON); Diabetes (EUPID); cardiovascular diseases (Eurociss); lung diseases (IMCA); Musculoskeletal disorders (MSD); oral health (EGOHID); injuries (WP accidents/injuries); perinatal health (Peristat); Child health (CHILD); reproductive health (Reprostat); health in intellectually disabled (POMONA); lifestyle indicators connected to cardiovascular diseases, diabetes, other major diseases (EHRM); Nutrition (EFCOSUM, Dafne and Public Health Nutrition); Environment and Health (ECOEHIS); Working Environment (Workhealth); health promotion (EUPHID).

OECD- Health Care Quality Indicators Project-HCQI: The objective of the OECD HCQI Project is to track health care quality by developing a set of indicators that are based on comparable data at international level (EU and other regions worldwide) and can be used to raise questions for further investigation on quality differences across countries. OECD has just released a data collection update report with data collected across 32 countries and a list of 19 indicators that seem to fit the purpose of making international comparisons on quality of health care.

ICHI - International Compendium of Health Indicators: ICHI is the collection of health indicators used by the international organizations WHO-Europe, OECD and the European Commission. The ICHI website allows the direct comparison of indicators and indicator definitions, and gives a full account of the ECHI indicator list proposed in the EU Public health Programme.

FEHES - Feasibility of a European Health Examination Survey: this project contributes to the development of a European Health Survey System by examining and analyzing the feasibility of carrying out a European Health Examination Survey (HES) or repeated HES in the EU Member States.
**EUHSID (European Health Surveys Information) database:** An inventory of nationally and internationally administered health interview and health examination surveys in: EU Member States, EFTA countries and some countries of other regions (USA, Canada and Australia). The database includes information on survey methodology, questionnaires, instruments and examination protocols, as well as recommendations.

**ISARE - Health Indicators in the European Regions:** A pilot project to test the feasibility of gathering health data at sub-national (regional) level within the EU. Over time, this project should lead to recommendations permitting easier integration of regional health data into the European databases.

**EUPHIX - European Public Health Information, Knowledge & Data Management System:** it is a prototype for a sustainable, web-based health information system for the EU, providing healthcare professionals, policy makers and other interested users with relevant, structured information on issues of public health across the EU, with particular relevance to health indicators.

**EUROTHINE - Tackling Health Inequalities in Europe:** The project aims at facilitating mutual learning by collecting and analyzing information from different European countries that will help policy-makers at the European and national level to develop rational strategies for tackling socio-economic inequalities in health.

**EHEMU - European Health Expectancy Monitoring Unit:** main aim of EHEMU is to provide a central facility for the coordinated analysis and synthesis of life and health expectancies to add the quality dimension to the quantity of life lived by the European populations, provide evidence of inequalities between Member States and highlight potential targets for public health strategies at both national and pan-European levels.
ANNEX 2
Definition of some proposed RD indicators, use, sources

A) Contribution of RD to morbidity/mortality

**Prevalence**

**Definition:** the number of persons affected by a certain disease in a given population (10,000;100,000) at a particular time. The current European definition of RD is based upon prevalence.

**Use:** surveillance of global health, particularly for chronic diseases. Establishing prevalence of RD is crucial to measure their impact as a public health issue; however, the sole use of prevalence can underestimate the burden of certain RD, e.g. conditions that are rapidly fatal. For these diseases, incidence is a better estimate. Differences in prevalence over time or between regions may reflect genetic or environmental differences, differences in diagnostic services, in quality of care, and in data collection methodology. Some important information in the field of RD can be generated by studying prevalence of a disease in certain age groups (e.g. perinatal) or in specific ethnic groups

**Sources/feasibility:** population-based registries, when available, are probably the best source for generating prevalence data, provided that the diseases are coded in the same way. Death certificates and hospital charts can be used, as already discussed in section 7, in combination with registry data. Alternative sources include literature data and scientific databases/clinical networks. Prevalence calculations can be tailored to the specific RD (e.g. prevalence rate at birth).

**Incidence**

**Definition:** the number of first events of a condition in a population (10,000; 100,000) during a specific time period. The period usually being one year, longer periods of observation might be necessary for conditions with a low rate of diagnosis (and with diagnosis delay), such as RD.

**Use:** due to the contribution of RD to children morbidity and mortality, incidence of RD in the perinatal period and the first years of life is very important information for policy-makers and the EU society at large. Incidence is a better epidemiological estimate than prevalence also in case of RD that is rapidly fatal, or acute/semi-acute, such as rare cancers. It is a very useful indicator to verify the effectiveness of prevention programs (e.g. prenatal screenings). The importance of incidence has been supported by the comments received during the public consultation on RD from several relevant stakeholders in the RD field. Note: due to the small numbers, an apparent “increase” in the incidence of some RD could result from improvement in the diagnosis and/or the classification of the disease.

**Sources/feasibility:** sources are registries and databases; information is reliable when registries are population-based. Incidence data in registries are often “cleaner” than prevalence data. As for prevalence, an integrated approach combining registries with hospital charts and mortality data can improve the validity of the information generated. Accredited genetic laboratories can be another possible source of information on incidence of genetic RD. For diseases for which data are not collected systematically, estimates of incidence can be made in some cases on the basis of the available literature data. The Orphanet report series of RD are important sources of data
concerning RD incidence and prevalence.

**Death rates (mortality)**

**Definition:** the number of deaths in a certain population (100,000), by age groups and sex. Reduction of mortality is one of the most important targets of any policy intervention. Death rates are fundamental health indicators, even more so are age-specific mortality rates, especially in younger age groups. Infant and perinatal mortality are particularly relevant indicators for RD and different definitions can be used for these purposes.

**Use:** death rates for RD are to be monitored over time and between countries. They can be broken down in 5-year or 10-year age groups, according to the type of situation studied (e.g. rapid fatal diseases versus slow progressing diseases). In the RD field, an overview of mortality due to RD as a whole would increase the visibility of RD, show their impact on public health, and identify geographical inequalities and areas of improvement. Mortality data of diseases characterized by high/rapid mortality (e.g. cancers, neuromuscular diseases) or mortality in infancy/childhood are necessary to stimulate health policies for these specific diseases.

**Sources/feasibility:** Death certificates are the most important source of data, usually available in all nations/regions. National/regional RD registries usually contain mortality data. Multiple-cause-of-death records can be very useful in the field of RD. Characteristics and limits of death certificates as sources of data have been discussed in section 7. Collection of mortality data is ongoing for some RD within ad hoc projects/networks (e.g. rare cancers, congenital anomalies). Scientific/clinical databases can be used as source of mortality data for RD that are not properly coded, however they are biased by several limitations (e.g. non-population based data).

**Hospital admissions/discharges**

**Definition:** the number of hospital admissions in a certain population (e.g. 100,000) for a certain disease.

**Use:** hospital admission is a very important indicator to drive health policy interventions. Depending on the use for which this indicator is defined, single episodes of hospitalization or multi-stay rates can be used. In the field of RD, hospital admission/discharged certificates can be used to calculate incidence and prevalence, in this case, attention has to be paid to avoid data duplication/overlap with mortality data. Information on multi-stay and re-admission rates can provide strong evidence of the public health and economic impact of RD with high level of disability and elevated co-morbidity, and possible changes over time due to new treatments/interventions.

**Sources/feasibility:** Hospital admissions/discharges are administrative data that are being collected in all countries. However, hospital certificates are sensitive to classification problems and to local (national) application of classification systems. A systematic collection of hospitalization data for RD is not performed at European level at present. The WGHI encourages the use of hospital admission rates as indicators for RD, per se and as source of data about prevalence and incidence of RD.

In the area of RD contribution to morbidity/mortality, information over RD contribution to mental/physical/neuro-sensory disabilities and contribution to transplantation where also considered by the WGHI as valuable information tools, in which data collection is feasible. Disability registries exist for most invalidating conditions (e.g. deafness, blindness); and rehabilitation registries could be another source of data. Similarly, dedicated registries/lists could
provide information over the contribution of RD transplantation. The information generated from these indicators will show the impact of RD in individually affected patients and their families, and on healthcare expenditure.

Other indicators discussed in the area of RD contribution to morbidity/mortality were: health expectancy, quality of life, functional health. **Health expectancy** (e.g. DALY: disability adjusted life years; PYLL: potential years of life lost) is a very important indicator at European level. Feasibility and sources of this indicator in the RD field are at present not very clear. Health expectancy might be calculated for some RD, where valid incidence, survival and mortality data are recorded (e.g. rare cancers). Similarly, data collected by clinical networks/databases can allow evaluation of quality of life over time for a very limited number of RD.

A) Socio-economic impact

**Frequency of consanguineous marriages**

**Definition:** in clinical genetics, a consanguineous marriage is defined as ‘a union between a couple related as second cousins or closer, equivalent to a coefficient of inbreeding in their progeny of $F \geq 0.0156$’. A common concern is that consanguinity leads to higher levels of mortality, morbidity in offspring due to the greater probability of inheriting a recessive gene. Consanguineous marriages in Europe are currently confined to particular ethnic groups.

**Use:** the WHO has recommended approaches to minimizing the negative effects of consanguinity on child health, i.e. the identification of families with a high risk of a genetic disease and the provision of prospective genetic counselling. Monitoring the frequency of consanguineous marriages can be used to understand geographical differences in prevalence/incidence of RD and to direct genetic counselling intervention.

**Sources/feasibility:** Genetic centres can usually provide data on the contribution of consanguinity to the occurrence of autosomal recessive diseases in the area they cover. Some voluntary centres may participate in monitoring this indicator over time.

In the area of socio-economic impact, the indicator ‘impact on families (economic, social, and psychological)’ has been discussed during the WGHI. More an information than an indicator per se, it is not easy in definition and quantification. However, information on the impact of RD on families is very important and lacking, therefore the WGHI stimulates efforts toward data collection in this field. The patients’ organization Eurordis performed a survey in several European countries to address this topic. This and similar initiatives can be the starting point for future assessment of the impact of RD on families.

The ‘**annual budget to cover orphan drugs**’, is regularly monitored by Eurordis.

C) (Availability of appropriate) Healthcare Services

**Genetic testing: Laboratories accredited/certified/participating in EQA schemes**

**Definition:** the number of laboratories for genetic testing accredited and certified at the EU level. In the past years, several efforts have been made to put in place networks for the assessment of quality standards of laboratories for genetic testing across Europe. In particular, EuroGentest and
the EMQN (European Molecular Genetics Quality Network) have had an important role in promoting and harmonizing quality testing and counselling in the field of rare genetic diseases. 

**Use:** the number of laboratories accredited for genetic testing is an indicator of quality of health services and provision of care since it gives information about genetic diagnostic provision (of certified quality) with geographical differences and changes over time. 

**Sources/feasibility:** Data on the number of laboratories can be obtained by the already mentioned networks of genetic laboratories, by several initiatives of the Commission and OECD, and by Orphanet. In the yearly reports, the number of laboratories can be divided in certified, accredited, and participating in EQA schemes.

**RD for which a diagnostic testing exists**

**Definition:** number of RD that can be diagnosed through a test. Diagnostic testing can be genetic, biochemical or metabolic.

**Use:** The availability of diagnostic tests for RD has an impact on diagnosis delay, and gives a better chance for early intervention, influencing health expectancy and epidemiological figures. Per se, this information tool reflects improvement in the knowledge of RD; inventories of the available diagnostic tests can be useful to identify areas not covered by ongoing research. The WGHI suggested monitoring **availability** of tests for RD (which test exists and in which countries are they available) and **accessibility**.

**Sources:** the existing tests and their availability per country can be regularly monitored by Orphanet, using as sources genetic labs and literature. For the monitoring of accessibility, an ad hoc survey is proposed by some WGHI members.

**Prenatal diagnosis**

**Definition:** the number of prenatal diagnostic tests for RD available/accessible; differences across countries and over time.

**Use:** Prenatal diagnosis can have a very high impact on RD epidemiological figures. EUROCAT has recently conducted a survey of prenatal screening policies across Europe and their impact, reporting very different implementation of this type of screenings and related policies on the basis of cultural factors. It is useful to have information on screening policies and programs in EU countries and their impact on RD, informing national policy makers and the society at large of the quantitative impact of prenatal screening policies.

**Sources:** international dedicated registries (EUROCAT); national/regional birth registries.

**Neonatal screening**

**Definition:** number of neonatal screenings (metabolic/genetic) available/accessible; differences across countries and over time.

**Use:** The implementation of population or targeted screenings is affected by many issues, such as the availability of an effective treatment/intervention for those screened, the prevalence of the disease and its severity, and the choice/value that society attributes to the screening. It is important to identify where screenings can provide a high impact on mortality, health expectancy and other indicators. The implementation of screenings can obviously have a tremendous impact on RD for which treatments/prevention measures exist. If a screening is proven relevant, number of screenings implemented (i.e. that become standard assessments at birth/first days of life) can indicate the quality of health services, with geographical differences and over time.

**Sources/feasibility:** Data over the availability and validation of screening are available through
dedicated sources such as the Human Genetic Society, which also releases recommendations and criteria for screening programs, information about availability of new screening methods is also provided by Orphanet. The number of screenings implemented in each country are easily accessible administrative data.

**Diagnosis delay/age at diagnosis**

**Definition:** an appropriate definition of age of diagnosis and diagnosis delay has to take into account diagnostic criteria for each disease and it can be difficult to calculate (delay) and/or to use as an indicator (age at diagnosis). Diagnosis delay refers to the interval between the first manifestations/lesions of a disease and the diagnosis (e.g. for breast cancer the interval between the first abnormal screen and the pathology confirmation of carcinoma).

**Use:** diagnosis delay is an indicator of the health service area. The delay in diagnosis is a very important prognostic parameter, and it can be crucial for diseases with severe outcomes which could be prevented by early intervention. Due to their situation of diagnostic complexity and scarcity of expertise, RD is particularly sensitive to diagnosis delays. Monitoring diagnosis delay across time and between countries is of great importance to evaluate progresses in the knowledge of RD, geographical inequalities which could be corrected though scientific networking/travelling of experts/training to primary care providers, areas to support with funding. Age at diagnosis can be used as a proxy (e.g. birth malformations that should be clinically recognized immediately after birth) and it is easier to monitor.

**Sources/feasibility:** Diagnosis delay can be difficult to assess and is sensitive to different definitions of first manifestations of the disease. Data on diagnosis delay/age at diagnosis are available in some registries, and some in dedicated international databases. Data of this kind are being collected by patients’ organizations; survey can be an appropriate tool to investigate this indicator. Diagnostic/genetic laboratories can be a good source of delay/age at diagnosis data.

**New orphan medicinal product designations**

**Definition:** the annual number of product that receive orphan medicinal designations by the European Medicine Agency (EMEA).

**Use:** monitoring the number of medicines approved as ‘orphan drugs’/year provides information about successful research and development in the field of treatments for RD, and the availability of new treatments at EU level. Policies to promote the creation of orphan drugs are being implemented in several EU countries (funds fore pre-clinical and clinical development) and the number of drugs produced/approved reflects also the efficacy of these policies.

**Sources/feasibility:** data are released and published regularly by the EMEA.

**Availability/accessibility of drugs with orphan designation**

**Definition:** orphan drugs that reach the market once they have received authorization by EMEA. Availability of/accessibility to orphan drugs can have an impact on e.g. RD mortality, life expectancy, quality of life, just to mention a few.

**Use:** once new treatments for RD are approved by EMEA, it is important to assess the real accessibility of orphan drugs for the patients, to identify the reasons of lack of availability (e.g. the new drug is not marketed) and accessibility (e.g. the new drug is not reimbursed) and of national/regional differences. Knowing about availability/accessibility of orphan drugs gives information on local health service provisions and aims at solving inequalities in the access to orphan drugs.
Sources/feasibility: EMEA post marketing surveillance, Eurordis observatory on orphan drugs, Orphanet.

**Number of patients’ organizations**

**Definition:** the number of patients’ organizations and associations in Europe. This definition might include only those organizations with legal status or any organized activity by patients’ groups. It has been proposed to evaluate also for which RD patients’ organizations exist.

**Use:** Nowadays patient organizations play an active and instrumental role in determining RD public health and research policies, suggesting provision of services and providing feedback on the quality of the services. The number of patients’ associations is useful in determining the degree of social concern about RD.

**Sources/feasibility:** there are over 1700 patients’ organizations in Europe, with different legal status and geographical coverage. They are listed on the Orphanet web portal. Eurordis is also monitoring RD patients’ organizations across Europe.

**D) Information, research, technology development**

**Number of RD with a code/classification**

**Definition:** Number of RD reported in an official classification system.

**Use:** monitoring the coding status of RD is at the basis of the generation of comparable data, and an information tool per se. This indicator is important for the recognition of RD as a health issue, to assure proper reporting mechanisms for RD, and can have great influence on health policies (e.g. reimbursement policies)

**Sources/feasibility:** the RDTF has a dedicated ‘Working Group on Coding and Classification’ and the chairman of the RDTF, Dr. Aymé, is collaborating with WHO in the revision of the ICD codes for RD to be implemented in the ICD 11. Therefore this indicator can be monitored; however, the next revision of ICD shall not be published any time soon. Initiatives are also recommended to assure proper classification of RD in other classification systems (SnowMed, MedDRA) and in assuring harmonized national transpositions of the international classifications.

Other indicators proposed by the WGHI in this area are: RD for which published practice guidelines are available; RD for which there is a registry with respective geographical coverage and RD for which there are ongoing clinical trials.

Regarding guidelines for RD, the level of evidence and the relevance of the sources can be assessed, and an ad hoc survey could be a possible instrument for data collection.

The number of registries (and databases) dedicated to a specific RD (or group of RD) is informative toward data collection initiatives, whether they come from public authorities (national/regional) or from scientific/clinical networks. Monitoring the number of registries, the diseases and the geographical areas covered by them is important to assess the status of information (data) collection in the field of RD, to avoid duplicate collections, and to identify which diseases are more ‘neglected’ among all RD. Monitoring the quality standards of registries and how many among the current registries are population-based is also important information. A survey of RD registries across Europe is regularly conducted by Orphanet. Information about the number of ongoing clinical trials for RD in the EU can most likely be provided by the EMEA.
E) Equity, EU initiatives

Countries with specific funding processes and plans for RD

**Definition:** the number of MS with specific funding processes and plans for RD, in the field of research, in the field of information, in the field of healthcare (e.g. orphan drugs), in the field of testing.

**Use:** it is an indicator of healthcare intervention measures. In the presence of national action plans, particularly when developed according to common guidelines and criteria of best practice, the patients are guaranteed equal service and treatment all across Europe.

**Sources/feasibility:** data on national plans and funding processes are accessible through member states and EU sources. A specific project on national plans (Europlan) will be carried out by a group of members of The RDTF; collaboration with this study will be useful to the development of this indicator.

Number of European reference networks for RD

**Definition:** the concept of European reference networks (clinical/scientific) is quite new and still evolving. Criteria for European reference networks are indicated by the RDTF (WG on Networks of Reference) and the High Level Group on Health Services and Medical Care of the EC. Some networks have been funded in FP6 and FP7 to test and further develop the concept of European networks of reference.

**Use:** not an indicator but an information tool which testifies the progression of knowledge in the field of RD, the provision and quality of dedicated health services. From Reference Networks guidelines for best practices can be generated for the specific RD, transmission of knowledge and training of professionals can be organized.

**Sources/feasibility:** the number of European reference networks is up to now limited and it is accessible through the EC.

EU/national funding programs for RD research and public health

**Definition:** the number of funding programs for RD at EU and national level.

**Use:** informative over health policy measures and research. Suitable for analysis over time, indicates also the level of political interest and impact of RD.

**Sources/feasibility:** inventory of funding initiatives for RD is easy to realize, and dedicated web portals collect information about funding initiatives.

Courses, congresses and seminars on RD

**Definition:** the number of congresses seminars, courses in the field of RD.

**Use:** informative over increase and transmission of knowledge in the field of RD. Not an indicator, it is information worthwhile to be collected over time, to monitor the visibility of RD, the attention given to them by scientific societies and public institutions, and to identify possible geographical differences.

**Sources/feasibility:** For a systematic quantitative monitoring of this parameter, an inventory of the available sources of data (e.g. websites, scientific societies) can be useful.
ANNEX 3

List of participants to the workshop

Gemma Gatta (RARECARE)
Jean Donadieu (EURO HISTIO NET)
Han Trang (Centre of Reference for Ondine Syndrome)
S. Simpson (European Huntington’s Disease Network) – 3,000 individual entries providing data on more than 12 HI.
Janos Sandor (Hungarian National Centre For Healthcare Audit and Improvement)
Laura Fregonese (Stichting Alpha1 International Registry)
M. Mazzacuto (Veneto Regional Registry of RD)
Anna Lisa Trama (Italian Center of Rare Diseases and EUROPLAN)
Arrigo Schieppati (Clinical Research Center for Rare Diseases)
Manuel Posada (Spanish Rare Disease Research Institute)
Antoni Montserrat (European Commission)
D. Schönfeld (German National Fabry Registry)
Yann Le Cam (EURORDIS)
Minutes

Meeting of the Rare Disease Task Force
Workshop on Patient Registries and Databases
Paris – March 13, 2008

On 12 March 2008, the meeting of the Rare Diseases Task Force (RDTF) Workshop on Patient Registries and Databases included the attendance of:

S. Aymé          A. Kole          J. Sándor
F. Bignami       O. Kremp       A. Schieppati
J. Donadieu      G. Mariani      S. Tanner
L. Fregonese     M. Mazzucato    A. Trama
S. Freisens      A. Montserrat    H. Trang
G. Gatta         C. Nourissier
S. Graham        R. Palla
H. Jansen         M. Posada

A. Welcome Agenda

S. Aymé introduced the two main goals of the workshop.
1. The summary of today’s discussion will be immediately introduced into the text of the Communication.
2. Many projects funded at the regional, national, or EU level have a registry component. Most often, project leaders discover the same obstacles concerning the creation, maintenance, and continuation of the rare disease (RD) registry after funding ends. As such, we have a duty to provide them with guidelines agreed upon today.

B. Context

Since for each RD a very small number of patients are affected, the need to collect patient data at an international level is great. The establishment of reliable patient registries will result in easily stored and retrieved patient data that can be used for collaborative efforts.

Participants agreed to elaborate on the purpose(s) of registries:

• Assess the feasibility of clinical trials
• Clinical heterogeneity
• Natural course / quality of life / time to diagnosis
• Treatment outcome / pharmacovigilance
• Assessment tools
• Quality of care
Establishment of biological markers
Genotype/phenotype correlation
Comparison between similar disorders
Epidemiology of the disease
Advocacy
Planning services / advise health authorities
Appropriate use of treatments
Basis for cohorts
Facilitating recruitment
Support to issue guidelines
Benchmarking tool
Build up a community

C. Issues

Issues surrounding the successful patient registries and databases include:
1. Typology of data collections and the importance of selecting the right type
2. The establishment and funding for data collection
3. Legal, ethical issues, and intellectual property rights

Participants discussed each issue and specific conclusions were incorporated into the RDTF report, Patient Registries and Databases in the Field of Rare Diseases: technical, legal and ethical issues.

D. Conclusions

Workshop participants ended the meeting by summarising their final contributions and conclusions:

O. Kremp stated that the fact that even patients who are not part of treatment in industry sponsored registries can be registered.

H. Trang pointed out the fact that the details of registry ownership are still unclear.

G. Gatta stated that registries must be population based and that since the data addressed public health issues, public funding should be provided.

S. Tanner added that given the great added value of RD data collection, the EC should sit up a mainframe for those who want to begin or maintain an existing registry can.

S. Simpson asserted the fact that data should be visible and given accurate ethical care.

J. Donadieu mentioned that sustainable registries are key to public health. Training of professionals for the collection of quality data should be encouraged, data should be shared at the EU level, continuity of funding should be ensured and a shared public/private responsibility, and
patients should be involved to make them more aware and thus more willing to participate.

L. Fregonese added that methodological tools should be created for e-health and written consent should be required in all cases.

F. Bignami emphasized the importance of ensuring the compatibility of registries.

M. Mazzucato reiterated the main goal of registries and databases in leading to public health tools, uses, and strategies.

G. Mariani disagreed with the majority of the group in his opinion that the plurality of registries is helpful and that one registry per disease does not foster competition and thus motivation.

S. Freisens stated that awareness should be raised in the value of registries in the field of RD and that industry, researchers, and patients should would together towards better transparency.

S. Graham emphasized the importance of the output of registries.

A. Trama stressed the importance of the quality of data, proposed asking the EC for alternative sources of support for the sustainability of registries, and expressed that post marketing surveillance of OD use should be organised by the EC (with the coordinated collaboration of high competent authorities).

The input of all workshop participants and additional experts will be incorporated into a final report published by June 2008.
PATIENT REGISTRIES AND DATABASES IN THE FIELD OF RARE DISEASES: TECHNICAL, LEGAL AND ETHICAL ISSUES

Background document for the Rare Disease Task Force
Patient Registries and Databases Workshop
13 March 2008
Introduction

Patient registries (PR) and databases are structured as searchable data collections of individuals with shared characteristics such as a disease or a gene defect.

Patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases (RD), to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients.

Registries of patients treated with orphan drugs are particularly relevant as they allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing.

When established, databases should be maintained and their use optimised through exchange of data between interested parties. However, the status of such databases is not well defined and most institutions have no written policies or agreements regarding this activity.

Regulations concerning registries in early stages in most European countries and, with the multiplicity of actors and of rules at MS level, the situation is difficult to comprehend. No guidelines are available yet on best practices for exchanging and sharing data. The notion of return of benefits to research subjects or communities is fairly recent.

Databases are expensive to establish and maintain. They require the cooperation of many healthcare providers and require careful management. PR should only be established when financial resources and expertise are present to support them. Furthermore, PR systems tend to have added value if the disease in question has a good prospect for intervention, control, prevention and for research that can lead to these ends.

They are of high interest to researchers, industrial partners, healthcare professionals and ultimately for the community. It is difficult to separate public and private research, as researchers from both sectors are often involved in the same projects. Whilst this enables effective technology transfer, it also gives rise to concerns about conflicts of interest. There is a need to promote confidence in research based on data collections.

Patient registries have been in place for several decades in sectors such as cancer, birth defects and cardiovascular diseases. This long and broad history of data collection is the basis on which to build guidelines for registration of patients with a RD although RD patient registries have some additional features which make them specific:

- most RD are genetic in origin and a large proportion of them are familial, which implies that family related cases have to be traceable;
- The scarcity of cases imposes a large geographical coverage of the data collection which implies multiple collaborations and exchanges of data, usually transnational;
The cost of establishing and maintaining a PR is nearly equal for a prevalent disease as it is for a RD, although budgets are more difficult to obtain for the latter.

To discuss these issues and produce recommendations from a health professional’s perspective, the Rare Diseases Task Force organised a workshop on 13 March 2008 in Paris, France, to which 23 experts from 10 European countries were invited. This document was created as a preparatory document for this workshop, served as a basis for discussion. Following the workshop, a new version of the document will be issued and submitted to a wider range of interested parties for comments. A final document will be produced after the consultation process which will propose guidelines on the establishment of PR and databases in the field of rare diseases.

The present document is based on a compilation of several previously published documents including:
- This document forms part of a BIOTECH programme financed by the Commission of the European Communities (CEE BIO4-CT98-0550).

Statements and recommendations

Typology of data collections
Several types of data collection exist and are reviewed below, each of which is designed for a particular type of use.

Patient information management systems: They help clinicians track patients with a certain type of disease. They are a clinical tool, adapted to counting patients using specific types of healthcare services. They are used by healthcare managers. They are not appropriate for research purposes.

Observatory of cases: It is defined as a permanent registration of patient information in a systematic way, done by healthcare providers on the basis of their referrals. It is a passive ongoing registration activity. The advantage of such a system is its low cost, as there is no cost attached to the identification of cases, as they are referred through the healthcare system. The limits of this approach include the fact that registered cases are not a true representation of the general population but rather a biased sample, usually toward more severe cases or cases from higher socio-economic classes. If the data collection is done properly, the data set may be of interest for some research purposes, but not suitable for epidemiologic studies, unless it can be established that all the cases are referred to the collecting centre. Observatories of cases are also called hospital registries.

Ad hoc surveys: The data collection is targeted at offering the possibility to answer one or more specific research questions. It is a one shot data gathering, which may be repeated in time. The data collected are in the exact format required for the anticipated analysis. The protocol of the survey is designed to ensure a clear answer to the research question(s). This implies an adequate definition of the sampled population,
an adequate size of the sampled population, and an adequate management of the survey to minimize the number of non-responders.

Ad hoc surveys are the most efficient instruments for research purposes as their protocol is well adapted to the research needs (the sample is fully representative and thus the results are conclusive) and the cost of the survey is much lower than any type of permanent data collection, as the survey takes place during a limited period of time. Ad hoc surveys are flexible instruments with protocols adapted to the most recent discoveries about the disease.

There are several types of ad hoc surveys, namely clinical trials, prospective cohorts, retrospective cohorts, case-control studies, cross-sectional (prevalence) studies, etc.

Patient registries: PR are ongoing, systematic and inclusive listings of all individuals with a disease from a geographically defined population. The collected data items tend to be stable over time to allow the analysis of variation through time. As they constitute exhaustive collections of cases, they are fully adapted to serve as sources of data for epidemiological studies. For the same reason they are very expensive and difficult to manage as the comprehensive nature is only achieved through systematic surveys of possible sources of data. Another limitation in the unchanged format of data collection is the inflexibility of incorporating state-of-the-art discoveries in the field.

Points of consideration in establishing a registry

The following points should be considered:

- Establishment of a registry must be justified, in particular with respect to its type of data collection if others are more flexible and less costly.
- A precise case definition of case eligibility for the registry is crucial. The criteria for inclusion and exclusion should be well-defined.
- Clinical objectives should be defined as the format of data will have to be adapted to these objectives.
- The proposed design of the registry should include a definition of the population under study, the direction of the study in time (retrospective, prospective or both), the method of case ascertainment, data sources, and whether the data collection will be passive or active.
- A list of variables to be considered and their format is a key aspect in the registry design. Their choice should be driven by the specific purpose of the registry and the availability of the data. The list should be kept as short as possible to avoid missing data.
- The resources to manage the registry should be considered carefully. The costs include the data collectors and managers, software robust enough for registry use, software programmers, data entry personnel, data analysts, office space, computers, publications, and administration of a registry committee.
- The type of software selected should be adapted to the specificities of the diseases and of the data collection. The possibilities include:
  - An off line system
    - A unique central database storing all the data (very secured system and inexpensive). When collected at distance, data can be sent by mail, by fax, by e-
mail. This is a less costly approach as commercial softwares for managing a unique
database are available and can be easily customised after a short training.

- As many local databases as there are entry points for data collection and the data
  are transferred from time to time to a central registry (EUROCAT model). This
  model is a bit more costly as there is a need for software at each point of data
  collection, but is still a relatively low cost approach.
  - An online system where all data collectors have the right to electronically submit data to
    the database. This is an expensive solution in terms of initial development and
    maintenance of the online system, raising many issues of security and legality when the
    data are collected in one country and stored in another.

Registrar’s scope of activity/responsibilities

The registrar assumes all responsibilities:

- For the quality control, safety and reporting of the registry
- To avoid missing cases
- For confirming the accuracy of data items
- Controlling and monitoring all access to the data
- Documenting any change to the data structure or to the data collection process
- Requesting archiving of the data
- Performing database searches
- Reporting and disseminating results to a wider public
- Ensuring proper comprehensive documentation on all management aspects

Types of Data

There are several types of data collected:

In anonymous data collections the data were originally collected without identifiers and are impossible to
link with their sources. This type of data collection is not applicable to clinical research of RD.

In anonymised data collections, data were originally identified, but have been irreversibly stripped of all
identifiers and are impossible to link to their sources.

In indirectly identifiable data collections, data are unidentified for research purposes, but can be linked to
their sources through the use of a code. This is the most common type of data collected for clinical
research.

In directly identifiable collections, identifiers, such as a name, patient number, or clear pedigree location,
are attached to the data. This is, for example, the care for hospital files.

Consent requirements for new collections

Informed consent is required for all types of data storage. When data is collected for research use,
oversight by an ethics review committee is required to assess and ensure that benefits of the goals of
research outweigh the risks of participation.
Information and consent should be obtained in writing and specific protections should be provided for vulnerable subjects and vulnerable populations, based on the general principle of acting in their best interest.

Individuals should be informed with respect to the types of research that will or might be carried out, the arrangements for access to or sharing of stored information, and the duration of storage.

Consent should be given freely, free from pressure or persuasion, based on information provided by trained staff.

Individuals should be given the right to withdraw from the research at any time, including destruction of their data.

Additional consent may be required at a group level through its representatives, namely patient organisations.

If the sampling is done by a group from a different country, regulations from both the country of origin of the data and of the country of origin of the researchers, should be respected in order to maximize the protection of the rights of the investigated group of patients.

As it is difficult to foresee all the potential research applications that a data collection may be used for, individuals may be asked to consent for a broad use. In this case there is no need to re-contact individuals although the subjects should be able to communicate with investigators should they wish to withdraw.

Consent requirements for existing collections
Previously collected anonymous samples, irreversibly anonymised may be used for purposes other than those originally intended.

The decision to strip samples of identifiers irreversibly requires careful consideration. The benefit of having unlinked anonymised samples is to ensure absolute confidentiality thereby allowing further use of the data. However, retaining identifiers, though requiring further consent from the subject, permits more effective biomedical research and the possibility of re-contacting the subject when a therapeutic option becomes available.

Anonymised samples are useful in allowing information sharing for research purposes with minimum risk. Anonymisation techniques should be standardized to ensure their robustness. Demographic and clinical data attached to anonymised samples should be coded with international nomenclatures, wherever possible.

In the case of existing collections, investigators should be required to re-contact subjects to obtain consent for new studies. If it is impossible or impractical to gain consent, an appropriate ethics review board must give its consent for the further use of the data.

Old collections should be regarded as abandoned and, therefore, useable for new research purposes as long as ethics review committee approval is obtained.
Management, quality control and security issues
The value of a database is proportional to the amount and quality of the information collected. The full benefits of data collection will be realized through maximizing collaborative high quality research. Therefore there is an ethical imperative to promote access and exchange of information provided confidentiality is protected. This includes the availability of catalogues.

The implementation of security mechanisms to ensure the confidentiality and long-term conservation of data are an absolute condition.

These mechanisms should be in place before the collection of data is initiated, including standardization of coding, patient tracking, computerization and encryption. The standards adopted should allow the sharing of information for research purposes with a minimum risk. Discussions should be encouraged amongst consortia to issue standardized protocols.

Databases should receive some form of authorization from institutions. Means of ensuring oversight may vary.

Authorization cannot occur without appropriate funding in place to ensure security, data protection and the ability to remove data if requested.

The managers of the database must balance protection of the data with distribution to research collaborators based on an agreed policy statement.

Professionals involved in storing data should have a written protocol describing the rights and obligations of all parties with respect to storage.

Provision should be specified to ensure continued care of the database under any circumstances.

In the case of academically based databases, governmental agencies should advise local institutional review boards to follow specified guidelines to ensure that databases adhere to uniform standards.

Commercial databases should adhere to a core set of rules.

Access / sharing / ownership
While protecting confidentiality, the free circulation and the availability of data for research should be promoted.

Agreements about ownership of data and access to data should be determined by multi-party contracts and not regulated by legislation. Practices should be based on the following principles:

  a. With respect to anonymised and identifiable data, the subject should always be considered as a primary controller of its data and information directly derived from it. Once the information has been processed, it becomes research data (i.e. data) unless there is agreed private ownership. The processor and/or principle investigator of data should be considered as the guardian of the data. As such, it is up to this person to take all the
b. Ownership of data implies an actual or potential financial return. A protocol including the donation of data by the subject to the researcher eliminates the subjects expectation of an individual compensation, but no the possibility of commercialisation by the researcher through traditional intellectual property rules.

c. Use of collections by third parties should be allowed providing that there is no transfer of ownership and that the use is in agreement with the present guidelines.

**Recommendations agreed upon in the Communication on a European Action in the Field of Rare Diseases**

Collaborative efforts to establish and maintain data collection should be supported, providing that these resources are accessible through agreed upon rules. Many research and public health networks financially supported by DG RTD and by DG SANCO have put in place such shared infrastructures, which have been proven to be very efficient tools in improving knowledge and organising clinical trials.

Areas to be supported by the MS and the European Commission include: quality standards, including development of strategies and tools for periodical monitoring of the quality of databases and for database upkeep; a minimum common set of data to be collected for epidemiological and public health purposes; attention to user-friendliness, transparency and connectivity of databases; intellectual property, communication between databases/registries (genetic, more generically diagnostic, clinical, surveillance-driven, etc). Importance should be given to linking international (European) databases to national and/or regional databases, when existing.

**Issues to consider for discussion**

The issues to consider are many
- data collection objectives
- typology, status
- linkages to other databases
- sponsors, funding
- public consultation and confidence
- adequate consent mechanisms
- common trends and divergences amongst databases
- definitions of anonymisation, levels of anonymisation
- coding, and linkages with other personal information
- “appropriate” security measures and software mechanisms
- quality assurance for confidentiality
- confidentiality issues related to sharing of data
- feedback of information to research subjects
- confidentiality and changes in the status or purpose of databases (e.g. termination)
- criteria for access for private and public researchers (scientific merit, ethics of proposed use, assurances of confidentiality, fees)
- control of data and research results
- licensing of commercial opportunities
  - business models
  - benefit sharing
  - issues surrounding the change in purpose or sale/transfer of database

- governance mechanisms
  - role of legislation, regulation, research ethics boards, central authorities
  - typology of governance structures
  - roles and mandates
  - composition of members
  - funding
  - powers, compliance, enforcement, sanctions
  - reporting requirements
  - assessment of security mechanisms
  - monitoring and accountability
  - international issues/options

- quality assurance
- validation and accreditation of research results
- feedback of research results to the database
- for profit, not-for-profit, and mixed databases
- ownership of data and research results
- protection of intellectual property/copyright
h. RDTF progress report to EC Services

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: 30 May 2007

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 20 June 07
2. Meeting of the Working Group on Coding and Classification of rare diseases on 2 May 2007 in Paris facilitating the collaboration between expert group members in order to assess the adequacy of ICD-10 codes for rare diseases and proposal of suitable changes to WHO.

3. Meeting of the Working Group on Orphan Drugs for rare diseases on 30 May 2007 in Paris facilitating the evaluation of the reality of access to orphan drugs in the EU27 and the debate of new products expected in the next ten years (pipeline of products in development), barriers and possible solutions.

| What were the main objectives* for the period July 2006 – December 2006, and to what extent have these objectives been achieved? |
|---|---|
| Objectives July 2006 – December 2006 | Has this objective been achieved? |
| | If not, please explain. |
| 1. To continue the activity of the Working Group on Coding and Classification | Yes | Very successfully as WHO has established a Rare Disease Topical Advisory Group for ICD-10 revision process which will be chaired by the leader of RDTF. |
| 2. To contribute to the Communication in preparation on the topic of orphan drugs | Yes | Conclusions of Working Group on Orphan Drugs meeting will serve to contribute to this Communication |
| 3. To publish 5 issues of our newsletter | Yes |

Please describe the progress* which has been made by your Task Force since January 2007.

1. We have published 5 new issues of our electronic newsletter for which we have 7,500 registered readers. In response to the satisfaction survey conducted during the first semester of 2006, we have modified the content of the newsletter to provide more information on research findings and have established a section on job opportunities.
2. We have established a group of experts to contribute to the revision of the coding and classification of rare diseases and organised a coding and classification workshop in Paris on 2 May 2007 in conjunction with the launch of ICD-10 revision process in the field of rare diseases. The expert group has a great range of expertise. The meeting was attended by representatives of the WHO and NIH. It has begun to tackle a systematic comparison of several coding and classification systems including the ICD, SNOMED-CT, MedDRA (used by FDA and EMEA), and MeSH. These coding and classification systems must continue to be harmonised through the exchange of data between participating institutions. A list of future activities was agreed on during the meeting in Paris:

- Cross-reference with UKGTN and CINEAS by the end of 2007. The end product will be a list of diseases with a code.
- Start revision comments in ICD10+, the tool developed by WHO to comment on ICD
- Create communication tools for WG: website and newsletter
- Look for funding for future activities as a lot of clerical work is required
- Liaise with colleagues world-wide through the NIH network

The next RDTF Coding and Classification WG Meeting will be held Tuesday 13 November 2007 in Luxembourg.

3. We organised another important workshop on orphan drugs with a group of experts representing RDTF, patient organisations, EMEA, national Health technology assessment agencies and Industry. We reviewed the state of the art in the field of orphan drugs in Europe and discussed possible scenarios for the future. A report of this meeting will soon be published to contribute to the Communication on orphan drugs.

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 all Working Parties and Task Forces to comment, in more detail, on the content of funded projects, their direction, and their methods (advisory only). An annual workshop of project leaders presenting their progresses and plans would be very useful as previously requested.

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

1. Publish 6 new issues of the newsletter and redesign the RDTF website

2. Prepare a workshop on Centres of Reference to produce a new report on possible methods for assessing the added value of theses centres and the added value of European Networks of Centres of Expertise. The workshop would be held in September 2007.

3. Organise another meeting for the Working Group on Coding and Classification
Do you foresee any problems in achieving these objectives? If so, please explain.

NO

Does the Task Force have a Work plan? | Yes
---|---
What is the date of the next meeting of the Task Force? | 20 June 2007

Please provide a summary of the projects that are 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 the WHO to act as a Topical Advisory Group (for rare diseases) in the revision of the International Classification of Diseases.

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

Task Force on Rare Diseases
Working Party Leader: Ségolène Aymé

(If necessary the boxes can be enlarged / rows can be added)

This form was completed by: Ségolène Aymé

Date: 28 December 2008

A. What are the main activities carried out/is the progress made by your Task Force since June 2007?
1. Meeting of the Task Force in Luxembourg on 23 October 07

2. Preparation of the draft of the Communication “Rare Diseases: Europe’s challenges” through two drafting group meetings: 18 July in Luxembourg and 15 October in Brussels

3. Continuation of the work on coding and classification of rare diseases in collaboration with WHO. A report of the work already achieved was provided at the WHO meeting in Trieste on 30 October

4. Organisation of a European Conference on Rare Diseases in Lisbon on 26-27 November with over 400 participants

5. Publication of 9 new issues of our electronic newsletter for which we have 10,000 registered readers.

B. What were the main objectives for the period June – Dec 2007, and to what extent have these objectives been achieved?

<table>
<thead>
<tr>
<th>Objectives May – Dec 2007</th>
<th>Has this objective been achieved?</th>
<th>If not, please explain.</th>
</tr>
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<tbody>
<tr>
<td>1. The main objective was to finalise the text of a Communication on rare diseases to be ready for public consultation before the conference to be held in Lisbon in November 2007.</td>
<td>This goal has been fully achieved. The text was ready on time and is now available for public consultation in 22 languages.</td>
<td></td>
</tr>
<tr>
<td>2. The second objective was to continue updating the community with scientific and political news in the field of rare diseases and orphan drugs.</td>
<td>This goal has been fully achieved as we have published 9 newsletters and the number of our readers has steadily increased.</td>
<td></td>
</tr>
<tr>
<td>3. The third objective was to organise a workshop on coding and classification.</td>
<td>This workshop has been postponed to February 2008 to protest against the fact that the application for funding this activity had not been selected, despite a good scientific review. The work on coding and classification has been done by Orphanet and reported to WHO as planned.</td>
<td></td>
</tr>
<tr>
<td>4. The fourth objective was to organise a conference on rare diseases in Lisbon</td>
<td>This conference was a full success, with over 400 participants.</td>
<td></td>
</tr>
</tbody>
</table>

C. Does the Task Force have a Work Plan for 2008? Yes for the first semester, not after, as there is no funding
D. What are the main objectives for the period Jan – June 2008?

1. Organise a workshop on coding and classification in Paris on 6 February 2008. This workshop will review the list of rare diseases which should have a specific ICD code in ICD11 and will establish a consensus on the classification methodology. The work is prepared by Orphanet.


4. Organise a workshop on methods to establish and maintain a shared data collection in the field of rare diseases in Paris on 13 March 2008. A report will be published later.

5. Finalise the text of the Communication on rare diseases, after the public consultation and continue to publish newsletters.

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

NO, as the funding is there.

F. What is the date of the next meeting of the Task Force? 28 February 2008

G. Were there projects that were finalized during the past six months? If so, please fill in the list below:

<table>
<thead>
<tr>
<th>Name project:</th>
<th>Was the final report of this project published as yet? (please provide link if possible).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Draft of the Communication on rare diseases of the European Commission</td>
<td>Published on the EC website for public consultation</td>
</tr>
<tr>
<td>2. EUGLOREH chapter on rare diseases</td>
<td>Not yet</td>
</tr>
</tbody>
</table>

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The Network of Working Party Leaders and the Network of Competent Authorities have separate meetings first, and subsequently a joint meeting. Both for the NWPL and the joint meeting you can raise issues for discussion. Please consider the specific audiences of the meetings when contributing, and note that issues will only be discussed if a representative of the TF that formulated the issue is present.

Future of task forces if funding is not provided for the activities
Sustainability of long term projects

Are there any issues concerning the progress of your TF you would like to discuss during the next NWPL meeting? If yes, explain:

Are there any issues concerning the progress of your TF you would like to discuss during the next joint NCA/NWPL meeting? If yes, explain:

- the necessity to support TF activities as a key factor for success
Editorial

Oh Happy Day - Today marks the very First European Rare Disease Day!

29 February - Paris, France - If you are reading these words today, be aware that celebrations are unfolding all around you as the very first European Rare Disease Day becomes a reality. Across Europe and beyond, a bevy of conferences, media events, marches, and workshops are drawing awareness to the theme of today’s historical event: A Rare Day for Very Special People. Visit the European Rare Disease Day website to find out what’s going on near you.

Orphanet, the European portal for rare disease and orphan drug information, has had its sleeves rolled up for the last two years, working hard to contribute to the effort being made for rare disease patients across Europe. The revamped site, undergoing a rigorous final testing process, is scheduled to be officially unveiled in mid-March. The new website is a work of art – a customised portal providing a multitude of information and services all available from the site’s homepage. The database of rare diseases and orphan drugs has been enhanced with new information, including prevalence, onset, mode of inheritance and genetics. Links to related information sources, such as Swiss-Prot, Hugo or EuroGentest are just a click away. A major feature of the updated website is the addition of a classification scheme that categorises and cross-references any given disease by scientific, medical and genetic criteria. This new capability will help professionals and other users to access information from a generic category and has the added-value of improving data capture that can be instrumental in future policy making and fund distribution decisions as well as vital to treatment development in both the public and private sectors. The new site also improves searching for a rare disease by clinical sign or symptom. The orphan drug section has been enriched to provide information on the stage of development for any particular molecule from the moment it receives EMEA orphan designation until its market authorisation in Europe. The website also now provides access to the list of on-going clinical trials by molecule and to all orphan indications of a designated molecule - a service strongly requested by patients. Finally, navigation of the new site has been simplified to adequately guide first-time users – a growing part of the website’s visitors as the word of Orphanet spreads. The portal is fully accessible to visually and physically impaired users.
Orphanet is one of many organisations throughout Europe dedicated to improving conditions for rare disease patients and their families. OrphaNews Europe takes the occasion on this special day to acknowledge the efforts of all the various information services, research projects, patient associations, networks of excellence, industry initiatives and government actions - each working hard in its own way to ultimately make life better for rare disease patients and their families. Together we can.

**Spotlight on...**

Interview

**Resuscitating a dream:**
An anaesthesiologist strives to improve access to rare disease information

Uta Emmig first considered the problem of accessing information for rare disease anaesthetics when she was a graduate student. Now a working anaesthesiologist, she is reviving her earlier pursuit of improving information for working with rare disease patients in her particular field.

Uta Emmig, a German anaesthesiologist who specialised at the University Hospital of Aachen and is now working in Italy, knows from firsthand experience that anaesthesiology information specific to rare disease patients can be hard to come by. She has spent many hours surfing the web for literature providing concrete information on administering anaesthetics or the necessity for specialised equipment specific to rare disease patients. Even when such information exists in the literature (via case reports, for example) if the hospital or institution does not have access to a particular journal, the information remains inaccessible.

It is one thing for an anaesthesiologist to know in advance that they will be working with a specific patient with a rare condition that will require special monitoring or equipment, but what about the emergency room professional who encounters a patient with a disease they know little or nothing about? To address this vital need, Dr. Emmig is working to improve the information available to professionals in her field. OrphaNews Europe met with Dr. Emmig recently and was able to learn more about this critical aspect of rare disease patient management:
OrphaNews Europe: How did you first become aware of the need for information for anaesthesiologists working with rare disease patients?

Dr. Uta Emmig: I have been studying the anaesthesiology information resources relevant to rare diseases since 1996. My thesis advisor (Pr. Manfred Abel, former professor of paediatric anaesthesia at the university hospital of Cologne, currently head of the anaesthesia department in a teaching hospital in Cologne-Porz) first drew my attention to this problem. He actually created an electronic database with anaesthesia-relevant information for paediatric rare diseases with the goal of offering a counselling service for professionals in the 1990s. Unfortunately, he had to abandon his efforts due to lack of funding and partners. For my thesis, I conducted a study of the literature as well as a survey amongst my colleagues. The outstanding result was that it was very difficult to find information.

OrphaNews Europe: What kind of information do anaesthesiologists need to work optimally with this category of patients?

Dr. Uta Emmig:
For elective interventions/planned surgery:
1. Before the anaesthesia: “Do I have to perform other examinations?”
2. During the anaesthesia: “Do I have to monitor/control organ functions that I usually wouldn’t control?”
3. After the anaesthesia: “Do I have to keep a watch on the patient for a longer period than usual? Do I have to monitor other organ systems, e.g. blood glucose level.

For emergency surgery:
1. “Can I get rapid access to information on a specific rare disease?”
2. “How can I know which possible medications a patient might be taking and access detailed information concerning interactions with anaesthetic agents?”
3. “Does the hospital or clinic where I am working have specialised equipment available if necessary? If not, where can I access such equipment?”

Read the full interview with Dr. Uta Emmig
EMEA implements electronic-only submission procedure

The European Medicines Agency (EMEA) has announced plans to implement an electronic-only submission procedure for information supporting marketing authorisation applications, leading ultimately to implementation of the Electronic Common Technical Document (eCTD) as the preferred format for electronic submissions. The change in procedures is expected to streamline application processing. Using the eCTD format in particular will permit standardisation and harmonisation and will facilitate navigation and lifecycle management capabilities. Thus, from 1 July, 2008, the EMEA will accept electronic-only submissions with no additional requirements for paper copies. From 1 January 2009, the EMEA will strongly recommend electronic-only submissions. From 1 July 2009, the EMEA will strongly recommend eCTD format electronic-only submissions. Read the question and answer document on electronic-only submissions.

A small but useful addition to the EMEA assessment report listing

Anyone visiting the European Medicines Agency A-Z listing of European Public Assessment Reports (EPARs) webpage might have noticed a new feature. Orphan designated products now have a small orange “O” icon next to their listing. Clicking on the “O” leads the reader to an information page on orphan medicines. EPARs provide a summary of the grounds on which the opinion was formed in favour of granting a marketing authorisation for a specific medicinal product.

National & International Policy Developments

Poland considers developing national rare disease programme

At the first meeting of the newly-elected Commission of Systemic Diseases, a working group of Poland’s paediatric scientific committee (the Committee of Human Development), working within the framework of the independent government-funded research organisation the Polish Academy of Sciences, it was decided to focus on rare disease issues, including the possibility of developing a national rare disease programme for Poland. Thus, rare diseases are to be included in the Committee of Human Development working programme for the coming four-year period. A first action toward this goal is the appointment of an Orphanet Advisory Board to the Committee in cooperation with the Polish Paediatric Society.

Luxembourg enlarges its neonatal screening programme

Luxembourg first implemented a neonatal screening programme in 1968. Testing currently
includes three rare disorders: phenylketonuria (since 1968); congenital hypothyroidism (since 1978); and congenital adrenal hyperplasia, (since 2001). Over the past twenty years, some 100,000 infants have been tested, 42 of whom were diagnosed with one of these three disorders. Early diagnosis and treatment are vital for a positive outcome for these illnesses. Now Luxembourg is adding to its repertoire. As of 1 January, Luxembourg has broadened its newborn screening programme to include medium chain acyl CoA dehydrogenase deficiency (MCAD), an autosomal recessive disorder characterised by acute episodes of hypoketotic hypoglycemia with hepatomegaly (pseudo Reye syndrome), triggered by fasting or infections. As with the other rare diseases that have screening, early detection permits adapted therapeutic intervention before serious and permanent damage occurs.

Other European news

East meets West to discuss rare disease patient needs

On 7 December, stakeholders from throughout Europe gathered in the charming old-world convent of Cenankel in Soesterberg, the Netherlands for a workshop organised by the Dutch Steering Committee on Orphan Drugs. The meeting sought to facilitate the exchange of information concerning the diversity of rare disease and orphan drug resources within Europe. Participants from Eastern and Central European countries were especially encouraged to share their experience and knowledge. Twelve different countries were represented at the event: Bulgaria, Czech Republic, Estonia, Finland, Hungary, Israel, Italy, Malta, the Netherlands, Romania, Slovakia, and the United Kingdom. Three keynote speakers were invited to discuss European-level collaboration in the areas of regulatory affairs, public health care, and research:

Regulatory affairs Dr. Dagmar Stará (State Institute for Drug Control, Bratislava) described her experience of Dutch–Slovak cooperation in the area of medicinal product regulation. Collaboration enhanced the implementation of new European guidelines at the Slovak Institute of Drug Control.

Public health care Dr. Wienke Boerma (Netherlands Institute for Health Service Research) has worked on many European projects. He shared his experience of the introduction of primary health care concepts to Eastern and Central European countries, where efforts are being made to improve funds for research and healthcare, re-structure health insurance systems, develop new equipment, and train doctors and nurses in order to reduce hospitalisation. This experience yielded information concerning health care indicators and why differences still exist.

Science and patient driven research Dr. Evelyn Schaafsma works for the Science Shop (Pharmacy) in Groningen, the Netherlands. She illustrated the different possibilities and added-value of Science Shops - demand-driven independent research units located at different universities and faculties. There are Science Shops (established or still in formation) in many countries, including Czech Republic, Denmark, England, Estonia, France, Germany, Latvia, Portugal and Romania. These shops conduct mostly patient-oriented research.
These examples reiterated that communication between stakeholders working on similar issues in different countries is one of the most important assets available. Yet identifying colleagues and understanding different perspectives takes time. In the three examples presented, collaboration was ongoing for at least 10 years, often because positive results led to a project being followed by a new collaboration. Exchanging experience, stimulating awareness and gaining new skills can be formalised by conferences, workshops and training. In the three examples presented, start-up funds were available (from MATRA or Era-net).

In the afternoon, participants split into small subgroups, according to the topic on which they wanted to focus (drug development, healthcare expertise, or patient-driven research). Four questions helped guide discussion: How can players collaborate to move forward on the different topics? What are the experiences on this topic throughout Europe and by country? What are possible pitfalls and bottlenecks? What really works (best practices)? Results were noted down and shared with the participants.

Some conclusions
In many EU countries, the discrimination of minorities (including handicapped citizens and rare disease patients) is a big problem, on a parallel with unequal access to treatment. Change takes time. It is an obligation for those involved in rare diseases to bring into the limelight the specific needs of patients with a rare disease. In many countries, there is a delay of several years before a correct diagnosis is determined. Without diagnosis, there is generally no treatment or care. Another problem is the lack of information and the shortage of reliable data (prevalence data, for example). Finally, small countries have a lack of expertise for some rare diseases, requiring patients or experts to travel.

Working together, stakeholders can create a powerful instrument. Patients, doctors, researchers, and the pharmaceutical industry can all facilitate communication to insurance providers, health care professionals, politicians and government agencies. Yet in some countries, this bottom-up approach doesn’t work. Rather, key people in government have been convinced to act to improve the situation for rare disease patients. These countries work more from a top down approach to health care for rare diseases. In countries where there are strong and well organised patient organisations, rare disease patients have earlier access to treatment and care. But small groups stand stronger when they combine their forces in umbrella patient organisations, either nationally or pan-European. In small countries (such as Malta and the Netherlands) more orphan drugs are
reimbursed. More active screening (such as cascade screening for genetic diseases) helps to diagnose (and treat) more people with a rare diseases.

One of the clearest conclusions is that great differences between European countries still exist. More pan-European awareness is needed. The European Commission Communication on *European Action in the Field of Rare Diseases* can help inform different European governments of important issues, such as the need for accurate diagnosis, registries, expertise centres, professional and medical student education, and the need for a research budget dedicated to rare diseases and orphan drugs. It is unnerving to note that not all European rare disease patients for whom an orphan drug is on the market are treated. Delays throughout the EU can be enormous. Differences exist from one country to another and also within certain countries (regional). The East Meets West workshop underscored that access to care and treatment remains one of the most important issues for rare disease patients.

French researcher wins international haematology prize

The prestigious William Dameshek prize, considered the highest award in the field of haematology, was awarded to Dr. William Vainchenker for his research on genetic mutations as activators of myeloproliferative diseases. In 2005, Dr. Vainchenker and his team identified a mutation responsible for polycythemia vera. This discovery has already changed the diagnosis and treatment of the disease and presents possible new therapeutic targets. Dr. Vainchenker is a director at the French national institute of medical scientific research (INSERM) and is based at the Gustave Roussy Oncology Institute. The American Society of Hematology awards the William Dameshek prize to significant contributions toward the understanding of blood-related diseases.

**Other International News**

The international genodermatoses project continues its work for Mediterranean-based patients

Genodermatoses are a group encompassing some 300 various genetic skin diseases, almost all of which are rare. The burden of severe genodermatoses is huge for patients and their family. Social exclusion, disability, and shortened life expectancy make this population very vulnerable. Prevalence is considered higher in the Mediterranean basin region due to a number of factors: consanguineous marital practices in certain regions, isolated cultural or religious sects, resistance to prenatal screening, and limited access to public resources. In 2003, the Fondation Rene Touraine (a European foundation promoting therapeutic advances in dermatology) and the Laboratoire Pierre Fabré launched an initiative entitled Genodermatoses and Mediterranean with the collaboration of specialists, scientists, policy makers and health officials from Euro Mediterranean and Middle Eastern countries. This initiative seeks to improve health care and social support, promote clinical research programmes, and foster networking in the field of severe genodermatoses. Each year, a Working Session is organised to bring together the project partners. In 2007, the Working Session was held in Alexandria, Egypt in late April. Eleven countries participated in the 2007 Working Session, in addition to three new countries that joined the initiative: Cyprus, Turkey and Saudi Arabia. Some achievements from the 2007 Working Session...
include involvement of new partners within many countries (geneticists, dermatologists, paediatricians, patient organisations, university clinics, et cetera); the finalisation of co-funding proposals at the European Union level in the fields of research and public health; specific social and healthcare training in various countries; the establishment of five working groups targeting diseases with a severe repercussion on quality of life: epidermolysis bullosa, severe ichthyosis, palmoplantar keratoderma, xeroderma pigmentosum, and other severe genodermatoses (a subgroup of eight other identified diseases); new referral centres in four different countries; the integration of genodermatoses into major health policies in various countries (rare diseases in Algeria; skin diseases in Morocco; handicap in Egypt and Tunisia; genetic diseases in France); and various research initiatives in different countries. The goals for 2007-2008 have been identified as the establishment of good practices, health care community networks, access to drugs and medical devices. The 2008 Working Session will be held in Rabat, Morocco, from 6-7 June.

New UN publication focuses on disability issues

Disability is an international health and social concern whose prevalence is hard to capture. It is well known, however, that a large number of rare disease patients suffer from mental and/or physical disabilities. The Economic and Social Affairs department of the United Nations has recently created a newsletter designed to keep readers up to date on initiatives to increase inclusion in work, school and social activities amongst this segment of the population around the world. The newsletter, Enable, also features new publications and upcoming events relevant to the topic of disability.

Orphanet News

New Texts

New Orphanet Journal of Rare Diseases publications

Multiple osteochondromas
Monosomy 18p
Primary intestinal lymphangiectasia (Waldmann's disease)
Syndromic (phenotypic) diarrhea in early infancy

New Syndromes

22q11.2 distal deletion: a new phenotype distinct from DiGeorge syndrome and velocardiofacial syndrome

Microdeletions within chromosome 22q11 have been linked to two syndromes: DiGeorge syndrome and velocardiofacial syndrome. The authors of this study have identified six patients
with a 22q11.2 distal deletion presenting a distinct phenotype. All have distinct facial dysmorphia perhaps linked to prematurity, pre-or post-natal growth delays, developmental delays and skeletal anomalies. Two patients also have cardiovascular malformations and a third has a cleft palate.

Read the PubMed abstract

Am J Hum Genetics ; 214-221 ; January 2008

Microtia, eye coloboma, and imperforation of the nasolacrimal duct: a new autosomal dominant syndrome

A Belgian team describes a family afflicted with an autosomal dominant syndrome characterised by microtia, eye coloboma, and imperforation of the nasolacrimal duct. This phenotype is linked to five tandem copies of a copy-number-variable region of chromosome 4p16. This is the first example of an amplified copy number variant associated with a Mendelian disorder.

Read the PubMed abstract

Am J Hum Genetics ; 181-187 ; January 2008

A new retinopathy linked to BEST1 biallelic mutations

The authors describe five families with a distinct retinal disorder, autosomal-recessive bestrophinopathy that is consequent upon biallelic mutation in BEST1 and is associated with central visual loss, a characteristic retinopathy, an absent electro-oculogram light rise, and a reduced electroretinogram. Heterozygous mutations in BEST1 have previously been found to cause the two dominantly inherited disorders, Best macular dystrophy and autosomal-dominant vitreoretinochoroidopathy.

Read the PubMed abstract

Am J Hum Genetics ; 19-31 ; January 2008

SERKAL syndrome: female to male sex reversal and renal, adrenal, and lung dysgenesis

The authors describe three foetus with a lethal autosomal recessive syndrome characterised by SEex reversal and Kidney, Adrenal and Lung dysgenesis. They identified a disease-causing homozygous missense mutation in the human WNT4 gene.

Read the PubMed abstract

Am J Hum Genetics ; 39-47 ; January 2008

New Genes

Familial erythrocytosis: hypoxia-inducible factor alpha 2 is at cause

Familial erythrocytosis is a primary polycythaemia characterised by an increase of haematocrit and haemoglobin levels. Hypoxia-inducible factor (HIF) alpha, which has three isoforms, is
central to the continuous balancing of the supply and demand of oxygen throughout the body. The authors describe a family with erythrocytosis and a mutation in the HIF2A gene, which encodes the HIF-2alpha protein. Their functional studies indicate that this mutation leads to stabilisation of the HIF-2alpha protein and suggest that wild-type HIF-2alpha regulates erythropoietin production in adults. HIF-alpha is a transcription factor that modulates a wide range of processes, including erythropoiesis, angiogenesis, and cellular metabolism.

Read the PubMed abstract

NEJM ; 162-168 ; January 2008

Lethal multiple pterygium syndrome has severe rapsyn function loss

Lethal multiple pterygium syndrome (MPS) is characterised by intrauterine growth delay, pterygia present in multiple areas (chin to sternum, cervical, axillary, humero-ulnar, crural, popliteal, and the ankles) and flexion contractures giving rise to severe arthrogryposis. Recessive mutations in the embryonal acetylcholine receptor g subunit (CHRNG) can cause both lethal and nonlethal MPS. The authors have identified a new homozygous mutation in the gene encoding rapsyn. Mutations in this gene have previously been identified in patients with congenital myasthenia. Whereas incomplete loss of rapsyn function may cause congenital myasthenia, more severe loss of function can result in a lethal foetal akinesia phenotype.

Read the PubMed abstract

Am J Hum Genetics ; 222-227 ; j

Autosomal-dominant snowflake vitreoretinal degeneration is caused by a retinal potassium channel gene mutation

Autosomal-dominant snowflake vitreoretinal degeneration is a progressive ocular disease affecting multiple tissues within the eye and characterised by fibrillar degeneration of the vitreous humor, early-onset cataract, minute crystalline deposits in the neurosensory retina, and retinal detachment. The authors have identified heterozygous mutations in gene KCNJ13, encoding a potassium channel localized to human retina and retinal pigment epithelium.

Read the PubMed abstract

Am J Hum Genetics ; 174-180 ; January 2008

X-linked infantile spinal muscular atrophy linked to defects in the ubiquitin-proteasome pathway

X-linked infantile spinal muscular atrophy (XL-SMA) is an X-linked disorder presenting with hypotonia, areflexia, and multiple congenital contractures (arthrogryposis) associated with loss of anterior horn cells and infantile death. The authors have identified missense mutations in UBE1 gene in two families and a synonymous substitution in three other families. In the case of the latter, gene expression is reduced and alters the methylation pattern of exon 15, implying a plausible role of this DNA element in developmental UBE1 expression in humans.

Read the PubMed abstract
Autosomal-recessive nonsyndromic hearing impairment: ESRRB gene may have mutations

Autosomal recessive nonsyndromic hearing impairments are a heterogeneous group of genetic disorders for which 67 loci, called DFNB, and 24 genes have been identified. In a Turkish consanguineous family, the authors identified locus DFNB35 and identified a homozygote duplication of seven base pairs in gene ESRRB. They confirmed the presence of mutations in this gene in four other families of whom the hearing impairment had already been linked to the same locus. ESRRB encodes an estrogen-related receptor protein. In mice, the orthologue protein is expressed during inner-ear development and is present postnatally in the cochlea.

Familial primary localised cutaneous amyloidosis has oncostatin M receptor-beta mutations

Familial primary localised cutaneous amyloidosis is an autosomal dominant disease characterised by chronic skin itching and deposition of epidermal keratin filament-associated amyloid material in the dermis. In three families, the authors identified mutations in gene OSMR, encoding oncostatin M-specific receptor beta, which is a component of two receptors: oncostatin M and interleukin 31, implicated in keratinocyte proliferation, differentiation, apoptosis, and inflammation.

Mitochondrial complex I: C6ORF66 is an assembly factor

The authors performed homozygosity mapping in five patients from a consanguineous family who presented with infantile mitochondrial encephalomyopathy attributed to a deficit of respiratory chain complex I. They identified a mutation in gene C6ORF66. Their research suggests that the gene encodes a respiratory chain complex I assembly factor.

X-linked scapulo-axio-peroneal myopathy: FHL1 mutated in three families

Two articles published in the American Journal of Human Genetics describe the identification of mutations in gene FHL1 in patients with X-linked scapulo-axio-peroneal myopathy. The patients studied present a particular phenotype of scapulo-peroneal weakness, pseudoathleticism or hypertrophy, and bent-spine syndrome. The gene FHL1 is highly expressed in skeletal muscle and may contribute to stability of sarcomeres and sarcolemma, myofibrillary assembly, and transcriptional regulation.
Research in Action

Fundamental Research

5q- myelodysplastic syndrome: identification of a causative gene via RNA interference screening

5q- syndrome is a subtype of myelodysplastic syndrome characterised by a defect in erythroid differentiation. The causative gene has not been identified to date. The authors describe an RNA-mediated interference (RNAi)-based approach to discovery of the 5q- disease gene in the normal haematopoietic progenitor cells. They observed that a partial loss of ribosomal protein RPS14 sufficed to mimic the phenotype seen in patients. This type of approach presents a strategy to identify gene dosage anomalies at the origin of diseases.

Clinical Research

Hemochromatosis: More men with C282Y homozygote mutation develop iron-overload related disease than their female counterparts

Hemochromatosis is a genetic disease characterised by an iron overload due to digestive hyperabsorption. It is caused by HFE gene mutations, of which allele C282Y is most frequently seen in patients. The authors demonstrate that C282Y homozygote men have a higher risk than women with the same genotype to develop a disease linked to iron overload (28.4% of men versus 1.2% of women).

Dysequilibrium syndrome: VLDLR gene may be the only one affected

Dysequilibrium syndrome is characterised by intellectual deficit, equilibrium and locomotive problems, strabismus and small stature. A homozygous deletion in the short arm region of chromosome 9, including two genes expressed in the brain, have previously been linked to this syndrome. In this study, the authors have identified a homozygous mutation that affects just one of these genes: VLDLR, encoding a very weak density lipoprotein receptor implicated in neuroblast migration in the cerebral cortex and the cerebellum.
Hypomyelilation and juvenile onset cataract: cataracts are not always present at birth

*DRCTNNB1A* gene mutations are responsible for an autosomal recessive disease associating hypomyelilation and congenital cataracts. The authors have identified an intragenic deletion in this gene in a family presenting juvenile onset cataract, thus broadening the phenotype for this disease. Congenital cataract is thus not an essential criterion for differential diagnosis.

Read the PubMed abstract

Spinocerebellar ataxia type 17: repeat configuration is a critical determinant for instability

Patients with spinocerebellar ataxia type 17 present ataxia, pyramidal and extrapyramidal signs, learning difficulties, psychosis and epileptic crises. This ataxia is due to expanded CAG nucleotide repetitions in gene *TBM*. The repetitions may be either continuous or interrupted. The authors observed that for a given stretch of repetitions, the instability of mutated alleles is two or three times higher when the repetitions are continuous. This information confirms the hypothesis that repetition configuration is a determinant of instability.

Read the PubMed abstract

Auriculo-condylar syndrome: mapping of a first locus and evidence for genetic heterogeneity

Auriculo-condylar syndrome, an autosomal dominant disorder of first and second pharyngeal arches, is characterized by malformed ears ('question mark ears'), prominent cheeks, microstomia, abnormal temporomandibular joint, and mandibular condyle hypoplasia. The authors have linked the transmission of the disease to chromosome region 1p21.1-q23.3 in a Brazilian family. However, in a second family no link could be established, demonstrating the genetic heterogeneity of the disease.

Read the PubMed abstract

Aicardi syndrome: incidence is around 1 in 100,000

Aicardi syndrome is a developmental disorder characterised by agenesis of the corpus callosum, retinal anomalies, seizures and developmental delay. It is transmitted as an X-linked disorder with presumed lethality in males. Using data from 408 patients gathered from different international sources, the authors calculate incidence to be 1 in 105,000 live births in the US and 1 in 93,000 live births in the Netherlands. The risk of mortality peaks at age 16 and the probability of survival at age 27 is 0.62.

Read the PubMed abstract
J Child Neurol ; Epub ahead of print ; January 2008

Autism: Two new susceptibility genes from the neurexin superfamily have been identified

Three independent studies published in « The American Journal of Human Genetics » have identified a new susceptibility gene for autism: CNTNAP2. This gene encodes a neurexin family protein and is expressed in areas of the brain instrumental to language development. A second gene, NRXN1, encoding neurexin 1, was identified in a fourth study published in the same journal.

Read the first PubMed abstract
Read the second PubMed abstract
Read the third PubMed abstract
Read the fourth PubMed abstract

Am J Hum Genetics ; 150-159 ; January 2008
Am J Hum Genetics ; 160-164 ; January 2008
Am J Hum Genetics ; 165-173 ; January 2008
Am J Hum Genetics ; 199-207 ; January 2008

Gene Therapy

Congenital erythropoietic porphyria: complete phenotype correction by gene therapy in mice

Congenital erythropoietic porphyria is a severe autosomal-recessive disorder characterised by a deficiency in uroporphyrinogen III synthase, the fourth enzyme of the heme biosynthetic pathway. The authors used a murine model to check the feasibility of hematopoietic stem cell gene therapy in this disease. They succeeded in achieving complete and long-term enzymatic, metabolic, and phenotypic correction of the disease.

Read the PubMed abstract

Am J Hum Genetics ; 113-124 ; January 2008

Diagnostic Approaches

Sézary syndrome: CD158K/KIR3DL2 is a differential diagnostic marker in patients with erythroderma

The distinction between Sézary syndrome and benign erythrodermic inflammatory diseases is difficult to make both clinically and on skin biopsies, since histomorphology can provide nonspecific results. The authors identified a marker specific to Sézary syndrome: CD158K/KIR3DL2. Using conventional and/or quantitative real-time reverse transcription (RT)-PCR analysis of skin biopsies allowed for distinction between Sézary syndrome and benign erythrodermic inflammatory disease.

Read the PubMed abstract

J Invest Dermatol ; 465-472 ; February 2008
Patient Management and Therapy

Advanced-stage mantle cell lymphoma: a new prognostic index

There is no generally established prognostic index for patients with mantle cell lymphoma (MCL) because the International Prognostic Index (IPI) and Follicular Lymphoma International Prognostic Index (FLIPI) have been developed for diffuse large cell and follicular lymphoma patients, respectively. Using data of 455 advanced stage MCL patients treated within 3 clinical trials, the authors examined the prognostic relevance of IPI and FLIPI and derived a new prognostic index (MCL international prognostic index, MIPI) of overall survival. According to the MIPI, patients were classified into low risk (44% of patients, median OS not reached), intermediate risk (35%, 51 months), and high risk groups (21%, 29 months), based on the 4 independent prognostic factors: age, performance status, lactate dehydrogenase (LDH), and leukocyte count. Cell proliferation was exploratively analyzed as an important biologic marker and showed strong additional prognostic relevance. The MIPI is the first prognostic index particularly suited for MCL patients and may serve as a tool to facilitate risk-adapted treatment decisions in patients with advanced stage MCL. Read the PubMed abstract

Blood ; 558-565 ; January 2008

Systemic Lupus Erytematosus: new treatment recommendations

EULAR, The European League Against Rheumatism has developed a new series of recommendations for the management of Systemic Lupus Erytematosus, an auto-immune disease characterised by the presence of anti-nuclear auto-antibodies. Read the recommendations

Ann Rheum Dis ; 195-205 ; February 2008

Orphan Drugs

Nine EMEA orphan drug designations for February

The COMP (Committee for Orphan Medicinal Products) adopted the following nine positive opinions on orphan medicinal product designation at its February meeting for the treatment of:

- retinitis pigmentosa
- Wilson disease
- small cell lung cancer
- Charcot-Marie-Tooth disease type 1A
- spina bifida
- pancreatic cancer
- amyotrophic lateral sclerosis
- ovarian cancer
- idiopathic pulmonary fibrosis

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

Grants

Call for proposals: European research projects on neurodegenerative diseases

ERA-NET Neuron has issued a call for proposals for European research projects on neurodegenerative diseases of the central nervous system. The deadline for proposal submission is 07 April, 2008.

For further information.

News from the Patients' Associations

An orphan disease review in Algeria

The Algerian Williams and Beuren Syndromes Association, founded in 2002 by parents of an afflicted child, has created a review dedicated to raising awareness for rare diseases in Algeria. The first issue of Maladies Orphelines provides basic information on an array of diseases, including a feature article on a little girl with Rothmund Thomsan syndrome, and also contains sections on psychology, social services, and patient testimonies. Five thousand copies of the first issue of the French-language review have been distributed, and an on-line version is in preparation. The review is scheduled to appear twice yearly.

What's on Where?

Rare Diseases: Channels and Transporters

Date: 8-12 March 2008
Venue: Sant Feliu de Guixols, Spain

The conference is devoted to channels and transporters involved in rare inherited diseases. Specifically TRP and CLC channels, connexins, mitochondrial transporters, heteromeric amino acid transporters, neurotransmitter transporters, ABC transporters and related diseases will be covered.

For further details

Second European Symposium on Rare Anaemias

Date: 13-14 March 2008
Venue: Nicosia, Cyprus

Sessions include current progress in prenatal and neonatal diagnosis of haemoglobinopathies, iron overload and chelation therapy, very rare anaemias, treatment of haemoglobinopathies, and
red blood cell hereditary disorders.
*For further details*

**Beyond Medicine: Providing Quality Genetic Testing Service for the Public in the World**

Date: 16 March 2008  
Venue: Tokyo, Japan

The purpose of the symposium is to exchange experiences and opinions on various issues relating to the provision of quality genetic testing services, such as information provided to consumers, regulatory schemes and genetic counseling.  
*For further details*

**Genomic Disorders 2008**

Date: 17-20 March 2008  
Venue: Cambridgeshire, UK

Topics to be discussed will include copy number variation and assays, structural variation predisposing to genomic rearrangement, mechanisms underlying genomic disorders, genomic rearrangements in common diseases and genetic syndromes, model organisms in the study of genomic disorders and potential therapeutic approaches.  
*For further details*

**Fifth International Congress on FMF and Systemic Autoinflammatory Diseases**

Date: 4-8 April 2008  
Venue: Rome, Italy

This conference will review current knowledge of the mechanisms of innate immunity and their relevance to the pathogenesis of autoinflammatory and other chronic diseases.  
*For further details*

**19th Conference of the German Society of Human Genetics**

Date: 8-10 April 2008  
Venue: Hannover, Germany

This year the main focus will be on the following subjects: Genetic origins of pain intensity, connective tissue disorders and complex infectious diseases; New therapeutic approaches to genetic diseases; The role of miRNAs and epigenetic modification; Proteomics; The structure of human genetic health care services in Europe.  
*For further details*

**International Ataxia-Telangiectasia Workshop 2008**
Topics include the roles of ATM and its related proteins in the DNA damage responses and in the tumorigenesis. The biological roles of ATM in the development of immune system, nervous system, and the stem cell systems are another essential area towards new therapies for A-T.

For further details

Second International Workshop on Minicircle-DNA

Date: 7-9 May 2008
Venue: Bielefeld, Germany

Following on the success of the 2007 conference, and focusing on technology and IP and application.

For further details

ICORD 4th International Conference on Rare Diseases and Orphan Drugs

Date: 20-22 May 2008
Venue: Washington, DC US

For further details

13th International Conference for Behçet's Disease and 5th Patients' Convention

Date: 24-27 May 2008
Venue: Klagenfurt, Austria

With presentations and discussions on oral, eye, genital and skin involvement, as well as paediatric patients, drug trials and future perspectives.

For further details

Myology 2008: Treatments – The Turning Point

Date: 29 May - 1 June 2008
Venue: Marseilles, France

Focusing on the development of therapies and the setting up of trials on humans for rare diseases in the field of myology.

For further details

First Conference on Translational Research in Paediatric Rheumatology

Date: 29 May - 1 June 2008
Venue: Genoa, Italy
Using the field of rare paediatric rheumatic disorders as a paradigm, Anticipating Changes in Drug Development for Children: Building on Paediatric Rheumatology will examine the medicine research and development process, from pre-clinical and early-phase clinical development, to biomarker validation, study design and management, data analysis, ethical review, regulatory submission and research governance. The conference is meant to further stimulate interaction among the three major stakeholders in the drug development process, namely, academia, industry and regulatory authorities.

For further details

5th International Congress of Rehabilitation in the Field of Neuromuscular Disorders

Date: 30 May – 1 June 2008
Venue: Marseilles, France

With sessions on gene-based therapies, patient evaluation, pain and fatigue management, and treatment options.

For further details

EuroGentest Genetic Testing Accreditation and Quality Assurance Programmes

Date: 30-31 May 2008
Venue: Barcelona, Spain

EuroGentest presents two workshops and a round table session on the topics of accreditation in genetic testing labs, quality assurance and managing the human side of change.

For further details

40th European Human Genetics Conference

Date: 31 May-3 June 2008
Venue: Barcelona, Spain

In conjunction with the European Meeting on Psychosocial Aspects of Genetics 2008. Programme will cover the latest developments in the field of human genetics that are of interest both for clinicians and research scientists.

For further details

14th International Conference on Prenatal Diagnosis and Therapy

Date: 1-4 June 2008
Venue: Vancouver, Canada

Conference sessions will include foetal imaging, cytogenetics, foetal DNA/RNA, PGD, screening, teratology, and legal aspects of prenatal diagnostics and therapy. The deadline to submit an abstract for this conference is 4 February 2008.
For further details

5th International Cystinosis Conference

Date: 27-28 June 2008  
Venue: Dublin, Ireland

World experts in the field of Cystinosis will attend and the latest research in this very rare disease will be presented. The event is unique as it combines a high-level scientific and medical conference as well as being a family and patient friendly conference. Deadline for abstracts: 11 April 2008.  
For further details

Fourth International Neuroacanthocytosis Symposium: Bridging Clinical and Basic Aspects

Date: 1-2 July 2008  

Including clinical aspects of chorea acanthocytosis and McLeod syndrome, muscle and nerve neuropathology and syndromes related to NA.  
For further details

Genetic Alliance Annual Conference 2008

Date: 11-13 July 2008  
Venue: Bethesda, MD, US

Brings advocates, health professionals, policy makers, industry representatives, researchers, and community leaders together for workshops and discussions.  
For further details

Fourth International Conference on Metals and Genetics

Date: 21-24 July 2008  
Venue: Paris, France

The main topics will include metal-associated diseases: molecular and systemic biology approaches; characterisation and speciation of metal in proteins and biological tissues; and metals and environmental health implications.  
For further details

Barth Syndrome: On Track Toward a Cure - 4th International Conference

Date: 21-26 July 2008  
Venue: Florida, USA
This conference will be dedicated to increasing knowledge and accelerating advances in research for this rare metabolic genetic disorder. It will bring together basic scientists, clinical researchers, treating physicians, other professionals, and affected individuals and families to focus on the syndrome through a series of carefully organised sessions.

For further details

15th Paediatric Rheumatology European Society Congress

Date: 14-17 September 2008
Venue: University College London, UK

The programme will cover four main topics through keynote lectures, abstract presentations and educational workshops: juvenile arthritis, juvenile dermatomyositis, vasculitis and pain. There will be novel symposia such as sport and exercise in young people.

For further details

6th World Rett Syndrome Congress

Date: 10-13 October 2008
Venue: Paris, France

Various aspects of Rett syndrome and MECP2 functioning, including fundamental, clinical and management topics.

For further details

Tenth International Meeting on Osteogenesis Imperfecta

Date: 15-18 October 2008
Venue: Ghent, Belgium

Topics include: Bone homeostasis, murine models/collagen biology/biophysics, classification, genetics: genotype-phenotype, prenatal diagnosis/preimplantation diagnosis, bisphosphonates, orthopedic management, hearing loss: physiopathology, surgery and imaging, other medical management issues, stomatology/dentistry, psychosocial aspects, new (therapeutic) perspectives.

For further details

Orphanews Europe, the newsletter of the Rare Diseases Task Force

Orphanews Europe is supported by the European Commission's DG SANCO and the French Muscular Dystrophy Association (AFM)

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