4th European Conference on Rare Diseases

Patients at the Heart of Rare Disease Policy Development

Conference Report
4TH EUROPEAN CONFERENCE ON RARE DISEASES

PATIENTS AT THE HEART OF RARE DISEASE POLICY DEVELOPMENT

CONFERENCE REPORT
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The organisers particularly wish to thank the following persons/organisations/companies for their role:

- Presidency of the European Union,
  Government of Portugal

- Ministro da Saúde -
  Direcção-Geral da Saúde Portugal

- European Commission, Public Health Programme,
  Dg Health and Consumer Protection
  Programme Of Community Action in the
  Field of Public Health (2003-2008)


The new programme is based on three general objectives: information, rapid reaction to health threats and health promotion through addressing health determinants. Activities such as networks, co-ordinated responses, sharing of experience, training and dissemination of information and knowledge will be inter-linked and mutually reinforcing.

http://europa.eu.int/comm/health

Interpretation in five languages (English, French, German, Portuguese and Spanish) and local transportation for participants with disabilities were provided thanks to donations from Novartis Europe and Swedish Orphan.
Executive summary

400 participants from 35 countries shaped the future of rare disease policies in Europe

The European Conference on Rare Diseases 2007 Lisbon was the 4th in a series of health and research policy conferences organised every two years. From the 27th to the 28th of November, more than 400 people from 35 countries shared their views and proposed actions for rare diseases.

The conference enabled patients, healthcare professionals, policy makers and industry representatives to interact with decision-makers from the European Commission and Member States. They debated key policies and actions to improve the lives of people affected by rare diseases.

The ERCD 2007 was organised by the European Organisation for Rare Diseases (EURORDIS) and its nine partners* in the framework of their common project “Rare Disease Patient Solidarity”. The event took place under the patronage of the Portuguese Ministry of Health, in the context of the Portuguese EU Council Presidency, and was supported by the Public Health Programme of the European Commission DG SANCO.

The programme of ECRD 2007 Lisbon was developed by an international committee of 14 members composed of patient representatives and health care professionals. The committee worked in conjunction with the DG SanCo Rare Disease Task Force and was supported by a local organising committee composed of national health authorities and patient group representatives.

→ THE EUROPEAN COMMISSION LAUNCHED ITS PUBLIC CONSULTATION “RARE DISEASES: EUROPE’S CHALLENGE”

The title of ECRD 2007 Lisbon “Patients at the heart of rare diseases policy development” was a perfect fit! ECRD 2007 Lisbon was the launching pad for an unprecedented Public Consultation regarding European action in the field of Rare Disease, initiated by the European Commission. This Public Consultation and its legislative outcomes will serve as a reference for all current and future rare disease policies in Europe for the next ten years.

→ A CONVERGING POINT TO INTEGRATE ALL ASPECTS OF RARE DISEASE POLICIES AND ARTICULATE EU AND NATIONAL LEVELS

The themes discussed covered a large spectrum: overviews of research and healthcare policies in EU Member states; patients’ needs in term
of medical, paramedical and social care; centres of expertise, European Reference Networks for rare diseases and future EU healthcare organisation; patient mobility in an enlarged Europe; success and challenges in orphan drug developments; the new regulation on advanced therapies and the advancements of gene and cell therapies for rare diseases; building on the success of EU research on rare diseases, orientations of the 7th Framework Programme and expectations of patients; emerging issues on quality assessment and innovative approaches; creation of European networks of specialised services of help lines, therapeutic recreation programmes and respite care services.

For each of these themes, presentations were based on two years of progress in policy development through national and European workshops or conferences, European working groups, projects lead by different stakeholders and partners and concrete experience. ECRD 2007 Lisbon was structured so as to allow in-depth presentations and discussions aiming to integrate national with European policies and to develop a patient-centred comprehensive approach to research and healthcare.

**→ PORTUGAL MADE THE FIRST PUBLIC PRESENTATION OF ITS NATIONAL PLAN ON RARE DISEASES**

The 4th European Conference on Rare Diseases 2007 Lisbon was the opportunity for the Portuguese Government to present its draft national plan on rare diseases and to launch a national public consultation – a first in Portugal. Everyone was able for two months to access the website of the Portuguese Ministry of Health and give his or her opinion to influence the future of people living with these diseases. The objectives of the plan are to improve prevention, diagnosis and access to health care services for rare disease patients. One of the main proposals is to create a rare disease information network through which it will be possible to share knowledge for more than 6000 registered rare diseases. Other proposals are to train health professionals and raise awareness in the general public as well as to create an integrated health information system.

**→ A MILESTONE IN THE PATH TOWARDS CENTRES OF EXPERTISE AND EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES**

The promotion of national centres of expertise was widely debated during the Conference. These centres are at the core of European Union vision on the future organisation of health services and medical care at European level.

The idea behind these centres is to gather information and share expertise about different rare diseases in order to reconcile the need of
geographical proximity with the need for highly-specialised care. The overall approach is to provide a framework for better quality care across Europe and for improved access to this care. Initially, knowledge should travel and patients should be able to travel, when necessary. The concept of a European Reference Network was developed first in the rare diseases health area where it will be applied. This was based on two years of discussions by the EU High Level Group on Health Services and Medical Care, the DG SanCo Rare Disease Task Force and EURORDIS’ 11 national workshops and one European Workshop in Prague in July 2007.

**RARE DISEASE PATIENT EXPERIENCE AND EXPECTATIONS REGARDING HEALTHCARE ACROSS EUROPE**

Rare diseases are complex; patients require a multidisciplinary approach to their disease and four to twelve essential medical services over a two year period. Rejection by health professionals is a major issue for people living with rare diseases; women are more likely to be discriminated against than men; rare disease patients needing specialised pain services have even more difficulty in accessing appropriate care. Patients can wait for more than five years before accessing proper social services. Rare disease patients need earlier access, in particular to the more specialised social services and they require a comprehensive approach integrating medical and social care.

These are few of the preliminary conclusions of the EurordisCare 3 survey carried out by the European Organisation for Rare Diseases (EURORDIS) in 23 European countries for 16 rare diseases involving 131 patient groups. Almost 6 000 people living with rare diseases responded to the questionnaire distributed in 15 languages.

When asked about their needs and expectations, 95% of respondents considered that sharing information between health professionals was crucial and 92% said that training of local professionals was also necessary to avoid having to travel abroad to find adapted care.

**NEW EUROPEAN NETWORKS OF SPECIALISED SERVICES FOR PEOPLE LIVING WITH RARE DISEASE**

After the ECRD 2007 Lisbon, the work concerning patients’ needs and expectations for centres of expertise and European Reference Networks, the creation of these networks is the third aim of the Rare Disease Patient Solidarity Project (RAPSODY) conducted by EURORDIS and funded by the European Commission and a consortium of partners*. The project’s objective is to improve the quality of life of rare disease patients and their
families by providing them with specialised services, information and assistance. Through the development and networking of help lines, the project also aims to fight patients’ isolation. The creation of therapeutic recreation programmes and respite care centres would allow patients and their carers to have a break from daily routine. Other services are being developed to help in the school curriculum and facilitate the transition of the provision of care from childhood to adulthood.

**BUILDING ON THE SUCCESS OF RARE DISEASE RESEARCH AND THERAPY DEVELOPMENT**

The European Commission DG Research presented a status report on achievements in the field of rare disease research policy. ECRD 2007 Lisbon offered the opportunity to report on the European Conference “Rare Disease Research: Building on Success” organised by DG Research in September 2007 in Brussels. This major multi-stakeholder event promoted rare diseases high on the research agenda of the Commission and has helped to establish the priorities for next few years. EURORDIS also reported on its European Workshop “Gaining Access to Rare Disease Research Resources” organised in May 2007 in Paris and supported by the Commission programme “Science & Society” to reflect on patient needs and priorities regarding research. This session was linked to another session on orphan drugs and advanced therapies. The major issues tackled concerned translational research and patient access across the EU to orphan medicines and later gene and cell therapies.

**POST CONFERENCE NOTE**

The Public Consultation on Rare Diseases that ended on February 14th, 2008 was a phenomenal success— the most successful ever in the field of public health in Europe. The Commission received 600 contributions from stakeholders across Europe and beyond; 460 answers to the consultation have been published on its website.

In 2008 the European Commission will present a “Commission Communication on European action on rare diseases” to the European Parliament, the Council of Ministers, the Economic and Social Council and the Council of the Regions. A Staff Working Document will be amended to it to detail each policy area based on the public consultation. An Impact Assessment Report will be published. The cornerstone of the Council Recommendations will be the promotion of national plans on rare diseases in each Member states.

The French EU Presidency has adopted rare disease as one of its health agenda priorities, together with the following EU Presidencies of Czech Republic and Sweden. It is expected that the Commission Communication on Rare Diseases will be adopted by November or December 2008, under the French Presidency, one year after ECRD 2007 Lisbon.

- Update on timeline:
  - 14 February 2008: end of Public Consultation
  - April 2008: impact Assessment
  - April-October 2008: Discussion in the European Parliament, Council, Economic and Social Committee and Committee of the Regions
  - Nov-Dec 2008: Expected adoption of the Communication under the French Presidency of the Council
THE ORGANISERS

EUORDIS / The European Organisation for Rare Diseases brings together 310 rare disease patients’ organisations from 34 countries including 23 EU member states. Eurordis is the voice of 25 million patients affected by a rare disease in Europe. It is one of the largest patients’ organisations in Europe. Eurordis’ objectives are to build a strong pan-European community of people affected by rare diseases, to be their voice at the European level, and to fight against the impact of rare diseases.

www.eurordis.org

AFM / Association Française contre les Myopathies. Created in 1958, the French Muscular Dystrophy Association (AFM) is a non-profit association whose members include patients and families affected by neuromuscular diseases. Its mission is to find a cure for these diseases, most of which are of genetic origin, and assist people affected by them. Supported by the generosity of millions of donors, AFM supports more than 400 research programs each year and has contributed to the emergence of policies and structures dealing with rare diseases in France and Europe.

www.afm-france.org

BARRETSTOWN / BARRETSTOWN is a specially designed camp, providing a programme of adventure, activities and fun - backed by the medical world - which helps children with serious illness regain their confidence and self-esteem. Barretstown provides challenging activity-based programmes for children affected by cancer and other serious illness and their families. These programmes are designed to re-build confidence, self-esteem, trust and courage, in a safe, fun and supportive environment.

www.barretstown.org

CLIMB / is committed to fighting metabolic diseases through research, awareness and support. CLIMB is the UK’s only dedicated organisation to provide advice, information and support on all metabolic diseases to children, young adults, families, carers and professionals. There are over 18 000 families affected by Metabolic Diseases in the UK over 38 000 throughout Europe. CLIMB is a national organisation working on behalf of children, young people, families, carers and support groups affected by metabolic diseases (genetic disorders). CLIMB currently provides information, advice and support on over 730 metabolic diseases.

www.climb.org.uk

FEDER / (The Federación Española de Enfermedades Raras) is a charity organisation which represents more than 90 rare diseases support groups in Spain. Since 1999 Feder has carried out activities to raise awareness on this health and social public problem, to support these families and improve their quality of life.

www.enfermedades-raras.org

FRAMBU / is a national competence centre for rare disabilities (covering approx. 100 different rare diagnoses). Frambu is a government-funded health and assistance programme. Frambu is a meeting place for families and professionals. Frambu’s offerings span the entire life cycle from childhood to old age. Frambu will gather, develop and disseminate knowledge about rare disabilities for persons who have been diagnosed, their relatives and healthcare professionals, so that children, adolescents and adults with impaired abilities can live a life in harmony with their condition, aspirations and needs.

www.frambu.no

FUNDACIÓ DOCTOR ROBERT / (Doctor Robert Foundation) is a training and advanced-services centre for Health and Life Sciences promoted by the Universitat Autònoma de Barcelona (Autonomous University of Barcelona) and the sanitary institutions that are part of its the Board of Trustees. The institutional mission of the foundation is to contribute to the professional development of health and life sciences’ organisations by looking for the synergies among the academic world and the health sector.

www.fdrobert.org

RARE DISORDERS DENMARK / RDD is an alliance of more than thirty national rare disease organisations. Rare Disorders Denmark works to improve the living conditions for people suffering from rare disorders and create a space for the mutual exchange of ideas and experiences.

www.raredisorders.dk

SUKL / (State Institute for Drug Control, Czech Republic) is the regulatory body in the Czech Republic responsible for the regulation and surveillance of human medicinal products. It is also involved in the regulation and surveillance of medical devices.

www.sukl.cz

EUROPEAN PARLIAMENT
Members of the Programme Committee

The Programme Committee of the 4th European Conference on Rare Diseases 2007 in Lisbon was composed of 14 members from 11 EU Member States, half patients’ representatives and half health care professionals. The Programme Committee was co-chaired by Mr Terkel Andersen and Prof Josep Torrent i Farnell.

Patient representatives

Françoise Salama, France
Françoise Salama is a volunteer, mother of 2 children, one of whom is young adult living with Duchenne muscular dystrophy. She is in charge of international affairs, AFM-Telethon. Former member of Eurordis board of directors. Member of the TREAT-NMD project.

Michele Lipucci di Paola, Italy
Michele Lipucci di Paola is a volunteer, parent of a young adult living with Thalassemia. He was a Eurordis Board Member from 1997 to 2006 and vice-president. Michele is a researcher in biological sciences at the University of Pisa.

Alicja Rostocka, Poland
Alicja Rostocka is a volunteer, mother of a child living with cystic fibrosis, and President of the Cystic Fibrosis organisation Poland

Paola Costa, Portugal
Paola Costa is a volunteer, mother of a child born with Cornelia de Lange syndrome, and President of Rarissimas

Tsveta Schyns, Austria
Tsveta Schyns is a volunteer, founder of ENRAH (EU Research Network for Alternating Hemiplegia). She is a biologist, but first and foremost she is a concerned mother. ENRAH groups patients, clinicians and geneticists.

Rik Serpentier, Belgium
Mr Rik Serpentier is a volunteer, Board Member, Belgian Association for the Parents of Children with Metabolic Disorders

Terkel Andersen, Denmark

Health Care Professionals

Dr Ségolène Aymé, France
Medical geneticist, director of research at the French Medical Research Council (INSERM), executive manager of Orphanet. She is the current chairperson of the Public and Professional Policy Committee of the European Society of Human Genetics and the leader of the Rare Diseases Task Force DG SANCO.

Prof Josep Torrent i Farnell, Spain
Member of the COMP. Member of the Rare Disease Task Force DG SANCO. General Director of the Dr Robert Foundation, Autonomous University Barcelona, organisation devoted to continuing medical education and postgraduate training. Full professor of Pharmacology, Therapeutics and Toxicology
Local Organising Committee

The organisers wish to thank the following organisations for their generous and volunteer participation to the Local Organising Committee that played such an important role in the preparation of the European Conference on Rare Diseases 2007 in Lisbon. The Local Organising Committee was composed of 9 persons from 8 Portuguese Rare Disease Organisations:

**Sandra Madeira**
Portuguese, 34 years old, works as Secretary of the Board and she is also ANPAR’s (Rett Parents and Friends National Association) President since February 2002.

**Ana Rita Dagnino**
Clinical Psychologist, Post Graduating in Brief Psychotherapies. Since 2004 she is founder and responsible for the Portuguese Haemophilia Society’s Psychology Department. She develops and works in projects aimed to improve the quality of life of people with rare diseases.

**Elvia Dias**
After her daughter Cristina was diagnosed with Rubinstein-Taybi Syndrome, she left her professional activity to become fully dedicated to the well being of her daughter. Because of this, she decided to create APART – Parent and Friends of Rubinstein-Taybi Syndrome Carriers Association, of which she is now President.

**José Pedro Cardoso Rodrigues**
José is 25 years old, living with Duchenne Muscular Dystrophy, software engineer, and active participant in APN since its beginning, in 1992. He is a Member of APN Board of Directors since 2003. In the scope of EURORDIS, participant in PARD 2 as document translator in 2001, participant in PARD3 as document translator and as an intervenient in an Workshop in Paris in 2003.
Volunteers

Maria Conception Maya
Maria da Conceição de Oliveira Miranda Maya, Portuguese, was born in Angola in 1951. She is a Kindergarten Teacher with a degree in Education Sciences. Founder and former President of the Portuguese Association of Parents and Persons with Haemoglobinopathies, she is now Vice President.

Marta Beirao
Marta is a volunteer, mother of three, a girl and two boys. Both the husband and daughter have Fabry’s Disease. She is Secretary of the Board of APL – Portuguese Association of Lysosomal Diseases.

Marta Jacinto
Marta Jacinto has a degree in Applied Maths and Computation and an MSc on IT, and works as an IT Specialist. She was diagnosed with PseudoXanthoma Elasticum PXE in 1997 and soon she became the PXE International representative in Portugal and works for the PXE cause in Portugal. She is also a Eurordis translator.

Paula Brito e Costa
Founder and President of the Board of Rarissimas is mother of a child carrier of Cornelia de Lange Syndrome. She is also Vice president of the World Federation of CdLS. She is the mentor of the fund raising national campaign for the construction of unique social equipment in the carriers of rare diseases world – “Casa dos Marcos” project, recognised by the First Lady of Portugal Maria Cavaco Silva.

Artur Madeira
Artur was born on 24th of March 1947 in Lisbon, married, with two sons and two granddaughters, is since 2005 a collaborator of RARÍSSIMAS – National Association of Mental and Rare Deficiencies. Since 1962 has been a volunteer in the area of sports.

Services

- Media Contact : Youngnetwork – Rita Branco and Joana Ricardo
- Event organiser in Lisbon : Mundiconvenius – Luisa Teixeira - Sofia Silva
- Marriott Hotel : Tomas Berger
- Photographer : Sylvain Gouraud
- For the conference web site :
- Graphics : Baptiste Ferrier - info@ferriergraphics.com
- Programming Php/MySql : Olf Software
- Programming XHTML/CSS/WAI, integration, project management : Gravelet-Multimédia
# The Conference programme

## Pre-conference workshops - November 26th
1. Workshop on Help Lines for Rare Diseases
2. Thalassemia International Federation and Pan-European Blood Safety Alliance Annual Meeting
3. Orphanet Network Meeting
4. Eurordis Council of National Alliances 5th Workshop
5. EuroWilson Meeting

## First day of the conference - November 27th

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MOBILITY IN EUROPE: FRAMING HEALTHCARE PATHWAYS TO PATIENTS’ NEEDS

Chair: Paula Costa, Rarissimas, Portugal

- A Patient’s Testimony
  Alicja Rostocka, Cystic Fibrosis, Poland

- The new rare disease challenges of patient migration and EU enlargements (testing issues, incidence and consanguinity, higher/lower European prevalence link to enlargement …)
  Dr. Jill Clayton-Smith, St Mary’s Hospital, UK

- Facing patient mobility needs in Europe
  Jaroslaw Waligora, DG Sanco, EU

Debate

Figure 1:
participants in ECRD 2007
### Second day of the conference - November 28th

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François Houyéz, Eurordis, EU |
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Pamela Davies, Climb, UK |
| - Assessing the quality of centres of expertise outcomes | - Fighting isolation for very rare disease patients (via help lines)  
Shane Lynam, Eurordis, EU |
| Prof Thomas Wagner, University Hospital Goethe-University Frankfurt, Germany | - The role of online communities for people living with a rare disease  
Dr Cécile Méadel, CNRS, France |
| - Assessing the quality of information on genetic testing | Debate |
| Alastair Kent, Genetic Interest Group, UK | Debate |

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| Dr Jose Robalo Directorate General for Health, Portugal | - Rare diseases at school  
Dr Anne Postel-Vinay, Integrascol, France |
| - New Italian actions | Debate |
| Dr Domenica Taruscio, Instituto Superiore di Sanita, Italy | - The French Emergency Project  
Dr Christophe Leroy, French Society Emergency Medicine, France |
| - The French Emergency Project | |
### SHAPING FUTURE POLICIES FOR ORPHAN MEDICINES AND ADVANCED THERAPIES

**Co-chairs:** Dr Ana Corrêa Nunes, COMP member and Infarmed, Portugal; and Dr Timothy Coté, Office of Orphan Product Development Office FDA, USA

- **Seven years of orphan drugs policy: what’s next?**
  Dr Kerstin Westermark, COMP Chairwoman, EMEA, EU

- **Preparing the European scenario for advanced therapies (gene therapy, cell therapy, future EU Regulation)**
  Dr Anne-Marie Masquelier, Genethon, France

- **Timely and equitable access to orphan medicines across Member States – The European HAS Workshop**
  Dr François Meyer, Haute Autorité de Santé, France

**Debate**

### TAKE HOME MESSAGES FOR ACTION.

The European society mobilised; member states partnering with each other and collaborating on European initiatives

Prof Josep Torrent i Farnell, COMP, Fundació Doctor Robert, Spain
Key Features of the Conference

420 participants from 35 countries, including 25 from EU/EEA: the 4th European Conference on Rare Diseases 2007 in Lisbon gathered participants not only from the European Union, but from the rest of Europe and of the world also. By countries of origin, the attendance was better distributed than for the previous conference in 2005 in Luxembourg: if France remains the country with the largest delegation, it represented 16.9% of delegates in 2007 compared to 30.4% in 2005.

An important contributor to the success of the conference in 2007 was the active participation of representatives of Portugal, the host country: Portuguese delegates represented 13.4% of delegates in 2007, compared to 1.1% in 2005 in Luxembourg. The decision to interpret the sessions in Portuguese was the key to this success.

Interpretation in five languages (English, French, Portuguese, Spanish and German) was also an important factor for registration: overall, delegates originating from France, United Kingdom, Spain, Portugal and Germany represented 52% of all delegates.

Figure 3: Participants European Conference on Rare Diseases
In terms of delegates’ categories, the composition of ECRD 2007 in Lisbon differed slightly compared to ECRD 2005 in Luxembourg: slightly less health care professionals in 2007 (39.7% versus 45% in 2005), and more representatives from the pharmaceutical and health industry in 2007 (11.9% versus 6.3% in 2005).

*Figure 04: Categories of delegates Comparison between ECRD 2005 in Luxembourg and ECRD 2007 in Lisbon.*

In terms of sex ratio, both conferences compared in equal terms:

*Figure 05: Comparison ECRD 2005 / ECRD 2007 Women and Men*
Funding

The 4th European Conference on Rare Diseases 2007 in Lisbon was mainly funded by the European Commission DG SANCO, registration fees and the Ministry of Health of Portugal in the context of the EU Presidency, for a total cost of 331,856 euros. Financial support from the industry helped providing on site interpretation in five languages and local transportation for participants with disabilities.

**Figure 06: ECRD 2005 Fundings**

- European Commission: 60%
- AFM: 6%
- Partners: 6%
- Registration fees: 28%

**Figure 07: Fundings ECRD 2007 Lisbon**

- European Commission: 60%
- Registration fees: 21%
- MofH Portugal: 21%
- Partners: 4%
- Novartis: 2%
- Swedish Orphan: 2%
Mr Terkel ANDERSEN, President of Eurordis, EU
Dr Ségolène Aymé, Director of Orphanet, France, and leader of the DG SANCO Task Force on Rare Diseases
Dr Catherine Berens, Scientific Officer, Medical and Public Health Research Unit, DG RESEARCH, EU
Dr Fabrizia Bignami, Therapeutic Development Officer, Eurordis, EU
Prof Jill Clayton-Smith, Professor of Medical Genetics, St Mary’s Hospital, Honorary Senior Lecturer, Manchester, UK
Dr Ana Corrêa Nunes, Coordinator of the Clinical Assessment-Department of INFARMED and COMP member, Portugal
Mrs Paula Costa, President of Associacao Rarissimas, Portugal
Dr Timothy R. Coté, Director, Office of Orphan Products Development, FDA, USA
Mrs Pamela Davies, Family Services Manager, Children Living with Inherited Metabolic Diseases CLIMB, United Kingdom
Dr Alexandra Fourcade, National Plan for Rare Diseases, Direction des Hôpitaux, Ministry of Health, France
Dr Francisco George, Directorate General of Health, Portugal
Mrs Birthe Holm, Vice-President Rare Disorders Denmark, Vice-chairperson of COMP, Denmark
Mr François Houÿez, Health Policy Officer, Eurordis, member of the Patients’ and Consumers’ Working Party at EMEA, EU
Mrs Lone Jensen, Chief Executive Officer, Rare Disorders Denmark, Denmark
Dr Edmund Jessop, Medical Adviser, National Commissioning Group, United Kingdom and member of the EU High Level Group on Health Services and Medical Care, member of the Rare Disease Task Force DG SANCO, EU
Mr Alastair Kent, Director, Genetic Interest Group, United Kingdom
Mr Yann Le Cam, Chief Executive Officer, Eurordis, member of the COMP, EU
Dr Christophe Leroy, Hôpital Louis Mourier, Emergency Unit, France
Mr Michele Lipucci di Paola, Thalassemia Organisation, Italy
Mr Shane Lynam, Project-Co-ordinator, Eurordis, EU
Dr Anne Marie Masquelier, Chief Executive Officer, Genethon, France

SPEAKERS AND CHAIR PERSONS
Dr Cécile Méadel, Researcher, Ecole des Mines de Paris, France
Dr François Meyer, Evaluation of Pharmaceutical Products, Haute Autorité de Santé, France
Mr Antoni Montserrat, Acting Head of Unit C-2 ‘Health Information’ Health and Consumer Protection General-Directorate (SANCO) Directorate C ‘Public Health and Risk Assessment, European Commission, EU
Dr Isabelle Moulin, Head of Medical Information, European Medicines Agency, EU
Prof Luis Nunes, Head of Genetic Department, Dona Estafania Hospital, Portugal
Dr Anne Postel-Vinay, Integrascol, Medical Genetics Department, Necker hospital, France
Dr Jose Robalo, Deputy General Director of Health, Directorate General of Health, Portugal
Mrs Alicja Rostocka, Vice-President, Polish Society against Cystic Fibrosis, Poland
Dr Andrzej Rys MD, Public Health Director DG SANCO, European Commission, EU
Prof Jorge Sequeiros, Director, Centro de Genética Preditiva e Preventiva, Division of Human Genetics Porto, Portugal
Dr Brigitte Soudrie, Head of department, Hôpital Marin d’Hendaye, France
Dr Eric Tambuyzer, Senior VP Corp. Aff. Europe & Int, Genzyme, Belgium
Dr Domenica Taruscio, Director, Istituto Superiore di Sanità, member of the COMP, member of the Rare Disease Task Force DG SANCO, Italy
Prof Josep Torrent i Farnell, Director Fundacio Dr Robert and member fo the COMP, Spain
Prof Thomas Wagner, Head of Department, University Hospital Goethe-University Frankfurt, Germany
Mr Jaroslaw Waligora, Administrator, Health Information Unit, Health and Consumer Protection, General-Directorate (SANCO) European Commission, EU
Dr Kerstin Westermark, Chairperson of the Committee for Orphan Medicinal Products, EMEA, EU
Dr Birgit Wetterauer, Scientific Officer, Federal Ministry of Education and Research, Germany
Dr Massimo Zeviani, Director, Molecular Neurogenetics Unit, Istituto Neurologico C. Besta, Italy
Dr Darko Žiberna, State Secretary of Health, Slovenia
Figure 8, 9, 10, 11: participants in ECRD 2007
1 OPENING SPEECHES

1.1 The word of the President of Eurordis

Ladies and Gentlemen,

It gives me much pleasure and it is a very great privilege to welcome you here in Lisbon, to welcome you to the Rare Disease Community which is, as you know a vibrant community that has not ceased to expand over the last few years. This has been demonstrated by the European level conferences which have been attracting an increasing number of participants, starting with Denmark in 2001, Paris in 2003, Luxembourg in 2005 (the first under a EU presidency) and now Lisbon in 2007.

Here we have managed to attract the largest number of participants from the largest number of countries ever. There are, in fact, more than 400 people meeting today from 35 countries, 23 of which are in the EU, plus Norway and Iceland. Not only is there an important geographical diversity, but also significant representation from all stakeholders. 49% of the delegates are patient representatives, 34% come from the health professional community, 12% from industry and 5% are policy makers at national and EU level.

These last years have been important to promote rare diseases as a public health priority. Major achievements have been recorded, not only in terms of community building, but also in terms of policy making. I’d like to mention just a few highlights which are worth remembering:

- the first Community Action Program, back in 1999
- the EU Public Health Programmes
- the EU Regulation on Orphan Medicinal Products, which led to the establishment of the COMP
- the adoption of the Regulation on Medicinal Products for Paediatric Use, 2007
- the EU Regulation on Advanced Therapy Medical Products, 2007
- the promotion and maintenance of Rare Diseases as a priority in the EU Public Health Programme and also in the EU Research Framework Programmes
- the EU has just released last week a Communication on “Rare Diseases : Europe’s Challenges”

This conference under the EU Presidency, with the support of the Portuguese government and the EU Commission, is the launching pad for a public consultation, offering you the opportunity to influence European action in the field of rare diseases. We encourage you to participate. The goal is to send a large number of contributions in order to show that
there is a real need for European initiatives which, together with Member State efforts, can be translated into concrete actions that can make a real difference for people living with rare diseases.

On behalf of the Programme Committee, which I’d like to thank very much for their effort organising the Programme of this meeting, I’d like to give you a brief overview of the two days to come:

Following the introductory speeches and the presentation of the draft communication by Mr Antoni Montserrat, acting Head of Unit C-2 ‘Health Information’ Health and Consumer Protection General-Directorate (DG SANCO-EC), we will learn about examples of Member States’ policies on Public Health and Research in the field of Rare Diseases. Then we will debate on National Centres of Expertise and European Reference Networks, following two years of intense European and local level discussions. This will lead us to issues of patients’ access to care, their experience and expectations, as well as issues on patient mobility in Europe and recent advances on quality assessments.

Given that this European conference has been organised by Eurordis, project on Rare Disease Patient Solidarity - the acronym is RAPSODY - the conference will address patients’ needs in a comprehensive approach - beyond medical care - displaying new European networks of specialised services. The two last sessions are especially important because they will wrap up a series of intense discussions and prior conferences in terms of making the most of EU research policy and shaping future policies for orphan drugs and advanced therapies.

Now beyond Lisbon…From the start of this conference, we need to keep in perspective the future in the promotion of public policies on rare diseases. In the next couple of years, the main challenge will be to transpose this dynamic to the local and national level in all Member States, leading to national plans in all Member States. A strong European Rare Disease Policy means strong Community and Member States’ policies. Then, another challenge will be to identify the five or six main priorities that we must focus on through the next years, which will be also one of the expected outcomes of this conference. Thirdly, to support the rare disease community and encourage the dialogue between all interested parties: patients, families, associations, health professionals, policy makers and the industry. Finally, to increase public awareness. This is important. There will be a specific opportunity where we can all share in on that. Next year, on the 29th February, we will celebrate the first
European Rare Disease Awareness Day and I invite you all to take part in that very fine activity.

To continue beyond Lisbon. The next EU Presidencies of Slovenia, followed by France, have assured us that they will follow up the good work of the Portuguese Presidency and continue supporting the cause of Rare Diseases. We are very honoured to have Darko Ziberna, State Secretary of Health from Slovenia here and also, as mentioned, Francisco George, Director General for Health from Portugal. The French Health Minister was not able to be among us today, but we have received a letter from the French Minister of Foreign Affairs, Bernard Kouchner, expressing the support of the French government to the Commission Communication on Rare Diseases and assuring us that, under their presidency, they will organise a debate that will lead to operational conclusions in the field of rare diseases.

We very much hope that the formal and informal discussions that will take place during this conference, will contribute to qualify these operational conclusions, and finally lead to their implementation.

This conference will encourage all stakeholders, here present I believe, to make their voices heard through their contribution to the draft Communication on Rare Diseases presented by the Commission.

Last but not least, I’d like to thank all those people who have made this conference possible. I mentioned the programme committee. I’d like to highlight also the nine partners of Eurordis in the Rapsody project. I’d like to specially thank the Portuguese Ministry of Health and also mention that this is a conference taking place under the Portuguese EU Council Presidency. I’d like to thank the Public Health Program of the European Commission and the DG Sanco as well as the Portuguese Rare Disease Associations that make up the local organising committee, and finally all the volunteers who you see all around wearing scarves with the logo of this conference.

By this, I hope you will really enjoy the next two days and that you will find inspiration for your contribution, to making the draft communication really fly and make true all our aspirations for rare diseases and the rare disease community in Europe.

With this I’d like to invite Francisco George the Health Director of Portugal to take the floor and to say some welcoming words.
1.2 The Directorate General of Health of Portugal

It is a pleasure and an honour for me to welcome you in our capital of Lisbon on behalf of our Portuguese Minister of Health. This conference, the work involved in it as well as its forthcoming positive outcomes and achievements mean a lot to us. Hopefully the weather will be fine and I hope everybody will enjoy their time here with us.

The Public Health’s commitment now is to make up for wasted time as it was realised that not enough emphasis was placed on the issue of rare diseases in the past. As a consequence, a year ago we took the decision to create a Committee in order to develop strategic measures, with the aim of enhancing early diagnosis, prevention and control which would, in time, contribute to better treatments of rare diseases as, although rare, are frequent among us.

Keeping in mind Eurordis’ great initiative for the organisation of this conference, and with the approval of the Portuguese Government, I would like to symbolically present you the first draft of the Portuguese Rare Disease Programme. First of all, to start this conference, I should say that the Portuguese Government decided to place the new programme for rare diseases up for public consultation and focus on aspects of prevention, early diagnosis and prompt treatment.

As all of us are aware, the problem of rare diseases has major repercussions on the National Health Services. Since the majority of rare diseases are chronic, severe and disabling and need specific and complex treatments, they are often considered as a burden to the Health system.

Our plan is up for discussion until January 31st and involves 3 pillars. Regarding the first one, emphasis will be put on intervention strategies, prompt diagnosis and treatment which implies the creation of a network of Centres of Expertise for rare diseases, and a network focused on the clinical and laboratorial aspects, bearing in mind that this is all occurring at a time of major reorganisation of the Portuguese Health services.

The second pillar, of no less importance, will deal with post graduation of medical doctors, nurses, and experts on pharmaceutical sciences of all communities.
The third pillar of this programme will be about information. In order to monitor and assess the development of our programme, and based on statistics, a system, led by outside resources, will be implemented.

Today, the programme was launched and presented for public consultation and we would like to encourage all specialists, patients and their representatives, citizens, stakeholders, and pharmaceutical industries’ representatives who are responsible for production and marketing of medicines for rare diseases to give their contributions.

In terms of Public Health, our next step is to make up for wasted time and we believe that, the work of Eurordis and forthcoming debates, as well as your participation in this conference and the countries you represent, will highly contribute to finalise all aspects and fine-tuning of our programme.

Regarding the European Commission, I would like to pinpoint that we have always had a good relationship with them and that their numerous contributions during our close work on many programmes such as those done for the European Council, are of great importance and we really feel the benefit of it all.

Thank you very much.

1.3 The State Secretary of Health of Slovenia

Dr Darko Ziberna welcomed the participants and presented some aspects of the preparation of the European Presidency by the Government of Slovenia in the first half of 2008. Intervention in Slovenian, not available for transcription in this report.
1.4 The European Commission – DG Health and Consumers’ Protection

European activities on rare diseases
27 November 2007, Lisbon

Ladies and Gentlemen,

First, I would like to mention that Markos Kyprianou, Commissioner for Health and Consumer Protection, had to attend other important meetings today. He asked me to pass on his warmest thanks to Minister Correia de Campos and Secretary of State Darko Ziberna for their personal involvement and for the support of the Portuguese and Slovenian Presidencies of the Council. He also wanted to thank the organising Committee, and particularly EURORDIS, for arranging and hosting this important European Conference on Rare Diseases. Finally he wanted me to express his best wishes to participants for the success of this Conference, co-sponsored by the European Commission and supported by the EU public health programme.

The focus on RD is a relatively new phenomenon in most Member States. Until recently, public health authorities and policy makers largely ignored these challenges due to the splintering of policy debates across many different Rare Diseases rather than the recognition of common issues for all the Rare Diseases.

The lack of information about rare diseases often means that sufferers, who together represent more than 6% of the total EU population (around 15 millions of citizens in the European Union with 27 Member States), do not always benefit from the health services they need.

Special combined efforts are needed to address rare diseases so as to prevent significant morbidity, early mortality or a considerable reduction in an individual’s quality of life and socio-economic potential. The life expectancy of Rare Disease patients risks to be significantly reduced if a strong European action it’s not implemented. Many rare diseases are complex, degenerative and chronically debilitating, whilst others are compatible with a normal life - if diagnosed in time and managed and/or treated properly. They affect physical capabilities, mental abilities, behaviour and sensorial capacities, and generate disabilities. Several disabilities often co-exist, with many functional consequences. These disabilities enhance the feeling of isolation and could be a source of discrimination and reduce any educational, professional and social opportunities.
At European level, rare diseases were tackled in a precursor programme on rare diseases adopted for the period 1 January 1999 to 31 December 2003. They had been a priority in the EU Public Health Programme 2003-2007 and remains as a priority in the new European Union Health Programme (2007-2013) recently adopted by the Council and the Parliament.

The Commission has also adopted in 2007 a very important Communication on Health Strategy which pointed rare diseases as a main priority for the action of the Commission in the next 10 years.

Also these same days the Commission is presenting in Brussels the proposal of Directive on Health Services where the aspects of mobility of patients and reference networks for diseases will have a strong influence in the rights of rare diseases patients in the new European space of free circulation of patients.

Since their creation in 1995 the European Medicines Agency (EMEA), has provided the European Union and its citizens with the best scientific assessments of the quality, safety and efficacy for hundreds of biotech or other novel products for human use. Twelve years ago, the EMEA initiated a new tradition of full transparency of its operation by publishing all its assessment reports and conducting a permanent dialogue with its stakeholders, including health professionals, consumers and patient groups.

Under the responsibility of the Commission and the EMEA a policy on Orphan Drugs is being implemented. The Orphan Medicinal Product Regulation from 1999 was proposed to set up the criteria for orphan designation in the EU and to create incentives to encourage the research, development and marketing of medicines to treat, prevent or diagnose Rare Diseases. The last report, published by the Commission in 2006 permits to say that the EU policy for orphan drugs is a success and one of the most successful EU policies overall.

In the period between April 2000 and August 2007, the EMEA has received more than 740 applications for orphan designation. As of July 2007, more than 40 different new orphan medicinal products have received a marketing authorisation for the treatment of more than 40 different life-threatening or chronically debilitating RD. In addition, more than 500 further medicines have already been designated by the Committee on Orphan Medicinal Products (COMP) as orphan me-
dicinal products, but are still undergoing clinical tests. The Commission knows very well that a lot of additional effort is needed in this area and a lot of problems for acceding in equal conditions to orphan drugs exists and measures in order to ensure equal access to everybody needs to be implemented.

In 2000, a Committee on Orphan Medicinal Products (COMP) was established in the European Medicines Agency, charged with reviewing the designation applications from persons or companies who intend to develop medicines for rare diseases. I had the pleasure to remember you that this committee was the first EU committee where patients are permanently represented. I will thank EURORDIS for the positive role played.

The Public Health Programme has supported since 1999 a total of 34 projects in the area of rare diseases with a funding around 10 million euros. Some of these projects are international references used extensively by experts and patients all around the World:

- I will only briefly refer to the database ORPHANET, the most important database for rare diseases and orphan drugs for the general public in Europe.
- The successive projects implemented by EURORDIS for building a public policy on rare diseases, improving quality information on rare diseases and orphan drugs, based on a survey, workshops and guidance documents.
- The EUROCAT network (Surveillance of congenital anomalies in Europe) that provides essential epidemiologic information on congenital anomalies and acts as a resource centre for people and professionals.
- The ENERCA (European Network for Rare Congenital Anaemia’s) and many, many others.

In parallel, the EU 7th Framework Programme (2007-2013) contains new open priorities permitting also to act in the field of rare diseases. Emphasis will be put on translational research (translation of basic discoveries into clinical applications including scientific validation of experimental results), the development and validation of new therapies, methods for health promotion and prevention. More specifically, the focus for rare disease research in FP7 is on Europe-wide studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions. Our colleagues of the DG Research will deeply present these priorities during the days of the Conference.

Under this EU Research Program, there is the EURORDIS Euro-BioBank project about the creation of a European network of Biological Resource Centres, where DNA, cell and tissue samples are collected, and information on the bio materials to support research
on rare diseases. This is an excellent example of how patient’s organisations can actively contribute to the action and the research in the field of rare diseases.

I want also mention the extraordinary role for supporting the EU action in the field of rare diseases played by the EU Task Force on Rare Diseases.

The commitment, the professionalism and the work of the experts involved in this Task Force has been and it’s always precious for the European Commission. This Task Force provides a forum for discussion and exchange of views and experience on information and knowledge in the field of rare diseases. The support of the Scientific Secretariat of the Task Force, leaded by Orphanet, and the particular role of the Task Force leader, Ms Ségolène Aymé, merits special mention and our fully recognition. I can give you the assurance that this scientific support to the Task Force on Rare Diseases will be continued from the Commission using the new financial facilities created by the new Public Health Programme.

The objective of the European Commission in the coming years is to sum up the necessary elements for an efficient policy addressing the important issue of Rare Diseases in Europe. The proposal for a Commission Communication (to be followed by a Recommendation of the European Council) for a European action in the field of rare diseases is a strategic objective of the EU. More details on the content of this proposal will be given in the session later.

Our main intention is to improving the chance for patients to get appropriate and timely diagnosis, information and care. This will in turn contribute to the growth in Healthy Life Years, a key Lisbon Strategy indicator.

This effort will requires to strength the cooperation between EU programmes: the EU Public Health Programmes, the Framework Programmes for Research and Technological Development, the Orphan Drugs strategy, the paediatric drug regulation, the advanced therapies strategy, the future Health Services Directive, the EU Statistical Programme and any other existing or future EU initiative. It will require also encouraging the development of national health policies to ensure equal access and availability of prevention, diagnosis, treatment and rehabilitation for people with RD. And will require, finally, to ensure that common policy guidelines are developed and shared everywhere
in Europe in areas such as research, reference networks, access to information, incentives for the development of orphan drugs and screening. The future Commission Communication is also expected to reinforce cooperation between MS, within a Community framework.

In 2003 the Commission invited all EU Health Ministers, representatives of the European Parliament and some European NGOs representing civil society, including European doctors and patients to engage in a high level reflection process on patient mobility and healthcare developments in the European Union. These activities have been taken forward through the High Level Group on health services and medical care established in July 2004. The High Level Group has agreed in principle to involve civil society participants in relevant working groups, and there is clearly a valuable contribution that organisations such as EURORDIS are making.

One of the Working Groups of this High Level Group addresses reference networks on rare diseases and is led by France. Fruitful exchanges have always taken place with the Task Force on rare diseases. Some principles have been developed regarding what should be these European Reference Networks on rare diseases, including their role in tackling rare diseases or other conditions and about some criteria that such centres should fulfil.

The Work Plans 2006 and 2007 for the implementation of the EU public health programme have introduced, as a priority in the area of Rare Diseases: the development of pilot project for these European Reference Networks. According to this priority some pilot Projects have been selected for funding: in Cystic Fibrosis, Rare bleeding disorders, Alpha 1 antitrypsin deficiency, Porphyries, Dysmorphology, Paediatric Hodgking’s Lymphoma, Histocytosis, and Paediatric Neurological diseases.

→ CONCLUSION

As I said the Commission has proposed in October 2007 a new health strategy for Europe together with ambitious plans under the new Public Health Programme 2007-2013.

A European Action in the field of Rare Diseases is one of the main priorities in this strategy. For this reason the Commission has decided to propose to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions the adoption of a Commission Communication for a European Action in the field of Rare Diseases. The adoption of this Communication requires from the
side of the European Union, to give to the civil society, to the patient’s organisations, to the health professionals, to the national, regional or local authorities and to any EU citizen the opportunity to provide ideas in order to prepare this document.

This is the mind of the process that we call Public Consultation. Since this week the European Commission has opened in the EU Health Portal and in the web site of DG SANCO the possibility to everybody to contribute to this future EU action in the field of rare diseases. The text is available in English and during December 2007 translations in 21 languages of the European Union will be also available in the mentioned sites. The date for closing this Public Consultation is the next 14th February 2008.

I have the pleasure to invite you to actively contribute to this public consultation. The Commission needs your opinions and suggestions and wants to implement their policy in a so important area with the maximum consensus and the most possible contributions from all the stakeholders involved in this field. It’s a real pleasure for me to declare today opened the Public Consultation on the European challenges on rare diseases and to ask your contributions. Don’t hesitate and express your opinions, your critics and your hopes.

This conference will focus today and tomorrow on the importance of EU actions on rare disease and review the progress made so far. Presentations during this conference will allow projects funded and carried out between European partners to be better known.

We expect an extensive exchange of information, experiences and best practices, in the different sessions. All participants are invited to contribute ideas for concrete recommendations on how to improve life expectancy and quality of life of persons living with rare diseases in Europe.

My colleagues in the Commission and myself look forward to continue working together with you and all the interested partners and European organisations represented here today. We keep an excellent memory of the previous 2005 European Conference on Rare Diseases in Luxembourg and I’m sure also that we will keep an excellent memory of this Lisbon Conference during our next 2009 Conference in Poland.

Thanks to every one of you, special thanks to EURORDIS and to the Portuguese Presidency of the Council and all my wishes of success to the 2007 European Conference on Rare Diseases.
2 EUROPEAN POLICY

2.1 The European Commission
Communication on Rare Diseases

2007 is a pivotal year for rare diseases. Member states and European Institutions are preparing this rendez-vous of national and European efforts in order to coordinate action and propose recommendations to improve the lives of people living with rare diseases. In this session, patients and their representatives, health care professionals and other stakeholders had a great opportunity to debate with representatives of the European Commission, and thus make their presence felt in this event.

Introduction and presentation of the communication

→ INTRODUCTION

The exact title of the Communication is: Proposal for a Commission Communication to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions on a European action on Rare Diseases.

A Commission Communication is a legal text presented by the European Commission to the other European institutions inviting them to take action in a certain field. In the case of this Communication on Rare Diseases, the long title represents exactly what the European Commission intends to do: invite the European Parliament, the Council, the Economic and Social Committee and the Committee of Regions to act in the area of Rare Diseases.

The concept of “rare disease” was used for the first time in 1978 in an article published by Holzman NA. Rare diseases, common problems: recognition and management. Paediatrics, 1978; 62(6):1056-1060. This was nearly thirty years ago and we have now entered a new area when the concept of rare disease is being consolidated.

The legal basis for the developments of Public Health Policy is Article 152 of the European Treaty. The Community Action Programme on Rare Diseases adopted for the period 1st January 1999 to 31st December 2003, pioneered a period of increasing changes for rare diseases in Europe. It was followed by the EU Public Health Programme 2003-2008 which included rare diseases as a public health priority.
However, it should be pointed out that the European Commission is not competent to organise health care systems at national level for patients with rare or chronic diseases. This is the responsibility of the Member States. It is competent to act in the areas defined by the European health strategies or by a Public Health Programme. The European Commission can only create a framework for cooperation between Member States to act in a specific area.

In 2007, the Commission adopted a new and more ambitious health strategy with rare diseases high on the agenda. Rare diseases have become a “normal” item to discuss between the different bodies at the European Commission.

Another example of this new awareness is the number of EU-funded projects supporting rare diseases. Under the 7th Framework Programme, thirty-four projects have been approved in public health. There is a good synergy between projects approved and supported by the European Commission from the Public Health Programme and projects supported in the area of research. This link between public health activities and research activities is important.

This article will provide a short overview of the impact of the Commission Communication, the DG SANCO priorities on rare diseases and how this Communication will be implemented.

The Commission Communication on Rare Diseases
Impact of the Commission Communication
A Commission Communication is not a legally binding document, but it can greatly influence the activities of the Member States. It gives all rare disease stakeholders a European text that can be used as a reference. Consequently, national authorities can be referred to this text to implement actions in the area of rare diseases.

These recommendations are sustainable, valid in legal terms and generally adopted across EU, i.e. the recommendations on electro-magnetic fields, cancer screening were adopted in almost all Member States. A communication means something the Commission will do. The Communication on Rare Diseases may be adopted under French presidency (2nd semester of 2008) or Czech presidency (1st semester of 2009).

One of the most important recommendations in this communication is the adoption of a national plan for Rare Diseases in all Member States. At
present, out of the 27 Member States only one country, France, has a national plan. Other countries are discussing the launch of one: Bulgaria, Italy, Portugal, Romania and Spain. This situation should be improved. This Commission Communication will not have much effect, if it is not accompanied by the rapid establishment of national and regional plans in all 27 Member States. The ambition of this text is to make it a moral obligation for the Council of Health Ministers to adopt this initiative at national and regional level.

Highlights on the DG SANCO priorities on rare diseases
Mr Montserrat highlighted the most important priorities. The exhaustive list of priorities can be found in his presentation.

1. Common definition of rare diseases in the EU
   It is important to consolidate a single definition that can be applicable across Europe

2. Common approach for a better codification and classification of rare diseases in the process of revision of the International Classification of Diseases

   In the existing international classification of diseases approved by WHO, only 300 rare diseases are classified and codified and 1,000 can be identified by deduction from other codes. The objective is to classify and codify all 6,000 – 8,000 rare diseases.

   A disease needs to be identified with a classification and a code. It is a way to give disease recognition and to facilitate reimbursement with the national health care systems for the patients.

3. Necessity of national plans for rare diseases in the EU Member States and European guidelines for the elaboration of the national plans for rare diseases

   There is a need for European guidelines on how to establish national plans for rare diseases. The EU-funded EuroPlan project launched in 2007 and lead by Domenica Taruscio from Italy aims to help Member States without a national plan to create guidelines and confront experiences in order to establish national plans for rare diseases in the future.

   Common databases and medical protocol for the identification of rare diseases: it is important that common databases and medical
protocols for the identification of rare diseases be translated to inventory and codification.

4. Common approach to the support of patient’s organisations

5. Creation of the EU Advisory Committee on RD
   There is a need for a European method to support the Rare Disease community.

   The High Advisory Committee on Rare Diseases was created for this purpose. The European Commission needs to increase support and funding for patient organisations.


   National/regional centres of reference were established to share knowledge and experience on rare diseases. The European Commission should facilitate the transfer of knowledge and the circulation of persons between the EU centres of reference.

   The following priorities need to be discussed:
   7. Development of e-Health in the field of RD:
      the EU insurance card could be an important tool in providing information on the patient.
   8. Availability and accessibility of accurate diagnostic tests, including genetic tests
   9. Evaluation of population screening (including neonatal screening) strategies for RD
   10. Primary preventive measures when possible (i.e. folic acid)
   11. Best practices on RD care
   12. Equal access to orphan drugs – access is currently unequal; some patients do not even have any access to them in some countries
   13. Orphan Medical devices and orphan diagnostics
   14. Health Technology Assessment of Orphan Drugs
   15. Coordinated compassionate use programme: they depend on industry and Member States, which is not acceptable.
   16. Specialised social services: the Action Plan for Disability includes rare disease patients who often suffer from serious disabilities
   17. Supporting databases, registries, repositories and biobanks Biomarkers
   18. Data protection
19. Networks of research for RD
20. Coordination between MS funding agencies
21. Intensifying Research
22. Common approach to the empowerment of patient organisations
23. Development of health indicators in the field of RD
24. Organisation of European Conferences on RD: conferences such as ECRD should become regular events
25. Creation of the EU Advisory Committee on RD
26. Rare Diseases in the EU budget
27. Establishment of a Community Agency for RD
28. Regular report on the situation of RD in the EU

Implementation of the Commission Communication
   A public consultation has been launched in English first, then in all languages, before adopting the recommendations. All stakeholders are encouraged to contribute, by email, in writing, anonymously or not. The Communication is available on the EC website. All contributions are important and will be used: they will be listed and summarised on the website. This is a great opportunity for the European Commission and the Rare Disease community to work together. The EU is involving its citizens. This is an invitation to respond.

2. How was the Communication developed?
   It was developed with the participation of a group of rare disease experts across Europe: Dr Ségolène Aymé, Dr Domenica Taruscio, Christel Nourissier, Dr Laura Fregonese, Dr Catherine Berens, Dr Rumen Stephanov, Dr Jordi Linares Garcia. It is therefore the fruit of a collective work.

   It is a long process before the adoption of a final version of the Communication: 1st draft, impact assessment, discussions with EU institutions, and finally, adoption of the Communication in November 2008.

1. Timelines:
   - June 2007: First Draft in consultation with Task Force
   - August 2007: Final Draft
   - September 2007: Process of consultation starts with specialised bodies
   - November 2007-February 2008: Public consultation
   - March 2008: Impact Assessment
   - March-October 2008: Discussion in the European Parliament, Council, Economic and Social Committee and Committee of the Regions
Debate with the audience

Dr Timothy Coté, Director of Orphan Products Development, Food and Drug Administration, started by mentioning bilateral collaboration between the FDA in the USA and the EMEA in Europe, as demonstrated by the common submission form to submit an orphan drug designation application that is now in place. Dr Coté welcomes the European initiative for a communication on rare diseases, as it may inspire the US policy in this domain.

Torben Grönnebaek, President of Rare Disorders Denmark, warmly thank the representatives from the European Commission: “It is the best Christmas present we ever had”. The draft communication seems very comprehensive and embracing all aspects that need to be tackled when addressing rare disease policy. The public consultation should help focusing on the top priorities and thus, a large number of contributions would be more than useful. Europe is not one country, and this communication should be seen as a tool to promote best possible care of rare diseases in our respective Member States. To focus on the importance of national plans for rare diseases is key to the cause.

For Jane Meijlink, International Painful Bladder Foundation, small grass root patient organisations always have a great deal of expertise on the disease their cover, but less experience and understanding of international health policy and the political process. Conferences such as this one are very useful tools to better understand these issues, and to see what role patient organisations can play.

Marco Meinders, from the ADCA-Association of the Netherlands and Euro-Ataxia, highlighted the need to support patient organisations both at national and at European level, as the networks can hardly sustain and thrive through good will and enthusiasm only. For example, the ADCA-Association of the Netherlands receives structural funding from the Dutch Ministry of Health.

George Constantinou, Thalassemia International Federation, called for more collaboration to define European treatment and care guidelines for each disease, to help diminishing differences in access to care and in quality of care throughout Europe.
Dr Martin Johnson, Thalidomide Trust UK, was concerned about resources: to him, the key resource is the knowledge. Barriers need to be broken down, and the DG SANCO initiative is creating framework to bring that knowledge into a level of harmony. Change does not come because there is money already available, change comes because the needs are identified and agreed on, and information shows that this is where the resources will go. “We need that level of free trade knowledge” said Dr Johnson. Speaking in his role of the Thalidomide Trust, Dr Martin Johnson shared his worries about a health care community based on the free trade in products for profits, whereas the purpose should be in free trade of knowledge for the benefits of the patients.

A delegate from Hungary suggested emphasizing the need to teach medical students and post graduated doctors. In his medical division, a training course was created six years ago focusing on diagnosing rare diseases. Among 800 medical students engaged in their 4th or 5th year of medical studies, 50 to 60 attend the course. Practising doctors can also take the course, and learn what resources exist to help them diagnosing rare diseases in their daily practice. Medical training should be at the heart of the communication.

Birthe Holm, Rare Disorders Denmark, also thanked the Commission representatives. The communication, when adopted, will be an important step forward, and an ambitious one: “We need ambitious goals to build something good”. A possible objective or indicator could be to have a national plan for rare diseases in each one of the 27 EU Member States by 2012. This communication is a basis to build collaboration at the EU level.

Flavio Minelli, Italian Rare Diseases Alliance and Eurordis, stressed the importance of paragraph 4.4 of the communication about Empowerment of patients. The importance to recognise the role of patient organisations and of the right for self-determination and self-decision of the patient should be underlined.

Alastair Kent, Genetic Interest Group UK, had diverging views on the communication: the communication may have too many aims, and if adopted, the work will only begin, but efforts might be diluted. The communication may results in a mechanism that will slow down rather than accelerating access to good quality care. For example, if enormous efforts have to be spent on classifying diseases, creating codes and defining categories before launching new registries, then these registries are
likely to be created much later than expected. Rather, the communication should be a vehicle for seeing the delivery of the EU ideal of equity of access: “let’s make sure this document is not just a series of high flowing words but a real roadmap to access good quality care”.

Dr Andrzej Rys⁹, Director of Public Health, European Commission DG SANCO, commented on the importance to perform an impact assessment (Evaluation of the extent to which a policy causes changes (e.g., economic, social, environmental) for a target population.), and to do so, data need to show that measures proposed in the communication can actually produce change and how to measure it. Numbers and figures are needed to convince that EU institutions, Member States and patients’ organisations are doing rightly what they want to achieve together.

Dr Darko Ziberna¹⁰, Secretary of Health of Slovenia, thanked the audience for its comments on the importance of the policy for rare diseases, as the Slovenian government will chair the EU Presidency during the first half of 2008.

Lastly, Terkel Andersen¹¹, President of Eurordis, called for sustainability of the actions, and their continued financing. If all Member States adopt a national plan for rare diseases by 2012, then adequate resources need to be allocated now and for the future. A suggestion could be to use the financial resources allocated in each Member State as another indicator, a sort of “Beauty contest” of Member States commitment to rare diseases. Member States capable of grasping the true added value represented by the European collaboration in order to make the best of our national policies would be rewarded.
2.2 Centres of Expertise and European Reference Networks for Rare Diseases

Centres of expertise are at the core of European Union thinking and experimentation on the future organisation of health services and medical care at European level.

The Rare Disease Patient Solidarity (Rapsody) project conducted by Eurordis and funded by the European Commission and a consortium of partners has created an intense dialogue on their usefulness and on possible recommendations for the identification of centres of expertise, their support and evaluation, both at national and European levels.

The EU High Level Group of Health Services and Medical Care made of representatives of member states presented its analysis and vision.

The patient perspective was also based on a large patient survey – EurordisCare 3 – to analyse patient needs and expectations for 16 rare diseases from 23 countries and on workshops that took place in 2007 in 11 member states.

Building a European policy addressing citizens’ needs

Abstract – Citizens as patients need prompt diagnosis, access to effective treatments and care or support. Early diagnosis is best achieved in centres of expertise. The European community can help these centres to communicate with each other through networks. Effective treatment requires first research and then often commercial developments. The Commission has already been active in this arena. Travel for treatment remains a problem. Social support is important but the added value of European action for care close to home is not obvious. Finally European policy must sooner or later address disparities in care between member states. This is difficult because levels of health care are closely tied to the overall wealth of the state, but it has been achieved for agriculture. Cows are equal in Europe, why not patients?

Keywords: Policy, networks, disparities.

→ INTRODUCTION

As citizens what do we need from our policy makers? Two things above all – fairness and consistency. We want policies to be fair – that is, to treat like cases alike and to treat special cases specially. And we want consist-
policy that remains stable over time: not for ever, of course, but long enough to build teams and develop excellence.

As patients we have certain other needs – needs for prompt diagnosis, for expert treatment and for care and support. How can European policy help to achieve these goals?

We need moral philosophers to engage with the ethical questions that we are facing: the dominant moral philosophy in the UK National Health Service is that we must use our money to do the greatest good for the greatest number of people. That is an acceptable ethic but it is not the only ethic, and obviously our concern today is to put as much resource as is needed for people with rare conditions. We need moral philosophers to articulate the ethic behind that very strong feeling that we all share because I can assure you that in the committees and the policy making and management teams it can be very difficult to defend putting let us say 30 million pounds towards a single simple group of patients when there are so many other claims on that money.

→ PROMPT DIAGNOSIS

Diagnosis of rare disease is often difficult. At present much of our European policy work is directed at better diagnosis. At first it seemed that the best way forward would be to identify the clinical teams or hospitals that were particularly expert in certain rare diseases. The Commission’s High Level Working Group readily agreed recommendations from the Rare Disease Task on the characteristics of expert centres [1]. These included matters such as a high number of cases, research activity, good relationships with patient groups, teaching and training, and so on. But the application of these criteria to specific hospitals was not so easy. Member states did not want experts acting for the European Commission to reach deep into their health systems to label the centres of expertise. We may need to rely on professional societies to achieve this goal. It has already been achieved in some spheres: there is for example a European scheme for European quality assurance in a number of laboratory services which has the effect of labelling the services which are first class and hence also indirectly those that are not.

Because member states did not want a Europe wide activity of labelling expert centres for rare disease, the Commission has focussed on helping experts to collaborate with each other. This information activity may directly benefit patients by allowing a diagnosis to be made by an expert from a different country – a good example of this is the dysmorphology
network [2]. Or the benefit may be less direct as the networks allow us to pool knowledge from many countries about the characteristics of very rare diseases – here the example is the network on rare bleeding disorders. We now have a series of pilot networks funded by the Commission which will allow us to explore the benefits to patients of different kinds of collaboration.

All of this work requires doctors to be open with each other, and willing to refer patients. This has not always been the case in the past!

So meeting patients’ need for prompt diagnosis depends on certain behaviours by doctors. Fostering the desired behaviour mostly depends on education and training but there may be a small place for regulatory policy. In the United Kingdom, the General Medical Council now includes in its list of duties of a doctor the rule that you must ‘recognise and work within the limits of your competence’ [3]. This helps to make sure that patients don’t get stuck with doctors who know little about their rare disease. Problems of ignorance remain. If a doctor does not even suspect a rare disease, he or she will not refer the patient on to someone with more expertise. One must have some sympathy here for the family doctor who sees 20 or 30 patients every day: only once in 50 years or more will one of those patients have some of the diseases we are talking about today. Indeed medical students have long been taught ‘When you hear hoof beats don’t look for zebras’ [4]. Perhaps our best safeguard is the another doctrine taught to generations of doctors: the best way to make a diagnosis is to listen to your patient (or in the case of children ‘listen to the parents’). ‘Listen to patients’ is a good rule for policy makers too!

**EFFECTIVE TREATMENT**

1. **Research**

   Before patients can benefit from effective treatment, the treatment must be discovered. This requires research, and we already have a good range of European policies and funding to support research in rare disease. For new therapies the next stage, after basic research, is commercial development and again the Orphan Drug legislation is designed to support this.

2. **Drug Therapy**

   Although the orphan drug legislation has helped to get drugs for rare disease to market, the next stage - access for patients - remains problematic. Some of these problems were explored at the EPPOSI workshop in Copenhagen [5] last month. Undoubtedly the very high cost of some
of these medicines is a major factor. On the whole member states seem to be prepared to pay very high costs provided the price is seen to be fair, though accurate information is difficult to obtain. Difficulties can arise at local level. In England a key instrument for funding very expensive drugs is to establish a national budget so that the cost does not fall disproportionately on local budgets. Italy also has a national list which helps to ensure uniformity in this field.

A key goal of European health policy must be to remove these disparities in access to treatment of proven effectiveness. It is less obvious what the correct mechanism is to achieve this policy goal, particularly if many of the problems arise at local level in devolved health systems.

3. Interventions and procedures
Pills and tablets are easy to ship around Europe to where the patient lives. But what if the required treatment is not a drug but an operation, for example a liver transplant or complex neurosurgery? It is not just a matter of flying a single surgeon out to do an operation – complex conditions require inputs of knowledge, skill and special equipment from many different expert teams. Although our main strategic goal is to spread expertise so that patients do not have to travel, nevertheless it will sometimes be necessary for the patient to travel to the centre of expertise. Patient mobility is the subject of a commission working group but attention has been focussed on holiday makers who fall ill abroad, or people who settle in different countries. Patients with rare disease have specific problems because they have to travel further than patients with common conditions to find the relevant expertise. So special policies may be needed.

Some of the policies on patient movement are being developed through judgements in the European Court of Justice [6]. This is good for prompting action in recalcitrant member states but policy development in the courts has two drawbacks. Firstly courts can only rule on cases which are brought before them. In the United Kingdom rare disease patient organisations have used legal processes (judicial review) with some success to prompt changes in local health policy, but legal actions are very costly. Secondly court judgements tend to establish rights rather than policies, and rights have to be exercised. Policies based on exercising rights tend to favour the affluent and well educated and fail the poor and ill educated. Exercising rights also requires plenty of spare time and energy – both are in short supply in households looking after family members with severe disease.
“Guérir quelquefois, soulager souvent, consoler toujours” - Cure sometimes, improve often, always support. For some rare diseases we have, alas, no cure. But support is always needed. Disabling disease places immense strain on families, and in the case of genetic disorders it is usually the mother who takes the main burden. We should recognise this in our policies.

For something as intrinsically local as social support, what is the role of Europe-wide policy? This is an area we need to explore and it will take time because I suspect that language will get in our way. ‘Treatment for haemophilia’ means the same throughout Europe: but what meaning is conveyed by the words ‘social services’? Do the words which are translated into English as ‘social support’ or ‘social services’ cover the same range of activities and policies in every one of the 27 member states?

Clarity is essential for good policy. And our difficulty here is not one of translation. It goes deeper than that. We are a community of many different systems and cultures. So the words may be translated correctly but convey different meanings in different health systems. It took me several years to realise what was meant by the phrase ‘centre of reference’ when spoken by a French health administrator!

Let me give another example of how important it will be to keep our language precise. Suppose we set up special arrangements for rare disease. The agreed definition of a rare disease in Europe is one which at any given point in time affects less than 5 per 10,000 populations. But actually most of us here mean a lot more than that when we say that we need policies for rare disease. We mean disease which is not just rare but also severe – fatal or severely disabling. And I suspect that we probably don’t mean to include rare cancers, because our focus is for the most part on genetic disorders. These distinctions may not matter much today but they certainly will if we succeed in setting up policies for rare disease which are strong and effective.

I said at the beginning that as citizens of a European community we want policies which are fair and consistent, so let me end with fairness. It is fair to ask for special treatment for special circumstances – such as rare diseases. But a community is fundamentally unfair if it fails to treat like patients alike. We must accept the fact that some member states of Europe are much richer than others – gross domestic product per person is around 20,000 Euros in, for example, the United Kingdom, France and
Germany but below 15,000 Euros in, for example, Portugal, Latvia and Lithuania. So on the face of it some member states can afford much more health care than others. This seems like an insuperable problem. But it has not prevented us from developing a common approach to farming – a common agricultural policy. I look forward to the day when we have a common health policy. Cows are equal in Europe – why not patients?

REFERENCES

Patients’ needs and expectations concerning access to health services - Eurordiscare 3 study

INTRODUCTION
The EurordisCare3 survey was launched to provide evidence on rare disease patients’ need for adapted health care. We needed to go beyond patients’ anecdotes or patient groups’ views in order to find out patients’ experience-based opinions with solid quantitative data. The aim is to contribute shaping patient-centred public health policy, health services and medical care, at a time when several European countries are involved in the (re)organisation of their health care provisions for rare diseases.

The objective of this EurordisCare survey is to describe and compare patients’ experiences and expectations regarding access to health services for a variety of significantly relevant rare diseases across Europe.

A UNIQUE APPROACH
The EurordisCare approach is unique because it is based on a scientific methodology to collect data from patients and families identified through the patient groups’ networks.
→ METHODS
The EurordisCare 3 survey is based on one common questionnaire, adapted to 16 rare diseases and to 23 countries and translated into 15 languages. A total of 20,022 copies were sent to 131 committed patients’ organisations from February to October 2008, and 5,963 questionnaires were filled-in and returned to Eurordis (30% response rate), representing 1,020,000 data recorded.

The 16 diseases involved are:
- Marfan syndrome
- Fragile X syndrome
- Williams syndrome
- Ehlers-Danlos syndrome
- Cystic fibrosis
- Prader-Willi syndrome
- Epidermolysis bullosa
- Tuberous sclerosis
- Myasthenia
- Osteogenesis imperfecta
- Huntington disease
- Friedrich Ataxias
- Aniridia
- Pulmonary arterial hypertension
- Chromosome 11q disorders
- Alternating hemiplegia

The 23 countries are:
- Austria,
- Belgium,
- Croatia,
- Cyprus,
- Czech Republic,
- Denmark,
- Finland,
- France,
- Germany,
- Greece,
- Hungary,
- Ireland,
- Italy,
- Luxembourg,
- Malta,
- Netherlands,
- Norway,
- Romania,
- Slovakia,
- Spain,
- Sweden,
- Switzerland,
- United Kingdom

And the questionnaire was translated in the 15 following languages: Croat, Danish, Dutch, English, Finish, French, German, Greek, Hungarian, Italian, Norwegian, Romanian, Slovak, Spanish, and Swedish.

→ PRELIMINARY RESULTS
All results of EurordisCare 3 survey will be analysed in-depth by Eurordis and by academic research teams.

All results will be provided early 2008 to each of the 131 patient groups for their patient and families. They will be able to compare their respective
results with patients with the same disease in other European countries as well as with patients affected by other rare diseases in their country.

The results presented at ECRD 2007 Lisbon are the three main findings and the four key expectations for centres of expertise for rare diseases, which are immediately coming up very high across the 16 rare diseases and the 23 countries studied.

**MAIN FINDING N°1 : RARE DISEASE PATIENTS NEED COMPLEX HEALTH SERVICES FOR COMPLEX DISEASES**

Patients reported an average of 9 different types of medical care or service over the last two years, on a daily, weekly, or monthly basis, or sometimes just on time over the period for each service. In 42% of cases the required service was a medical specialist consultation, in 33% the service was a medical test or an examination, and in 25% the service was a specialised care. This average varied from 5 to 6 different types of medical care or service for Fragile X, Aniridia or Huntington and up to 10 to 12 different types for Ehlers Danlos, Prader Willi, Marfan Syndrome, Cystic Fibrosis, Pulmonary Arterial Hypertension and Tuberous Sclerosis.

1. Access to the 8 most needed medical services was difficult or impossible for patients in 26% of cases as shown in figure below:

![Figure 13: Difficulties in accessing medical services](image)
For patients reporting that access was impossible (11%), the lack of referral (69%) was the main reason for not accessing the medical services, followed by unavailability of services (52%) and waiting time (41%). It is important to note that the impossibility of access is not linked to a single obstacle but two cumulated obstacles on the average the lack of access is due to at least two reasons.

Figure 14: reasons for not accessing medical services

Among factors that drove difficulties in accessing care, family income was an important one. Families with lower income have more difficulties in accessing care, as reported by other studies. Lowest income families have twice more difficulties to access care compare to families with highest income.
2. Most needed medical services properly addressed patients’ expectations in only 50% of cases.

![Figure 15: relation between income, education and difficulties in accessing medical services](image)

20% of patients were not satisfied with the medical services offered (11% because they had no access, 2% because they were not at all satisfied and 7% because they were poorly satisfied). 30% of patients were partially satisfied. This leaves only 50% of patients and families fully satisfied regarding their most needed medical services; these results are even lower for other medical services needed but not most needed.

Some types of care were particularly problematic:

- For pain control, 37% of the patients needing it had not access at all.
- For rheumatologic care, access to care was impossible for 26% of patients and 23% were not at all satisfied or poorly satisfied.

**Finding N°2: Rejection by health professionals is a major issue for rare disease patients.**

Based on their experience, 18% of rare disease patients were rejected by health professionals because of their disease. The main reason for rejection given to patients was the complexity of the disease (69%).
Reasons for rejection varied in great proportions between diseases, as shown on the figure below: for Ehlers Danlos, rejection was reported by more than 40% of respondents. Patients with Ehlers Danlos, Epidermolysis Bullosa, 11q Chromosome disease are mostly rejected based on the complexity of their diseases when patients with Huntington, Tuberous Sclerosis, Fragile X, Williams Syndrome or Prader Willi Syndrome are mostly rejected because of their aspect, their behaviour or their communication deficiencies.

Figure 17: causes of rejection, by disease
1. Female patients are more rejected
All together, females were 34% more likely to be rejected than males: 20.1% female patients experienced rejection by health care professionals as opposed to 15% of male patients.

2. Patients needing pain control are far more rejected
Patients needing pain control were even more rejected: 42.4% of rare disease patients needing pain control services were rejected as opposed to 15.5% of patients not needing pain control. Patients needing pain control services were about 3 times more likely to be rejected by healthcare professionals throughout Europe.

3. Patients with lower income are more rejected
Income was a strong factor related to rejection, as was education to a lesser extent. The lower the income, the higher the rejection.

→ FINDING N°3: RARE DISEASE PATIENTS NEED SOCIAL ASSISTANCE AS MUCH AS MEDICAL CARE

29% of patients needed to meet a social worker over the last 12 months, and the frequency of this need varied by diseases, as shown below:

*Figure 18: % of patients needing social services, by disease*
1. **Huge difficulties and extremely long delays to access social assistance for patients with rare diseases**

Still, 32% of patients said it was difficult or impossible to access social assistance.

In average, delays to obtain social assistance were far too long: from the moment the patient starts experiencing the rare disease, it takes more than 5 years to have real access to social assistance. Dissatisfaction was higher for specific assistance (purchase of wheelchair, home adaptation, medical consultation abroad) than for general assistance (social, legal and financial rights).

2. **Four specific patients’ expectations regarding centres of expertise for rare diseases**

1. Rare disease patients agreed that specialised centres are essential to address their needs: **95% of patients agreed with the statement that medical information sharing and coordination between all professionals who care for her/him in the specialised centre is useful or essential.**

2. For the training of health care professionals, **92% of patients declared that training of local professionals on specific needs of patients is essential or useful.**

3. **93% of patients** agreed with the notion that the mission of a specialised centre is to **inform patients about their rights and to guide them towards services, schools, leisure activities.**

4. Lastly, **91% of patients** stated that the mission of a specialised centre is to **create materials for teachers, employers, social services, insurance companies and the general public,** to inform them about patients’ needs and improve social integration of patients.

**→ CONCLUSION**

Key messages for Centres of Expertise and European Reference Networks for Rare Diseases

To address the major issues of lack of access to most needed medical services, poor satisfaction for these medical services, rejection by health care professionals, barriers and delays in accessing social assistance and lack of specific social assistance,
Rare disease patient are expecting that centres of expertise for rare diseases:

- Know their disease well and accept to treat it
- Have a multidisciplinary approach to address all their essential needs
- Share and coordinate patients’ medical information between professionals
- Integrate medical care and specific social services linked to the rarity of the disease in a comprehensive approach
- Provide training for local professionals
- Provide information material about their disease and guide them in order to improve social integration

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Paving the road for integrated policies - the RAPSODY workshops’ outcomes

→ OBJECTIVES OF THE RAPSODY PROJECT

- To engage and to develop dialogue between patients, health care professionals, health care systems experts and health authorities
- To address needs and expectations primarily of patients and families but also health professionals and policymakers regarding centres of expertise for rare diseases
- European reference networks of centres of expertise
- To develop recommendations for
- Principles and criteria for the identification of national centres of expertise and European reference networks
- The evaluation of their respective outcomes

→ ENGAGING DIALOGUE

Dialogue on National Centres of Expertise and European Reference Networks was facilitated both at National and European level.
At National level, series of one day workshops were organised in 11 Member States from March to July 2007, with same agenda, same format, and same composition of the audience. Overall, 272 participants (133 patient representatives, 106 health care professionals and 35 policy makers participated).

At European level, a workshop took place on 12-13 July 2007 in Prague, under the auspices of the State Institute for Drug Control of the Czech Republic, SUKL, with 80 participants from 13 countries.

→ MAIN OUTCOMES OF THE DIALOGUE

11 national workshops

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<th>Member State</th>
<th>Date</th>
<th>Organiser</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Rep.</td>
<td>2nd March</td>
<td>SUKL</td>
<td>37</td>
</tr>
<tr>
<td>Denmark</td>
<td>26th March</td>
<td>RDD</td>
<td>19</td>
</tr>
<tr>
<td>France</td>
<td>29th March</td>
<td>Alliance Maladies Rares</td>
<td>26</td>
</tr>
<tr>
<td>Germany</td>
<td>19th March</td>
<td>ACHSE</td>
<td>20</td>
</tr>
<tr>
<td>Italy</td>
<td>24th March</td>
<td>UNIAMO</td>
<td>18</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>22nd March</td>
<td>ALLAN asbl</td>
<td>11</td>
</tr>
<tr>
<td>Spain</td>
<td>23rd March</td>
<td>FEDER</td>
<td>37</td>
</tr>
<tr>
<td>Sweden</td>
<td>16th March</td>
<td>Swedish Alliance</td>
<td>28</td>
</tr>
<tr>
<td>Netherlands</td>
<td>11th April</td>
<td>VSOP</td>
<td>22</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>28th March</td>
<td>GIG</td>
<td>29</td>
</tr>
<tr>
<td>Portugal</td>
<td>30th March</td>
<td>Ass. Haemophil Portugal</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Total 272 participants</strong></td>
</tr>
</tbody>
</table>

1. Pre-conditions
Two essential pre-conditions were drawn. The first pre-condition related to professional qualifications of health care professionals practising in specialised care centres, both on clinical and scientific experience. Proven qualifications could be documented by publications, grants, pre-existing certification or an accreditation process. A second condition should be the commitment to cooperate and to share information. The importance of an “atmosphere and attitude” of trust rather than competition among experts to ensure effective cooperation was also largely highlighted.
2. **Patients access to a multidisciplinary team of experts**

It was felt that universal competence does not exist in any single member state, both at the level of centres of expertise and European networks and therefore a cross-disciplinary approach is needed to meet rare disease patients’ needs. Only multidisciplinary approaches can be effective in providing adequate care.

Rare diseases are complex diseases involving different medical specialties and a wide range of paramedical healthcare professionals working in close collaboration with social workers. Centres and networks that succeed in organising care through a multidisciplinary approach are on the right track.

3. **Importance of communication and coordination between professionals**

This coordination is needed:

- within centres, between all professions
- between centres, highly specialised ones and less specialised ones that are easier to access or closer to where the patient lives
- within networks, combining European and international knowledge of rare diseases to adopt consensus guidelines on how best to treat individual rare diseases and to co-ordinate research
- Between care and research activities
- An intelligent way of circulating information and organising the continuum of activities can be obtained by placing the patient at the centre of the system, and by optimising the use of existing expertise and resources, in order to improve the quality of care and to reduce the psychological burden of the patient (feeling lost in the system, lack of support, language barriers).
- Between medical care and social care
- Social support is often underestimated and European networks should have the specific administrative tasks to support patient mobility for cross-border care, addressing the reimbursement issue.

No patient should feel neglected because he cannot be treated at a well-known highly specialised centre led by a leading international expert which is situated hundreds or thousands of kilometres from where he or she lives. No patient should think that the local hospital where he or she can be treated rapidly when the need arises is a stopgap or second-best. Other medical teams could instead give better care to their patients by learning from care centres designated as expert. Any centre applying for qualification or accreditation in line with a set of standards established for the care of a given disease or group of diseases would thus ensure that patients benefit from the network’s expertise of care. It will no longer be necessary to travel long distances to see an expert, in fact the expert will communicate with the treating practitioner and medical team via telemedicine, training seminars, treatment consensus conferences and medical staff exchanges etc.
4. **A critical mass of patients**

Centres and networks should target to pool patients with similar conditions, as this is a condition for increasing scientific and medical knowledge on each disease. The identification of unknown aetiologies will help the management of complex and rare situations, but at the condition that enough patients can be enrolled in trials.

5. **General expectations**

The development of best practices, standards and guidelines for diagnosis, treatment and care of rare diseases at international level was most welcome. Dissemination of European reference diagnostic and therapeutic protocols will ensure equity at European level by reducing the impact of the” postcode lottery” and will increase trust in local services. Provision of expert opinion for the confirmation of diagnostic and therapeutic options should also be possible.

6. **Research activities at European and International level**

Organising networks of integrated care and research, combining higher numbers of patients and multidisciplinary expertise on the disease will generate progress via different methods:

- Multi-centre clinical studies and facilitation of partnership with pharmaceutical companies
- Shared databases, shared biological resources (DNA, RNA, tissues, cells), registries (harmonisation of procedures), international epidemiological surveillance, pharmacovigilance
- Participation in EU-funded research projects
- Perform education and training

Reference networks and centres of expertise should have a role on information to the public and the primary health care professionals (to improve referrals and follow up), and communication outreach activities are essential to achieve this. Training activities for health professionals, including staff exchanges, meetings and conferences to exchange best practices, to harmonise processes and to disseminate standards and guidelines should also be in the mandate of centres of expertise.

7. **Activities to empower patients**

To build patients’ and families’ capacity to manage the medical and social aspects of their rare disease, to enhance their autonomy, increase their compliance and help improve their quality of life, the centres should propose educational activities in close cooperation with patients’ organisations.
The cooperation with patients’ organisations should be articulated at different levels:

- Patient organisations contribution to the management and evaluation of networks
- Facilitation of the creation of patients’ groups
- Enhancement of exchanges between professionals (care and research) and patients
- Promoting links between European reference networks, research networks and patient organisations

8. A general agreement is that

European reference networks should be:

- Initially evaluated and accredited at EU level via an agreed set of criteria (minimum set of standardised criteria and objectives)
- Regularly assessed on common indicators with soft values and hard values
- There is a need to develop methods and tools for European reference networks to perform regular self-evaluation. Proposed soft values and hard values could be:

<table>
<thead>
<tr>
<th>Soft values</th>
<th>Hard values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperation with patient org.</td>
<td>Time to diagnose</td>
</tr>
<tr>
<td>Patient oriented approach</td>
<td>Waiting time</td>
</tr>
<tr>
<td>Improved outcomes</td>
<td>Genetic consultation</td>
</tr>
<tr>
<td>Improved atmosphere</td>
<td>Multidisciplinary approach</td>
</tr>
<tr>
<td>Improved quality of life</td>
<td>Cooperation with other centres</td>
</tr>
<tr>
<td>Avoiding unnecessary complications</td>
<td>Guidelines / recommendations</td>
</tr>
<tr>
<td>Awareness and knowledge dissemination</td>
<td>Quality control</td>
</tr>
<tr>
<td>Information provision to local centres</td>
<td>International /national networking</td>
</tr>
</tbody>
</table>

9. Economic and management aspects

of European reference networks

Reference networks were perceived to be cost-effective, they need proper funding for their specific European and international activities, they need long term sustainable public funding, they should be encouraged to share good governance practice (organisation, leadership, regulation, steering committee) and coordination practice between them. They should be able to disclose their procedures and their outcomes.

10. Importance of flexibility when selecting types of centres belonging to the networks and flexibility in relation to the geographic coverage of the networks

There should be no obligation for a network to have centres in all Member States, and the density of centres will depend on the population.
size. European networks could play an active role in the accreditation of national centres of expertise. Patients’ agreement to travel should be confirmed, detailed and responded to.

Different suggestions were made on the structure of the networks, with ”leading centres” and ”associated centres” and possible” sub-national networks” with ”centres of competence”. Different type of centres and with different related diseases could be grouped within a European network. An excellent contribution of new member states to European reference networks is foreseen.

➔ IN SUMMARY

1. **Main criteria for the designation of centres of expertise**

   Two essential pre-conditions:

   • Professional qualification: both clinical and scientific experience. Proven qualification documented by publications and grants and pre-existing certification or accreditation.

   • Commitment to cooperate and share information.

2. Patient access to a multidisciplinary team of experts
3. Combine research and care
4. Report volume of relevant activity
5. Importance of coordination between professionals
6. Importance of global approach (holistic, comprehensive) integrating medical and social aspects
7. Participation in research activities at European and international level
8. Perform education, information and communication outreach activities with the public and primary health care professionals
9. Perform training activities for health professionals
10. Perform activities to empower patients and collaborate with patient organisations

➔ ADDITIONAL CRITERIA FOR THE FUNDING OF EUROPEAN REFERENCE NETWORKS

• Capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control

• Involvement in epidemiological surveillance, such as registries

• Close links and collaboration with other expert centres at national and international level and capacity to network

• Appropriate arrangements for referrals of patients from other Member States established within a framework
Methods for Evaluation

A general agreement is that European reference networks should be:

- Initially evaluated and accredited at EU level via an agreed set of criteria (minimum set of standardised criteria and objectives)
- Regularly assessed on common indicators with soft values and hard values

Centres should define their goals when applying for designation and these goals should serve for the evaluation of their activities: have they met their objectives after three or five years?

Acknowledgements: Advisory Committee

1. Patient representatives
   - Simona Bellagambi - Italy, Tuberous sclerosis Organisation and UNIAMO
   - Christel Nourissier - France, Prader Willi and Alliance Nationale Maladies Rares
   - Rosa Sanchez de Vega - Spain, Aniridia and Federacion Española de Enfermedades Raras FEDER

2. Health care professionals
   - Prof. Dian Donnaï - UK, Medical Genetics, St Mary’s Hospital
   - Prof Birgitta Strandvik - Sweden, Inst.of the Health of Women and Children, Goteborg University
   - Prof Olaf Rieß - Germany, University of Tuebingen / Department of Medical Genetics

3. Health policy makers
   - Dr Alexandra Fourcade - France, Ministry of Health & EU High Level Group on Health Services and Medical Care
   - Dr Ségolène Aymé - France, Orphanet and DG SANCO Rare Diseases Task Force
   - Dr Edmund Jessop - UK, Department of Health, National Specialist Commissioning Advisory Group (NSCAG) & DG SANCO Rare Diseases Task Force
2.3 Mobility in Europe: Framing healthcare pathways to patients’ needs

Rare diseases have no frontiers; they affect people from all parts of Europe and beyond.

The construction of Europe and the establishment of a single market for goods and services, the abolition of internal frontiers and the exchange of information have created a new kind of traveller: the patient in search of quality care. In this session, patients explained why they can be tempted to move to a different state when affected by a rare disease, health care professionals explained how they organise health services for foreigners, and the impact of population displacement. Patients’ mobility needs are now fully part of the evolution of our health care systems.

A patient’s testimony: Lung transplantation for cystic fibrosis in Poland

Cystic fibrosis (CF) is the most common, life threatening inherited disease amongst the Caucasian population. There are estimated 100,000 suffers worldwide and 1 in 2500 live births of children with cystic fibrosis. In developed countries average life expectancy for people with CF is approximately 30 to 33 years but in Poland the life expectancy falls below 18.

Since the early 1980s, lung transplantation has been pursued as an option to improve the quality of life for people with end-stage pulmonary disease including CF. The first patient with CF to receive a heart-lung transplant was performed in 1984. But although there are 4 transplant centres in Poland there is no CF patient who has received lung transplantation in Poland till now.

When Iga was 16 years old it was obvious that the only rescue for her was lung transplantation. Her parents decided to send an application to Polish Ministry of Health. Waiting for the answer they got in touch with one of Polish Transplant Centre. They got a positive answer and Iga was listed for transplant.

But after one year waiting Iga’s parents realised that Iga had minimal chance to get a transplantation because there were only a few lung donors a year in Poland. Nobody had told them that before.
They decided to ask for help a transplant centre abroad. The Vienna centre answered positively. It was the last possible moment when she received “new lungs”. But the parents had to pay all cost of transplant – more than 100,000 Euro.

The transplant was performed 2 years ago. Iga feels very well now. But she has a post-transplant treatment in Vienna because there is no one who could do it in Poland. And her parents have to pay for it full price.

Iga has a national insurance. But she has to pay for her treatment full price. Theoretically she could have received lung transplantation for free in Poland but it was obvious that it was only theoretically. She would have died before getting transplant in Poland for sure.

The new rare disease challenges of patient migration and EU enlargements

Many thanks for asking me to speak today on the subject of patient migration within the EU and the challenges which arise as a result. First of all, I’d like to make clear that I am speaking as a clinician who works with families who have rare diseases on a day to day basis, rather than an expert in patient migration. My talk today is therefore based on real life scenarios which demonstrate some of the situations we face as a result of increasing movement of individuals within the progressively enlarging EU.

During this presentation I am going to address the various problems which may be encountered as a result of patient migration and I am also going to attempt to discuss how some of these are currently being solved, or might be solved in the future with the appropriate resources.

Migration in the EU

The rates of both immigration and emigration to and from many of the partner countries of the EU are progressively increasing as more countries are accepted into the EU and individuals then become free to move from one EU country to another. At the moment, there is net movement into some of the original EU countries, with net movement out of some of those which later accession. I cannot discuss all these figures in detail here but the MPI Data Hub has a website with reasonably up to data figures of numbers of migrants and what percentage of the population of each country they make up. For most EU countries it’s somewhere between 5 and 20%. This graph shows the pattern of immigration and emigration for the UK, where 600,000 legal immigrants were known to have entered
in 2006. There are of course many reasons why people choose to move from one country to another. Studies have shown that the main reason is for better employment prospects, although escaping war, natural disasters and famine also play a part. Securing better educational opportunities and better housing are also significant reasons. Finally, a small but significant proportion move countries to obtain better healthcare.

→ MIGRATION AND HEALTH

It’s well established that there are mutual economic benefits for both migrants and the countries they are accepted into, as migrants gain a better standard of living but provide skilled labour and become tax payers.

Migrants moving to a new country carry with them their own particular patterns of health-related issues, however, referred to by some as a health “footprint”. As many of them are moving to escape poverty, the health profile they bring with them is often that associated with poverty, for example heart disease and some infectious diseases such as TB. Statistically speaking, rare diseases form a relatively small proportion of the health burden of migrants, but it’s a very important one because of the specialist services they require.

→ CHALLENGES IN THE CLINIC

I’d like to demonstrate the need for some of these specialist services by looking at some examples from the genetic clinic. In this first scenario a young couple present with a severely disabled first child who is small with a small head size. A brain scan has shown an abnormal brain with the presence of calcium within the brain tissue.

→ TWO POSSIBLE SCENARIOS

I’d like to demonstrate how the approach to this would differ depending on whether you were dealing with a family from your own local population or a migrant family. In the normal situation you would have easy access to previous medical notes written in your own language to verify the history and find out further information. There would be no language barrier when you were taking the history from the couple and discussing your conclusions with them. You would make a diagnosis based on the most likely scenario for a couple of that particular ethnic background, and in this case it would be very likely that congenital infection was the cause of the baby’s problems.

In the second scenario you are faced with a baby with identical problems but this time the parents do not have English as a first language. The
baby was born abroad and treated there initially but you have no information about this. You manage to take a history with the aid of an interpreter, but the interpreter does not understand some of the specialist terms you use and so the consultation is difficult. You are concerned that this baby might have the autosomal recessive disorder Aicardi-Goutiére syndrome which mimics congenital infection but the baby’s original brain scans are not available and you have to arrange more. You discuss with the family the fact that this condition may have a 1 in 4 recurrence risk. As there are numerous first cousin marriages within the family you also explain that other family members may be at risk but you need to take care not to be judgmental so that they do not perceive that they are being blamed because they have married a cousin. You want to write them a summary letter but will have to make arrangements for this to be translated at significant expense or it will be no use to them.

Thus, you have two babies presenting with very similar problems, but the way you approach these situations to make sure that both of them were managed in the best way would be very different.

→ WHAT ARE THE CHALLENGES?

This case demonstrates many different challenges; how the way we think in terms of differential diagnosis varies and the difficulties that we encounter when families move from one country to another leaving their medical details behind them. Working with interpreters can be difficult, especially when you are dealing with complex situations like rare diseases. Family members may volunteer to translate but you cannot be sure that they will not have their own agenda which means that they could pass on biased information. Sometimes, it’s the children in the family who have the best English and end up taking on the responsibility of translating for parents. There may be a clash of cultures between healthcare professionals and the family, with different value systems. This requires sensitivity when discussing issues such as consanguinity and prenatal testing with the option of termination of pregnancy. We have to try not to be too paternalistic, however, and you cannot assume for instance that all people from a certain cultural background would refuse prenatal testing, they need to be offered a choice even if we feel uncomfortable discussing it. These cultural issues require healthcare staff to have appropriate training.

→ CONSANGUINITY AND RARE DISEASES

I wanted to make a point of mentioning the issue of consanguinity. In some communities, for example the Middle East, Southern Asia, Turkey
and Irish Traveller families, first cousin marriages are the cultural norm. Often, this goes back to the old-fashioned dowry system where a father had to pay money to marry his daughter into a man’s family, and marrying a cousin kept the money within the family. Another reason for consanguinity is isolation, with rates of consanguinity being much higher in rural populations, where there is no-one else unrelated to marry. This table reflects the varying rate of consanguineous marriages for several ethnic backgrounds:

<table>
<thead>
<tr>
<th>% consanguineous</th>
<th>rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>22</td>
</tr>
<tr>
<td>Spain</td>
<td>6.8 (26)</td>
</tr>
<tr>
<td>British Pakistani</td>
<td>69</td>
</tr>
<tr>
<td>White UK</td>
<td>0.4</td>
</tr>
<tr>
<td>Scotland</td>
<td>2.6</td>
</tr>
</tbody>
</table>

A large study carried out by the late Sarah Bundy and colleagues in Birmingham in the UK in the 90s demonstrated that the rate of birth defects among the offspring of first cousins was doubled compared to the general population risk and that this increase was accounted for by the increased incidence of autosomal recessive disorders in the consanguineous couples. In this situation both parents carry a single copy of the same gene fault. When present in a single copy the gene fault causes no problems but if both parents pass the gene fault on to a child, who therefore has a double dose, then problems will arise. The risk of this happening is 1 in every four pregnancies. For consanguineous couples where there is no history of recessive disorders in the extended family, the risks are still relatively low, but if a previous baby has been born into the family with a recessive disease, then the risks to another related couple are considerably higher. The cornerstone of management of these families is to be able to identify which couples might be at risk, based on their extended family history and to target them for counselling.
In this second scenario we are faced with a couple of Pakistani origin who present with a family history of cystic fibrosis. Remember that in some EU countries migration on a large scale has not just occurred from other EU countries but from countries outside the EU.

**ISSUES ARISING IN FAMILY 2**

In this family, again we have no medical records, so it’s difficult to get confirmation of diagnosis and perhaps unlikely that previous genetic testing has been done. We can therefore only screen this couple for the commonest CF mutations. We have to make sure, however, that we screen for the common mutations in their particular ethnic group, so that we can give them a relevant carrier risk if they screen negative. This has significant implications for the laboratory. When we counsel the family, the information we provide about CF and the long term outlook depends on where that child will receive care. If the family plan to move back to rural Pakistan, then specialist care may not be so good and prognosis may be poorer. If we did identify a mutation we may not be able to follow our usual practice of offering cascade screening if other family members were still in Pakistan.

**FAMILY 3 : FLOPPY BABY**

In this third scenario we are again faced with two babies who have a similar presentation, that of a floppy baby. In this case, one of the fami-
lies was a migrant couple from a Roma population. They denied consanguinity in this case. Their baby has very rare condition of congenital myasthenia, an autosomal recessive disorder with a particularly high gene frequency in the Roma population but one which we virtually never see in our own UK population. We knew this because the family has had a previous affected child, but to be honest, it would have been very difficult for us to make the diagnosis without that clue. It emphasized the importance of doing some background reading about the health problems that are common in the migrant population of the families you are seeing.

*Figure 20:*

→ **LESSONS FROM FAMILY 3**
If you finally do make the diagnosis, it’s difficult accessing specialist help or investigations for an affected child if there is no demand for a service within your country, and the parents may feel very isolated if there are no other families with the same condition to share their experiences with and no local support group.

→ **FAMILY 4 : A DYSMORPHIC CHILD**
Even clinical assessment of patients with rare diseases can be difficult when it depends on recognising physical features that may vary from one population to another. Both of these patients have the Prader-Willi Syndrome, for example, but it’s so much more difficult to recognise in
the child of a different background when you are not use to knowing what is normal for that ethnic background. For rare syndromes, finding literature for the family in a suitable language can be difficult, too.

**→ HOW CAN WE IMPROVE THINGS?**

I’ve flagged up a lot of problems but how can we improve things? There is no doubt that establishing Networks of experts in rare diseases and rare disease registers which might record clinical data, can prove invaluable as a source of information. Training in ethnicity issues is important and not always well done. I would suggest also that interpreters working with families who have rare diseases merit some specialist training, and there is a need for specialist genetic counsellors to work with these families, particularly if they can also speak another useful language. Support groups can provide useful resources for clinicians who do not have specialist clinical experience of rare diseases. I attend lay support group meetings quite regularly, however, and am struck by the fact that often families from ethnic minority groups do not engage with the support groups as much as they might. I suspect that this is because of language and cultural issues and also financial constraints. One explanation is that culturally, making contact with other families is not so acceptable or important to them. It may be, however, that they are less likely to have internet access at home, that the patient literature is not useful to them because it’s not in their language or that the expense of attending a meeting is prohibitive. These latter issues could be addressed. Finally, getting genetic tests done for rare disorders can be difficult at the best of times. It makes sense to centralise this type of testing in accredited laboratories where there is most experience, and I believe that these should be funded on a service basis in diagnostic labs so that the results can be used for genetic counselling, rather than being fitted in when time and resources allow as part of a research project.

**→ ARGUMENTS FOR TARGETED SCREENING PROGRAMMES**

Finally, the issue of screening. We are all aware that some conditions occur with greater frequency in some populations than others, in the case of Smith Lemli Opitz syndrome, for example there is a particularly high incidence in Poland. For other diseases such as the thalassaemias and cystic fibrosis, screening programmes have been established successfully in countries with a high incidence. If you move from a country of high incidence, however, you would miss out on screening. Do we need to think about organising targeted screening for specific rare diseases in countries where migrants make up a significant proportion of the population?
In conclusion, although healthcare is not the main reason for migration, the current scale of migration has significant implications for those managing rare diseases. This has resource and training issues. The rare disease networks and associations also have a major role to play in underpinning best management of migrants with rare diseases.

### Facing patient mobility needs in Europe

#### Introduction

In 2003, European health ministers and other stakeholders invited the European Commission (EC) to explore how legal uncertainties in the domain of health care could be improved following European Court of Justice decisions on the reimbursement of treatment and care in other Member States than the Member State of residence.

The EC proposal on general services in 2004 included the free movement of patients. This approach was rejected by the European Parliament and Council. Thus, the European Commission developed a policy initiative specifically targeting health care services as a separate issue. Moreover, rulings of the European Court of Justice in the recent years have made clear that even though Member States are primary responsible for health services, those services must comply with Community Law, particularly for the internal market enabling goods, services, persons and capitals to circulate freely within the EU.

#### Importance of the Issue

The EC conducted a EuroBarometer survey in May 2007 which reported that among respondents 54% were open to travel to another EU country to seek medical treatment. Currently, care provided abroad represents 1% of public expenditure on healthcare. A public consultation followed, and more than 270 responses were received from governments, regions,
international and national organisations, social security institutions, universities, industry and individuals. Debates were also continued at the European Parliament and Council: Informal ministerial meeting (November 2006), Informal Council in Aachen (April 2007), EPSCO Council (May 2007), and at the European Parliament, a resolution in March 2007, the ‘Vergnaud Report’ in May 2007.

The elements of the Community Framework for health services are to develop common principles in all EU health systems, a framework for cross-border healthcare, European cooperation on health services.

A Directive on Health Services should be adopted by the Commission at the beginning of 2009.

→ COMMON PRINCIPLES

- Fundamental elements for ensuring quality and safety of healthcare are in place
- Patients can make an informed choice between providers
- Clear rules and obligations exist to deal with harm arising from healthcare
- Continuity of care is ensured through transfer of relevant health data, and
- Patients from within and outside domestic systems are treated on a fair basis

→ FRAMEWORK FOR CROSS-BORDER HEALTHCARE

- Clear entitlements of patients: the right to access health services in other Member States should be realised in practice
- Limits that Member States can place on such health care abroad
- Reimbursement: right for reimbursement for services provided in other Member States

→ EUROPEAN COOPERATION ON HEALTH SERVICES

- Cooperation in border regions
- Providing for medical recognition of prescriptions issued in another Member State
- Establishing European networks of reference centres for rare diseases
- Sharing assessments of new health technologies or techniques
- Setting standards for the use of ‘e-health’ (information technology in healthcare, such as tele-radiology)
- Collecting data to enable comparable and comprehensive monitoring of cross-border healthcare, to allow its integration into the planning and management of health services overall

→ THIS POLICY IS COHERENT WITH OTHER COMMUNITY POLICIES:

- Regulations for coordination of social security schemes
- Framework for mutual recognition of professional qualifications
- Community framework for the protection of personal data
- E-health
**LEGAL BASIS**

- Legal basis
- Articles 16, 95 and 152 of the EC Treaty
- Subsidiarity principle: if any action can be undertaken more efficiently at the National level, there should be no initiative at the European level. Lack of Community action would undermine safe and efficient provision of cross border health care and would leave Member States without the capacity to manage and steer their Health Care Systems as a whole. This policy is in line with the subsidiarity principle.

- Proportionality principle: the Community action should not go beyond what is necessary in order to achieve the objectives. This proposal sets out only general principles creating a framework but leaving a wide margin for its implementation for the Member States. If a Member State decides not to provide a particular treatment, the mechanism should not force the Member State to reimburse it if the patient decides to purchase it in another Member State.

**IN CONCLUSION:**

despite the limitations of this policy, the Commission is confident this initiative will help patients seeking care in another Member States in full respect of the rulings of the European Court of Justice.
Policy and Implementation: European, Regional, State and Local Policy

Member states’ policies and actions in the field of rare diseases are rapidly evolving.

They share common features but diverge in some areas. This session proposed an overview of policies in two different domains: general policies, and research.

Europe is rich in its diversity. Any new initiative that arises in a member state can rapidly give birth to similar actions in all member states. This session highlighted three examples of national action that can be multiplied by 27: the Portuguese plan for rare diseases, the Italian actions for rare disease research, and an emergency Project for rare diseases.

3.1 Overview of Member States public health policies for rare diseases: a 2007 update

European collaboration for the delivery of health care and medical services in the field of rare diseases (RD) has major potential in bringing benefits to European citizens. It overcomes the limited experience of professionals confronted with very rare conditions; it improves access for European citizens to treatment requiring a particular concentration/pooling of resources (infrastructure and knowledge) or expertise; it offers patients the highest possible chance of success through the sharing of expertise and resources; it maximises cost-effective use of resources by concentrating them where appropriate; it supports the sharing of knowledge and provides training for health professionals; it acts as a benchmark to help develop and spread best practice throughout Europe; and it helps small countries with insufficient resources from their health care sector to provide a full range of specialised services of the highest quality. European collaboration, however, cannot be possible if there are no initiatives at the Member State (MS) level targeted at developing services dedicated to RD.
In the past years, several countries have taken action to support the development of orphan medicinal products (OMPs) and adapt their health care systems to meet the needs of the RD patient community. Article 9 of Regulation (EC) No 141/2000 on OMPs requires MS to communicate detailed information concerning any measure enacted to support research into and the development and availability of, OMPs to the European Commission (EC). A first inventory of these initiatives and incentives was published in January 2001, and made available in all European Community languages in June 2001. In 2005, MS were asked to communicate details on any measures introduced or in effect beginning in 2002 through the end of 2005. The information collected was published in 2006 and follows the recently published general report on the experience of the first five years of application of the regulation.

The OrphaNews Europe editors also attempt to survey new initiatives introduced in Europe by soliciting news at the MS level. Contributions to the newsletter by leaders in the RD community presenting recent initiatives in MS are published bimonthly.

This overview is based on the data, either published in the 2006 EC report or more recently published in OrphaNews Europe and may be incomplete. As such, this inventory should be considered as a provision of examples of public health policies in the MS rather than a comprehensive overview.

**INITIATIVES IN ORGANISING CENTRES OF EXPERTISE**

With regard to centres of expertise, there are three categories of countries in Europe: those which have a specific policy regarding RD and have established centres of expertise within this framework; those which have established centres of expertise, though not specifically for RD and those which have no centres with these denominations, although they have centres with all characteristics of a centre of expertise.

Only the following four European countries have officially adopted the concept of centres of expertise for RD within the context of a national policy regarding RD: Denmark, France, Italy and Sweden (Figure 22).

Within the national health system, Denmark has a designation system for referral centres/ highly specialised centres for a number of different conditions (diseases or procedures). The system takes the form of a catalogue from the National Board of Health made in collaboration with the local health authorities and medical experts. The general criteria used in
establishing such referral centres are rareness, complexity, multidisciplinarity and costly diagnosis and treatment of the disorders considered.

France launched its National Plan for Rare Disease in November 2004, to be in affect from 2005-2008. The plan includes a specific provision for care management of RD. The provision was intended to improve the previously unstructured system of care. Currently, criteria for national centres of expertise are focused on their provision of expertise, not the provision of direct care as such. The calls for proposals for designation of centres of expertise are intended only for university/teaching hospitals. Through the first four annual calls, 132 such centres were designated. Each centre is designated for five years, with a mid-term evaluation after three years and again after five years. Centres receive a specific budget to run their coordination activities corresponding to approximately two or three additional staff. Decrees are currently in preparation to designate other expert clinics accepting to work in a network coordinated by the centre of expertise with the intention of increasing the geographical coverage of the centres of expertise and preventing unnecessary traveling of patients.

In 1998, the Italian Government approved the National Health Plan in which RD were indicated as a priority for public health. Since 2001, more than 250 regional centres of expertise have been established by official regional decisions following the governmental regulation on RD. These centres do not receive an extra budget for their activity. The National Network is almost completed, although the criteria used by the regions to identify centres were highly heterogeneous throughout the national territory. Only centres established by regional decisions are officially recognised by the Italian Health System for the reimbursement of patients affected by RD. In the future it is expected that a coordination centre will be established in each region. An official agreement between the Ministry of Health, Istituto Superiore di Sanità and each region has been established in order to coordinate and harmonise the regional network activities. The same national committee, established within the agreement between the Italian Government and the regions, is currently reviewing the list of conditions which will receive free diagnosis and treatment.

Sweden’s system of care for RD is concentrated in specialised centres within an overall decentralised system run at the county level (there are 20 counties in Sweden). The National Board of Health and Welfare, based on an agreement with the Federation of County Councils in 1990,
sets out the providers of specialist care in a catalogue, which is intended to provide a reference point for local administrators. The catalogue lists around 75 of these specialist centres, which concentrate on clinical care – diagnosis and treatment of rare disorders – rather than research. Their services are offered to a broad geographical area, beyond the local catchment area, to ensure sufficient flow of patients. Counties can decide to buy in healthcare from centres located in other counties. In addition to the medical centres of expertise, the catalogue also includes specialised regional resource centres. Recently a committee has been set up by the Swedish National Board of Health and Welfare to work on the future organisation of highly specialised medical care.

In eight countries (Belgium, Croatia, Czech Republic, Finland, Greece, Ireland, Portugal, and the United Kingdom) clinical centres are designated as Centre of Expertise in areas relevant to RD, but were established outside any specific policy regarding RD (Figure 22).

In the remaining European countries, no clinical centres are designated as “centres of expertise” although many centres act as such without any specific support.

→ INITIATIVES TO PROVIDE INFORMATION TO PATIENTS AND PROFESSIONALS

In several MS, public information measures have been taken through the provision of web-based information and telephone helplines. Web-based information services are accessible in national language(s) in Bulgaria, Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden and the United Kingdom (Figure 23). Only in France and in Sweden have health authorities provided significant resources to develop information on a large number of diseases. The French information database has been translated into five other languages (English, German, Italian, Portuguese, and Spanish) and has thus become a truly European resource.

Helplines are established in Denmark, France, Italy, Netherlands, Norway, Spain, Sweden and the United Kingdom, although their resources vary considerably.

→ INITIATIVES TO IMPROVE ACCESS TO TREATMENT

Among MS, major disparities are observed initiatives in improved access to treatment. Although all OMPs receive market authorisation at the EU level, their accessibility at MS level depends both on marketing decisions as of the product in the country and the willingness of health authorities in each MS to quickly establish OMP prices and reimbursement rules.
A few MS have established multi-stakeholder forums of discussion to review possible actions in the field of orphan drug development and accessibility (Figure 24).

The Netherlands has had a Steering Committee on Orphan Drugs since 2001. It was implemented by the Dutch Minister of Health, Welfare and Sport (VWS) for a minimum of four years, in accordance with Article 9 of the European Regulation No. 141/2000 on Orphan Medicinal Products, which states that individual MS of the EU must implement measures to encourage the development of OMPs. The construction of such a national structure was one of the suggestions made in 1998 by the Dutch Advisory Council on Health Research (RGO). The VWS Minister asked this council for advice on the coordination, prioritisation and stimulation of research in the Netherlands with respect to OMPs. Based on a positive evaluation of the steering committee activities, the Minister decided at the end of 2004 that the committee could continue for three additional years (2005-2007).

In February 2001, the Irish Platform for Patients’ Organisations, Science and Industry (IPPOSI) was established in Ireland at a meeting held in Dublin on the subject of Therapeutics – How will Ireland Contribute – Opportunities and Threats. Since then, five further meetings have been held on topics such as the European Regulation on Orphan Medicinal Products; the Commercialisation of Health Research; the EU Clinical Trials Directive; and most recently on the Development of a National Clinical Research Infrastructure. IPPOSI was supported in the 2001 Irish Government Health Strategy document, Making Knowledge Work for Health, and was a contributor to the Advisory Council for Science, Technology and Innovation’s 2006 Report “Towards Better Health: Achieving a Step Change in Health Research in Ireland”.

In France, fee waivers can be granted in the case of drugs which fulfil the criteria for an orphan medicinal product, but do not have the designation. Free scientific advice is available for orphan medicines, from the French medicine agency (AFFSSAPS). Sponsors of OMPs are exempt from several taxes such as the tax on promotion of pharmaceuticals, the tax paid by the laboratories for the AFSSAPS, the safeguard clause for medicinal products, the tax on sales and the tax on distribution of medicines. Designated OMPs can benefit from compassionate use programme approximately 36 months before their marketing authorisation. The accelerated process for pricing has been reduced to 15 days. Reimbursement measures are also in place for compassionate use.
In Germany, the 14th amendment to the German drug law, which came into force in September 2005, allows for pre-authorisation access to OMPs.

In Hungary, a committee on the treatment of rare conditions has been set up within the scientific health council.

In Italy, a special legislation was passed in Italy in 2001. The legislation has several components, including a specific list of RD subject to systematic registration for which care and treatment is fully covered by health authorities. The list of RD includes 581 diseases or groups of diseases which can be broken down to 2,138 more specific diseases.

In Poland, a national forum on the treatment of orphan diseases was created at the beginning of 2005, mainly dedicated to the treatment of lysosomal storage diseases.

→ Initiatives to Empower Patient Organisations

With the exception of a few countries such as Denmark, France, the Netherlands, Spain and Sweden, most of the initiatives to empower patient organisations came from the patient organisations themselves without official support from governmental bodies.

Patient organisations have grown in number and have enlarged their membership. There are currently 1,740 organisations registered with Orphanet. They are dedicated to one disease or a group of diseases and are often part of an international network. At the MS level patient organisations in Bulgaria, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands, Romania, Spain, and Sweden have established national umbrella organisations to host all organisations concerning rare diseases (Figure 25). These national alliances and other disease-specific organisations have developed fund raising, political lobbying, targeted services including helplines, and information systems. They now play a very significant role in the provision of health care for RD patients.

→ Coordinated Public Health Policies in the Field of Rare Diseases

To date, France is the only country which has implemented a 2005-2008 National Plan on RD in the context of its national law on public health (Figure 26). This plan was allocated a budget of over 100 million Euros for the four year period. A few other MS are currently discussing the content of a possible national plan, namely Romania, Portugal, Italy, Spain, and Greece (Figure 26). A few more MS, including Bulgaria, Ireland, the Netherlands, Sweden, and Slovenia are laying the groundwork for this discussion (Figure 26).
Monitoring the outcome of the existing national plans will be of high relevance to convince MS not yet considering a similar approach to start consulting the stakeholders of their country about their expectations and proposals.

→ CONCLUSION

The EU as a whole and several individual MS have well identified the needs of patients affected with a RD and have defined policies to address these needs. Such initiatives should be continued as they not only correspond to the Lisbon Strategy, but have also proven to be effective. The European health care model based on equity and solidarity is particularly adapted for the problems raised by RD.

The European Commission is currently defining the elements for a policy on RD in Europe through a public consultation. The general aims of this policy are: to strengthen the cooperation between the EU programmes; to encourage EU MS in developing national health policies; and to ensure that common policy guidelines are shared everywhere in Europe. The attainment of these goals will require the improvement of knowledge and identification of RD; lead to improvement in diagnosis and care of patients with RD; accelerate research and developments in the field of RD and OMPs; empower patients with RD at the individual and collective level; encourage coordination of policies and initiatives at MS and EU level.

Pressure for change in this direction comes from all stakeholders in the RD community. There are difficulties, however, in establishing and funding such cooperation, as health services and medical care are not derived from a European competency and any type of European-wide cooperation could have strong influences on the structure of national/regional health care systems. Nevertheless, it is strongly urged that the EU assess the added-value of an EU approach through the case study represented by RD as RD have been and continue to be paradigmatic.
Figure 22: EU Member States with initiatives in organising centres of expertise (CE)

Figure 23: EU Member States with initiatives to provide information to patients and professionals
Figure 24: EU Member States with initiatives to improve access to treatment

Figure 25: EU Member States with initiatives to empower patient organisations
3.2 Overview of national research policies and collaboration between Member States

Abstract – Rare diseases are defined by their low prevalence (< 5/10,000). Except for their rarity there are few common denominators for rare diseases: the 5000-8000 different diseases themselves are heterogeneous, as well as the state of knowledge about them. Research funding needs to be flexible to accommodate the heterogeneous requirements. Translation of knowledge from basic science to the clinic requires special attention. However, clinical research suffers more than other research domains from infrastructural difficulties such as difficulties to gather patient cohorts due to the scattering over large areas, and the necessity to organise interdisciplinary approaches for patient relevant research due to the complexity of most phenotypes. Translational research requires networking between (basic) scientists and clinicians. Therefore support for networks of researchers is a major activity on the national and international scale. Few countries have funding initiatives dedicated specifically towards rare diseases. However, funding volumes in programmes which do not specify disease types may be considerable. To coordinate
national funding programmes on an international scale, a consortium of national funding agencies is supported by the European Commission as an ERA-Net on rare diseases “E-RARE”. Its activities include transnational calls for proposals on rare diseases. It will further address issues like access to research infrastructures as well as rotational positions for clinical scientists.

Keywords: research funding, ERA-Net, member states.

→ INTRODUCTION
There are an estimated 5000 to 8000 distinct rare diseases, the great majority of them being of genetic origin. Although individually rare, taken together, rare diseases affect more than 20 million people in Europe. They represent a major issue in health care since a large percentage of these diseases cause chronic illness with a large impact on quality of life and the health care system. Furthermore they lead to a significant decrease of life expectancy. Therefore research on rare diseases is needed, but it is hampered by lack of resources at several levels: (1) Few scientists work on one specific disease. (2) There are few patients scattered over a large geographic area, causing difficulties to gather cohorts required for studies. (3) Existing databases and material collections are often local, small, and not accessible or standardized. (4) Diseases mostly have complex clinical phenotypes and require interdisciplinary approaches to treatment and interdisciplinary cooperation for research.

Research on rare diseases is funded mostly by public funding bodies and charities. As a first approximation, basic science on rare diseases seems to be reasonably established. This seems especially true in systems which have a strong bottom-up approach of funding. Strengths can be seen for example in the number of identified genes whose variants cause genetic diseases. Clinical sciences are less well established, since clinical descriptions of diseases may be too imprecise for clinical studies, diagnostic procedures are evolving (e.g. genetic testing) and treatment options are underdeveloped.

Research on rare diseases is mostly funded within programmes which do not specify the disease (neither type nor prevalence). Only few countries have research programmes which are specific for rare diseases. These countries attempt to overcome fragmentation on a national level. However, due to the small number of patients affected by a specific rare disease, efforts in each individual European country may still be limited in objectives and power. Therefore, rare diseases are a prime example of a research area that can strongly profit from coordination on a transnational
Europe should be enabled to realize its potential by coordination across country borders: reorganizing and combining scientific expertise, research infrastructure, well defined patient cohorts and biological material. Nine partners from various European countries (Table below) have thus decided to join their efforts into the Coordination Action “E-Rare” to overcome the inherent difficulties of research on rare diseases and to complement existing national initiatives and the research framework programme of the European Commission. The general goal of E-Rare is to coordinate existing research programmes and to prepare joint and strategic activities to overcome some of the limitations imposed by scattered funding and fragmentation between national programmes. This article will provide a short overview over the national activities on research funding for rare diseases and the above mentioned consortium of funding agencies.

DISCUSSION

In 2000 the Lisbon strategy was forged: to transform the research landscape of Europe into a coherent unit, and to allow Europe a leading position in international comparison. Since the funds distributed via the research framework programmes of the European Commission, amount to 4-5% of the total F&E budget within Europe, most of the funds for extramural research projects are managed by the Member States (MS). Therefore, to reach the Lisbon goals, coordination between member states is necessary. To facilitate coordination steps between research funding organisation of the individual member states, a new instrument was created within the 6th framework programme for research, the so called ERA-Nets. Within ERA-Nets, the European Commission supports research funding organisations, such as research ministries, research councils, which manage extramural research programmes. Support is provided for different types of activities: increasing mutual knowledge about MS programmes, strategies and management and evaluation procedures, as well as opening of national programmes and funding of transnational research by common calls for proposals.

In 2005 a cooperation was started between the GIS-Institut des Maladies Rares (France), the PT-DLR (Germany) and the Institute of Health Carlos III (Spain), which managed the research programmes on rare diseases of their respective countries. This transformed soon into a larger initiative of organisations from eight countries including in addition Belgium, Italy, Israel, The Netherlands and Turkey (Table 1). In addition, organisations from Russia and the Italian Region of Lombardia participate as affiliated partners. The description of the national funding activities on rare
diseases will be limited to Partner organisations of the E-RARE, since knowledge stems from an analysis performed within this ERA-Net.

Participating organisations of the ERA-Net on rare diseases.

<table>
<thead>
<tr>
<th>Country</th>
<th>Organisation</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>France (coordination)</td>
<td>GIS Institute for Rare Diseases/ National Institute for Health and Medical Research (GIS Institut des Maladies Rares)</td>
<td>GIS-IMR</td>
</tr>
<tr>
<td>Belgium</td>
<td>The National Fund for Scientific Research (Fonds National de la Recherche Scientifique)</td>
<td>FNRS</td>
</tr>
<tr>
<td>France</td>
<td>National Institute for Health and Medical Research (Institut National de la Santé et de la Recherche Médicale)</td>
<td>Inserm</td>
</tr>
<tr>
<td>France</td>
<td>National Research Agency (Agence National de Recherche)</td>
<td>ANR</td>
</tr>
<tr>
<td>Germany</td>
<td>Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung)</td>
<td>BMBF</td>
</tr>
<tr>
<td>Germany</td>
<td>Project Management Organization in the German Aero-Space Centre (Projekträger im Deutschen Zentrum für Luft und Raumfahrt)</td>
<td>PT-DLR</td>
</tr>
<tr>
<td>Israel</td>
<td>The Chief Scientist office of the Israeli Ministry of Health (Lishkat Hamadaan Harashi, Misrad Habriut)</td>
<td>CSMOH</td>
</tr>
<tr>
<td>Italy</td>
<td>The Italian National Institute of Health (Istituto Superiore di Sanità)</td>
<td>ISS</td>
</tr>
<tr>
<td>Netherlands</td>
<td>The Netherlands Organisation for Health Research and Development (De Nederlandse Organisatie voor Gezondheidsonderzoek en Zorginnovatie)</td>
<td>ZonMw</td>
</tr>
<tr>
<td>Spain</td>
<td>Institute of Health Carlos III, – Fund for Health Research / Institute for Research on Rare Diseases (Instituto de salud Carlos III / Fundación para la Cooperación y Salud Internacional Carlos III)</td>
<td>ISCIII/FCSAI</td>
</tr>
<tr>
<td>Turkey</td>
<td>The Scientific and Technological Research Council of Turkey (Türkiye Bilimsel ve Teknolojik Araştirma Kurumu)</td>
<td>TÜBİTAK</td>
</tr>
</tbody>
</table>

Only few countries run a programme specific for rare diseases. However the volume of research funding on programmes which do specify neither disease nor prevalence should not be underestimated. Due to the genetic origin of most rare diseases, programmes addressing genetic diseases are highly relevant to rare diseases and may even have a preponderance for rare diseases. Examples of this kind of programmes are “Translational Gene Therapy” (The Netherlands), “Genetic diseases, Disease
and Therapy Models (Spain), or “Innovative Therapies” (including gene therapy or cell therapies) and “Molecular diagnostics” (Germany).

Most research programmes within the above mentioned countries are publicly funded. In France charities actively collaborate in a significant extent. Only in France the research programme on rare diseases is currently embedded into a “National Plan for Rare Diseases” which includes health care as well as research, although in some countries such National Plans are either in preparation (e.g. Italy, Portugal, Romania,) or discussed (e.g. Spain). In France, Germany, Italy and Spain, research programmes are implemented which are dedicated specifically to rare diseases, while in other countries, research on rare diseases is performed as a part of “generic” programmes, which do not specify neither types nor prevalence of the disease. Although the goals of the research programmes may vary in scope and breadth, they usually include basic research such as the identification of new syndromic entities, genotype-phenotype correlations, identification and characterization of mutated genes and (precompetitive) development of new drugs and therapies. Funding instruments for individual research projects as well as networking of researchers are common.

→ FRANCE

The French research programme on Rare diseases is managed by the Inserm via the GIS “Institute for Rare Diseases” (GIS-IMR), which was created in 2002. The GIS “Institute for Rare Diseases” is a consortium of the major public bodies and charity organisations involved in rare disease health care and research: the Ministries for Research, for Health and for Industry, the National Centre for Scientific Research (CRNS), the Inserm, the National Public Health Insurance System (CNAMTS), the French Muscular Dystrophy Association (AFM) and the Rare Diseases Alliance. The major goals of the Institute are to promote new research on rare diseases, to coordinate the activities of research teams and institutes, to optimize the use of research infrastructures and technological platforms (such as the “mouse clinic” for phenotyping of animal models, small molecule screening and high throughput screening facilities), to promote exchange of know-how and to organise access to small molecule collections from industry (ERDITI initiative). From 2002 to 2004, the GIS-IMR organised yearly calls for proposals to establish disease-oriented networks and to develop interdisciplinary research projects. Over this period, a total of 117 research projects (including 70 networks) were funded by the French Foundation against Myopathies in association with public funding bodies with 4 to 5 million per year. In
2005 the new French Research Agency (ANR) was established and concomitantly the National Plan for Rare Diseases was put in action (2005-2008). Thereafter the GIS-IMR continued to organise and administer the yearly calls for rare diseases launched by the ANR. Since 2005, 106 projects have been funded with 30 million € by the ANR (in association with the AFM) on diverse aspects as gene identification, pathophysiology and research on therapies.

→ GERMANY

The Federal Ministry of Education and Research (BMBF) of Germany funds - among others activities - research programmes in life sciences and health research. Part of the funding for health research is embedded in the national framework programme Health Research – Scientific Research for the People which includes an initiative on rare diseases. This initiative funds national networks in order to coordinate scattered resources for rare diseases, including manpower of researchers as well as research infrastructures (databases, tissue- and DNA collections, diagnostic services). The main goal is to foster interdisciplinary collaboration between basic scientists, clinicians and health care researchers. The call for proposals was open to all disease types and a bottom-up mode of selection of research topics and diseases. In a highly competitive evaluation ten networks were selected for funding in 2002 (http://www.gesundheitsforschung-bmbf.de/de/416.php). Total funds allocated to this programme are 30 million € in 5 years. The 10 networks comprise a total of about 90 projects which combine basic science projects to identify disease genes, genotype-phenotype correlations and biochemical-cell/biological experiments with clinical data collection on disease progression, building of patient cohorts, comparison of diagnostic tools and treatment studies. In 2007 the initiative was continued for further funding and is now open for new proposals.

→ SPAIN

Rare diseases are one of the research priority of the new National Plan of Spain for Research, Technological Development and Innovation (2008–2011) within the Strategic Action for Health Research (AES). The Spanish national programme for rare diseases is managed by the Instituto de Salud Carlos III (ISCIII), which has its mission in all fields of Biomedical and Health Research as well as Public Health. The aim of ISCIII is to develop and offer scientific-technical services and research of excellence, for the National Health System and the Society (http://www.isciii.es/). It manages intramural and extramural research programmes. Funding of Research on rare diseases follows several approaches: (1) the general
extramural research funding on Biomedical and other Health Sciences Research (grants for research project and infrastructures, research job contracts and fellowships) within the National Plan for Research, Technological Development and Innovation of Spain, based on yearly competitive calls for proposals. These calls are not specific for rare diseases, but rare diseases are included as a call priority. (2) In addition, ISCIII managed twelve networks which were funded as a part of the rare diseases programme with 6 million from 2003 to 2006. These networks either focus on a specific (group of) disease (e.g. genetic macula degeneration), or are centred on research methods (e.g. genotyping, epidemiology). (3) A “Network Centre for Research in Biomedicine” (CIBER) specialised in rare diseases was launched in 2006 with a 4 year grant. The centre will encompass 47 Spanish research groups with an annual budget of 6 to 7 Mio. Its main objective will be to provide applied research and constitute an international reference centre. (4) Furthermore there is intramural funding for a branch of ISCIII called Institute for Research on Rare Diseases (IIER) The mission of the IIER in this field is to guarantee quality health care and increase the knowledge on aetiology, epidemiology and clinical evolution of the rare diseases. IIER has a strong experience in the design and development of databases. It has published the first Spanish information system on rare diseases (SIERE) (http://cisat.iiier.sciii.es/er/) and has created a DNA and biological sample bank.

→ ITALY

In Italy, the Ministerial Decree No. 279 (18 May 2001) established the National Register Rare Diseases at the National Institute of Health (Istituto Superiore di Sanità – ISS) in order to contribute to health planning and to ensure the surveillance of rare diseases. Epidemiological data collected by regional centres, designated to manage rare diseases patients. Data are sent to a regional coordination centre that will further transfer them to the national register at ISS. If a coordination centre is not available, the Region will forward the data to the ISS.

Two major initiatives fund research projects after public calls for proposals:

1. By the Italian National Medicines Agency (AIFA) (bando per la ricerca indipendente promosso dall’Agenzia Italiana del Farmaco). According to Art. 48, law 326/2003 pharmaceutical companies are obliged to devote 5% of their promotional expenditure to a fund for independent research. This fund is managed by AIFA. The objectives include clinical research on drugs, in particular orphan drugs; comparative studies are aimed at assessing relative efficacy.
2. By the Ministry of Health and the National Institute of Health. The MoH and the ISS launched two national calls for proposals (2004 and 2006) dedicated to rare diseases in the frame of a bilateral agreement between Italy (ISS-National Centre Rare Diseases) and the USA (National Institute of Health-Office for Rare Diseases). The agreement includes collaboration in research as well as in public health.

The topics of the calls include models to study primary, secondary and tertiary prevention of rare diseases, characterization of nosological entities and conditions without a certain diagnosis, development of new diagnostic and prognostic approaches, experimental models for the development of new therapies (pre-clinical phase) and for the evaluation of their safety and efficacy, epidemiological and clinical research (using as basis the Italian Register of Rare Diseases), validation and optimisation of models to evaluate quality of life of rare diseases patients and quality of the supplied services. Fifty four research projects were selected for funding by the MoH/ISS call in 2004 and 82 in the 2006 call.

### Experiences with the national funding initiatives can be summarised as follows:

<table>
<thead>
<tr>
<th>National Plan</th>
<th>GIS-IMR (France)</th>
<th>ISS (Italy)</th>
<th>ISCIII (Spain)</th>
<th>BMBF (Germany)</th>
<th>ZonMW Netherlands</th>
<th>TUBITAK (Turkey)</th>
<th>CSO MOH (Israel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>programme specific for RD</td>
<td>In action 2005-2008</td>
<td>In preparation</td>
<td>In discussion</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>5-10 Mio. €</td>
<td>2004-2006 3,5 Mio. €</td>
<td>2006-2008 8,2 Mio. €</td>
<td>6-8 Mio. € /year</td>
<td>5-6 Mio. €</td>
<td>in preparation</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>generic programmes</td>
<td></td>
<td>6-8 Mio. €</td>
<td>&gt; 9 Mio. € per year</td>
<td>ca. 2,5 Mio € per year</td>
<td>ca. 0,5 Mio € per year</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>deadlines for applications</td>
<td>every year</td>
<td>ad hoc</td>
<td>every year</td>
<td>2-3 years</td>
<td>every year</td>
<td>every year</td>
<td>every year</td>
</tr>
<tr>
<td>funding for</td>
<td>projects and networks</td>
<td>projects and networks</td>
<td>projects, networks and net centre CIBER</td>
<td>networks</td>
<td>project and networks</td>
<td>projects</td>
<td>projects</td>
</tr>
</tbody>
</table>
There is a large diversity in the proposals, concerning disease types as well as the type of research approaches deemed appropriate by the applying scientists.

From many projects a clinical impact can be expected. Frequent research goals are better diagnosis and thorough description of the natural history of specific rare diseases as preparatory work for treatment studies or characterization of the pathogenesis processes. Clinical treatment trials are relatively rare, but in this respect there seem to be differences between different countries with more trials where funds are specifically earmarked.

There is a large scientific potential in the research landscape, even among the proposals which have not been selected for funding.

The national approaches to fund research on rare diseases are different concerning a variety of variables (generic versus specific for rare diseases, the timeline of the programmes and periods for application as well as the funding instruments).

→ THE TRANSNATIONAL INITIATIVE OF THE ERA-NET “E-RARE”

Because of the geographic distribution of patients suffering from rare diseases and researcher working on a specific diseases, it is quite obvious that research on rare diseases can profit from Europe-wide coordination and especially from a “one stop shop” for researcher applying for transnational collaborative projects, which avoids time delays and frictions when applying to different national agencies. One of the tasks of the ERA-Net is to open national programmes for international collaborations. The new call for proposals in Germany has already enlarged the options for international cooperation. However on the large scale adjusting and opening national programmes is an administrative. Therefore the launching of a new transnational call to complement the national initiatives was a faster and more appealing way to implement transnational collaboration on rare diseases, rather than to adjust the national programmes themselves. Shortly after the E-RARE consortium was established in its current composition (in mid 2006, see Table 1), a call for proposals for transnational projects was launched in March 2007. The prerequisite for participation in the call was that teams from at least two different countries must participate in a collaborative project, which shall clearly create an added value by the international collaboration. The call was open to all types of diseases except rare cancers and infectious diseases. Projects could address a broad spectrum of research approaches, with no pre-selection of diseases:
1. Collaborative research using or constituting cohorts of patients/families for:
   - Definition of new nosological entities, epidemiological studies, genotype-phenotype correlations.
   - Characterization of the genetic/molecular basis of specific diseases.

2. Basic research on rare diseases including genetic and pathophysiological studies with clinical relevance.

3. Research on diagnosis and therapies for rare diseases: biological targets, screening systems, model systems, gene or cell therapies.

4. Patient oriented research in the area of social and human sciences - e.g. psychological, psychosocial and behavioural research – as well as health services research and health economy research in the field of rare disorders.

125 proposals were submitted, of which 13 were selected for funding in a common evaluation procedure with a volume of 10 Mio € from all agencies. The participating researchers currently receive the required funds from their national agency should start their work in the beginning of 2008.

→ CONCLUSION

1. Similar to the national funding initiatives, the transnational call for proposals reveals a large scientific potential.

2. Due to the heterogeneity in type of disease and state of knowledge on the individual disease, a bottom-up approach for funding is most promising.

3. Translation of knowledge from basic science to patients must be improved (bench to bedside and back).

4. Translational research needs networking between (basic) researchers and clinicians, as well as interdisciplinary in methods.

5. Efficient use of limited resources needs networking (e.g. access to technological platforms and facilities, sharing of databases).

6. Generic calls should include and encourage research on rare diseases, while calls specific for rare diseases might mainly address networking.
7. Therefore, the ERA-Net will continue its efforts to enable transnational research projects and will also address issues like access to research infrastructures as well as rotational positions for clinical scientists.

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3.3 Portugal - a national plan for rare diseases centred on patient needs

In the European Union diseases with a prevalence of less than 5 cases per 10 000 inhabitants are considered rare diseases.

Using this prevalence, all diseases with estimated cases not exceeding 5000 will be considered rare when this concept is applied to the Portuguese population.

As it is probable that there are between 5 000 and 8 000 different rare diseases one could estimate that there will be between 600 000 and 800 000 cases of this type of pathologies.

In most cases the prevalence is below 1 in 100 000 cases, i.e. less than 100 cases for our population. However, the social cost is high, especially in the case of the more severe incapacitating and hard to control diseases, as it involves immediate family members as well as other care givers.

It is worthy of note that adequate treatment is only possible in 40% of the cases.
In view of the above the Directorate-General of Health (Direcção-Geral de Saúde) decided to elaborate a National Program for Rare Diseases (Programa Nacional de Doenças Raras: PNDR) in collaboration with a group of specialists within the framework of the National Health Plan (Plano Nacional de Saúde) running from 2004 to 2010.

This program was later submitted to the Health Minister, and was approved for public consultation.

The purpose of this project is to create better understanding in areas such as epidemiology, early diagnosis, etiology, clinic and the treatment of this type of diseases, with optimization and access according to the available resources, in view of an adequate and effective response.

**OBJECTIVES**

The National Program for Rare Diseases (Programa Nacional de Doenças Raras: PNDR) proposes to reach the following objectives:

**General**
1. Improve the response at the national level of the unfulfilled treatment requirements of those persons suffering from rare diseases and their families.
2. Improve the quality of treatment to those persons affected by rare diseases.

**Specific**
1. Create a national network of referral centers for rare diseases
2. Improve access to adequate treatment for those affected by rare diseases
3. Improve the mechanisms of integrated management for rare diseases
4. Improve knowledge and national research on rare diseases
5. Promote therapeutic innovation regarding medication for rare diseases
6. Ensure transnational cooperation between the European Union and the CPLP (Communities whose official language is Portuguese)

**TARGET POPULATION**

The National Program for Rare Diseases aims at answering the needs of the target population: all individuals affected by a rare disease regard-
less of sex or severity of the illness, over the entire span of their life cycle, considered within the framework of their families and communities.

→ **TIMEFRAME**
National Program for Rare Diseases, an official document of the National Strategic Plan is part of and in accordance with the National Health Plan with a timeframe horizon to 2010, including an initial implementation plan over 2008-2010 and 2010-2015 as a consolidation period.

→ **INTERVENTION STRATEGIES**
The strategies of this project follow 3 main directions: intervention, training, data collection as well as information analysis.

1. Define eligibility criteria for national referral centres in rare diseases;

2. Structure a national network of referral centres and promote their accreditation;

3. Define criteria for the adequate referring of the patients to the referral centres;

4. Propose specific financial rules and regulations for the accredited referral centres;

5. Define criteria for the early diagnosis of rare diseases;

6. Elaborate criteria to consistently identify the unfulfilled health needs of those with rare diseases;

7. Propose planning, authorisation, financing, organisation and follow up rules for the screening of rare diseases by the responsible authorities;

8. Propose rules for the facilitation, rationalisation and access to genetic tests, including their utilisation within the framework of medically assisted procreation, namely for pre-implantation diagnosis;

9. Propose measures to improve the access in real time to health services for carriers of rare diseases including positive discrimination in the case of the more incapacitated;

10. Guarantee medium and long term health and social care to carriers
of rare diseases regardless of age as laid down in the National Network for Integrated Continuous Care (Rede Nacional de Cuidados Continuados Integrados);

11. Propose specific measures for the support and social integration of school age children with rare diseases;

12. Propose support measures for the families with rare disease members, namely through respite centres and supported residences;

13. Promote the training of people with rare diseases in view of their professional qualification and employability;

14. Divulge the social benefits, the existing available EU resources as well as their access mechanisms for carriers of rare diseases;

15. Support the creation, development and networking of Patients’ Associations including the constitution of a National Federation as essential partners to achieve gains in health care;

16. Produce and divulge technical guidelines for good professional practice conducive to clinical quality and safety of the person with a rare disease;

17. Identify and quantify the direct financial costs related to patients with specific needs;

18. Propose the inclusion of specific financing for rare diseases in the contract-programme for hospitals;

19. Propose support measures for the development of ORPHANET-Portugal thus making it the reference portal on rare diseases in Portuguese;

20. Promote Research, issue guidelines, propose pluriannual financing for specific projects pertaining to rare diseases along with the collaboration of private and public structures having responsibilities or vocation in this area;

21. Propose measures to safeguard data confidentiality, informed consent and individuality and dignity of the rare disease carrier;

22. Propose monitoring systems for the efficiency and safety of orphan medication;
23. Propose the establishment of contractual policies with the pharmaceutical industry holding the AIM for medication designated as orphan, with the aim of establishing better price and supply conditions;

24. Propose measures of facilitation and accompaniment of research on orphan drugs in Portugal particularly in view of submission for designation as orphan medicaments; and dissemination of EU subsidies for the development of new products;

25. Propose legislative measures for the improvement of the national policy of incentives for the development of medicines for rare diseases;

26. Follow and participate in the decision making process at EU level on development policies as regards medicines for orphan diseases as well as, within the frame work of the EMEA, the scientific evaluation of new substances under consideration for orphan designation;

27. Create wider reaching partnerships between the EU and the CPLP in conjunction with public and private structures dedicated to the prevention, treatment and rehabilitation of rare diseases;

28. Promote the divulgment of existing resources in Portugal as regards the prevention, treatment and rehabilitation in rare diseases;

29. Participate and collaborate with the European institutions on scientific aspects of rare diseases;

**TRAINING STRATEGIES**

Training strategies will focus on actions of informative, pedagogical and instructional nature directed at health professionals, the educational community as well as persons affected by rare diseases, their families and the general population, the purpose being to allow them to manage and control rare diseases in their many dimensions and aspects.

30. Propose a curricular re-formulation in the many areas of health sciences pre-graduate studies in order to increase awareness to rare diseases;

31. Propose the inclusion of the rare disease carriers and/or their next of kin into the curricular program of Internal Medicine of General and Family Medicine, Pediatrics, Neurology, Hematology, among others, for the basic training required for the identification, support and referring for referral centers;
32. Promote the increase in the number of vacancies for Genetic Medicine Internships and other important specialties with the National Commission of Medical Internships (Comissão Nacional do Internato Médico), The Order of Medical Doctors and the central entities for the planning and coordination of the Health Ministry, for the carrying out of the PDNR;

33. Promote specific training for health professionals in rare diseases;

34. Create pedagogical tools for health professionals on rare diseases;

35. Produce and divulge technical guidelines for the support of children carriers of rare diseases to school health care teams as well as educational agents;

36. Produce and diffuse self-help manuals for carriers of rare diseases and their families;

37. Develop information campaigns through the media on rare diseases to stimulate more empathetic solidarity, less stigmatising and non-discriminatory behaviors vis a vis rare disease carriers and their families;

38. Divulge pertinent scientific information as well as existing resources, namely the referral centers, to health professionals by means of, among others, the resources of the Health Ministry (Direcção-Geral de Saúde) as well as those from ORPHANET-Portugal

 STRATEGIES FOR DATA COLLECTION AND INFORMATION ANALYSIS
Data collection and information analysis allow for the advancement of knowledge on rare diseases over the span of the entire life cycle. To carry this through, all agencies, public or private, and R&D financiers in the Health sciences must be called upon.

39. Adopt the nomenclature and classification system on rare diseases that may come to be adopted within the framework of EU initiatives (Rare diseases Task Force, OCDE ...);

40. Establish an inventory of existing data bases on rare diseases and promote mechanisms of compatibility and access;

41. Implement epidemiological monitoring of rare diseases;
Propose the creation of a national observation centre for rare diseases;

Develop partnerships between health services, research centres and patient associations, the aim being to implement the registration of rare diseases;

Create integrated information support and management systems on rare diseases;

Monitor the health gains achieved through the development of the programme;

Determine that information necessary for the establishment of the program’s starting point in 2008, in view of its subsequent evaluation.

ACCOMPANIMENT AND EVALUATION

The coordination and accompaniment of the Rare Diseases Program are the responsibility of the Directorate-General of Health (Direcção-Geral da Saúde), with support from a national commission to be created by the Health Minister.

The periodic evaluation of the PNDR will be carried out according to the indicators below:

1. Total number of accredited referral centres;

2. Proportion of accredited referral centres in the country relative to those accredited in the EU per rare disease or group of diseases;

3. Proportion of patients with a rare disease and with access to orphan drugs made available by the National Health Service (Serviço Nacional de Saúde);

4. Total number of Technical Guidelines for good professional practice that have been elaborated;

5. Total number of contract-programs with specific financing that have been drawn up with hospitals for rare diseases;

6. Total number of rare diseases with integrated management;
7. Calculation of the frequency of diseases covered by integrated management during the program implementation period (2008-2010);

8. Calculation of the incidence and prevalence of rare diseases with integrated management over the consolidation period of the program (2010-2015);

9. Total number of annual visits to the ORPHANET- Portugal portal;

10. Total number of articles published in indexed scientific journals;

11. Total number of registered occurrences of secondary effects from the use of orphan drugs;

12. Total number of contracts celebrated with the pharmaceutical industry on medicines carrying the designation of orphan;

13. Total number of active substances that have been researched and patented by national groups and that have been attributed the designation of orphan medicines by the EU;

14. Total number of partnerships created between the EU and the CPLP on rare diseases;

**CONCLUSIONS**

This project will be up for public consultation until January 31st, 2008. It can be consulted and contributions may be given at the Directorate-General of Health’s website as well as at the Health Portal (Portal da Saúde).

The Directorate-General of Health (Direcção-Geral da Saúde) will also promote meetings with the stakeholders of this kind of diseases.

After having benefited from the different contributions, the final draft will be presented to the Health Minister for evaluation and eventual approval.
3.4 New Italian initiatives for rare diseases

Abstract – The Italian Government promulgated a Regulation on Rare Diseases (RD) (Ministerial Decree 279/2001, «Institution of the national network of rare diseases»). The Decree identifies approximately 500 RDs for which patients are diagnosed and treated free of charge and lists the criteria for the establishment of the centres designated to manage RD. Regional centres have been identified in the entire national territory. A permanent inter-regional technical group including Regional Representatives, Ministry of Health (MoH) and National Institute of Health (ISS) was established to optimise the function of the regional networks.

The National Register Rare Diseases was established at the ISS to contribute to the national and regional health planning and to ensure the surveillance of RD. The National Register Orphan Drugs was established at the ISS with the aim of establishing a post marketing surveillance system of orphan drugs available in Italy.

The Low 326/2003 requires to the Italian pharmaceutical companies to donate 5% of their promotional expenditure to a specific fund established within the Italian National Medicines Agency (AIFA). The AIFA used the fund to launch 3 calls for proposal (in 2005, 2006 and 2007) including orphan drugs among the priorities. The MoH and the ISS launched two national calls for proposals (2004-2006 and 2006-2008) on RDs and in 2007 contributed to support the first trans-national call for European projects on RD (E-Rare project).

The Italian Minister of Health has established a “Consulta” of RD patients’ organisations in order to provide a forum for strengthening the dialogue between patients’ organisations and MoH.

Keywords: Italian national network of rare diseases, national register rare diseases, research, patients organisations.

→ INTRODUCTION
In 1998, the Italian National Health Plan indicated rare diseases (RDs) as a priority for public health. In 2001 a specific national low (Ministerial Decree No. 279, 18 May 2001) established the Italian National Network for RDs to tackle the problem of prevention, surveillance, diagnosis and treatment of RDs. The Decree identifies approximately 500 RDs
for which patients are diagnosed and treated completely free of charge, lists the criteria for the establishment of the centres designated to manage RDs patients (regional centres) and establishes the National Register Rare Diseases at the National Institute of Health (Istituto Superiore di Sanità – ISS)

In July 2002, as part of the State-Regions conference a permanent inter-regional technical group including Regional Representatives, the Ministry of Health (MoH) and the ISS was established with the objectives of optimising the function of the regional networks and to safeguard the principle of equality in healthcare for all citizens.

→ MAIN INITIATIVES

1. Regional Centres for rare diseases patients management
Regional Centres are expressly identified by the Regions among those possessing:

- documented experience in diagnostic and/or specific therapeutic activities for single or groups of RDs
- adequate support structures and complementary services (emergency services and services for biochemical and genetic-molecular diagnosis)

Regional centres have been identified in the entire national territory. The list of the regional centres identified in the national territory is available on the National Centre Rare Diseases (ISS) website (http://www.iss.it/cnmr).

2. The National Register of Rare Diseases
The national register rare diseases was established at the National Centre Rare Diseases (ISS) in order to contribute to the national and regional health planning and to ensure the surveillance of RDs. In particular the national register aims at:

- estimating the prevalence and incidence of RDs
- knowing the spatial and temporal distribution of RDs
- estimating need for services (burden of disease and patient’s migration)
- monitoring diagnostic and therapeutic protocols

Epidemiological data are collected from all regional centres officially identified by the Region. From the different centres data are sent to the regional coordination centre that will than send data to the national register of the ISS. When a regional coordination centre is not yet available, the Region will be responsible for sending the data to the ISS.

The functioning of the surveillance system and of the national network has been recently confirmed by a specific agreement signed at the State-
Regions Conference (10 May 2007) establishing new commitments:

- establishment of regional registries in the Regions where not yet available by 31/03/2008
- identification of regional and/or interregional coordination centre
- institution of a working group on orphan drugs including Ministry of Health, Italian Medicinal Agency and Representatives of the Regions

3. The National Register of Orphan Drugs
The national register orphan drugs was established at the ISS with the aim of: 1) establishing a post marketing surveillance system of orphan drugs available in Italy and 2) monitoring and collect information on orphan drugs efficacy, safety and appropriate use. In addition, it will be an opportunity to define the number of patients treated in Italy.

The register is in its pilot phase and is focusing the data collection on the following orphan drugs:

- Aldurazyme (mucopolysaccharidosis I – MPS1)
- Fabrazyme and Replagal (Fabry disease)
- Somavert (Acromegaly)
- Ventavis and Tracleer (pulmonary arterial hypertension - PAH)

Up to November 2007:

- 117 Centres prescribing drugs have been registered (25 Fabry; 71 PAH; 21 MPS1)
- Diagnostic and follow-up treatment data are available for 105 patients with PAH (Figure 27)
- Diagnostic and follow-up treatment data are available for 27 patients with Fabry diseases (Figure 28)

Figure 27: Numbers of patients with PAH registered by Region
Figure 28: Numbers of patients with Fabry disease registered by Region
The National Centre Rare Diseases, established at the ISS, ensure the functioning of the National Registers and leads several activities at national level. In addition, the Centre officially represents Italy at the Committee for Orphan Medicinal Products (COMP) of the European Drug Agency (EMEA) and is involved in the coordination and development of EU projects.

The main activities of the Italian National Centre Rare Diseases (http://www.iss.it/cnmr) are briefly described as follows:

- Research activities on selected RDs
- Quality assurance of genetic tests
- Primary prevention of congenital defects and folic acid
- Surveillance of RDs at national level (national register rare diseases)
- National register orphan drugs
- Development of guidelines for diagnosis and treatment of specific RDs
- Studies on accessibility and quality of health and social services for the patients with rare diseases

- European project (NEPHIRD http://www.iss.it/cnmr; E-Rare http://www.e-rare.eu; TEDDY http://www.teddynoe.org; EUROPLAN)
- Projects/activities on narrative medicine
- Provision of information to patients, families and to the general population
- Training and continuous education of health care operators

RESEARCH ON RARE DISEASES

The Italian National Medicines Agency (AIFA) activities

The Law 326/2003 requires Italian pharmaceutical companies to donate 5% of their promotional expenditure to the AIFA in order to establish a fund to promote independent research.

In 2005, the AIFA officially established how to use the fund and launched the first call for proposal including among the priority areas orphan and neglected drugs. In 2006, a second call for proposal was launched including again orphan drugs and rare diseases among the research priorities. A third call was launched in 2007 and the evaluation of the proposals is actually in progress.

Twenty independent research projects in the area of rare diseases and orphan drugs have been selected for funding by the AIFA in 2005 and 24 projects in 2006 (Table 1).
The Ministry of Health and the National Institute of Health activities

The MoH and the ISS launched two national calls for proposals (in 2004-2006 and in 2006-2008) on RDs in the frame of a bilateral Italy (ISS-National Centre Rare Diseases) – USA (National Institute of Health-Office for Rare Diseases) agreement on joint research and development of public health actions.

Fifty four research projects were selected for funding by the MoH/ISS call in 2004 and 82 in the 2006 call.

In addition, the MoH and the ISS contributed to support the first transnational call for European projects on RDs launched within the framework of the E-Rare project.

PATIENTS’ ENGAGEMENT

The Italian Minister of Health has formally established (5 July 2007) a “Consulta” of rare diseases patients’ organisations.

The Consulta is made up of 34 representatives of the associations of patients; it collaborates with the Rare Diseases National Centre and other competent authorities with the aims of:

- advise on rare diseases issues,
- strengthen collaboration and ameliorate the rare diseases network functioning and
- contribute to the identification of rare diseases challenges and priority needs.

The Consulta dedicated 5 months (June-November 2007) to the definition of priorities and gaps that need to be addressed by the Ministry of Health.
Different working groups have been established and supported scientifically by the National Centre Rare Diseases to identify future activities to address the following priority areas:

1. provision of care
   - integration of social and health care services
   - strengthen of the regional network
   - equality of the health and social services provided for all
   - access to orphan drugs

2. professional training

3. scientific research

4. development and distribution of information on rare diseases

The Consulta presented the results of the working groups to the Ministry of Health during the International Conference on rare diseases and orphan drugs organised by the National Centre Rare Diseases from the 5th to 8th November 2007.

**ITALIAN COMMITMENT TO RD**

Following the Ministerial Decree (No. 279, 18 May 2001), RDs and the implementation of the national network have been included as priorities in all Italian National Health Plans (2003-2005; 2006-2008).

Within this framework, the following priority actions have been identified by the Italian Minister of Health for the year 2008:

1. development of the Italian National Plan for RD
2. establishment of an institutional help line for RD at the National Centre Rare Diseases
3. celebration of a national awareness day for RD (February 29th)

**REFERENCES**

[1] DECRETO 18 maggio 2001, n. 279. Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell’articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998 n. 124. (Regulation of the institution of a national network for rare diseases and the exemption from patient participation in the costs of the relevant healthcare)
3.5 The French Emergency Project

Rare diseases in emergency situations: the Orphanet Emergency guidelines

During the process for establishing the “French National Plan for Rare Diseases” patient organisations have noticed a lack of information available to emergency physicians regarding rare diseases management in emergency care. Like any other patient, a person suffering from a rare disease can find itself in a situation requiring emergency care. The nature of the emergency can be related or not to the rare disease but solely the existence of the special pathology requires emergency particular measures. The patient or their entourage can sometimes provide useful information regarding the disease but it is usually difficult for them to be heard in an emergency room.
For patients bearing a rare disease, special measures are required in order to address these special situations. Several situations can be encountered:

- The diagnosis of rare disease is well known and the emergency is related to the pathology (i.e. an aortic dissection in a patient with Marfan Syndrome)
- The diagnosis of rare disease is well known but the emergency is not related to the pathology (i.e. a trauma resulting from a car crash in a patient with haemophilia or a surgical emergency requiring a general anaesthesia in a patient with porphyria)
- The diagnosis of rare disease is known and the patient presents an acute medical condition of minimal gravity but its management should be adapted in order to avoid complications of the rare disease (i.e. a febrile condition in a child with adrenal insufficiency)
- The diagnosis is known but the patient is unable to communicate
- The diagnosis is not known and it is revealed by the emergency situation

Orphanet, the main documentation service dedicated to rare diseases, was chosen to remedy to this situation of lack of information.

A survey conducted by Orphanet and the French Society for Emergency Medicine (SFMU) aimed towards identifying the current behaviour of physicians having to gather information about a rare disease in the emergency room and their needs. The survey was constructed in three parts: a description of the activity of the participant, data concerning prior experience with rare diseases, and the physicians wishes with regards to the information in these situations. This survey was realised through a web questionnaire put on the French Society for Emergency Medicine web site.

207 physicians participated in the survey, 75 % had a joint activity (in and out hospital emergency system) and the activity range was from 10 000 to 40 000 patients/year.

Nearly 54 % of the emergency physicians had managed a patient with a rare disease during the past year and 8 % of them managed more than 10 patients. Information about the disease was obtained in nearly 70% of cases, either using Internet (60% of cases) or by contacting a specialist (38 % of theses cases). This information led to a change in patient management in 42 % of the cases and prevented complications in 12 % of the cases. In more than half of the cases, it was considered just interesting but not useful in the emergency situation.

The expectations of emergency specialists are useful to adapt the project to the physicians' needs. The survey proposed five different information models. The two sources of information preferred were Personal health-
care cards carried by the patients (91%) and emergency guidelines available on Internet (75%).

The French General Directorate for Health (DGS, from the French health ministry) started the edition of personalised healthcare cards to be distributed to patients by centres of reference. These cards include recommendations for emergency situations and provide a phone number of a centre of reference for the disease, as well as the address of the orphaned website.

Orphanet together with the Emergency Medicine Societies are working on synthetic good practice guidelines for emergency situations. A steering committee was established for this project. It is constituted by representatives of the French ministry of Health, the French High Health Authority (Haute Autorité de Santé), patients’ organisations (Alliance Maladies Rares, Fédération des Maladies Orphelines and Association Française contre les Myopathies), learned societies (French Society of Emergency Medicine, SAMU de France, French Society of Paediatrics and French National Society of Internal Medicine) and Orphanet. The methodology for the development of these charts follows the recommendations of the French High Health Authority (Haute Autorité de Santé). These charts, useful in pre-hospital care as well as in emergency departments, will be available on the Orphanet website (www.orphanet-urgences.fr). Beyond the recommendations of emergency management they provide also the special emergency phone contacts - if available- as well as the bibliographical references, useful to satisfy the need for further information, once the emergency is resolved. These short charts are structured as follows:

**THE PRODUCTION PROCESS IS AS FOLLOWS:**

- A short description of the disease
- A specific page for the physician medical dispatcher (SAMU)
- Guidelines for emergency situation:
  - management of emergency situations related to the rare disease
  - drugs precautions
  - anaesthetic precautions
  - complementary guidelines for hospitalisation
  - recommendations for organ donation
  - emergency call numbers and centre of reference
  - bibliographic resources

The experts from the centre of reference and patients organisations are asked to write a draft following a standardised layout Orphanet provides the experts with the bibliography. A reading committee is constituted by learned societies. Orphanet warrants that the guidelines are written according to the layout, and put together the comments of the different
readers. The experts and the patients’ organisations validate the final version of the document which is putted online on the Orphanet website.

This project resulting from the cooperation between the emergency professionals and Orphanet, wants to be a stepping stone in the creation of an information system regarding the management of rare diseases in emergency situations in order to improve the quality of emergency room services offered to the patients.

In a near future all European physicians will be able to access this database which is currently accessible in French only but which will be translated in five other languages soon.

*Figure 29: the French Emergency Project*
4 EUROPEAN RESEARCH AND NETWORKS

In this session devoted to research on rare diseases, speakers addressed the need for coordination between European and national research policies, explained the broad spectrum of research in biomedicine, public health, social science, and ethics, and called for a favourable environment to transfer discoveries from academia to industry.

Various workshops took place in 2007 on this theme, with the participation of European Commission DG Research, patients, and industry.

4.1 DG Research Conference on Rare Diseases 2007 - Outcomes

Catherine Berens presented what DG Research had been doing in previous years during their FP6 programme and what they will be doing in the coming years with their FP7 programme. She explained that there has been a historical support to research on rare diseases by the European Commission. DG Research being a European public body funding research, they are funding research in areas where research is most needed and where the European added value is most important. She said that the historical low input of the private sector in research on rare diseases and the very important European added value it represents are really two good reasons for the European Union to be involved in funding such research.

During the FP6 programme, their first priority was health and they had four calls for proposals altogether. Out of these four calls for proposals, they have been able to support roughly 60 projects, relevant to rare diseases. Included in these projects is the ERA-Net, a project coordinating national programmes on research on rare diseases presented yesterday by Dr Birgit Wetterauer as well as dedicated programmes such as the Science and Society programme which will be presented by Dr Fabrizia Bignami later on. These projects have accounted for more than 230 million euro, which is a substantial increase compared to their previous 5th FP (more than 3 times) budget, and it is an important step-forward during their FP6 programme. They had a few more projects, not three times as many projects as they had in the 5th programme thus the size of these projects has increased quite a lot.
All projects can be found on their Cordis website: http://cordis.europa.eu/lifescihealth/major/cardio.htm.

Mrs Berens went on to talk about the achievements and the great success of FP6 programme and how they have mobilised top researchers all over Europe, enabling them to tackle fragmentation of research, produce new knowledge, coordinate the field at EU level (e.g. Orphan platform, ERA-Net), better liaise at EU level. Hopefully all these projects will deliver new knowledge on which future research will be based on and later on lead to development of new therapies for rare diseases. She said there was of course room for improvement - for instance, they had not funded a lot of clinical research in the FP6 programme. They published focused topics in FP6 and this needs to be kept in mind for FP7 programme.

They realised it was difficult for emerging consortia to find their way through in FP6. Mrs Berens talked about their new programme called:

→ BUILDING A EUROPE OF KNOWLEDGE : SEVENTH FRAMEWORK PROGRAMME (2007-2013)

This new programme was launched end of 2006 and will last 7 years. The global budget is roughly 54.000 million and the biggest part of the project is dedicated to collaborative research. Within this collaborative research area, 6.1 billion will be allocated to research on health. The aims of the Health Theme is of course to improve health of European citizens but also answer more global challenges like emerging epidemics and furthermore contribute to increase competitiveness of European health related industries.

Ten themes have been identified for collaborative research:

1. Health
2. Food, agriculture and fisheries, biotechnology
3. Information and communication technologies
4. Nano-sciences, nano-technologies, materials and new production technologies
5. Energy
6. Environment (including climate change)
7. Transport (including aeronautics)
8. Socio-economic sciences and humanities
9. Spaces
10. Security
Mrs Berens gave details of the Rationale for the construction of their programme. A huge amount of new data has been accumulated over the last years due to the sequencing of human genome and recent advances in post genomics research. These data now have to be translated into really concrete deliverables for patients; international multi-centred trials require a European approach. As a novelty in the programme, health policy-driven research should be reinforced in order to be able to compare the national policies – this being very important as it might lead to new public health policies. She said that if the competitiveness of industries and SME’s has to be strengthened in order to create new jobs for a stronger Europe, the EU based-biomedical research should be strengthened through FP7.

The Health Theme has been structured in the following 3 sub-themes:

11. Sub-theme: Biotechnology, generic tools and medical technologies for human health
12. Sub-theme: Translating research for human health
13. Sub-theme: Optimising the delivery of health care to European citizens

It is noted that rare diseases have now a dedicated bullet-point and the fact that they are fully recognised nowadays is a good political sign that their specificities are fully recognised now.

Mrs Berens then reminded the participants of the workshop held in April 2005. Its purpose was to identify the priorities and research needs of rare diseases in the scientific community.

They had gathered a number of stakeholders, researchers, clinicians, patients’ organisations, scientists, representatives of industry and had asked them what type of projects they wanted to be funded and the size of these projects. Concerning the research priorities, should the topics be focused on specific diseases or should they concentrate on horizontal issues relevant to a number of rare diseases?

The results of this workshop were recommendations to the European Commission. It was felt that collaborative research projects were very important for rare disease research and also that small projects but also bigger types of projects, like integrated projects, were needed. Funding networking is important too. Specific attention should be paid to emerg-
ing teams and emerging topics. The priorities being as follows:

- Infrastructures
- Natural history
- Physiopathology
- Pre-clinical and early clinical studies
- Therapeutic interventions
- Social sciences

**FOCUS & IMPACT**

Throughout FP7, research on rare diseases will focus on natural history, pathophysiology and on development of preventive, diagnostic and therapeutic interventions.

The expected impact: this area should help identifying and mobilising the critical mass of expertise in order to shed light on the course and/or mechanisms of rare diseases, or to test diagnostic, preventive and/or therapeutic approaches, to alleviate the negative impact of the disease on the quality of life of the patients and their families, as appropriate depending on the level of knowledge concerning the specific (group of) disease(s) under study.

This will be followed continuously during evaluation of proposals and the projects in FP7.

The first call for proposals focused on:

- Natural course and pathophysiology of rare diseases (collaborative projects)
- Research capacity-building in the field of rare diseases in order to provide the emerging teams a platform
- Out of these topics, eleven projects have been selected for funding for roughly 30 million €.

Rare disease is not the necessary keyword to identify relevant topics in the work programme.

In order to make sure they were heading in the right direction, DG Research organised a conference on rare diseases in Brussels on 13/9/07 to increase awareness of the field which gave the rare disease community an opportunity to express their needs, and provide a sound basis for future calls for proposals. Catherine said the conference was a big success. The needs that have been reiterated are similar to those in 2005, so they’re heading towards the right direction.

In conclusion, Mrs Berens said that there will be opportunities for research on rare disease during FP7 programme; this will require active involvement of all stakeholders. She stressed the fact that all of us have to be active and continue the good discussions we have had in the past in order for us to try and stick to your needs and for you to develop good research in order to deliver the new therapies that the patients need so much.
4.2 Expectations and Contributions from patients – The European Workshop outcomes May 2007 Paris

The European workshop ‘Gaining Access to Rare Disease Research Resources’ held in May 2007 in Paris was organised by Eurordis in the context of the CAPOIRA project funded by the European Commission under the Science & Society programme (FP6)

→ INTRODUCTION
The CAPOIRA project (Capacity Building Activities for Patient Organisations in Research) aims at increasing patients’ capacity in the research field, by training them on clinical trials and on the funding schemes for research available at the EU level. The 5 partners collaborating in this project are issued from three different Member States. Three of them are national alliances of rare disease patients (FEDER-Spain, Rare Disease Denmark –Denmark and Uniamo –Italy), one partner, INSERM (France), is a public research institute, while Eurordis coordinated the whole project.

During the European Workshop organised by Eurordis in Paris in May 2007, representative from the EU Commission, together with organisations partners in European projects, provided information about the rare disease research funding opportunities in Europe and explained the vocabulary & jargon used in this field. They also gave indications on how research policy is decided at the EU level. Mr Hallen, Head of Unit for Medical & Public Health Research at DG Research- EU Commission, presented the investments of the European Union in the field of rare disease research over the years and the plans for the future.

The instruments that are prepared by the Commission in order to fund research were presented in detail by Dr C. Berens responsible for the projects on rare diseases at DG Research., The majority of the 270 participants of this two-day meeting, were patient representatives.

→ CONTENT
This workshop was also coupled to the Eurordis’ 10th Anniversary, thus it offered also the opportunity to go through the last ten-year achievements of the organisation in the field of rare disease research.

In addition, Yann Le Cam, Eurordis’ CEO, presented how the capacity
of patients in this field can be increased, and how Eurordis is directly involved in rare disease research.

In order to give concrete examples of patient organisations’ direct involvement in the research area, the successful collaboration between the NIH (National Institute for Health) (USA) and patients organisations was presented, as well as three successful stories of patient driven research projects at the EU level.

The workshop explained the instruments and how funding for research can be obtained once the patients themselves have created their own network of specialists and how the European Commission sees the involvement of civil society (which of course includes patients) in high level discussions about the definition of strategies including those for research.

Patient representatives were given a view of existing tools for rare disease research in one of the two parallel sessions of the meeting. In particular, the E-Rare and the ECRIN projects were presented. This last is an important clinical research infrastructure also dedicated to rare diseases. Professor H. Lochmüller presented the Eurobiobank network, the unique biobank infrastructure making biological samples from rare disease patients available to researchers across and beyond Europe. The important issue of databases and registries was also raised at the end of the session.

Another approach where those patients already involved in European projects presented their own experience was used for the second parallel session. The speakers described their experience to other patients, how they had the idea of creating a new project and where they looked for funds. Last but not least, the patients exchanged important information on how patient organisations have succeeded in getting funds from donors and companies, how they tried to best use these funds to boost the research on their own disease, and which type of pitfalls and error should be avoided in this context.

**GENERAL RECOMMENDATIONS**

In order to collect contributions, three questions were asked:

- What are the basic requirements and tools that a patient organisation should have to best contribute to research on its disease?
- What can patient representatives contribute to European research projects?
- How and which structures and context can patient representatives be involved in research strategy?
The majority of stakeholders agreed on the need to push for national plans for rare disease not only for care but also to stimulate basic and fundamental research at member states level. Since most of funding for research usually comes from the Member States, more awareness of rare disease research among the decision makers and why research on rare diseases has to be made at European level needs to be addressed on a larger scale.

Provide more opportunities for patients and decision makers to meet and discuss new strategies together and establish EU-wide committees for rare diseases rather than national ones.

Promoters of clinical trials have difficulty with Member States in obtaining the agreement of ethics committees because of lack of competence in this field. Clinical trials need to be conducted at a national as well as international level because of the rarity of disease and they need to be treated, analysed and agreed by – possibly – a European ethics committee.

Availability of Information in national languages is important.

Develop new tools to facilitate debate and exchange of information and to promote joint research projects between lay patients and scientists is also an important aspect.

Operating grants for patients’ organisations with the creation of new networks implies a lot of time-consuming and resources and patients’ organisations, most of the time, do not have these resources.

Create long-term support for research projects.

Develop more research projects on quality of life for patients and social impact of the disease. Many of these recommendations have already been taken into account by DG Research in the new frame of the programmes which is very encouraging.

Because bureaucracy at EU level (although simplified) still remains a burden for patients’ organisations not specialised in this area, to implement a two-step approach could be useful: expression of interest first and full application when pre-selected.

Publish a simplified ‘who’s who’ of the European Commission as it
is not easy to navigate on their website. Alternatively, the creation of a portal for specific rare diseases or patient organisations or a helpdesk dedicated to development of rare diseases projects could be developed.

11. In collaboration with partners like INSERM, training sessions have already started and these sessions should be developed in the future.

→ SPECIFIC RECOMMENDATIONS

12. Rare disease bio banks and clinical trials - Results are not good sometimes and they are wasted and lost. Thus scientists have no interest in publishing them but negative results should be published in order not to repeat the same errors and not to involve people again in useless clinical trials.

13. Patients’ databases and registries – organise training sessions for patients’ representatives, write and disseminate EU guidelines on the creation of databases, develop databases linking genotypes and phenotypes that can be operated or supervised by patient groups with the support of specialists.

14. Patient organisations should be involved in research at EU level because they know best about diseases and they can really contribute in avoiding errors and in planning trials and even research. They can help in reaching out to patients and create a patient-orientated research to provide a better quality of life and life expectancy of patients, help in disseminating results of this research by translating it in more understandable words, and communicate with European citizens by explaining the reasons and achievements of this research.

In conclusion, the main outcome of the workshop is that patients can really make the difference for research on rare diseases to be successful.
4.3 Expectations and Contributions from pharma & biotech industry on the future of Orphan Drugs in Europe

Abstract – Industry’s key messages concerning the Orphan Medicines include: ensuring clearer messaging including that it is understood by all those involved that an orphan drug is a product for which no alternative exists in the EU or if it does, it provides a significant benefit for those affected over the existing product; promoting early, timely and equitable access; promoting and supporting that more awareness is given to rare diseases and their impact on patients and their quality of life; collecting data about all rare disease initiatives and orphan drugs in Europe; more clearly explaining that market exclusivity does not mean a monopoly as there is room for products with different modes of action and for clinically superior products; understanding the need for more research on rare diseases and the risks to develop them; ensuring that policy makers understand that market exclusivity gets eroded by delays in access to market; encouraging partnerships with other stakeholders.

Keywords: EuropaBio, Biotechnology industry, Contributions to the framework of Orphan medicines.

→ Introduction

his presentation considers industry’s priorities, expectations and contributions for the framework of Orphan Medicines in Europe.

The seven-year history of the EU Orphan Medicines Regulation has delivered significant results. Today, there are more than 500 EU orphan medicine designations and already 42 orphan drugs with EU marketing authorisation. About 1/3 is in the field of oncology and slightly less in the field of metabolic disease. The EU is now catching up to the US in terms of annual designation and approval numbers. The promise of orphan medicines is delivering results to patients.

But we need to address perceptions with clearer messages. Orphan medicines are treatments for life-threatening or serious and chronic diseases for which no alternatives exist, or if such alternatives exist, have a significant benefit over existing products – so there is no real choice of treatment available where there is an orphan drug available. A second message of high importance is that in reality rare diseases lie within a continuum of rarity,
with research and treatment complexity increasing with rarity. Definitions of rare, common or ultra-rare are just based on a societal agreement for a cut-off. The third important message is that there is no “avalanche” of orphan drugs coming, but rather a steady annual increase – as was discussed at length at the recent EPPOSI workshop in Copenhagen, in November 2007.

The spirit of EU Orphan Drug legislation is to provide timely and equitable access to therapies for patients with rare diseases, and to balance the risk of developing new medicines by providing economic (and other) incentives to industry. The message enshrined in this legislation is that patients with rare disorders deserve the same care and the same safety, efficacy and quality of products as patients with more common diseases. The European Union has also chosen to further support the concept of rare diseases and of orphan drugs. This is exemplified by the fact that rare diseases are again a public health priority under the European Health Programme 2008-2013 of the European Commission’s Directorate General for Health and Consumer Protection, and by the Public Consultation on a proposed action plan “Rare Diseases: Europe’s Challenges”. But also by the approval of the Advanced Therapies Regulation in Europe, of which many will be orphan, and by the special provisions for orphan drugs in the Paediatrics Regulation, as many rare diseases are genetic in origin, and therefore may affect many children. Furthermore, there is policy continuity through EC guidelines on Regulation 141/2000 and by the remarkable work of the COMP and EMEA and its scientific body, the CHMP. Last but not least, EuroGen-test, the large European project on genetic testing, also touches upon the diagnosis of rare diseases, as this is a very critical factor in the field.

Industry is substantially contributing to the field of rare diseases through innovation for these unmet medical needs, and is a major source of the orphan drugs receiving market authorisation in the EU. Meanwhile, industry is also active in creating access for patients to these products, and also in organising compassionate use programmes. Apart from the patient benefits of these therapies, industry’s activities also lead to societal wealth and employment. Yet, to date, industry’s positive contributions to the field of rare diseases have been poorly communicated, and there is definitely more we can do to be proactive in this regard.

The strategic focus of industry in the field has been discussed at a recent strategy workshop of the Joint EBE/EuropaBio Industry Taskforce. This was set up to assess the current status of the field and, in particular, to identify areas that still need to be addressed in order to deliver fully on the promise and spirit of the orphan drug legislation.
Patient access to orphan drugs is a top priority. Orphan drugs are receiving market authorisation, but are still not getting to patients in all Member States. Extended discussions on pricing and reimbursement in some countries are slowing patient access to orphan drugs. Eurordis has also noted that the smaller the country, the more difficult it is to access orphan medicines. Regionalisation of healthcare makes access even more difficult, as larger countries are split up now in smaller regions. The definition and application of Health Technology Assessment (HTA) to orphan medicines is another question, and it needs to be discussed whether such methods are appropriate, given that the results they generate may not be meaningful because of the degree of uncertainty associated with the lack of data, an issue of increasing importance with increasing rarity of the disease. A harmonised approach of all the factors determining access to orphan drugs for patients is needed, and we have some ideas about workable European models which could be applied to this process.

Other regulatory issues are impacting on the delivery of orphan drugs. The EU Clinical Trials Directive\(^1\) is one such example—industry would like to work on broadening regulators’ understanding of trial complexities and results where orphan drugs are concerned. International harmonisation of regulatory requirements is also required, with the recently agreed joint FDA/EMA application form as a good start. More could also be done to protect incentives in relation to off-patent products and to clarify how decisions relating to “clinical superiority” and “significant benefit” are made.

Another aspect is the need for better communication about the economic and social value of orphan drugs. There is a need to consider the full picture, and not just the direct benefit to the individual patient. Orphan drugs have an impact on a broader level than just the healthcare system, for example by bringing people into the workforce who may never have contributed otherwise, by affecting the involvement level of carers, and by facilitating the work of family members who were looking after them. Orphan drugs also generate knowledge on new mechanisms and possible treatments for diseases which can be applied elsewhere. Increasing awareness of this point is essential to improving access to these treatments. And economic incentives to the field should be continued and strengthened instead of eroded or questioned.
Industry’s key messages are therefore quite simple:

1. We should ensure that it is understood by all those involved that an orphan drug is a product for which no alternative exists in the EU, or if such alternative exists, is of significant benefit to patients above and beyond what already exists on the market, and that therefore access should not be lightly denied.

2. We should all promote and support that more awareness about the rare diseases and their impact on patients and their families as well as on the impact of rare diseases left without treatment on national healthcare systems is needed.

3. We should more vigorously collect data about all rare disease initiatives and orphan drugs in Europe, in order to develop best practices and models for this field.

4. We should more clearly explain that market exclusivity does not mean a monopoly as there is room for products with different modes of action and for clinically superior products. And that the promised market exclusivity gets eroded by important delays in access to market.

5. There is also a need for more research, including about understanding risk.

6. And finally, we should encourage and promote the building of partnerships with other stakeholders.

To expand on the last two points, development of orphan medicines is not without risk, due to the fact that many of these therapies are the first in human history, and are exploring into hitherto uncharted territory. And being able to ensure the sustainability of a business in this environment is highly important, not only for investors, but even more so for patients. Indeed, finding these patients is difficult enough, and necessitates by itself proper use of diagnosis and screening techniques. On top of this, there is a need to improve the undeveloped care “infrastructure” for rare diseases.

A closer look needs to be taken on such areas as the impact of orphan drugs on, and the denial of access to, families. The whole notion of “value” and “value for whom” needs to be examined, as do communication
tools to create awareness about the ramifications of not granting access to these treatments. There is a need for more work on the epidemiology of the diseases, as well as on their natural history. The potential to involve payers already at the time of the design of the clinical trials, and the use of clinical registries as tools for further improvement of the therapy as well as for payers, should similarly be considered.

Another important factor is the definition and applicability of transparency from the perspective of the different stakeholders, as well as the reality of such perspective in discussing issues such as prices.

Therefore, trust building among all stakeholders in orphan medicines is needed, based on awareness and correct information. Successful drug models can act as a catalyst, generating further interest in the field. But it must be understood that, because of the risk involved, in the field of orphan medicines there is a real possibility that projects may fail, but their costs remain. And as a result, companies may fail as well, and then they are no longer seen in the equation. For a company to thrive and grow, it is important that it does not lose sight of the expectations of its shareholders. As a result, these products may only be one of many in a company’s strategy/portfolio, since it is very seldom that such a product is being developed on its own.

As a consequence, we should openly communicate, and not shy away from also discussing controversial topics – of which a few were raised – as they tend to come back. Open discussions, such as those during the EPPOSI conferences, are very helpful in this regard.

**Conclusion**

To conclude, we can summarise that industry is proud of what it has already achieved in the field of orphan drugs in Europe, and is committed to continue to focus even more on rare and neglected diseases, and to continue to innovate. Industry will also communicate more clearly about the achievements so far, while continuing its programmes on access, community relations and patient support. But we will also need to communicate more clearly about our focus, difficulties, and prices.

But we also need all other stakeholders in parallel to step up to the plate. All stakeholders must focus first of all on the needs of the patients. In addition, transparency from everyone about the issues, both positive and negative, surrounding orphan medicines can only help patient access. Dialogues among all stakeholders should be promoted to find solutions
for issues – joint communication of messages increases their strength, especially when being delivered by and to politicians (whose support is critical). And if we engage personally, our messages will come across stronger and with more impact.

Orphan medicines can improve the lives of rare disease patients across Europe. And through them, the lives of other Europeans. The legislation regulating their development must now take the final steps towards delivering on this ultimate reward.
5 NEW TREATMENTS AND ORPHAN DRUG DEVELOPMENT

The European policy for Orphan drugs is one of the most successful policies of the European Union. This session presented a brief status report as of 2007 and challenges identified by the Committee for Orphan Medicinal Products (COMP) for its 3rd mandate 2006-2009. One hurdle is unequal access to orphan drugs and the diverging national policies for health technology assessment. The outcomes of an important European workshop organised by the French National Health Agency was presented. The voice of the rare disease community will also be heard in the shaping of the future EU policy on advanced therapies – gene therapy and cell therapy.

5.1 EU and USA Shared Interests in Orphan Drugs

- Shared interest for defending the Spirit of our Acts and Regulations from Mischief
- Harmonising Operations

Joint FDA/EMEA Application for Orphan Drug status: it took five years to create it, and is a powerful tool to demonstrate both agencies’ good will to collaborate. Industry can now submit a designation application to Europe and to USA at the same time.

Conceptual Framework for Prevalence/Medical Rationale for designation

- Confronting post-designation barriers to full approval
- The Clinical trial for Orphan Drugs is special!
- Jointly re-examine what has stymied drugs designated but not approved
- Linking Patient Groups Internationally
- Tropical Disease Medicines are Orphans Too. These diseases are considered as rare under our rules, however they are a concern for a large part of the human population
- Global Outreach to other Orphan Drug Activities (Japan, Australia, etc).

Dr Timothy Coté,
Director, Office of Orphan Products Development, FDA
5.2 Seven years of orphan drugs policy: what’s next?

Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients.” But “the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions” As “some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product (…) would not be recovered by the expected sales” (from (EC) No 141/2000 and (EC) No 847/2000).

An orphan medicinal product should be for a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 individuals in the Community or that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment. No satisfactory method of should be authorised in the Community or, the medicinal product should be of significant benefit. The tasks of the COMP include: opinions on applications for orphan drug designation; advise to the Commission on orphan drug policy; assistance to the commission in liaising internationally on orphan drugs and with patient groups.

The EU Commission provides incentives for orphan designated drugs, e.g. market exclusivity for 10 years from the time of marketing authorisation, fees reduction for drug development and via the mandatory centralised procedure, access to all 27 EU member states. Extended incentives for Small and Medium-sized Enterprises are available post authorisation. Priority to EU research programs is given. The regulation also calls for national incentives for orphan designated drugs.

After 7 years of orphan drug policy, it is fair to conclude that the Orphan Drug regulation has been a success. Up to November 2007, 759 orphan drug designation (ODD) applications have been received, 523 of which have gained positive opinion by the COMP, whereas 12 had a negative opinion and 193 applications were withdrawn by the sponsor. So far, 42 new products have received market authorisation, 3 are in decision making by the EU Commission. Three applications had negative opinions and 22 applications were withdrawn. The predominant therapeutic areas corresponding to the designated orphan medicinal products are rare cancers (c:a 50%), whereas e.g. metabolic disorders amount to c:a 10%. More than half of the products designated are potentially for paediatric use.
WHAT’S NEXT?

1. **In drug development?**

Currently there is a strong trend - from “one drug fits all” blockbuster model - towards targeted treatments solutions for patients with particular diseases. This concept concerns innovative medicines (around 1/5 of orphan drug designations), advanced therapies, targeted and personalised medicines where orphan drug development could act as models. Such a development would benefit not only from a close collaboration between different companies contributing in their specific areas but also from a close collaboration between academic researchers and industry - in order to make real progress.

Orphan designated medicinal products comprise several examples of advanced therapies, such as gene therapy products for hereditary diseases, e.g. Duchenne’s muscular dystrophy, SCID (Severe Combined Immunodeficiency) and for rare cancers, e.g. glioma and renal cell carcinoma. Cell therapies have received orphan designation, e.g. for the treatment of acute liver failure, and even tissue therapy - for epidermolysis bullosa.

2. **In economic development?**

According to the EU Commission report, the orphan drug regulation has resulted not only in more jobs in the EU, notably in SMEs but also in a marked increase in R&D expenditure.

3. **In collaboration?**

The first and very important steps have been taken to a collaboration between the EMEA and the FDA; parallel protocol assistance/scientific advice between the EMEA and the FDA is already in place; recently, the Common EMEA/FDA application form for orphan medicinal product designation, in order to simplify simultaneous ODD application. The potential for an extended transatlantic work in parallel will be explored, as will also the possibilities for global collaboration with e.g. Japan and Australia.

4. **For the COMP?**

The role of the COMP as a “meeting point”/”initiation site” for collaboration and development between stakeholders – industry, patients, health care professionals/academia - is steadily increasing. The role of COMP members – at the EMEA in e.g. Scientific Advice Working Party (SAWP); in the EU Commission Rare Disease Task Force; as advisors to the EU Commission (DG Enterprise/SANCO/Research) is becoming
more and more important - as well as their roles in the member states as “ambassadors” for rare diseases and orphan drugs.

→ OPPORTUNITIES AND CHALLENGES

The incentives under the regulation - market exclusivity, protocol assistance and access to Community research programs has made it possible also for small enterprises to develop new drugs and bring them to the market. In the EU only, the orphan regulation could benefit some 15 million people suffering from rare conditions. Moreover, since the designation criteria also allow for the designation/development of conditions prevalent in developing countries but rare in the EU, the impact of the orphan regulation could be even greater. Further, by learning from the rare, common conditions might benefit from orphan drug development. Thus, the impact of the regulation has far exceeded the expectations at the beginning of the COMP mandate in April 2000. The challenges are several: allowing for the necessary profitability to stimulate research in drug development to achieve even more and better orphan drugs - yet keeping costs at a level where the drugs can still be affordable and available to the patients.

Annex document: Orphan Medicines authorised in the EU as of 26/11/2007 (centralised procedure)

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>MA Sponsor</th>
<th>Authorised Therapeutic Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabrazyme</td>
<td>Genzyme BV</td>
<td>Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (-galactosidase A deficiency).</td>
</tr>
<tr>
<td>Replagal</td>
<td>TKT Europe AS</td>
<td>Replagal is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (-galactosidase A deficiency).</td>
</tr>
<tr>
<td>Trisenox</td>
<td>Cell Therapeutics (UK) Ltd</td>
<td>TRISENOX is indicated for induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptoralpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy.</td>
</tr>
<tr>
<td>Tracleer (Bosentan)</td>
<td>Actelion</td>
<td>Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms inpatients with grade III functional status. Efficacy has been shown in: Primary PAH PAH secondary to scleroderma without significant interstitial pulmonary disease</td>
</tr>
<tr>
<td>Tracleer (Bosentan)</td>
<td>Actelion</td>
<td>Treatment of new digital ulcers in patients with systemic sclerosis and active digital ulcers</td>
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</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.</td>
</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Glivec is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.</td>
</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Glivec is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).</td>
</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Treatment of adult patients with unresectable recurrent and/or metastatic dermofibrosarcoma protuberans</td>
</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) as monotherapy</td>
</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR gene re-arrangement</td>
</tr>
<tr>
<td><strong>Glivec</strong></td>
<td>Novartis Europharm Limited</td>
<td>Treatment of adult patients with hypereosinophilic syndrome (HES) and chronic eosinophilic leukaemia (CEL)</td>
</tr>
<tr>
<td><strong>Somavert (Pegvisomant)</strong></td>
<td>Pharmacia Enterprises SA</td>
<td>Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.</td>
</tr>
<tr>
<td><strong>Zavesca (Miglustat)</strong></td>
<td>Oxford GlycoSciences (UK) Ltd (transferred to Actelion)</td>
<td>Zavesca is indicated for the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.</td>
</tr>
<tr>
<td><strong>Carbaglu</strong></td>
<td>Orphan Europe Sarl</td>
<td>Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.</td>
</tr>
<tr>
<td><strong>Aldurazyme (Laronidase)</strong></td>
<td>Genzyme Europe BV</td>
<td>Aldurazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPSI; a [alpha]-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease</td>
</tr>
<tr>
<td><strong>Busilvex</strong> (Busulfan)</td>
<td>Pierre Fabre Medicament</td>
<td>Conditioning treatment prior to haematopoietic progenitor cell transplantation in adult patients.</td>
</tr>
<tr>
<td><strong>Ventavis</strong> (Iloprost)</td>
<td>Schering AG</td>
<td>Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.</td>
</tr>
<tr>
<td>Drug</td>
<td>Manufacturer</td>
<td>Description</td>
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</tr>
<tr>
<td>Onsenal (Colecovib)</td>
<td>Pharmacia-Pfizer EDIG</td>
<td>Reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP) as an adjunct to surgery and further endoscopic surveillance.</td>
</tr>
<tr>
<td>Photobarr</td>
<td>Axcan Pharma International BV</td>
<td>Photodynamic therapy (PDT) with porfimer sodium is indicated for: Ablation of high grade dysplasia (HGD) in patients with Barrett’s Oesophagus (BE)</td>
</tr>
<tr>
<td>Litak (Cladribine,B)</td>
<td>Lipomed GmbH</td>
<td>Treatment of hairy cell leukaemia</td>
</tr>
<tr>
<td>Lysodren (Mitotane)</td>
<td>Laboratoire HRA Pharma</td>
<td>Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.</td>
</tr>
<tr>
<td>Pedia (Ibuprofen),M</td>
<td>Orphan Europe SARL</td>
<td>Indicated to close a patent ductus arteriosus in preterm newborn infants</td>
</tr>
<tr>
<td>Wilzin</td>
<td>Orphan Europe SARL</td>
<td>Treatment of Wilson’s disease</td>
</tr>
<tr>
<td>Xagrid (Anegrelide Hydrochloride)</td>
<td>Shire Pharmaceuticals Ltd</td>
<td>Reduction of elevated platelet counts in at risk essential thrombocythemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.</td>
</tr>
<tr>
<td>Orfadin (Nitisinone)</td>
<td>Swedish Orphan Int.</td>
<td>Hereditary tyrosinemia type 1</td>
</tr>
<tr>
<td>Prialt® (Ziconotide)</td>
<td>Elan Pharma Int.</td>
<td>Ziconotide is indicated for the treatment of chronic pain requiring intrathecal (IT) analgesia in patients who fail to obtain adequate analgesia and/or suffer intolerable adverse events with systemic opioids</td>
</tr>
<tr>
<td>Xyrem (sodium oxybate)</td>
<td>UCB Pharma Ltd</td>
<td>Treatment of cataplexy in patients with narcolepsy.</td>
</tr>
<tr>
<td>Revatio (sildenafil citrate)</td>
<td>Pfizer limited</td>
<td>Treatment of pulmonary arterial hypertension. Revatio has been shown to improve exercise ability and to reduce mean pulmonary arterial pressure.</td>
</tr>
<tr>
<td>Naglazyme (N-acetylgalactosamine 4-sulfatase,A)</td>
<td>BioMarin Europe</td>
<td>Naglazyme is indicated for long term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux Lamy syndrome) to treat the clinical manifestations of the diseases.</td>
</tr>
<tr>
<td>Myozyme (recombinant human acid alpha-glucosidase)</td>
<td>Genzyme Europe</td>
<td>Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid alpha-glucosidase deficiency)</td>
</tr>
<tr>
<td>Evoltra (2-chloro-9-[2 deoxy-2-Fluoro-β-D-Arabinofuranosyl]adeniteL)</td>
<td>Bioenvision Ltd</td>
<td>Treatment of acute lymphoblastic and acute myeloid leukaemia</td>
</tr>
<tr>
<td>Nexavar (Sorafenib tosylate)</td>
<td>Bayer Healthcare AG</td>
<td>Treatment of advanced renal cell carcinoma</td>
</tr>
<tr>
<td>Drug</td>
<td>Manufacturer</td>
<td>Indications</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sutent</td>
<td>Pfizer Limited</td>
<td>Treatment of gastrointestinal stromal tumour (GIST)</td>
</tr>
<tr>
<td>Sutent</td>
<td>Pfizer Limited</td>
<td>Treatment of advanced and/or metastatic renal cell carcinoma (MRCC)</td>
</tr>
<tr>
<td>Savene (Dexrazoxane)</td>
<td>Topo Target A/S</td>
<td>Treatment of anthracycline extravasation</td>
</tr>
<tr>
<td>Thelin (Sitaxentan sodium)</td>
<td>Encysive (UK)</td>
<td>Treatment of idiopathic pulmonary arterial hypertension (IPAH) or pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Exjade</td>
<td>Novartis Europharm Limited</td>
<td>Treatment of chronic iron overload due to blood transfusions (transfusion haemosiderosis) in adult and paediatric patients (aged 2 years and over)</td>
</tr>
<tr>
<td>Sprycel (dasatinib)</td>
<td>Bristol-Myers Squibb Pharma</td>
<td>Treatment of chronic myeloid leukaemia (CML) and philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL)</td>
</tr>
<tr>
<td>Sprycel (dasatinib)</td>
<td>Bristol-Myers Squibb Pharma</td>
<td>Treatment of adults with chronic accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate</td>
</tr>
<tr>
<td>Inovelon (Rufinamide)</td>
<td>Esai Limited</td>
<td>Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years and older</td>
</tr>
<tr>
<td>Diacomin (Striomentol)</td>
<td>BIOCODEX</td>
<td>Treatment of severe myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>Elaprase (iduronate-2-sulfatase)</td>
<td>TKT UK</td>
<td>Treatment of Hunter syndrome (Mucopolysaccharidosis II)</td>
</tr>
<tr>
<td>Cystadane (betaine anhydrous A)</td>
<td>Ophan Europe</td>
<td>Treatment of homocystinuria</td>
</tr>
<tr>
<td>Revlimid</td>
<td>Celgene Europe Ltd</td>
<td>Treatment in combination with dexamethasone of multiple myeloma patients who have received at least one prior therapy</td>
</tr>
<tr>
<td>Soliris (Eculizumab)</td>
<td>Alexion Europe</td>
<td>Treatment of paroxysmal nocturnal hemoglobinuria (PNH)</td>
</tr>
<tr>
<td>Siklos (hydroxyurea)</td>
<td>Addmedica</td>
<td>Prevention of vaso-occlusive crises in patients with symptomatic Sickle Cell Syndrome</td>
</tr>
<tr>
<td>Increlex (Mecasermin)</td>
<td>Tercica Europe Ltd</td>
<td>Treatment of growth failure</td>
</tr>
<tr>
<td>Atriance (Nelarabine)</td>
<td>Glaxo Group Ltd</td>
<td>Treatment of T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)</td>
</tr>
<tr>
<td>Gliolan (5 aminolevulinic acid hydrochloride L)</td>
<td>Medac GmbH</td>
<td>Visualisation of malignant tissue during surgery for malignant glioma</td>
</tr>
<tr>
<td>Yondelis (Ecteinascindin 743 L)</td>
<td>PharmaMar SA</td>
<td>Treatment of advanced soft tissue sarcoma</td>
</tr>
</tbody>
</table>
5.3 Preparing the European scenario for advanced therapies (gene therapy, cell therapy, future EU Regulation)

This presentation addressed:

**Gene / cell therapy : emergence**
- Orphan drug designation
- On-going clinical trials
- 1st MAA on going

**Regulations on advanced therapies : update**

**Development and marketing on advanced therapies : Key issues, bottleneck, reflections to be addressed**

> **GENE / CELL THERAPY : EMERGENCE AND ORPHAN DRUG DESIGNATION**

To obtain the orphan drug designation, 5 to 7 months are necessary: an initial meeting at the European Medicines Agency (EMEA), then 2 months to submit the file (disease information, proof of concept, 1st pre-clinical results), and finally the evaluation that can last for 3 to 5 months in the absence of questions.

When the orphan drug designation is granted, the product becomes a priority for regulatory agencies, the orphan designation receives 10 years of exclusivity in all Member States, protocol assistance at EMEA,

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<table>
<thead>
<tr>
<th>Orphan Medicine</th>
<th>Company</th>
<th>Description</th>
<th>Mutual Recognition Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dudopa (Levodopa/Carbidopa)</td>
<td>NeoPharma</td>
<td>Treatment of advanced levodopa-responsive Parkinson’s disease with severe motor fluctuations and hyper-dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results</td>
<td>Sweden</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recognised by: Austria, Denmark, Finland, France, Germany, The Netherlands, Norway, Portugal, Spain</td>
</tr>
<tr>
<td>Impavido (Miltefosine, P)</td>
<td>Zentaris AG</td>
<td>Treatment of visceral leishmaniasis caused by Leishmania donovani after failure of standard therapy</td>
<td>Germany</td>
</tr>
</tbody>
</table>

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**Dr Anne-Marie Masquelier, Chief Executive Officer, Genethon, France**
direct access to the centralised procedure for the assessment of the risk/benefit for marketing authorisation, and fee reduction for the centralised procedure.

The table below summarises advanced therapies that are designated as orphan:

<table>
<thead>
<tr>
<th>NPN Indication</th>
<th>Indication</th>
<th>Prev /10000</th>
<th>Sponsor</th>
<th>Designation date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome P450 isoform 2B1 gene transfected human embryonic kidney 293 cells encapsulated in polymeric cellulose sulphate</td>
<td>Treatment of pancreatic cancer in combination with ifosfamide</td>
<td>1</td>
<td>FSG BTnologie Austrianova GmbH</td>
<td>30/06/03</td>
</tr>
<tr>
<td>herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes</td>
<td>Adjunctive treatment in haematopoietic cell transplantation</td>
<td>0,2</td>
<td>MolMed SpA</td>
<td>20/10/03</td>
</tr>
<tr>
<td>HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor</td>
<td>Treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients</td>
<td>3,6</td>
<td>CellC ApS</td>
<td>21/06/04</td>
</tr>
<tr>
<td>human autologous mesenchymal adult stem cells extracted from adipose tissue</td>
<td>Treatment of anal fistula</td>
<td>1,8</td>
<td>Cellerix SL-CSIC</td>
<td>26/08/05</td>
</tr>
<tr>
<td>human heterologous liver cells</td>
<td>Treatment of acute liver failure</td>
<td>3,36</td>
<td>Cytonet GmbH &amp; Co. KG</td>
<td>11/04/06</td>
</tr>
<tr>
<td>Autologous CD34+ cells transfected with retroviral vector containing the human gr91 (phox) gene</td>
<td>Treatment of chronic granulomatous disease</td>
<td>NA</td>
<td>Vision 7 GmbH</td>
<td>28/08/06</td>
</tr>
<tr>
<td>allogenic (human) tumor cells, transfected with MIDGE vectors for the expression of IL-7, GM-CSF, CD80 and CD154, in combination with dSLIM immunomodulators</td>
<td>Treatment of renal cell carcinoma</td>
<td>3,5</td>
<td>Mologen AG</td>
<td>23/10/06</td>
</tr>
<tr>
<td>L-asparaginase encapsulated in red blood cells</td>
<td>Treatment of acute lymphoblastic leukaemia</td>
<td>0,5</td>
<td>Erytech Pharma S.A.</td>
<td>27/10/06</td>
</tr>
<tr>
<td>ex-vivo cultured adult human mesenchymal stem cells</td>
<td>Treatment of acute graft-versus-host disease</td>
<td>1</td>
<td>Quintiles Ltd</td>
<td>20/02/07</td>
</tr>
<tr>
<td>NPN</td>
<td>Indication</td>
<td>Prev /10000</td>
<td>Sponsor</td>
<td>Designation date</td>
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</tr>
<tr>
<td>autologous dendritic cells loaded with autologous brain tumour cell lysate</td>
<td>Treatment of glioma</td>
<td>1</td>
<td>Dorian Regulatory Affairs BV</td>
<td>15/02/07</td>
</tr>
<tr>
<td>autologous CD34+ cells transfected with lentiviral vector containing the human ARSA cDNA</td>
<td>Treatment of metachromatic leukodystrophy</td>
<td>NA</td>
<td>Fondazione Telethon</td>
<td>13/04/07</td>
</tr>
<tr>
<td>human heterologous liver cells</td>
<td>Treatment of ornithine-transcarbamylase deficiency</td>
<td>0,1</td>
<td>Cytonet GmbH &amp; Co KG</td>
<td>14/09/07</td>
</tr>
<tr>
<td>retroviral gamma-c CANA containing vector</td>
<td>Treatment of Severe Combined Immunodeficiency (SCID)-XI Disease</td>
<td>0,003</td>
<td>Genopoietic S.A.S.</td>
<td>30/05/01</td>
</tr>
<tr>
<td>adenovirus-mediated herpes simplex virus-thymidine kinase gene</td>
<td>Treatment of high-grade glioma with subsequent use of ganciclovir sodium</td>
<td>0,7</td>
<td>Ark Therapeutics Ltd</td>
<td>06/02/02</td>
</tr>
<tr>
<td>recombinant adenovirus carrying a gene coding for the human interferon gamma</td>
<td>Treatment of cutaneous T-cell lymphoma</td>
<td>0,63</td>
<td>Transgene S.A.</td>
<td>09/07/03</td>
</tr>
<tr>
<td>herpes simplex virus lacking infected cell protein 34.5</td>
<td>Treatment of glioma</td>
<td>0,8</td>
<td>Crusade Laboratories Ltd</td>
<td>09/07/03</td>
</tr>
<tr>
<td>adeno-associated viral vector expressing lipoprotein lipase</td>
<td>Treatment of lipoprotein lipase deficiency</td>
<td>0,02</td>
<td>Dr. Aart Brouwer</td>
<td>08/03/04</td>
</tr>
<tr>
<td>vascular endothelial growth factor-D gene in an adenoviral vector for use with a collagen collar</td>
<td>Prevention of stenosis in synthetic grafts used in haemodialysis</td>
<td>0,4</td>
<td>ARK Therapeutics Ltd</td>
<td>08/06/04</td>
</tr>
<tr>
<td>adeno-associated viral (AAV) vector containing the human gamma-sarcoglycan gene</td>
<td>Treatment of gamma sacroglycanopathies</td>
<td>0,2</td>
<td>Généthon</td>
<td>21/10/04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NPN</th>
<th>Indication</th>
<th>Prev /10000</th>
<th>Sponsor</th>
<th>Designation date</th>
</tr>
</thead>
<tbody>
<tr>
<td>adeno-associated viral vector containing modified U7 sn RNA</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>0,5</td>
<td>Genethon</td>
<td>27/07/05</td>
</tr>
<tr>
<td>autologous CD34+ cells transfected with retroviral vector containing adenosine deaminase gene</td>
<td>Treatment of ADA-deficient SCID</td>
<td>NA</td>
<td>Fondazione Telethon</td>
<td>26/08/05</td>
</tr>
<tr>
<td>Gene Therapy Clinical Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Treatment of wiskott</td>
<td>0.01 Genethon</td>
<td>24/01/06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aldrich syndrome gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of calpainopathy</td>
<td>0.1 Genethon</td>
<td>06/04/06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adeno associated viral vector containing the human calpain 3 gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of Li Fraumeni Syndrome</td>
<td>0.05 Gendux AB</td>
<td>23/10/06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adenoviral vector containing human p53 gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of congenital alpha-1 antitrypsin deficiency</td>
<td>2.5 The Matthews Consultancy Ltd</td>
<td>20/03/07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recombinant adeno-associated viral vector expressing human alpha-1 antitrypsin gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of renal cell carcinoma</td>
<td>3.6 Oxford Biomedica Ltd</td>
<td>26/01/07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recombinant modified vaccinia virus Ankara expressing human ST4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of Pompe Disease</td>
<td>2.7 The Matthews Consultancy Ltd</td>
<td>09/07/07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recombinant adeno-associated viral vector expressing human alpha-1 antitrypsin gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of epidermolysis bullosa</td>
<td>0.4 Cellerix SL</td>
<td>28/05/06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilayer engineered skin composed of keratinocytes from the patient (autologous) and fibroblasts from a donor (allogeneic) embedded in a plasma matrix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ CLINICAL RESEARCH : CLINICAL TRIALS IN PROGRESS, TOWARDS MARKETING AUTHORISATION APPLICATION

<table>
<thead>
<tr>
<th>Phase III (updated 11/2007)</th>
<th>22 enrolling (out of 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monogenic diseases : 0</td>
<td></td>
</tr>
<tr>
<td>Phase II/III (updated 11/2007)</td>
<td>6 enrolling (out of 13)</td>
</tr>
<tr>
<td>Monogenic diseases : 0</td>
<td></td>
</tr>
<tr>
<td>Phase II TG (updated 11/2007)</td>
<td>95 enrolling (out of 169)</td>
</tr>
<tr>
<td>Monogenic diseases : 1</td>
<td></td>
</tr>
<tr>
<td>Phase VII (updated 11/2007)</td>
<td>131 enrolling (out of 258)</td>
</tr>
<tr>
<td>Monogenic diseases : 12</td>
<td></td>
</tr>
<tr>
<td>Phase I (updated 11/2007)</td>
<td>473 enrolling (out of 801)</td>
</tr>
<tr>
<td>Monogenic diseases : 31</td>
<td></td>
</tr>
<tr>
<td>Total of enrolling trials</td>
<td>727</td>
</tr>
</tbody>
</table>

→ REGULATIONS ON ADVANCED THERAPIES : UPDATE

Advanced therapies are medicinal products based on genes, cells, and tissues: tissue engineering, cell therapy, and gene therapy, as opposed to products based on biotechnologies and chemical products.
The European regulation for advanced therapies responds to the market segmentation that undermined industrial development until recently. Patients’ access to new treatments was therefore hindered. Public consultations in 2002, 2004, and 2005 revealed public expectations for clear European rules in this domain, and this was true for all stakeholders: the need for a specific, harmonised and coherent EU regulatory framework.

**COMMITTEE FOR ADVANCED THERAPY (CAT)**
With the Regulation, a new committee has been established at the EMEA, pooling Community expertise. This is a multidisciplinary group: biotechnology, medical devices, risk management, ethics ….

**SPECIFIC PROVISIONS FOR SMES:**
For Small and Medium-sized enterprises, the current legislation Reg EC N° 2049/2005 provides fee reduction and deferrals, handling of translations, general administrative assistance, workshops and training sessions. In addition, the legislation will also provide certification of quality and non-clinical data.

The Legislation on Advanced Therapies defines clear rules, smooth procedures and a European wide market. Particular attention is given to certain categories of stakeholders such as academic teams or SMEs. Detailed requirements and guidance also influence the implementation and its economic impact. The Legislation keeps the pace with new scientific developments.

**DEVELOPMENT AND MARKETING ON ADVANCED THERAPIES: KEY ISSUES, BOTTLENECK, REFLECTIONS TO BE ADDRESSED**

1. **Development of Advanced Therapies**
Special clinical investigation centres for Gene Therapy and Clinical Trials must be supported: very few exist in Europe (particularly for Gene Therapy), imposing to patients to travel when they want to participate in these trials, but difficulties due to the pathology, the lack of familial environment, or the cost are limiting factors.

Patients’ registries need harmonisation, rapid patient enrolment, feedback to patients’ organisations.

2. **Regulation**
A unique IMPD file (Investigational Medicinal Product Dossier for the centralised mutual recognition should be created and a same entity should evaluate the Clinical Trials Application and the New Drug Application.
SUSAR should be reported to EMEA only, and there should be no reporting duplication to national competent authorities. National Ethics Committees will address cultural differences within Member States.

Good Manufacturing Practices Production sites for clinical trials: very few exist in EU for Gene Therapy and Clinical Trials, and with limited capacities.

Funding is limited, and creative solutions are needed to increase the research capacity, associating Pharmaceutical industry, Biotech companies, National, European, Venture Capital, business angels, private equity partners.....

3. **Compassionate use / Marketing Authorisation Application**
The EMEA now has the possibility to give an opinion on Compassionate use (indication, eligible patients…). However compassionate use programmes have a cost, and the Legislation states that unauthorised products can not be charged for. Exceptions exist, and Member States have different compassionate use systems. As most advanced therapies are developed by SMEs or Academic teams, logistical issues and cost issues are obstacles to patients’ access to compassionate use.

Information on treatments, clinical sites and on-going or planned clinical trials should be more transparent. Patients’ representatives and industry initiatives should link together to improve information in this domain.

The reimbursement of marketed products varies across countries, and this creates inequity in access to treatment throughout Europe. Furthermore, the development and manufacturing costs of advanced therapies are likely to be substantial.

**CONCLUSION**
- EU Regulatory is coming > advanced therapies are really coming
- Objective to facilitate and harmonise EU rules for development and MAA
- Clear Objectives to get equity across countries to get access to treatment
- Main issues: harmonisation across MS, funds, different ways of reimbursement across MS
5.4 Timely and equitable access to orphan medicines across Member States – The European HAS Workshop November 2006, Paris

→ INTRODUCING A NEW DRUG IN THE EUROPEAN HEALTHCARE SYSTEMS

Even though all products evaluated through the European centralised procedure are authorised the same day in all Member States, they are not all actually placed on the market at the same time. The marketing authorisation is the first step, and then the introduction into national healthcare systems is the second step, under the responsibility of Member States for the pricing, reimbursement, financing and implementation.

The availability of medicinal products after the marketing authorisation has been granted is the result of a chain of actions: appraisal (of the therapeutic value), listing (on the reimbursement list), pricing (free pricing policy, regulated pricing schemes), financing (budget for the purchase of the product), and appropriate health care organisation (product available in hospitals only, restriction to specialised doctors or not...). These decisions are taken at the national level, and sometimes at the regional level.

→ HAUTE AUTORITÉ DE SANTÉ WORKSHOP, NOVEMBER 2006, PARIS

Orphan Drugs in the EU: Toward a Common Approach for a Fair and Sustainable Patient Access

The French agency in charge of health technology assessment organised this workshop in November 2006. All stakeholders were represented, except the pharmaceutical industry. Four working groups gathered to address the following themes:

- WG 1 The epidemiology of rare diseases to assess the needs, chaired by Dr Ségolène Aymé
- WG 2 The assessment of the potential clinical benefit in the pre-marketing phase and of the real benefit after marketing authorisation
- WG 3 The economic evaluation of OD
- WG 4 The sustainability of the system

→ ECONOMIC EVALUATION

The group discussed the adequacy of the assessment methods for rare diseases and orphan drugs. A seminar with leading health economists to see how to best address some of these issues was proposed. For economic evaluation of orphan drugs, experts are debating ethical issues about the apparent opposition between collective choices and individual preferences.
Does rarity have an economic value, as opposed to severity? The criteria on which decisions are made should be made clear and publicly available, and discussed. Research into society’s values with respect to rarity compared to severity has to be fostered, with a comparative analysis between Member States.

The issue of risk-sharing in research and pricing should be discussed more thoroughly: when uncertainty prevails, who should accept the financial risk? The health care system alone or the health care system sharing the responsibility with the patient? Or with the marketing authorisation holder in case the product is not as effective as initially thought at the time of assessment?

→ SUSTAINABILITY OF THE SYSTEM

The need to clarify key concepts such as “market exclusivity” and “significant benefit” was recognised by all participants. To be in the best position to foresee future health expenditures, health care systems need more transparency from the industry on medicines and their cost. The weight of failing developments in these costs should be addressed.

An informal network of national authorities in charge of orphan drug pricing could be created. Common sets of criteria could be adopted for the pricing negotiations, so that a European ex-factory reference price could be proposed.

Nevertheless, the decision making will remain at the national level due to market and organisation of care specificities: other elements such as taxes, distribution mode, volume, other products in portfolio of the marketing holder, etc. should be considered.

Greater public investment in research and risk sharing on development costs should be promoted to contribute to ensure long term sustainability of the system.

→ ASSESSMENT OF THE CLINICAL OR THERAPEUTIC VALUE OF MEDICINAL PRODUCTS

- Necessity to increase knowledge of the natural history of Rare Diseases, for example in the absence of a comparator in the trials (comparison with historic cases and untreated patients)
- Assessment of the therapeutic value and natural history of the disease should take place before the placing on the market, without delaying development
- Importance to improve the quality of data on the product, and clinical end points in clinical trials are needed. Surrogate markers can only be used for the appraisal of therapeutic value only if they relate to clinical endpoints.
• Randomised clinical trials are the reference, but alternative methods exist
• Improve cooperation in the field of Health Technology Assessment: towards common assessment of some Orphan Medicinal Products within existing networks. MEDEV is an informal network that could play this role. Networking within HTA (EUnetHTA DG SANCO project) can be helpful.
• Importance to manage uncertainty with post marketing data collection

→ CONCLUSION OF THE WORKSHOP

Cooperation between EMEA (COMP-CHMP) and HTA agencies on the assessment of significant benefit, relative effectiveness, choice of endpoints for clinical trials, and pharmaco-epidemiological studies is greatly needed.

→ HTA IS PERFORMED WITHIN A GIVEN NATIONAL CONTEXT

<table>
<thead>
<tr>
<th>FRANCE</th>
<th>ENGLAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% of drugs are evaluated before decision</td>
<td>Limited number of drugs evaluated, topic selection</td>
</tr>
<tr>
<td>Two step procedure: clinical value first assessed by HAS, then a different committee negotiates the price with the marketing authorisation holder</td>
<td>One step procedure (NICE)</td>
</tr>
<tr>
<td>HTA (performed by HAS) focused on clinical effectiveness. Price not (yet) taken into account.</td>
<td>Freedom of pricing</td>
</tr>
<tr>
<td>Price decided by Economic Committee after negotiation with the company, and based on the results of HAS’ assessment.</td>
<td>Assessment/appraisal of the drug includes cost-effectiveness (based on the price decided by the company) Cost/QALY threshold? (Quality Adjusted Life Years)</td>
</tr>
<tr>
<td>National Budget</td>
<td>Primary Care Trust</td>
</tr>
</tbody>
</table>

The EUnetHTA is organising a conference in France at the end of 2008. In parallel, a public Consultation on Future EUnetHTA Collaboration beyond 2009 is open.

More information is available at: EUnetHTA http://www.eunethta.net/
6 INFORMATION SERVICES

6.1 Involvement of patients in Norway

Birgitte Bjerkely, Jostein Fredriksen and Mads Bjerke, from the Centre for Rare Disorders in Norway, reported on the involvement of patients in the description of their own disease in booklets, videos. When patients express the need for a new publication, a brainstorming session is organised at the Centre for Rare Disorders, with health care professionals representing all medical and paramedical specialities. From the brainstorming session, a storyboard is developed. And a working group is established, with patients (both young and older patients) and health care professionals.

During the writing process, quality assurance is performed by the professionals, and patients check the understandability at all stages. Manuscripts are sent to the reference groups, and also for the choice of illustrations. Once edited, patients are invited to participate in the booklets’ dissemination. This sharing of information ultimately builds a solid base of competence and knowhow around the patients in their everyday life, usually not found in ordinary textbooks.

More information at: www.rikshospitalet.no/sjeldnediagnoser

6.2 Information both in Swedish and English

The Swedish Rare Disease Database, currently providing information on around 225 rare diseases, is published by the Swedish National Board of Health and Welfare. The material is also being published in English. The number of users is steadily increasing, and the database now serves around 50,000 visitors monthly.

Leading experts on each diagnosis produce the information, which is also reviewed by a scientific advisory board before publication. Patient organisations are important partners. All texts offer detailed descriptions of medical, psychological, social and educational aspects of the disorders, and the information is continuously updated and enlarged.

The database is a resource for patients and their families, healthcare professionals, public authorities and anyone interested in learning more
about rare diseases. The Swedish Information Center for Rare Diseases produces and edits the database, and also provides information, printed materials and referrals to other resources. The center is managed under the auspices of the Sahlgrenska Academy at Göteborg University and can be contacted by email, phone, fax or post.

More information at: www.socialstyrelsen.se/ovanligadiagnoser

### 6.3 Practical education in biology

Do you have trouble understanding the time scale of research? Would you like to know precisely what DNA is and unravel its mysteries? Tous Chercheurs offers a training to familiarise with biology, genetics and the world of research, all in an enjoyable setting.

The association “Tous Chercheurs” has developed practical trainings in molecular biology and genetics for rare genetic disease associations.

These 3-days sessions take place in a laboratory where the trainees work as researchers, under the guidance of experienced tutors. They learn to observe, formulate hypotheses and carry out experiments. In addition to the practical work, each session includes discussions with specialised researchers. The trainees thus understand concretely the work and constraints of researchers.

Since 2004, Tous Chercheurs have trained 130 patients from very diverse associations, highlighting a strong need for this kind of training.

The development of this innovative action was made possible by the support of partners: AFM (Association Française contre les Myopathies), Inserm (Institut de la Recherche Médicale) and CNRS (Centre National de Recherche Scientifique).

Aim of education for rare disease associations to reinforce the dialogue between disease associations, researchers and physicians

- A basis in biology and genetics
- Clear explanations on the origin and transmission of genetic diseases
- An understanding of scientific methods and the specificities of research (time scale …)
6.4 The Orphanet directory of services: activities related to rare diseases across the United Kingdom

Orphanet is an information centre for the rare disease community.

Orphanet is the non-profit, European Commission funded, official portal offering information and specific services for rare diseases. The website, which is now the largest database dedicated to rare diseases in the world, is accessed daily by more than 20,000 users from 170 countries. The website is freely available in a choice of six languages: English, French, German, Italian, Portuguese and Spanish.

The objectives of Orphanet are to:

- Contribute to improving diagnosis, treatment and management of patients suffering from rare diseases
- Accelerate the development of research
- Reinforce the participation of concerned rare disease stakeholders
- Improve existing resources
- Contribute to improving diagnosis, treatment and management of patients suffering from rare diseases
- Accelerate the development of research
- Reinforce the participation of concerned rare disease stakeholders
- Improve existing resources

→ ORPHANET OFFERS:

- A list of more than 7000 rare diseases, over 2000 of which feature encyclopaedia entries describing the condition. Entries for the encyclopaedia are produced by international experts in the field and validated by an editorial committee.
- A directory of services providing information on specialised consultations and centres of reference, clinical laboratories, research projects, clinical trials, professional networks, disease registries and patient support organisations.
- Many related services such as the bi-monthly OrphaNews Europe e-newsletter, the peer reviewed academic journal, Orphanet Journal of Rare Diseases and a registration service where patients can volunteer to participate in relevant research projects and clinical trials.

For more information on the Orphanet database or any related services, please visit the website (www.orpha.net) or contact the Orphanet team in your country.

Figure 30: This map illustrates the 35 Orphanet partner countries and the year in which they joined the consortium. In addition to collecting data for the directory of services in their respective countries, the partners also ensure the relevant pro professional, patient and public communities in their country are aware of the Orphanet portal and related services.
The directory of services is a vital part of the service Orphanet provides:

- It aids health professionals and patients by providing information on currently available clinical and laboratory diagnostic services.
- It facilitates collaboration in the research and development of future treatments for rare diseases.
- It allows patients and their families to feel less isolated by providing the means to find relevant support organisations. The Orphanet partners are responsible for gathering information for the directory of services from their respective countries (see map). The Orphanet directory of services currently contains the details of over 26,000 activities related to rare diseases. The UK Orphanet team began collecting the details of any ongoing relevant activities from health professionals and patient support organisations in January 2005. As they were collected, these activities were added to the Orphanet website.

The collection of UK activities has so far been successful. Highlights of the activities collected so far include:

- Every test provided by the UK Clinical Molecular Genetics Society network of laboratories is now listed on the Orphanet database.
- Orphanet contains details of the outpatient clinics provided by over 75% of UK Clinical Genetics centres and over 50% of UK National Specialist Commissioning Advisory Group (NSCAG) services.
- Over 90% of UK patient support organisations are now listed in the Orphanet directory of services.
6.5 Experience from psychosocial (Re)habilitation in Finland

The Concept of Psychosocial (Re)habilitation

For a family with a member with a rare disease or disability, proper examination, diagnosis, therapy and medication are essential. These are basic requisites for the growth and development of the individual but only part of the total picture. In order to become empowered and find their own place in the family and society, disabled/chronically ill person also needs psychosocial support and (re)habilitation. This gives him/her the possibility to develop as a person with solid self-esteem interacting with the environment and managing his/her own life. In addition, abilities and skills to use services are needed to make their everyday life functional.

Psychosocial (re)habilitation supports a person’s self-respect and overall well-being. Essential is to give him/her measures for empowering and to advance and exercise social skills.

Conditions for Good (Re)habilitation

- Accessible physical and social environment
- Respecting opinions, feeling and experiences of the participants
- Taking care of basic needs (e.g. assistance)
- Meeting other people with a disease or disability
- Multiprofessional approach
- Professional attitudes and continuing development

When is Psychosocial (Re)habilitation Needed

- A changed life situation (e.g. newborn baby with a disability, accident)
- Transition periods (e.g. school start, new marriage)
- Interaction threatened (e.g. isolation)
- Questions on own personality and identity emerging (role as man/woman/parent, mental health)

Content of Psychosocial (Re)habilitation

- Identity
- Empowerment
- Close personal relationships and interaction
- Relationships with peers
- Functional everyday life.

Typical Methods of Psychosocial (Re)habilitation

- Group discussions and activities
- Support by peers having experienced similar life situations
- Learning by doing
- Sharing of information and implementing it in one’s everyday life

Poster presented by

Merja Monto, Marjaana Suosalmi, Hely Strong, Finnish Association of People with Mobility Disabilities (FMD), Lahti Rehabilitation Centre
9 parents of children with a rare disease or disability and 15 adults with a rare disease or disability were interviewed while they participated in a (re)habilitation course in July-October 2007. The courses were financed by National Insurance according to the law. Participants were asked whether the course did have an impact in their life in relation to identity, empowerment, close personal relationships and interaction, relationships with peers, and functional everyday life.

Interviewed person represented the following rare diseases: Arthrogryposis multiplex congenita (AMC), Ataxia cerebellaris, Cartilage-hair hypoplasia, Dysplasia diastrophica, Lymphoma of the central nervous system, Malformation congenita membrorum, Marfan syndrome, Morbus Legg-Calvé-Perthes, Myopathy mitochondrialis, and Osteogenesis imperfect.

The main results of these interviews highlighted the importance of meeting others with a rare disease for feeling of togetherness, for sharing experiences and exchanging information, particularly for useful information in day life activities, and to interact with people.

6.6 Centre for Rare Diseases in Bulgaria: a model for an integrated approach

Healthcare systems in EU member states differ greatly in respect to their structure, organisation and funding. They share common difficulties in addressing rare diseases though: specific problems and needs of people living with a rare disease for prevention, diagnosis, treatment and rehabilitation. Bulgaria is an example of a new MS with action of significant importance and activities in the area of rare disease policy and organisation.

At the end of 2004, the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) started as a project of a non-government non-profit organisation (www.raredis.org). This Centre highlights the importance of working simultaneously in 6 main directions – information, education, awareness, support, networking and lobbying. Currently, a National health plan for rare diseases is in the process of review and approval.

The Centre for Rare Diseases as a successful model for integral rare disease approach that can be adapted and applied also in other countries.
Member State’s health policy initiatives for rare diseases must be encouraged by the European commission, should germinate by initiative groups within each country and develop in the suggested above 6 directions.

6.7 Design of a Web-enabled System for Managing Clinical Information in Hemophilia Care

**Keyword(s)**: Hemophilia; Patient Treatment; Patient Registry; Home Therapy; Shared Care; Web Application;

Nowadays, Information Systems combined with the Internet, have a significant role in data storage, as in the efficiency and promptness of data transfer and can offer a large contribute in managing and manipulating the information resulting from treatment and attendance of chronic patients, as hemophiliacs. On the other hand, the Internet also created the opportunity of patients to insert data concerning home treatments.

This work briefly describes the design process of a Web-based information system to help the management of inherited bleeding disorders integrating, diffusing and archiving large sets of information from heterogeneous sources in scope of the hemophilia care at the Hematology Service of Coimbra Hospital Center, in Portugal.

Healthcare is characterised by a highly complex environment where the process of patient care requires an unusual amount of communication between different health care professionals (HCPs). For a better patient care, various HCPs have to cooperate, a processed often called shared
care (Garde & Knaup, 2006; Schabetsberger et al., 2006). Nowadays, there is an increasing incorporation of a heterogeneous set of Information Systems - paper-based and computer-based - on the daily work of HCPs, in order to retrieve information about patients (Coiera, 2003; Van-Bemmel & Musen, 1997). The complexity of the patient care process combined with the heterogeneity of the information resources leads to a paradigm of data redundancy in the healthcare services in general, and hemophilia care in particular.

Hemophilia is a chronic disease that affects about 400,000 people worldwide; however, most of these people do not have access to adequate treatment (Evatt, 2005). A system for patient registry is a critical tool for monitoring, identification and diagnosis of these patients; furthermore, it serves as an essential tool for managing their treatment. A registry is a database or a collection of records of people identified as having hemophilia or inherited bleeding disorders. The purpose of a registry is to define the population demographics and collect observational data on specific hemophilia health concerns such as the prevalence of viral infections, factor inhibitors and implementation of prophylaxis for children or different product.

Portugal, in spite of having about 1,000 patients with hemophilia, does not have a hemophilia national patient registry and most hemophilia treatment centers do not have a specific system to store and manage information concerning this pathology. In order to help the management of this information at the Hematology Service of Coimbra Hospital Center (in Portugal), as well as to facilitate communication between
HCPs and patients and improve the utility and quality of clinical data and treatment information, a Web-based Information System under study has been presented.

→ IN THE MODEL :

- The patients’ personal data is important object to record the data obtained from the medical program routines (appointments) and medical diagnosis.
- Patients’ data are stored with a unique identification.
- Each patient can undergo many treatments.
- Treatments consist of infusion of blood products which are in stock.
- When a blood product is consumed in the sequence of a treatment, the system should register this occurrence and automatically update the stock.

→ ULTIMATE GOALS :

- Patients can have direct access to the system, allowing them to view their clinical history.
- Patients can introduce treatment data in the system through the Web.
- The process of management and stock control of the products used in treatments can also be improved.
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- The process of management and stock control of the products used in treatments can also be improved.

7 PATIENT DRIVEN INNOVATIVE PROJECTS FOR RARE DISEASES

7.1 National Centre of Competence for Rare Diseases, the adult programme

The demands of having a high quality of life have increased among adults with a rare disease in Sweden. The need for more knowledge about rare diseases among professionals concerned is strong.

One out of three persons with a rare disease experience a wrong diagnosis from the start, 5,6% have still no diagnosis, and one out of three experience an inadapted treatment. Over 40% report experience of being rejected, and 30-50% report experience of difficulties in accessing care.

Since 2005, Agrenska has developed the Adult program as a project together with Riksförbundet Sällsynta Diagnoser (The National Association for Rare Diseases). The project is partly financed by the Swedish inheritance fund.
ABOUT AGRENSKA

Since 1989 Agrenska has successfully developed and provided programs for children with rare diseases, their families and professionals concerned.

Agrenska is a National Centre of Competence for Rare Diseases. Its aims are to build not only knowledge but to build competence among targeted groups. By being a progressive and creative meeting place between needs and knowledge, the programme contributes to spreading information to targeted groups of children, adults and families as well as to professionals. Working methods are multi-dimension:

- Knowledge transfer from experts in a number of fields concerned
- Exchange of experiences
- Reflections

The ambition is to empower and building competence/capability for life.

OBJECTIVES

- To improve the quality of life for adults with rare diseases
- To empower adults with rare diseases
- To increase the access for adults with a rare disease and professionals concerned to information about adults with rare diseases and the consequences of having a rare disease

METHODS

The Adult programme lasts for three to four days for adults having the same rare disease. The adults learn about the medical, social, educational, and psychological aspects of their situation. Six programmes are run per year.

During the programme an editor is documenting all lectures and the discussions. During sessions, information about the everyday life of having a rare disease are collected, and documents become available on a website. The target groups are people with rare diseases, their relatives, professionals concerned and other interested.
The intervention programmes are designed to improve the competence for adults with a rare disease. The programmes are based upon scientific proof and/or reliable experience. Documents based on interviews and on lectures about each rare disease are published and disseminated via a web-based helpline.

RESULTS


Experiences from the adult programs: adults have to explain and defend their problems/disorders due to the rarity, describing themselves as outsiders. Adults need to receive different information following the different phases of life. Adults need to discuss possibilities and solutions rather than problems. Adults living with a rare disease need to meet with other adults with the same situation – in this group they are the normality.

7.2 Collaborative Experience of the Romanian Prader Willi Association with Medical Specialists

Keywords: Genetic counselling, education, genetic services, public policy

One of the aims of the Romanian Prader Willi Association is to focus on the encouragement of a collaborative effort between Higher Education Medical Universities, medical specialists, and NGOs serving beneficiaries in the rare diseases sector through a multidisciplinary approach.

The goal is to provide adequate medical support and consultation for understanding and diagnosing various rare genetic diseases. The organisation was founded in 2003 by family members of children living with a rare disease. Over the past 4 years, in collaboration with professionals, specialists, patients and their families, the organisation has been working to improve the life for those affected by rare diseases in Romania.
RESULTS:

- In 2005, the 1st Center for Information about Rare Genetic Diseases in Romania was open;
- In 2007, RPWA organised the 6th International Prader Willi Syndrome Conference and The 1st Rare Diseases Conference in Cluj-Napoca, 348 participants attended from 38 countries;
- On August 9th, 2007, these efforts lead to the creation of the Romanian National Alliance for Rare Diseases (RONARD) with 32 founding members representing patients and specialists in the field of rare diseases;
- On November 2-3 (2007), the association organised the Rare Diseases National Conference and debate of the National Plan for rare Diseases;

In the absence of a national governmental strategy for Rare Diseases, an EU priority for Romania, the collaboration of local and national NGOs and medical specialists is essential. As a National Alliance with cooperation from the Romanian Ministry of Health, RONARD will act as a single, powerful voice for all of those affected by rare diseases in Romania and work to provide equal access to early diagnosis, quality treatment and rehabilitation services.

Developing awareness about the needs of people with Rare Diseases within the European framework of EURORDIS’ “Rare Disease Day” and engaging the public in a shared strategy for the development of genetic services will ensure a collaborative international approach in sharing expertise and experience.

7.3 A Pilot Project for a European Patient-driven Network for Congenital Limb-Reduction Deficiency: ECRD 2007 Conference

Abstract - This paper reports a pilot project developed by the Thalidomide Trust to create a Health Support Service capable of being expanded to support all Congenital Limb-reduction Deficiency (CLD) patients within the EU. The planning parameters of the project included: worldwide availability of the service, identifying relevant clinical specialists, gathering available recorded information (published and unpublished) relevant to the support of CLD, and identifying gaps in the capability of primary care provision to prevent duplicating existing services. The intended outcomes of the project include: improved quality of life for CLD patients, establishing the range of CLD-specific health problems...
and reducing the incidence of these problems. It also expects to identify appropriate areas for research, and increase the awareness of CLD-specific health issues among primary care providers and patients. The problems associated with identifying and evaluating Centres of Excellence are discussed. Technology issues include: AAA website accessibility standards, electronic patient records, and an on-line patient registry. It also reviews the development and use of an on-line Instant Medical History tool, for improved diagnosis. The progress of this project at the end of the first 3 years is reported, including 9 months of a clinical evaluation involving some 60 (UK) patients. Delays, costs, frustrations among the patient group, and pressures to change methods are discussed, as well as the next steps for expanding the network into other national groups.

Keywords: Congenital Limb-reduction Deficiency; Electronic patient records; On-line patient registry.

INTRODUCTION

The Thalidomide Trust initiated a project in 2003 to create a Health Information Service capable of being expanded to support all Congenital Limb-reduction Deficiency (CLD) patients within the EU. The majority of thalidomide survivors suffer from CLD, while there is also a wide range of damage to other organs. These cases are characterised by complex and compound physiological and health issues. The approach being developed results from widespread experience among the patient group of a lack of knowledge and experience on the part of health care professionals, with consequent failure to provide appropriate treatments and risk to life and well being. The project began with creating a database capable of recording the extreme anatomical variations present in the patient group, and then the very challenging task of populating that database with accurate information. In parallel with this, work began to identify all relevant medical and scientific publications on the subject of Thalidomide damage (and CLD in general), and to identify specialists and centres experienced in care for CLD patients. This activity exposed a lack of expertise within the UK, and led to the discovery of specialists and centres in other European countries: most of these contacts were facilitated by patient groups in these countries. This has resulted in the development of a network among similar patient groups in other European countries, which has been formalised as a European Forum. The logical extension of this process has involved the creation of web-deliverable electronic patient records and the trialling and development of an internet based medical history-taking tool. The second major development began in 2007, following a patient group request for an

Advisory service, capable of delivering expert advice to patients and clinicians, when a pilot trial was commissioned. The pilot work shows the range and complexity of networking and sharing information in improved patient care, and the benefits of involving the patient group in the process.

→ EUROPEAN FORUM FOR CLD

A series of surveys and reports concerning the thalidomide survivors within the UK conducted during the period 1995-2005 showed a pattern of health problems which included musculo-skeletal pain affecting one third of the group. The initial attempts to find reliable ways of relieving this particular problem involved making contacts with representatives of similar groups in Sweden and Germany. It was found that in Sweden a centre of excellence had been established specialising in this subject, while one orthopaedic surgeon in Germany had developed considerable experience in the field of CLD problems. The UK group, on the other hand, had access to a larger body of historic information, coupled with direct access to the individual patients in a way not possible for the other two groups. This led to an agreement between the three groups in 2004 to initiate a network organisation intended to benefit all CLD patients within the EU, the European Forum for Congenital Limb-reduction Disability, with the Föreningen för de Neurosedynskadade (Sweden) and the Bundesverband Contergangeshäditger (Germany) and the Thalidomide Trust as founder members. These three organisations support about 25% of the 15,000 people estimated to be affected by CLD within the EU. Work has continued to identify more patient groups concerned with CLD throughout the EU.

→ PLANNING PARAMETERS

The planning parameters of the project included:

- Worldwide availability of the service: because the Thalidomide survivors wanted to be able to access expert and relevant advice wherever they may be.
- Identifying relevant clinical specialists and centres.
- Gathering available recorded information (published and unpublished) relevant to the support of CLD, and identifying gaps in the capability of primary care provision to prevent duplicating existing services.

→ INTENDED OUTCOMES

The intended outcomes of the project include:

- Improving quality of life for CLD patients.
- Establishing the range of CLD-specific health problems and reducing the incidence of these problems.
- Identifying appropriate areas for research.
- Increasing the awareness of CLD-specific health issues among primary care providers and patients.
HEALTH ADVISORY SERVICE PILOT PROJECT

The main purposes of this project are:

- data collection of the health problems being encountered by Thalidomiders
- to support individual Thalidomiders with their health problems
- to provide a ‘Referral’ service for the Thalidomiders, to assist them

so they obtain appropriate health care from their local providers

- gather Statistics of the current health problems to assist Trust board in understanding emerging problems

The project was initiated in January 2007 using an Occupational Therapist trained in CLD issues as coordinator, under the supervision of a medical General Practitioner experienced in Thalidomide cases. All individuals who have entered the process have formally consented to take part in this study. Reporting has included very senior medical experts assisting the Thalidomide Trust. 60 referrals have been dealt with to date, statistics on 52 are provided below.

The process begins with an individual’s health data being collected, and then the cases are discussed with the medical supervisor to ensure that appropriate advice, case support and referrals follow.

The ethos of the process is to support individuals accessing local NHS services. Where local healthcare providers demonstrated a lack of expertise we attempted to create links with specialist expertise in other areas of the country, or the EU. These included the Ex–Center (Stockholm), the National Orthopaedic Hospital (Stanmore), and a specialist orthopaedic centre in Nurnberg. Cases have also been referred to specialists in Ergonomics and Assistive technology and Mobility; and to the Trust’s own Volunteer Visitors for welfare support. Areas of need where NHS provision has been found unsatisfactory include:

- the availability of experienced physiotherapists to treat those with upper limb pain and muscle damage,
- an exercise routine that suits the group (particularly those with CLD affecting all four limbs)

Feedback to date indicates that the Thalidomiders using the HAS appreciate it facilitating better access to local health provision rather than having to travel to a clinic outside their locality. In the few cases where the referral is to a specialist clinic the individuals are prepared and supported appropriately. A summary of areas of concern identified among the first 59 patients is in table below:
The Thalidomide Trust has long experience of working with specialist centres. The French National Plan\(^1\) for rare diseases is modelled on the expectation that specialist centres will be created in each country for all main rare disease groups, but the experience in UK is that such centres tend to have a limited life. This is because the creation of such a centre results from the specialist interest of a very small number of clinical staff, and when the key individuals leave, the centres usually close soon afterwards. This is probably a function of the lack of patients of the rare disease group, or the lack of awareness by other patients further afield of the availability of the service, or unrelated management matters. The concept of an information network helps to overcome these problems, and while adapting to the changing existence of specialist centres, may also help them to survive (by channelling in patients from a wider area).

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\(^1\) Ministère de la santé : French National Plan for Rare Diseases 2005-2008 : Ensuring Equity in the access to diagnosis, treatment and provision of care. Ministère délégué à la recherche, Paris 2005
From a clinical point of view, the most important single ingredient for the understanding of the range and details of symptoms in patients with complex physical disabilities is the availability of a multidisciplinary team experienced in working together. Individual experts can contribute much more when members of such a team than when working alone. It has been our experience that the identification of effective therapeutic teams, as for example in University-linked centres, is only a beginning, since sufficient opportunity and motivation to take on a new patient group is rarely present. The alternatives include the creation de novo of a new special interest team, with all the problems of funding, location, recruitment and professional links. Without a great deal of funding we view this alternative as impractical.

The identification of experts in different disciplines (e.g. Orthopaedic surgery, Clinical Rehabilitation, Occupational therapy, Physiotherapy, Clinical Psychology, etc.) recruited at appropriate times in their professional careers and irrespective of location, but brought together by an electronic network with face to face opportunities whenever possible has developed into a promising, increasingly effective method. Experience is shared with other professionals lacking previous experience of the patient group, with enhancement of clinical practice.

Figure 34: Thalidomide Trust Health Information Management
Technology issues include the design and build of a site that meets AAA website accessibility standards; collection and build of electronic patient records; and build of an on-line patient registry.

Each area of requirement had to be designed in conjunction with the others especially allowing for data security and access control. A web based secure messaging system, and a case management system, have been identified but remain to be configured, user tested and finally implemented. Involvement of the users during the phases is proving essential.

Advancing security requirements coupled with changing software standards tend to run counter to the positive trends of rapidly increasing communication bandwidths and computing power, and the falling cost of data storage. The challenge of meeting AAA website accessibility standards is eased because of the improvements in a wide range of web software packages. Figure below illustrates the bank of information accessible to all users in the Public area; and the secure flow of communication between the specific beneficiary users and the component parts of the information service providers:

Figure 35: Thalidomide Trust health Advisory Service

Figure below illustrates the advisory service functions and the flow of communications between the specific beneficiary users and the providers:
→ INSTANT MEDICAL HISTORY

The Thalidomide Trust has been impressed with an online questionnaire tool that has been developed in the US over the last 20 years. This tool collects a sophisticated medical history from a user and then presents that history to a clinician for review, to aid their diagnostic and planning process. There is much evidence from both sides of the Atlantic that this approach is valid and acceptable to patients\(^1\). The Trust has anecdotal evidence that Instant Medical History will be useful to the Thalidomide community and is therefore including this in the suite of tools that it is making available to help individuals document, monitor and improve their health and their experience of the Health Care Systems they interact with. Instant Medical History will not only gather a sophisticated history but it will also score, where appropriate, evidence based peer reviewed scales and this has already been shown to be very helpful. Using such an instrument as part of a secure messaging service between the Thalidomide and the advisors adds another exciting dimension to this project. The aim would be to facilitate such communication between users and their health care providers where ever they are situated.

Anecdotal evidence from a small number of Thalidomide users has shown that even the process of filling in the questionnaires can be useful and therapeutic and there is wider evidence that this process can certainly better prepare people for a subsequent face to face consultation.

→ PROGRESS IN FIRST 9 YEARS

There are some solid achievements. The Centre of Excellence (The Ex Centre) in Stockholm has been made accessible for the British patient group via the NHS. Occupational Therapists have learned from the experience, acquiring specialist expertise. A search for comparable Centres of Excellence in UK has been unsuccessful, as a result of a lack of spare capacity among those centres visited and a lack of appropriate experience. However, a number of individual specialists of different disciplines have been recruited, and are cooperating as an embryo multidisciplinary team.

A Database detailing the ‘Body Map’ of the roughly 450 Thalidomiders living in UK will shortly be tested for accuracy and completeness, and this will much facilitate research. The Instant Medical Record initiative is already helping individuals when seeking medical assistance. EURORDIS has been joined.

→ CONCLUSIONS

The basic organisation necessary to assist patients suffering from rare conditions is the same, whatever the nature of the disorder. Irrespective

of the pattern of national health care provision, the presentation of someone with a previously unmet condition and additional symptoms, from common conditions or from ones specific to the rare condition, challenges many doctors and may impair their capacity to help. The availability of expertise appropriate to the rare condition should ideally be available and not too far away from any individual requiring specialist assistance, but this could be impractical in view of the number of different rare conditions and their intrinsic scarcity.

An alternative system to provide help for one rare condition, Thalidomide Embryopathy in UK, appears to be promising, since the electronic availability of the necessary members of a multidisciplinary team can be achieved and effectively deployed. The recruitment of the necessary individuals, the training of volunteers from required disciplines, ongoing research and collegiate professional development can all be supported by an electronic network of increasing sophistication. The cost of supplying such a service to any or all of the rare conditions met in Europe or worldwide is likely to be more containable than with alternative strategies.

7.4 An analysis of the results of a questionnaire among patients with Autosomal Dominant Cerebellar Ataxia (ADCA) in the Netherlands in 2004

The study has been commissioned by the ADCA patients’ association in the Netherlands.

→ SUMMARY

The purpose of this article is to show that a questionnaire among the members of a patients’ association can give much information. Thanks to the information gathered we know the problems faced by the affected members and the way they cope with their impairment.

A quality of life study is an affordable activity that can be carried out at low cost by the patients’ association without applying and waiting for grants.

The poster deals with the set-up and organisation of a questionnaire. It also shows a number of results and recommendations for patients’ or-
ganisations. I hope that this study will stimulate other patients’ associations to organise quality of life studies among their members.

**INTRODUCTION**

The ADCA patient association in the Netherlands wanted to know more about the patients’ group and their needs. In order to collect the required information a questionnaire survey was used as the main tool to gain the information.

It was decided to use the SF-36 health survey format, a validated instrument for this kind of studies. This was completed with some questions of the Rotterdam handicap scale and questions put forward during a patient and care givers meeting.

The questions were put together in a questionnaire and send to all members of the patients’ organisation with the request to return them duly filled out.

**RESULTS**

The 653 questionnaires that were sent to the members resulted in 304 adequately filled out copies.

Physical constraints in:

- Balance and coordination 87%
- Walking 76%
- Stair climbing 70%
- Writing 70%
- Housekeeping 63%
- Working 58%
- Speech, slurring 54%
- Driving a vehicle 52%
- Seeing 45%
- Eating, drinking, swallowing 38%
- Washing, showering 36%
- Urination 26%
- Toilet routines 20%
- Other constraints 18%

Means of support

- Walking aids as canes and walkers 47%
- Wheelchairs 27%
- Special cutlery 7%
- Adapted keyboard 7%
- Adapted home facilities 5%

Home adaptations

- Adapted toilet, bathroom 57%
- Ground level house 43%
- Lowered threshold/ramp 37%
- Elevator, automatic door 15%
- Adapted kitchen 10%
- Staircase lift 10%
Social relationships

- Reliable people that can be called upon 90%
- Contact with a reliable care taker 81%
- Shrinking circle of friends 33%
- Sense of loneliness 30%
- Feeling of desolation 30%
- Loss of cosiness 29%
- Missing a good friend 23%

Spiritual feelings

- Frequent emotional eruptions 44%
- The feeling of not being taken seriously 44%
- Depression 37%

Caregiver

- Partner 44%
- Children 16%
- Friends, acquaintances 9%
- Brother of sister 7%
- Parents (in law) 4%
- Neighbours 4%
- Other family members 4%

Caregiver duties

- Travelling 38%
- Housekeeping 33%
- Keeping company 30%
- Washing and dressing 14%
- Other 13%

Therapies apart from symptomatic drugs:

- Physiotherapy 44%
- Speech therapy 17%
- Fitness etc. 11%
- Food supplements and diets 9%
- Alternative therapies 4%
- Yoga 2%

> FINANCE

About 20 percent of the patients report to have financial problems because of their disease.

> CONCLUSION

The quality of life of ADCA patients is analysed according to three main items, functional status, wellbeing and general health.

In the subscale of physical functions the ADCA patients have a relative low score.

Abilities such as mobility, walking, writing, coordination and keeping one’s balance are seriously impaired. Social dysfunction and role impairment are a result of the physical impairment. This is well illustrated by the fact that 30% of the respondents have found their social network...
being diminished as a consequence of their physical impairment. Mental health and vitality are heavily affected. Caretakers have a major role in the lives of 50% of the ADCA patients and they are often involved in travelling activities. Physiotherapy is the most frequent used therapy next to symptomatic drugs. About 20% of the diseased have financial problems as a result of the disease.

**Figure 36: diagnosis delays in ADCA in the Netherlands**

Number of years between the first symptoms and 127 genetically confirmed diagnosis in percentages

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<td>&lt; 1 year</td>
<td>26%</td>
</tr>
<tr>
<td>1 - 2 year</td>
<td>26%</td>
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<tr>
<td>4 - 5 years</td>
<td>10%</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>26%</td>
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</table>

→ **RECOMMENDATION**

A quality of life study as a tool for the patients’ association

Much money and effort is spent on getting financial support for basic research on rare diseases. A quality of life study among the patient organisation’s members can provide information that give an insight in the daily life limitations caused by the disease concerned. Such a study will also provide the solutions that have been found by the individual members. The data can be used as a base level study, to measure the influence of certain interventions on the quality of life. The study can be carried out by the patients’ association with little support or even with the help of a simple handbook.

The study I carried out with a student was financed by the patients’ association at a cost of about 3200 €.
7.5 European Consensus Conference on Primary Immuno-deficiencies

The International Patient Organisation for Primary Immunodeficiencies (IPOPI) has taken the lead on a joint project with the International Nurse Group for Immunodeficiencies (INGID), the European Society for Immunodeficiencies (ESID) and the European Federation for Immunological Disorders (EFIS).

The poster was prepared thanks to an unrestricted grant from Baxter.

The World Health Organisation currently recognises more than 100 Primary immunodeficiency diseases (PIDs), and they represent a class of disorders in which there is an intrinsic defect in the human immune system. In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly. They are genetic conditions that range in severity and bare the clinical hallmarks of persistent, recurring infections. Left un/misdiagnosed, PIDs lead to a lifetime of chronic illness, permanent organ damage, disability or even death.

With funding from the European Commission’s 2005 Public Health Programme, IPOPI, ESID, INGID and EFIS held an EU PID Consensus Conference in June 2006. The aim of which was to increase recognition of PIDs as a public health issue, and create a forum for experts to discuss and propose a consensual public health approach to PIDs.

Treatments in the form of antibody replacement therapies (immunoglobulins) are available, and have a long history of proven efficacy, leading to reductions in illness and burden on healthcare provider resources. The core issue with PIDs is therefore one of chronic under diagnosis, with symptoms often not recognised by doctors, sufferers or their families.

The European PID Consensus Conference successfully brought together clinicians, patients, policy makers, regulators and manufacturers, and is an outstanding example of how the EU Public Health Programme can enable cooperation among organisations who play different roles in supporting improved care for a rare disease.

→ PIDS AS A EUROPEAN PUBLIC HEALTH PRIORITY

The recognition of PIDs as a European public health priority has gained momentum over recent years thanks to the support of the European Com-
mission and European Parliamentarians such as Antonios Trakatellis MEP, John Bowis MEP, Caroline Jackson MEP, Godelieve Quisthoudt-Rowohl MEP, Peter Liese MEP, Stephen Hughes MEP, Catherine Stihler MEP and Chris Davies MEP. Their support gave confidence to the umbrella organisations working with patients, nurses and physicians in this field to collaborate on a project that would aim to develop a European framework for a public health approach to PIDs, and then articulate this to national policy makers, public health experts, researchers and the general public.

→ THE EUROPEAN PID CONSENSUS CONFERENCE

The project developed to meet these aims was the European PID Consensus Conference. This was held on 19-20 June 2006 at the Paul-Ehrlich Institute in Germany. The Conference convened 100 experts and delegates in clinical immunology, PID care, public health, genetics, EU/national ministries of health and agencies, academic centres, public health laboratories, professional organisations and patient groups, to identify and develop public health strategies that can be applied to PIDs.

→ EU PID CONSENSUS STATEMENT, RECOMMENDATIONS AND REPORT

At the conference, the multi-discipline experts concluded that:

- PIDs are widely undiagnosed and there is a lack of awareness of PIDs among the general public, healthcare professionals, healthcare policy makers and implementers.
- Effective therapies for PIDs exist and early treatment saves lives, prevents morbidity and improves quality of life. There is also evidence that early treatment is cost effective.
- There is a significant disparity of care within and across EU member states.

The multi-discipline experts developed a Consensus Statement containing these conclusions and also approved a series of recommendations that focus on three key areas where priority action is needed to be taken by Member State governments of the EU:

**Priority Action 1 : Awareness and Education**

- Clinical protocols to reliably identify PIDs
- Epidemiological studies into the prevalence and incidence of PIDs and their impact on public health and costs.
- International patient registries expanded to assess the clinical presentation, natural history and genetic patterns of PIDs.
- Health campaigns developed to raise awareness of PIDs among the general public.
- Education programmes targeting the general public, healthcare professionals and healthcare policy makers and implementers.

**Priority Action 2 : Screening and Diagnosis**

- Practical tools for efficient diagnosis of PID made available in every country.
- Evaluation of diagnostic tools for PID and research into the feasibility of screening programmes to prevent damage.
Priority Action 3: Treatment and Management

- EU guidelines developed to provide equal access to treatment and assure an optimum standard and quality of patient care in the appropriate treatment setting.
- Cross country initiatives set up to allow exchange of expert experience and education.
- EU treatment centre networks established in order to determine disease outcomes.
- Safest immunoglobulin treatments available to all patients who require antibody replacement.

Given these conclusions a Statement, Recommendations and Report were developed. A key part of this communication was the development of a Consensus Conference website: www.eupidconference.com. The website is an online forum, available in 5 EU languages, that provided pre-conference information and online registration as well as post-conference documentation and outputs.

Following the Conference, the European PID Consensus Statement, Recommendations and Report was subsequently launched in October 2006 at the ESID/IPOPI/INGID bi-annual meeting in Budapest.

At the Conference a well attended press conference was held, which combined with launch activities of the Consensus Statement, resulted in sixteen significant news pieces in countries that included: Austria, Germany, the Netherlands, Portugal, Belgium, Hungary, France and Italy.

The EU PID Consensus Statement, Recommendations & Report was also made available in 10 EU languages (Spanish, Portuguese, French, German, Dutch, Hungarian, Polish, Swedish, English, Italian) on the Conference website and on CD Rom. This CD Rom was then circulated to all Conference attendees and over 400 key health policy decision makers in each of the EU Member States.

7.6 I.B.EA – The Italian bioBank for Alternating Hemiplegia

a tool for the promotion of the research on a rare disease

→ BACKGROUND

Alternating Hemiplegia (AHC) is a very rare disorder characterised by early onset, recurrent episodes of hemiplegia affecting alternatively both sides of the body, occurrence of paroxysmal phenomena such as
tonic and dystonic attacks, oculomotor and autonomic disturbances. It is a highly chronically debilitating suffering with deleterious effects on the quality of life of the affected patients.

A.I.S.EA, the Italian Patient Association for AHC, was created in 1999 with the main goals to support the families, spread the knowledge about the disorder, promote and support the research.

Since the beginning, the association realized that the best way to achieve this last goal was to provide the research groups with an easy, non exclusive access to the clinical data and blood samples of as many AHC cases as possible.

At the same time, the patients of the associations wanted to safeguard their rights to the privacy, to the correct use of their data and samples and to the information about the results of the research projects using the Bank.

Therefore I.B.EA - the Italian bioBank for AHC, has been created, a project coordinated by A.I.S.EA, in collaboration with its Scientific Committee.

→ THE ITALIAN BIOPAN FOR ALTERNATING HEMIPLEGIA,
I.B.EA IS COMPOSED OF THREE SECTIONS :

B.1 Personal Data Base - managed by A.I.S.EA
It contains the personal data of the patients and the link between such data and the related CID, the anonymous, numeric code used to reference the information kept in the following two sections.

B.2 Clinical Data Base – managed by Dr Giuseppe Gobbi, Child Neuropsychiatry Unit, Maggiore Hospital, Bologna.
It contains the clinical data, the video recordings and the photographs of the participating patients, to be used for clinical and therapeutic studies. All these data are identified only by the CIDs.

B.3 Biological Bank – managed by Dr. Maria Teresa Bassi, Laboratory of Molecular Biology, Scientific Institute E. Medea (LC).
It contains the biological samples of the participating patients (DNA, RNA and cellular lines) and of their parents (DNA), to be used for genetic research. The samples are identified only by the CIDs.

A subset of the Data in the Clinical Data Base is also copied in the European Registry for AHC, under the management of ENRAH, the European Network for Research on AHC.
Figure 37: The Architecture of I.B.EA. The three sections B1 – B2 – B3 are physically separated but logically joined by means of the CID, the Patient Identification Code.
The protocol of the Italian bioBank for Alternating Hemiplegia I.B.EA consists of the following steps:

1. **Enrolment of the patients, their parents and their treating physicians**
   A.I.S.EA collects the consent forms from the participating patients and parents and from their treating physicians, for the processing of their data (Italian National Law 30.06.2003 Nr 196). A CID is assigned by A.I.S.EA and notified to each participant. Only A.I.S.EA can communicate personally with the participants.

2. **Collection of the Clinical Data and the Blood Samples**
   The treating physicians receive from A.I.S.EA the questionnaires to fill with the clinical data of their patients and to send to the Clinical Data Base. The questionnaires are labeled only with the CIDs of the patients, thus protecting their anonymity.

   With the collaboration of the physicians, also the blood drawing is organised and the samples, labeled by the CIDs, are sent to the Biological Bank.

   A.I.S.EA updates the list of the available CIDs on its web site: this way, the patients can easily check their presence in the Bank.

3. **Validation of the Diagnosis**
   At least once a year, A.I.S.EA organises a video-session, during which new suspected AHC cases are presented by their physicians and discussed by the Scientific Committee of the association and all the physicians participating to I.B.EA.

   If the diagnosis is validated, the patient and the presenting physician are enrolled in the Bank.

4. **Access to the Bank**
   Any research group can request to use the Bank, by filling a form and sending it to A.I.S.EA.

   The request is evaluated by the Scientific Committee of the association and by the Ethic Committee of the Scientific Institute E. Medea, within the following two months.

   A Material Transfer Agreement (MTA), based on the evaluation comments
and proposed by A.I.S.E.A, must be signed by the research group, before accessing the Bank.

→ RESULTS
At present, I.B.EA contains the complete clinical documentation and the biological samples of more than 30 Italian patients.

Three clinical studies and two genetic research projects are currently using the Bank: A.I.S.E.A also agreed with their managers, through the signing of the MTA, that the results will be delivered to the patients, kept in the Bank and shared with the scientific community through publications.

I.B.EA is also the central node of a network inside which a better circulation of information and ideas is fostered, thus further promoting the start of coordinated and collaborating research projects and activities.

In particular, through the collegial validation sessions and the active participation of the treating physicians, correct and early diagnoses and a better care of the patients have been promoted.

→ CONCLUSIONS
New enhancements for I.B.EA have already been planned. In particular, a new project I.B.EA on-line has already started, to build a Clinical Data Base accessible via Internet in a secure and controlled way.

This will allow a more efficient data entry and management and easier data retrieval.

Also interfaces to the ENRAH European AHC Registry and to the Public National Registry for Rare Diseases will be developed for the automatic data transfer.

I.B.EA on-line will be available also in English, to facilitate the access by international research groups.

→ ACKNOWLEDGEMENTS
A.I.S.E.A wants to thank the members of its Scientific Committee, its advisors and all the treating physicians of I.B.EA, for their active participation to this important project.

Many thanks to the Azienda ASL – Ospedale Maggiore, Bologna for hosting the Clinical Data Base and to the Scientific Institute E. Medea,
Bosisio Parini (LC) for hosting the Biological Bank. Thank you also to the Managers of these two sections of I.B.EA.

A special thank to the Ethic Committee of the Institute E. Medea for their participation to I.B.EA and for their precious advice to the association.

8 ADDRESSING ALL PATIENT NEEDS, BEYOND MEDICAL CARE

For chronic and severe diseases, care is not restricted to medical and paramedical care. Patients and carers require other types of care throughout their entire lives: information and support via help lines, tools to break their isolation, leisure activities, respite care services, programmes to help their school curriculum, and organisation of the transition of the provision of services and medical treatment from childhood to adulthood.

8.1 Rare Diseases Help Lines

Rare disease helpline representatives from all over Europe have formed a network that aims to increase awareness and best practices. Series of meetings and activities have been taking place since September 2006 in the context of the Rare Disease Patient Solidarity Project. Rapsody aims to create or develop networks of services for patients living with a rare disease in Europe.

The network is composed of Tuy Nga Brignol AFM-Myoinfo (France), Inge Kristensen Centre for Små Handicapgrupper (CSH, Denmark), Helen Segura, European Network of Rare Congenital Anaemias (Enerca, Spain), Vanesa Pizarro FEDER SIO (Spain), Thomas Heuyer and Marie Claude Bergmann Maladies Rares Info Service (MRIS, France), Pam Davies, National Information Centre on Inherited Metabolic Diseases (Climb, UK), Christina Greek-Winald, Smagrupps Centrum Sweden, and Simona Bellagambi, Uniamo (Italy) and coordinated by Eurordis, François Houyez and Shane Lynam. These organisations are located as shown in figure below from www.rapsodyonline.eu.
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Why a help line network?

The main reasons to create the network was to pool best practice resources especially regarding training and experience and also to share information with European associations aiming to set up a help line service (workshop, online resource) or to improve and change an already existing helpline. Another network’ objective was to link together rare disease patients and their families.

Figure 38: Rare Disease Help Lines in the Rapsody project, as located at www.rapsodyonline.eu
WHAT HAS BEEN ACHIEVED SINCE SEPTEMBER 2006?

With these objectives in mind, the network has further developed best practice tools such as guidelines for the organisations of information services for rare diseases (Pard III), a self-evaluation form for help line respondents, a brochure describing the help lines, an online tool (www.rapsodyonline.eu) for help lines to work more closely together, including a cartography of help line services, developed a caller profile analysis, organised a training session on finding validated health information resources on the internet, and has organised a specialised workshop on November 26th, 2007, just prior to this conference.

CHARACTERISTICS OF THE NETWORK' PARTICIPANTS

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<tr>
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<th>SIO</th>
<th>Danish National Centre for Rare Disease and Disabilities</th>
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### Maladies Rares Info Services

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*Figure 39: the brochure on the European Network of Rare Disease Help Lines*

*Figure 40: training session for help line respondents, 20 October 2007, Alicante, Spain*
PROPOSALS
The members of the European Help lines network and the workshop participants have contributed to the following proposals for EU Member States and to the European Commission.

1. Encourage member states to support and develop Help line services for rare diseases, in particular to commit to long term plans.
2. To go towards the same level of service in all Member States
3. Encouraging European initiatives on help lines.
4. Support Help lines for rare diseases networks beyond Rapsody
5. Release funds for the training and the funding of help line operators and training of doctors and other professionals in the knowledge of rare diseases (“knowledge of knowledge”)
6. Target the continued development of common tools for help lines and common regulation of validation and patient confidentiality
7. Make existing resources available in all European languages
8. Specific initiatives to promote national or European help line numbers
9. Support the creation of a common European help line number: 116 number
10. Continuing to support the creation and development of connections between European rare disease patients and in particular patients without diagnosis – is another concern as they are so exposed, or without associations

IN CONCLUSION
The network needs to maintain the vitality of help lines, in order to empower patients to be involved in their care, to be their voice and to give reliable information.

The network has created a climate which facilitates exchanging expert information from the help lines and patient’s families/families. The help lines for the rare disease community are gradually becoming a voice for European information services. It is crucial that the network is listened to at the decision making level (European and national). Information and support services should be willing to follow up after when life ends. When policies begin and end, we remain.
8.2 Contacting someone with the same condition and fighting isolation- via help lines

One of the issues that the European Network of Rare Disease Help Lines attempted to address was the ever present issue of isolation in the lives of rare disease patients. From very early on in the project the network members discussed the best approach to networking European isolated patient services. The Contact Forum at the The Danish National Centre for Rare Disease and Disabilities (55 associations for rare diseases have 400 people in the Contact Forum, covering approximately 150 diseases) and the Milor service at Orphanet were present to offer their invaluable experience in dealing with this issue. This presentation also served as a chance to go into more detail about www.rapsodyonline.eu and compliment Pam Davies’ presentation of the help line network. www.rapsodyonline.eu and how to break isolation for European rare disease patients are two strongly inter-related issues.

Breaking isolation, the best approach?

Rare disease patients often feel isolated by their condition. By definition rare implies isolated and how to break that isolation is an issue which comes up on a very regular basis for those who seek to try and address the needs of rare disease patients. The goal of this particular aspect of the Workpackage was to increase the chances of patients living with rare disease ‘finding someone like them’. It is self evident that working at European level on an issue like this is crucial. By widening the pool of possible matches the chances of finding someone with the same disease or same issue is increased as services join the network.

Isolation in rare disease addresses a huge variety of issues. The following are examples of the sort of issues that the patient can be faced with: diagnosis can make a patient feel different, rare diagnosis makes a person even more different, lack of a cure and little hope for their future family, their life may be taken over by the condition, they may not be able to live full, active, healthy or ‘normal’ lives, they may have to take medicines that no-one else does, they may look different, they may have no peers to look up to with the same condition they may be the oldest with this condition,, they may choose not to have children and stop the family
line, they are not told what is happening to them, they know they will die early or their life may be very short. These are all issues that can make the rare disease patients feel isolated.

Sometimes just knowing that you are not the only one can offer a patient huge relief. Often, relieving isolation and benefiting from the experiences of other patients with a similar concern/disease can be enough to trigger a patient getting his/her life back on track.

The Danish Contact Forum Denmark for example with its 55 associations for rare diseases have 400 people in the Contact Forum, covering approximately 150 diseases, contacted via the help line. Scandinavia has particularly strict regulation on the exchange of private data.

www.rapsodyonline.eu

Figure 41:
Rapsodyonlinehomepage
The ENRDHL will exist beyond Rapsody, Eurordis and its partners are actively looking for new sources of funding. However even without this funding the Rapsody project has created a tool to ensure that help lines will continue to exchange best practice and experience, a website dedicated to rare disease services.

**TOWARDS A EUROPEAN CONTACT FORUM**

When the final version of [www.rapsodyonline.eu](http://www.rapsodyonline.eu) is launched, European rare disease help lines will be invited to join the network and the number of members will continue to grow. Once a help line shows an interest in joining he will be sent a welcome pack and invited to agree to the terms and conditions of membership, this will, for example include the regular sharing of statistics. The network will include the possibility to share resources on best practice and eventually a document portal will be created, with crucial documentation and advice on the running of a help lines. The goal is to eventually create a roadmap for patient groups wishing to create a new help line. The site will also include a cartography of services for finding information on the existence of help lines in a given region and European help lines tools to record calls installed on the help line’s local server, a caller profile analysis: a common European database to produce statistics on the amount of activity help lines represent. This information will allow the network to give concrete statistics when seeking future funding opportunities for the network.

**ISOLATED PATIENTS FORUM**

Another aspect of the site is a tool to coordinate European help line’s isolated patient’s services. This will help patients find a patient or a family with the same problem as theirs, not just in their region but in the whole of Europe. When the patient contacts a local Help line participating in the Rapsody network and seeks assistance in establishing contact with a person with the same disease or same concern, the local help line will ask a few questions and check if there are patients with the same disease or issues in its own database. If not it will contact other European Help to check whether they have received a query regarding the same disease. In concrete terms the helpline will add the name of the disease or issue to a list which is circulated by email on a regular basis amongst the participants in the network. Then if a match is found the respondent will create a forum which will be created by the respondent through Rapsody online, after giving the caller a login and password, the respondent will encourage the patient to login and start exchanging information with the other European patient below. See figure below.
One of the key issues that the network had to deal with from early on was how to deal with the problems that exchanging personal information across borders can create. Throughout the project we have been receiving advice from a European law expert in private data, base in Brussels, on how to approach this issue. With regard to the central database, potential problems will be avoided by ensuring that the network members do not centralise any personal information, just statistics on the numbers of calls, reasons for calling, region, sex, age. However the module dedicated to networking isolated patients was a more challenging exercise. After a lengthy reflection it was decided that, as mentioned above, the most secure method would be to put isolated patients in contact with anonymous logins through an online forum. This ensures that no private data is exchanged across borders unless the patient volunteers the information directly to the patient he has been put in contact with. One of the preconditions to help lines joining our network is that they have checked that they are respecting local legislation on the private data.

Figure 42: Rapsodyonline, putting isolated patients in contact with each other
What about language? Firstly we hope the patient find a match with a person living in their own country. If they find a match through rapsodyonline we hope that they will find a common language to exchange. However if this is not the case an automated translator service will be provided with a rough translation of what the patients wishes to express.

What are the prospects for the ENRDHLs? With rapsodyonline these service now have a common cross-country contact opportunity. As more helpline join and the newer services learn from the more experienced, the level of service that the patients receive can only improve.

8.3 The role of online communities for people living with a rare disease

→ INTRODUCTION

Internet plays presently an evermore important role in the health information: health issues are a major motivation for Internet consultation with the proliferation of websites and diversity of producers. The proliferation of services and activities are an important concern for professionals, as quality, quantity and the use of web based information is often put into question: is it creating chaos and confusion or really helping web surfers who seek for medical information?

The question on the impact on the relationships between health care professionals and patients is a concern, and the creators of web sites and online tools have a responsibility in this respect.

Mailing lists (or discussion lists) are one the existing tools. It is a “closed” forum, where registration is required. Anonymity is not the rule, and these lists do not require specific technological or computer science skills, as they are a very simple tool. I will show that those groups explore a new and interesting way to involve lay people in health question. Those discussion lists act in three directions: as support, as producer of knowledge and as collective actor.

→ KNOWLEDGE PRODUCTION

We can briefly distinguish two principal forms of knowledge inside the discussion groups:
A large amount of information posted on the list is produced outside the group, passed on by members, eventually translated, summarised and analysed.

An another amount of “personal” information: for example, biographical account, collective inquiry address to the members, confrontation of various treatments, precise observation on physical symptoms, etc.

One could question whether this is developing valuable information. A partial response has been published in the BMJ in 2006: “Accuracy and self correction of information received from an internet breast cancer list: analysis of posting content” by Esquivel, Adol, Meric-Bernstam, Funda et Bernstam, Elmer V, BMJ, 2006, 10, 1136.

**Collective Action**
These collective actions have an ambivalent mechanism: they have no well defined position or clear agenda, and actors are often reluctant to act as a structured group. Their identity is often fuzzy and labile, and some exert some kind of political action. Patients’ mailing lists are laboratories for information and convictions.

**Issues for Regulation**
Three particular topics that tackle the issue at stake and enlighten the functioning of such groups:

1. The crucial role of moderators to maintain the group and protect the members has been underlined by all authors.

2. Regarding the necessary limits to what can be said, we observe that the group comes very easily to a responsible consensus.

3. The relationships with clinicians is based on mutual respect and distance.

**To Conclude: Relevance and Value of the Health Mailing Lists**
The mailing lists are places where information is debated, where opinions are confronted, and where discourses and arguments are elaborated. These common tools are sometimes constructed, exploiting the specific resources provided by the medium.
Mailing lists are specific organisations, with a fussy and labile identity. They rely on an informal commitment (which can be huge however). Their debates can impact existing organisations, but indirectly or tangentially. Therefore, the patients’ organisations will benefit of the mailing lists’ work as long as they do not try to regulate the debate, so as to keep the discussion open and the involvement of the list members informal.

**8.4 Respite care**

— so that patients and their carers can have a break from daily routine

Respite care is provided on a short term basis for disabled people who normally live at home, so that their carers can have a break, and so that patients can be taken care of by other persons.

One of important purpose of respite is to give family members time and temporarily relief from the stress they may experience while providing extra care for a family member living with a rare disease. Another important purpose is to give the person living with the disability/rare disease a place to experience/recreational and meaningful activities away from their parents/other caregivers.

Respite care can be an active part of the empowerment process. The transition from childhood to adulthood is more difficult for those with
developmental disabilities or diseases. For many families respite care will act as a first step towards increased independency.

Respite care services enable families to have planned temporary, intermittent, substitute care, allowing for relief from the daily responsibilities of caring for the person living with the rare disease. Respite care services should offer meaningful and satisfactory activities, such as recreational activities, habilitation and learning according to each individual.

Respite care includes nursing care delivered to inpatients needing assistance with daily living tasks, on a continued basis due to chronic impairment and a reduced degree of independence.

Short term temporary relief for disabled people who normally live at home

Includes nursing care, physiotherapy, (re) habilitation, recreational activities

They target patients from mental retardation (behavioural management) to highly medicalised cover

WHERE CAN RESPITE CARE BE PROVIDED?

There are different approaches/services to offer respite care, these are:

- Residential respite : the person living with a rare disease goes away to be looked after by someone else : a “respite care family” for a while
- Domiciliary care : “home care”, when services offer a care giver to come to the family’s home and take over care for a while so the care giver(s) can have some time off
- Others require that the individual go to a day care centre, respite group home, with assisted living facilities or go to a nursing home/institution (inpatient stay)
- Emergency respite services : parents/spouses/family/staff need to be able to access services at short notice, in the event of an unexpected emergency

THE RAPSODY PROJECT AND RESPITE CARE SERVICES

The Rare Disease Solidarity project has brought together Respite Care Services representatives from Ireland, France, Norway and Sweden to form a network that aims to increase awareness, efficiency and best practice for its members. The group has been meeting on a regular basis since December 2006.

TEMPORARY STAYS UNIT WITHIN AN HOSPITAL CARE SETTING

At the Marin Hospital Marin in Hendaye, a building was opened in 2003 (Ribadeau-Dumas building), with 40 beds to accommodate patients who are severely handicapped.
It offers rooms with bathroom/shower, TV, internet and special automated devices for handling the patients.

From 2003 to 2007, 645 patients were accommodated in this building.

This is accomplished as a partnership with patients’ advocacy groups:

- AFM (Association Française contre les Myopathies)
- ARS (Association for Research on Lateral Amyotrophic Sclerosis)
- ALIS (Association for Locked-in-Syndrome)
- AFAF (Association for Friedreich Ataxia)
- ASL (Association for Strumpell-Lorrain syndrome)
- CSC (Cerebellar syndromes)
- Huntington France
- Groupe Polyhandicap France (GPH)
- Prader-Willi France

In average stay, the duration of a stay is one month, and patients can come once or twice a year, on doctor’s or social workers’ or family’s request. Patients originate from France only, 100% of the stay is reimbursed by the National Social Coverage service (Sécurité Sociale).
For Neuro Muscular Diseases, for example Spinal muscular atrophy type 2 & 3 and congenital muscular dystrophies, the partnership with AFM was key to ensure the success of the organisation of care on site.

The same applies to Gamma-sarcoglycanopathy with respiratory rehabilitation.

For all projects, actions are prepared through a constant dialogue between patients and caregivers.

→ ACHIEVEMENTS OF THE RAPSOXY PROJECT

The creation of a network or respite services in Europe, a definition of respite care services for rare diseases (Centre based or home based), a brochure, an online cartography of respite care services in Europe linked to a database (www.rapsodyonline.eu) and best practices guidelines are some examples of the achievements of the Rapsody project from May 2006 to April 2008.

The participants have decided to make proposals for the improvement of respite care services in Europe:

- Resource Centres, Sheltered Workshops
- Supported Accommodation, Residential Services
- Autism Services…

1. Establish by law the right to receive respite care services

2. There should be a larger range of services

3. Hospitals/centres should aim to provide the right combination of services (centre based, home based, etc.)
4. A cost/benefit approach could be useful to demonstrate the utility of such services
   • with positive impact on quality of life and health outcomes

5. Raise awareness about the importance of respite care services among decision makers and professionals

→ FRAMBU, NORWAY

Figure 48: patients with neuro muscular diseases at the Hendaye hospital

Frambu is a national centre of excellence for people with rare disorders and disabilities catering for approximately 100 different rare disorders.

• Frambu provides services, funded by the government, that are supplementary to the normal treatment and care to which everyone is entitled.
• Frambu is place for families and professionals to meet.
• Frambu’s services span the entire life cycle from childhood to old age.
AGRENSKA, SWEDEN

Agrenska is a national centre of competence for rare diseases and its aim is to build not only knowledge but to build competence among target groups. By being a progressive and creative meeting place between needs and knowledge Agrenska contributes to spreading information to target group children, adults and families as well as to professionals. By its method of working in several dimensions:

- Knowledge transfer from experts in a number of fields concerned
- Exchange of experiences
- Reflections

The ambition with these programmes is to build competence/capability for life.

Since 1989 Agrenska has developed programmes for children and adults with rare disorders, their families and professionals concerned. Agrenska wishes to contribute and provide knowledge to the families to enhance the coping process. Agrenska strives to develop and make proper tools available to patients suffering from any rare disease, in order to improve their everyday life.

Agrenska has since 2005 a special consultative status within the UN. It is located on the west coast in Sweden.

REHABCARE, IRELAND

Figure 49: Agrenska national centre

Figure 50: supported accommodation at Rehabcare, Ireland
RehabCare is the provider health and social care services that facilitate people who are disadvantaged to participate in the life of their local community in ways that match their choices, aspirations and needs.

Users are typically people with disabilities (learning disabilities, physical and sensory) or with mental health issues, or older people, marginalised groups in the community, carers and people who wish to work in the Health and Social Care Sector.

Services include resource centres, sheltered workshops, supported accommodation, residential services, centre based respite, home based services, and Autism services.

8.5 Rare Diseases at School

Dr Anne Postel-Vinay introduced the IntegraScol project in France, aiming at improving schooling for 250,000 handicapped or sick children/adolescents in France. This project stresses the need to train the school staff adequately.

It is intended for teachers and other members of the school staff, and all people concerned by welcoming sick or handicapped children at school.

This project is conducted by medical doctors, and its objective is to produce targeted and validated information to school teachers and staff, so that they are aware of the diseases that may affect one of their pupils. It is conducted in close collaboration with patients’ organisations to best document on practical experiences.

It receives the support of the Ministry of Education, and coordinated by the INS-HEA, the National centre specialised in teaching methods for children with a disability, which is also hosting the web site www.integraScol.fr (Institut national supérieur de formation et de recherche pour l’éducation des jeunes handicapés et les enseignements adaptés).

→ HISTORY

The project started in March 2003, with a first meeting with representatives of the Ministry of Education and of the Ministry of Health. Fi-
Financial support was dedicated to the project in March 2004, including 35 000.00 euros from the Ministry of Education, and 15 600.00 euros from the French organisation for children with diabetes.

The web site was launched in October 2005.

**CONTRIBUTORS**
The editorial team consists in 3 medical doctors and 3 teachers. As of November 2007, 27 medical doctors and 8 teachers wrote articles, and 26 patients’ organisations contributed.

**COMMON AND RARE DISEASES OR CONDITIONS COVERED AS OF NOVEMBER 2007**
Asthma, paediatric cancers, congenital cardiopathies, cerebellar syndromes and Friedreich ataxia, Crohn’s disease, insulin dependent diabetes, sickle-cell anaemia, epidermolysis bullosa, epilepsy, limb-girdle dystrophy, children in a wheelchair, osteogenesis imperfecta, G6PD deficiency, celiac disease, hydrocephaly, injections at school, renal insufficiency, general information on rare diseases, cystic fibrosis, neuro-muscular diseases, achondroplasy, Prader-Willi syndrome, paediatric rheumatism, corticoid treatment, and Down syndrome.

**WEB SITE ORGANISATION**
The first sections addresses medical aspects covering 24 themes, a second one covers pedagogical aspects with 15 themes, and the last one covers patients’ organisations information.

1. **Medical aspects**
Medical aspects: name of the disease, its physiopathology, its aetiology, its frequency, its symptoms, possible treatments, consequences for school life, when to be careful, how to improve the school life…

2. **Pedagogical aspects**
Experts have developed recommendations for school professionals on how to accommodate children living with a rare disease and how to teach them, e.g. reading tools for children with visual field reduction. These recommendations come with testimonies provided by patients’ organisations.

3. **Patients’ organisations**
This section contains information on patients’ organisations, their contact details, links to their web site etc. Some organisations also provide additional information on the disease.
FUTURE DEVELOPMENTS

New themes will be developed, with news diseases, possibly translation into English. Collaboration with other projects is also expected, but these initiatives need to be identified and contacts need to be established. For example, a visit to Ăgrenska in Sweden was very useful. Ăgrenska is running the “Web-Academia” project for rare diseases and disabilities. A further analysis of children’s need, at school and pre-school, is in progress.

8.6 Therapeutic Recreation Programmes

Introduction: the Rare Disease Patient Solidarity “RAPSODY”

The Rare Disease Patient Solidarity Project is committed to:

- offering quality information provided by rare disease help lines throughout Europe
- helping very isolated persons make contact with others suffering from a similar disease
- standardising the quality of therapeutic recreation programmes for children and young adults living with a rare disease
- guiding school professionals on how to accommodate children living with a rare disease
- identifying respite care centres as well as creating networks for severely disabling rare diseases
- participating in the European reflection process on national centres of reference and European networks of reference of rare diseases
- increasing awareness/credibility of therapeutic recreation programmes, for example within member state’s medical communities
- Learning from each other and creating ‘best practice’ guidelines and standards.

The Rare Disease Solidarity Project has brought together therapeutic recreation programmes representatives from Ireland, France, Germany and Italy to form a network that aims to increase awareness, efficiency and best practice standards for its members. The group has been meeting on regular basis since October 2006.

The Rare Disease Patient Solidarity Project brings representatives of these programmes together to create a European network with the goal of:
• Creating an online service with a cartographic representation of the various services and their location

• Facilitate the movement of patients across European borders to an ever increasing range of different types of programmes.

**Figure 51: the network of therapeutic recreation programmes for rare diseases**

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Country</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georges Biheng</td>
<td>L’Envol</td>
<td>France</td>
<td></td>
</tr>
<tr>
<td>Oliver Engel, Gabriele Geib</td>
<td>Waldpiraten-Camp</td>
<td>Germany</td>
<td><a href="http://www.waldpiraten.de/">http://www.waldpiraten.de/</a></td>
</tr>
<tr>
<td>Marta Spanevello</td>
<td>Fondazione Dynamo</td>
<td>Italy</td>
<td><a href="http://www.fondazionedynamo.org">http://www.fondazionedynamo.org</a></td>
</tr>
<tr>
<td>Tamas Fuzesy</td>
<td>Bator Tabor</td>
<td>Hungary</td>
<td></td>
</tr>
</tbody>
</table>
Most rare diseases affect children: about 50% of all people affected by rare diseases are less than 19 years old. Starting life with a condition that will impact quality of life, life expectancy, social relations, ability to move, to learn, to accomplish daily life activities is a hurdle that becomes more unbearable with often invasive and complex medical interventions.

Personal development, education and learning cannot fully thrive if the life of a child is centred around a disease: children need to enjoy other activities. Children need to play, develop artistic skills, and they need to have fun with other children with or without the same condition as their own.

Siblings also need attention. Leisure and recreational activities will help a child to gain self-confidence: it will open new fields of activities and new horizons in the life of the child.

Ultimately, children need a break. They need to spend some days in an environment where they can stop thinking about their disease, where they can meet, socialise and play with other children.

\textbf{A QUALITY OF LIFE ISSUE}

“Camping” programmes afford children with chronic illnesses, and their siblings, the opportunity of spending time in supportive environments where they participate in a variety of recreational activities. In so doing, they seek to provide a positive experience for these children and this, in turn, may have a salutary impact on their physical, psychological and/or social well-being.

The models convey that in assessments of the impact of therapeutic recreation services including camping programmes, important domains to measure are:

- quality of life
- physical functioning as it pertains to health status
- psychological functioning, for example, cognitive and emotional well-being and self-esteem
- social functioning, particularly social skills
- leisure functioning
The main objective of a therapeutic recreation programme:
Entertainment! Fun! Leisure! Recreation!

- I can trespass my borders.
- I can do something, even if I haven’t done it before.
- I can get along well with the others!
- First I have to get to know the other kids, before I judge them.
- I can count much more on others than I thought I could before.
- Now I know how it feels, to have real good friends.

In an environment that differs from day to day life.
American camping programmes have acted as a template for the development of European camping programmes. However, there is little information, especially within a European context, regarding the nature of these programmes, and a limited body of evidence regarding their effectiveness.

→ NEW PROGRAMMES IDENTIFIED DURING THE RAPSODY PROJECT MAY 2006 – APRIL 2008

- France : ALPAS, Association Service Loisirs Vacances, ASRIM, AFDE, AFH, ASSYMCAL, VML
- Norway : Frambu
- Slovakia : Organizácia muskulárnych dystrofík v Slovenskej republike
- Belgium : International NF summer camps for teens
- United Kingdom : The Calvert Trust Exmoor and Kielder
- Italy : Antonello Viti De Angelis, Associazione Sindrome di Crisponi e Malattie rare, Associazione Bambini, Cri du Chat Onlus, Associazione Cornelia de Lange
- Germany : Bundesverband Herzkranke Kinder e.V, Kindness for Kids, Kleine Helden e.V., BVHK-Geschäftsstelle
- Spain : Eusebio del Castillo Romay

Collection of information on the programmes

- People served : Season of the year, caregivers/siblings, countries …
- Camp programme staff
- Volunteers : Total number, % return volunteers, age range…
- Campers on waiting list
- Programmes : Activities, hospital outreach

Collection of information on medical aspects

- Diseases groups : blended or single-disease sessions, unexpected challenges or rewards, most costly session to host…
- Medical staff : Average camper/medical staff ratio, medical volunteers’ training, psych/social person on staff, full time year round or seasonally employees…
- Supplies : Top medical supplies needed as a donation, items available for swapping with other camps
- Research projects
- General : Instances when outside (off-camp) medical help was sought, How far away is the hospital to which you transport in an emergency

→ SOME ACTIVITIES

Figure 59 : at Barretstown, Ireland
Some European Camp Association Activities in 2007-2008

The European Camp Association Outreach programme is aiming at serving more children and children that are more seriously ill. Any camp wishing to become a member of the Association will have to meet criteria in three areas: Programme, Medical and Facility.

European Standards: a set of minimum standards for camps and programmes working with children with serious illness in Europe. In summer 2007, two such camps (L’Envol France and OTW UK) were assessed against this template. In 2008 two more camps (Bator Tabor Hungary and Limestre Italy will be assessed.

The European Camp Association organised an International Conference on Therapeutic recreation for children with serious illness and other special needs.

The association also conducts research programmes: Barretstown, with the University of Nottingham, is conducting a longitudinal research study into the benefits of Therapeutic camp programmes for children with serious illness (Study will be completed at the end of 2009).

Rapsody Outcomes

The main outcome of the Rapsody project is the creation a European network of Therapeutic Recreation Programme for children and young adults living with a rare disease, with a database. This network is linked to the European Camp Association. During the project, participants have identified rare diseases organisations running such programmes, proposing quality standards, increasing awareness on the existence of these programmes. The ultimate goal is to improve efficiency and training in order to ensure a solid basis to develop hosting capacities in the future.

The Rare Disease Solidarity Project is a project funded by the Public Health Programme of the European Commission, DG SANCO, and led by Eurordis, the European Organisation for Rare Diseases and its partners: Fundacion Doctor Robert UAB (Spain), Children Living with Inherited Metabolic Diseases Climb (United Kingdom), Federacion Española De Enfermedades Raras FEDER (Spain), Barretstown (Ireland), Frambu (Norway), Rare Disorders Denmark (Denmark), State Institute for Drug Control SUKL (Czech Republic), Association Française contre les Myopathies AFM (France), and Inserm Orphanet (France).
It is supported by the Baxter International Foundation, Sigma Tau Pharmaceuticals USA, Actelion Pharmaceuticals Europe, and Groupe Initiatives Mutuelles UGIM.

Figure 61: Cartography of European Therapeutic Recreation Programmes
9 RECENT ADVANCES
QUALITY ASSESSMENT
RELEVANT TO
RARE DISEASES

“First, do not harm. Possibly, do good”. But how to do better? To best use medicinal products, quality information is essential. The same applies to specialised centres for rare diseases: evaluation is needed to provide the best possible care. Information on genetic testing is also key to their usefulness. In this session, speakers demonstrated the importance of quality assessment relevant to rare diseases.

9.1 Assessing the quality of information on medicines to patients

Abstract - The European Medicines Agency (EMEA) is responsible for the evaluation and supervision of medicines in the European Union. Amongst its principal activities the EMEA, involves representatives of patients, healthcare professionals and other stakeholders in its work and publishes impartial and comprehensible information about medicines and their use. The EMEA’s provision of information on medicines to patients is foreseen by the EU pharmaceutical legislation and follows the recommendations stemming from the Agency’s patients’ and consumers’ organisations working party (PCWP). Various projects are now in place to actively and systematically involve representatives of patients’ and consumers’ in the provision of information to patients. These are user testing while the product information is being prepared by the pharmaceutical industry, and the involvement of patients in assessing package leaflets and EPAR summaries for medicines. The EMEA also involves patients and consumers in other activities, on occasional basis, relevant to provision of information. In this respect the involvement of patients’ and consumers’ representatives has proven to be an added value. Certain procedures, that already have been put in place have proven to be positive and may be developed further.

Keywords: ECRD 2007, EMEA, package leaflet, EPAR.
THE EMEA

The European Medicines Agency (EMEA) is the European Union (EU) body responsible for coordinating the existing scientific resources put at its disposal by the Member States of the EU for the evaluation, supervision and pharmacovigilance of medicinal products.

The mission of the EMEA is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

Amongst its principal activities the EMEA, involves representatives of patients, healthcare professionals and other stakeholders in its work, to facilitate dialogue on issues of common interest and publishes impartial and comprehensible information about medicines and their use.

EUROPEAN PUBLIC ASSESSMENT REPORTS AND PRODUCT INFORMATION

The EMEA, which is a scientific body, is responsible for the evaluation of medicines through the so-called centralised procedure. In the centralised procedure, a pharmaceutical company submits an application for the evaluation of a medicine directly to the EMEA, to obtain a single marketing authorisation valid throughout the EU.

The EMEA’s Committee for Medicinal Products for Human Use (CHMP), supported by its various working parties, assesses the application and expresses an opinion. Based on the CHMP’s opinion, the European Commission may issue a marketing authorisation valid in all Member States.

The marketing authorisation for a new medicine includes key documents that constitute the ‘product information’ for a medicine. Theses are:

- the summary of product characteristics (SPC), which provides information on the product addressed to the prescribers and pharmacists;
- the package leaflet which includes the information addressed to patients;
- the labelling (the information appearing on the boxes).

European legislation dictates the way in which the product information documents are written and presented as well as the way they are developed and updated during the ‘life cycle’ of a medicine. They are initially drafted by the pharmaceutical company, according to official templates, and then assessed and revised by the EMEA as part of the marketing authorisation application.

After the final positive opinion of the CHMP, the product information is published as part of the European public assessment report (EPAR). This is a collection of documents, which includes the scientific discus-
sion, an in-depth explanation of how the CHMP reached a positive opinion for the medicine and on which data this opinion was based.

A similar assessment report is also published if the CHMP reaches a negative opinion or when the company applying for the examination of a medicine withdraws its application.

→ THE EMEA AND INFORMATION ON MEDICINES: MORE INFORMATION AVAILABLE TO THE PUBLIC

The EMEA’s provision of information on medicines to patients and the general public is foreseen by the EU pharmaceutical legislation and follows the recommendations stemming from the Agency’s patients’ and consumers’ organisations working party (PCWP). This is a permanent platform of exchange between EMEA and patients’ and consumers’ organisations. To provide information adapted to patients’ needs, to develop appropriate communication tools, and to increase the awareness of the public in relation to the use of medicines were, in fact, all objectives included in the EMEA Road Map 2010 (http://www.emea.europa.eu/htms/general/direct/roadmap/roadmapintro.htm).

The legislation and the recommendations of the PCWP, have progressively made possible to provide the public with more information. The EPARs used to be technical documents which were not easily accessible for the layperson. However, they now include a summary written in language understandable by the public in the form of a question-and-answer document called the EPAR summary. All new medicines approved through the centralised procedure since the start of 2006 have their own EPAR summary, and work is currently underway to create EPAR summaries for previously-approved medicines.

New measures have also been set up to systematically publish question-and-answer documents summarising the status of applications withdrawn prior to the CHMP opinion, and following any negative decisions.

Further initiatives have been created, or will be put in place to improve the levels of public access to information on medicines approved by the EU including:

- an increased level of publication of information on safety issues aimed at the general public, in the form of question-and-answer documents;
- improvements to package leaflets and labelling;
- public access to Eudravigilance (the European database of adverse drug reactions);
The importance of the active contribution of patients and consumers in the provision of information directed towards patients and the public is recognised by the EMEA. Their input is now actively sought by the Agency.

There are currently two main projects that actively and systematically involve representatives of patients’ and consumers’ organisations in the provision of information to patients. These are user testing while the product information is being prepared by the pharmaceutical industry, and the involvement of patients in assessing package leaflets and EPAR summaries for medicines after they have received a positive opinion and are reviewed by the EMEA.

1. Involvement of patients during the development of the Package Leaflet while the Product Information is prepared by the pharmaceutical company

Patients are involved in testing package leaflets while the product information is being drafted by the pharmaceutical company. This activity is enshrined within European Pharmaceutical Legislation and is commonly known as ‘user testing or ‘user consultation’.

The purpose of user testing is to test the readability of a package leaflet specimen with a group of selected test subjects. During the test, the specimen is presented to the group, which is then asked to answer specific questions on the use of the medicine to assess its level of comprehension. The objective is to identify whether the information presented conveys the correct messages to the patients and allows them to act appropriately. Testing itself does not improve the quality of the information but it indicates any problem areas that could be improved.

This procedure is the responsibility of the pharmaceutical company, but its results are included in the marketing authorisation application. The CHMP assesses the results of the tests during the evaluation of applications that fall under the centralised procedure.

User testing is a relatively new requirement, having been compulsory since November 2005. Prior to that date, the readability testing of package leaflets was optional and reports submitted by companies were re-
viewed by the Quality Review of Document (QRD) group. The new user testing requirements have proven themselves to be a good starting point for the standardisation of the assessment of readability. However, as the procedure is relatively new, both industry and regulators of medicines are still building up experience of how user testing works in the EU and how it could be improved. In two workshops in organised by the EMEA and the member states 2006 and 2007, it was clear that considerable experience in user testing has been gained in a relatively short time, and that a relatively harmonised approach has been established throughout the various Member States. At this stage, the QRD group and the assessors are ready to further progress with new initiatives, such as developing tools to promote a best practice in presenting the information in the Package Leaflets.

2. Involvement of patients while the Product Information is reviewed by the EMEA

Since May 2007, patients have also been actively involved in the review of information following a positive opinion, specifically EPAR summaries and package leaflets. This activity is also based on the Pharmaceutical Legislation and it is a further development coming from the Framework of interaction between EMEA and Patients’ and Consumers’ Organisations (EMEA/354515/2005).

Experts from patients’ and consumers’ organisations have been actively involved in the review of the English versions of EPAR summaries (on medicines that have received a positive opinion from the CHMP, and of the English versions of package leaflets at the time of the renewal of the marketing authorisation (usually five years after a medicine was first approved). The primary objective of this exercise is to ensure that the information is clear and understandable by the patients and the general public. Patients or consumers involved in theses activities are officially designated as ‘experts’ by the EMEA and are nominated by their organisation.

The EMEA selects the experts for each document on a case-by-case basis, matching each EPAR summary or PL to the expert’s area of expertise. The experts are free to give any comments that they believe could improve the comprehensibility of the document. Feedback is provided to them clarifying which comments could be taken into account, either immediately or in the future.

All of the organisations involved fulfil the criteria laid down by the EMEA for involvement in the Agency’s activities (see http://www.emea.
The EMEA checks declarations of interest and confidentiality from all experts and organises a yearly training session to review the procedure and discuss the objectives of the exercise.

3. EPAR summaries
The first draft of the EPAR summary is prepared by the EMEA within a short timeframe after the CHMP has adopted a positive opinion. According to the internal procedure for the preparation of EPAR summaries, the first draft is scrutinised internally by the assessors of the medicine and by experts from patients’ and consumers’ organisations. The document is then sent for information to the company that manufactures the medicines and finally, before publication on the EMEA website, is translated into all official EU languages.

4. Package leaflets
The PL is developed by the company that will submit an application for marketing authorisation. The same procedure applies when a marketing authorisation has to be renewed and changes to the original PL are proposed, i.e. when new information about the medicine is available. At present, experts from are only involved at the time of the renewal of the marketing authorisation. The experts from patients’ and consumers’ organisations perform the review of the English version of the document in parallel to the scientific assessors. The comments are then compiled and sent to the company marketing the medicine.

5. Ad hoc involvement of patients in other EMEA activities
Apart from the systematic involvement of experts from patients’ and consumers’ organisations in the review of documents addressed to patients and the public, the EMEA also involves patients and consumers in other activities relevant to provision of information. For example, the PCWP often contributes to the review of safety communication aimed at patients and the general public.

6. A good example: anti-inflammatory drugs and thrombotic risk
One example of this interaction is the review of information on non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and thrombotic risk. As part of its continuous monitoring activities, the EMEA, during the 2007, reviewed newly available cardiovascular safety data on these medicines, which include naproxen and diclofenac. Non-selective NSAIDs have been available on the market for many years and are mainly used in the treatment of painful conditions. The review concluded
that non-selective NSAIDs are important for the treatment of arthritis and other painful conditions, but that a small increase in the absolute risk of thrombotic events could not be excluded, especially when they are used at high doses for long-term treatment.

Following this conclusion, additional wording for package leaflets for non-selective NSAIDs was prepared, which was then circulated to the members of the PCWP. The PCWP reviewed the first draft and acknowledged that communication to patients on this topic was necessary, but that the wording required some improvement to increase clarity and comprehensibility. A simplified common wording for all NSAIDs was agreed by the PCWP and subsequently implemented.

7. Other examples
A similar approach was taken later on for antidepressants, which were under scrutiny for a possible increased risk of suicidal behaviour. Since depression itself can itself lead to suicide or suicide attempts, this has generated considerable debate amongst the scientific committees, which is still ongoing. At present, the CHMP and its Pharmacovigilance Working Party is of the opinion that an increased risk for some individuals cannot be excluded and wishes to reflect this in the PL of all antidepressants. Again, the input of the PCWP was sought and experts from patients’ and consumers’ organisations answered promptly, improving the ‘fine tuning’ of the message and its clarity.

Other examples of consultation with experts from patients’ and consumers’ organisations helping to tailor information to their needs took place during 2007. New medicines containing thalidomide and lenalidomide (an analogue product which shares a similar chemical structure to thalidomide) have been under assessment by the EMEA, and representatives of patients and victims of thalidomide were invited to discuss the risk management plan. They also provided input on the information for the package leaflet and for the labelling of the new medicines.

Patients were also consulted during the preparation of the communication plan at the time of the temporary withdrawal from the market of Viracept (nelfinavir), a medicine for treatment of HIV infection. Viracept was withdrawn from the market because some batches had become contaminated with a toxic compound. It was therefore of the utmost importance to give the most appropriate information to patients taking the medicine.
CONCLUSIONS

With regard to provision of information, the EMEA will continue to work towards the provision of high quality information for patients and to the improvement of the level of interaction to tailor its information to their needs. In this respect the involvement of patients’ and consumers’ representatives has proven to be an added value. Certain procedures, such the review of EPAR summaries and package leaflets, have proven to be positive and may be developed further. Nevertheless, the EMEA clearly needs to receive more systematic feedback confirming that the ongoing initiative contribute to the rational and safe use of medicines and improve adherence to treatment for all the patients in EU.

REFERENCES


[2] Article 78(1) and 78(2) of Regulation (EC) no. 726/2004

9.2 Assessing the quality of centres of expertise outcomes

The concept of centres of reference is not compatible with the federal structure of Germany and networks are therefore better adapted. Cross-border referral of patients should be avoided, and experts should be in a position to exchange information and medical opinions. Networks of experts are in a best position to train the local experts.

For cystic fibrosis, a European consensus of care has been established. It is a complex multi-organ disease involving: airways (mucus impaction, infection and inflammatory reaction), liver (cirrhosis), pancreas (p. insufficiency), diabetes, bowel (obstruction, fatty stools), reproductive system (infertility), skin (increased secretion of sodium chloride). Outcomes variables are numerous: airways with pulmonary function, and bowel/nutrition with body weight and body mass index.

Quality of care increased during the last decades, with an increase in the proportion of patients with cystic fibrosis who reach adulthood: 2% in 1980, 55% in 2006.
European Centres of Reference Network for Cystic Fibrosis (CF) ECORN-CF16 is a network associating partners of the CF care team and of the patient organisations from GER, UK, BE, NL, SWE, ROM, POL, LIT, CZE and collaborating partners from ITA, FRA, ESP, SLO, AT, DK, GR, TUR etc.

The project is structured with 7 work packages, 3 standard and 4 specific ones: Expert advice to patients, Expert advice to care team members, Quality control measures and Evaluation of Quality of Life, utilisation, implementation of European consensus.

All collaborating partner-countries provide expert advice to patients and care team members. Transfer of knowledge and expertise throughout Europe to guarantee the same level of expert advice in all partner countries.

The scheme below explains the processing of information in the project to ensure its quality, accuracy and translation.

*Figure 62: processing of the medical information in the ECORN-CF network*
By providing expert advice and quality program, the network raises the level of expertise and facilitates access to information. This model can be applied to other rare diseases; it does not interfere with the national interests of Member States. It really yields European added value. ECORN-CF only targets patients with access to internet.

This project should also be linked to a research project (submitted), including LAM and Lung transplantation, expert advice and quality program, optional cross border referral, clinical study networks and patient registries.

### 9.3 Assessing the quality of information on genetic testing

**→ INTRODUCTION**

When looking at issues of quality in respect of genetic testing services clearly no-one would aspire to providing a service that is not of the highest possible quality given the state of current scientific knowledge and the resources available to the service provider. However, from a patient and family perspective, it is important to recognise that quality in much more than a narrow, technical question. Of course technical matters are important, but a simple “Does it do what it says on the tin?” approach to quality assurance will neglect a number of very important elements in the provision of services that are able to respond to patients’ and families’ legitimate needs and expectations.

**→ NEEDING A GENETIC TEST**

Notwithstanding the emergence of over-the-counter testing available from internet and other suppliers, and the rise of public interest in genealogy, for most people at risk of serious health problems arising from genetic abnormality getting a genetic test is still not a curiosity driven activity. Rather the need arises because of a growing awareness of the existence, or the possible existence, of a problem which may affect the individual, a family member or a child (who may yet be unborn). This awareness may happen for a variety of reasons – perhaps as part of routine ante-natal care, due to knowledge of the disease in the family, as a consequence of some other medical investigation, or for some other reason. Whatever the rehabilitating factor the patient and the family are likely to arrive at the genetics clinic stressed, anxious and uncertain. If they have had no previous experience of clinical genetics services they
may also have only a hazy understanding of what to expect, and what
genetic diagnosis may be able to do for them. They may even have wildly
unrealistic expectations based on media representations about the pow-
er of genetics and the state of our current knowledge!

For most people, their arrival at a genetics clinic will be accompanied
by a fervent desire that they will be told that everything is OK – that
the signs and symptoms that appeared to indicate a problem can be
explained, and that there really is nothing to worry about – at least from
the genetic perspective. And of course it must not be forgotten that for
many of those referred this is precisely what happens. The value of an
“all clear” cannot be over-stated when considering the quality of genetic
services because it allows patients and families to go away and get on
with their lives free from this particular worry.

Whilst giving good news is a pleasure, for some the news they receive
from the geneticist will not be that which they are wishing and hoping
to hear. Those who do receive the news that they, or their loved ones have,
or have a significant chance, of developing a genetic disorder that may
well limit life substantially in terms of its quality and quantity also have
to go home and get on with the rest of their lives – sometimes after hav-
ing to make some very hard decisions, and learning to accept a future for
themselves and their family that may be very different from the one they
were hoping for before they crossed the threshold of the genetics clinic.

In such a situation, the need for a quality service is of the utmost impor-
tance to patients and families needing to make use of the advice, support
and whatever else may be on offer.

**TEN DIMENSIONS OF QUALITY**

Whilst the list that follows may not be exhaustive, and others will and
should expand upon it, nevertheless from the point of view of the pa-
tient, if a service provider can put ticks in the following ten boxes then he
or she can be reasonably confident that their service, whilst it will not be
perfect, has taken reasonable account of patient and family needs.

1. Access to the service must be TIMELY. Once the need for genetic test-
ing has become apparent patients and families should not be kept
waiting longer than is absolutely necessary. If there is a delay prior to
a first appointment then contact and an explanatory letter should at
least be sent in order to reassure them that they are in the system and
not left dangling in limbo.
2. Services must be AVAILABLE. Whilst patients and families will often be prepared to travel great distances to see someone who is an acknowledged expert in “their” condition, it is far better that that which can be done locally is done locally, reserving the need to travel for those things that cannot be done close to home. Conversely, unnecessary barriers to families seeing acknowledged experts (for organisational or financial reasons perhaps) should not be erected in the way of those needing to move around the country to get access to the help and support they need.

3. The environment in which services are delivered must be USER FRIENDLY. Genetics can often seem like “scary science” operating at the edge of scientific knowledge. Because of this, consideration needs to be given to ensuring that the environment is both comfortable and comforting – for example by providing consulting rooms that are big enough to accommodate families without cramming people together, with comfortable, non institutional furniture as far as possible. A private space where families can go after the consultation session, to digest what they have been told, have a cup of tea and brace themselves to walk out into the world again can be invaluable.

4. The content of the encounter must be PATIENT AND FAMILY FOCUSED. Patients need to be able to use their time in the clinic to express their worries and needs, and feel that these are being responded to by the geneticist or the genetic counsellor, clinical encounters also provide an opportunity for the professional to impart important information which experience has shown that families need to know. Clinical consultations are not one-way but two way streets – sessions which should be paced according to patients’ needs and abilities. Under stress even those who are highly competent professionals in other areas of their lives tend to regress, and need things expressed more simply and in a greater variety of ways than would normally be the case were they to be functioning at the top of their game. Sessions need to be non-judgemental, paced and reinforcing for patients and families so that they can have the best chance of adjusting to the situation in which they now find themselves – something which may have been changed dramatically by the very process through which they have just been!

5. The service must be ROBUST. In other words it must be capable of delivering good information in coherent and consistent ways appropriate to the needs and abilities and (legitimate) demands of the pa-
tients who use it. This should apply between diseases – given the limitations of current understanding of the specific condition, with regard to the language in which it is communicated (both in terms of the language level and the mother tongue of the hearer) and with steps taken to ensure that the messages given to different members of the same family (and to different families with the same condition) are consistent even when this happens in different places or at different times.

6. Services must be EVOLUTIONARY, so that patients and families can be confident that they have incorporated new knowledge arising from research that may impact on the options open to them and the choices they make between these – and that if things have altered materially since their initial encounter with the service as a result of this new knowledge in ways that would be relevant to them then they will be contacted. The annual updating of genetic registers, where these are maintained, provides a good opportunity for regular re-contact in a non-threatening way. It also creates a positive opportunity for patients to opt out if they feel that that is what they want to do, rather than just drifting away in a manner that creates uncertainty and is ultimately unsettling to professionals and families alike.

7. The organisation and delivery of services must be RELIABLE. This is not just a matter of scientific reliability, assessed by appropriately validated procedures to proper standards of performance, but also clinically, administratively and managerially, ensuring sufficient skills, resources and personnel are in place to deliver the service promised to the standards of performance that have been claimed for it.

8. PROCESS AND OUTCOMES need to in balance. Whilst patients and families will often not care how the specific steps to arriving at a diagnosis are carried out. Providing they believe the “back office” and the systems are in place to ensure that all the relevant steps are taken in a logical order by people with the appropriate skills, knowledge and equipment to reach a result that is true and accurate then many will not care if how precisely this point is reached. Trust in the process, however is essential if patients and families are to be able to contextualise the information shared in the clinical encounter, because they need to know that what has been done has been done well and is fit for purpose if they are to believe and act upon it.

9. Service providers must be HONEST. This is especially important with regard to things that are not done or which may take some time to do. Families tend to know that there is variability between patterns of service delivery in different parts of the country and also in the time that the same thing may take in differ-
ent regional centres. Families may not like the variability in service provision, but if they understand why and how it has come about then they are in a better position to do something about it – be that adjusting and being patient, campaigning for service improvement or whatever. Honesty is always important, but honesty about difficulties in service provision arising from issues such as a test moving from research into clinical service delivery, and the commissioning issues this creates, or skills, knowledge and resources gaps arising because the supply of skilled professionals and the provision of equipment lags behind the expanded need created by new scientific possibilities is particularly important.

Services must strive to be FAIR and to be seen to be fair. Families do not choose to have conditions that may be difficult to diagnose, expensive to test for or otherwise make substantial demands on the capacity of genetics services to meet their needs. Nor do families in different services’ catchment areas differ significantly in the totality of their needs (though the specifics may vary substantially). In order to protect the trust between patients and professionals that is the cornerstone of clinical genetics service delivery there should be clear, transparent and challengeable policies in place to ensure that equity of access – between diseases and between families with the same disease – are in place, known to all relevant staff and adhered to.

**THE ACCE FRAMEWORK**

The ACCE Framework, developed by Prof. Wylie Burke and others see for example Burke (2002) and Haddow & Palomaki (2004) to provide a systematic methodology for evaluating genetic tests as fit for purpose has proved an important tool in raising awareness of the importance of quality standards for genetic testing services. This framework looks systematically at:

- Analytical validity
- Clinical reliability
- Clinical utility
- Ethical, legal and social aspects

It has provided a useful tool for quality commissioning decisions, and will serve to support the logical decision making frameworks put in place by, for example the UK Genetic Testing Network.

However, as was said at the very start of this paper, genetic testing, from a patient point of view is a means to an end. It is one aspect of a quality genetic service, and as such perhaps genetic services need their own
ACCE Framework – though in the context, it stands for:

- Available
- Comprehensible
- Compassionate
- Equitable

Such a framework, with appropriate targets, properly monitored and enforced would create pressure for improvements that would enhance the health gain to be had from quality genetic testing. It would give confidence to professionals, commissioners and the health care system as a whole that resources made available for genetic services are being used to best advantage, because they would provide robust confirmation that services are delivering things that are useful to, and valued by patients and families. In the context of health care systems that are increasingly patient centred, user led, consumer friendly and accountable to an engaged public this cannot be a bad thing.

**REFERENCES**


10 CONCLUSIONS

The European society mobilised: member states partnering with each other and collaborating on European initiatives

As co-chair of the Programme committee, Prof Torrent i Farnell started by a big thank you to all the delegates and speakers. Special thank to participants coming from outside of the European Union, to the Local organising committee and volunteers from Portuguese patients’ organisations, to the Portuguese Presidency of the European Union, to the Portuguese Ministry of Health & National Competent Authorities, to the European Commission, to Programme Committee members and to Eurordis staff.

THE EUROPEAN CONFERENCE ON RARE DISEASES:
THE EUROPEAN RARE DISEASE RENDEZ-VOUS

The rare disease community in Europe is steadily growing and getting stronger. This is largely due to the European Conferences on Rare Diseases since 2001:

- 2001 Copenhagen
- 2003 Paris
- 2005 Luxembourg
- 2007 Lisbon

We can discuss with authorities, industry, patient organisations, researchers and the society at large.

THE EU POLICY FRAMEWORK IS ABOUT TO BE IN PLACE

- EU Regulation on Orphan Medicinal Products 2000 +
- EU Regulation on Paediatric Use of Medicines 2007 +
- EU Regulation on Advanced Therapies 2008 +
- EU Research Framework Programme: RD = priority 2007-2013
- EU Health Policy Strategy: RD = priority 2008-2013
- EU Directive on Health Services & Patient Mobility 2008 ?
- EU Commission Communication on Rare Diseases 2008 ?
- EU Recommendations on Rare Diseases 2008 ? 2009 ?

THE EUROPEAN COMMISSION COMMUNICATION TO EP AND COUNCIL FOR RARE DISEASES

- Brings a new tool and new hope for coordination
- Offers a common reference political framework
- Horizontal articulation (at EU level)
- Rare Disease Research
- Therapy Development
- Public Health
Rare diseases require specific actions and initiatives at national levels but also need a true European dimension and an international perspective. For the future, we need strong national political commitment; we need to continue collaboration between all stakeholders, and from Lisbon 2007 to Poland 2010, 27 national plans for rare diseases in all Member States!!!
ABSTRACTS
Centres of Expertise and European Reference Networks for Rare Diseases

Red blood cells disorders diagnosis and prevention - experience of the Congenital Anaemias Unit - Hematology Department in Centro Hospitalar de Coimbra, Portugal

Author: Dr Celeste Bento - Departamento de Hematologia, Coimbra, Portugal

Keywords: red blood cell (RBC) disorders; prenatal diagnosis; Haemoglobinopathies’ screening

Summary:
The Congenital Anaemias Unit, Haematology Department, Centro Hospitalar de Coimbra (CHC), Portugal, is a reference centre for red blood cell (RBC) disorders. A multidisciplinary team provides the diagnosis, medical advice, treatment and prevention of the severe forms. Among the severe forms Thalassemia intermedia, Sickle cell disease and PK deficiency are the...
most frequent. We performed several prenatal diagnosis studies on these pathologies and also on TPI deficiency, sideroblastic anaemias and congenital pure red cell aplasia. We implemented a Hemoglobinopathies screening program in the central region of Portugal. Severe forms of RBC disorders are relatively rare and should be investigated and treated in clinical/laboratory units with technical expertise and clinical experience.

**Text:**

The Congenital Anaemias Unit, Haematology Department, Centro Hospitalar de Coimbra (CHC), Portugal, is a reference centre for red blood cell (RBC) disorders. A multidisciplinary team provides the diagnosis, medical advice, treatment and prevention of the severe forms. The biochemical and molecular diagnosis cover the haemoglobinopathies, defective RBC metabolism (enzymopathies), membrane disorders (Hereditary spherocytosis and elliptocytosis), sideroblastic anaemias, pure red cell aplasia, erythrocytosis, phenotype modulating factors related to iron overload (Haemochromatosis), hyperbilirubinemia (Gilbert syndrome). Prenatal diagnosis is provided when indicated. The methodology used for RBC disorders investigation is mainly based on the clinical history, family data, haematological parameters, including RBC morphology, and all the standard biochemical and molecular tests for RBC disorders studies.

Apart from patients from CHC, many samples are received from other Hospitals all over the country and abroad. Among the severe forms Thalassemia intermedia, Sickle cell disease and PK deficiency are the most frequent. We performed several prenatal diagnosis studies on these pathologies and also on TPI deficiency, sideroblastic anaemias and congenital pure red cell aplasia.

Recently, we implemented a Haemoglobinopathies screening program in the central region of Portugal. The target population are young adults and pregnant women attending the primary care medical centres and Obstetrician Units. We developed a new procedure to study capillary blood samples by HPLC methodology. We identified several couples at risk of having children with severe forms of the disease that were referred to Prenatal Diagnosis Units. The frequency of beta-chain haemoglobinopathies carriers was 2%, among the 19000 samples studied (Bento et al., 2006). Severe forms of RBC disorders are relatively rare and should be investigated and treated in clinical/laboratory units with technical expertise and clinical experience. Correct diagnosis, made as early as possible, can prevent many complications associated with the disease. Carriers screening, genetic counselling and prenatal diagnosis should be available.
The outcome of haemathological parameters and organomegaly under imyglucerase treatment Romanian type 1 Gaucher patients

Author: Dr Victoria Cret - First Paediatric Clinic, Cluj-Napoca, Romania

Keywords: Type 1 Gaucher disease, Romanian patients, Imyglucerase treatment, outcome

Summary
ERT with Imyglucerase in Romanian type 1 Gaucher patients for a mean of 28 month shows a significant improvement of haematological parameters and organomegaly

Text:
Aim: This study aimed to evaluate the outcome of haemathological parameters and organomegaly in Romanian type 1 Gaucher patients under imyglucerase treatment, which has recently been available in our country.

Patients and methods: 30 patients with type 1 Gaucher disease (age: 31.74 + 12.02 years; range: 13 – 53) and 1 patient with type 3 have been treated by now, with 20–60 units/Kg/dose of Imyglucerase, every two weeks, for a minimum of 6 month (28.43 + 11.39 month). Haemoglobin (g/dl), platelet count (/mm3), spleen and liver volume were assessed every 6 month.

Results: Haemoglobin level has a significant increased from the start of ERT (11.40+1.87g/dl) to 6 month of treatment (13.47+1.44g/dl) and after 28 months of treatment the value is 13.9+3.11g/dl. 12 patients were splenectomized before start of therapy. 18 patients, of whom 17 did not undergo splenectomy, had thrombocytopenia (average 68700+ 28940/mm). After 6 months of therapy the platelet count increased at 116560+66290/mm and up to 158420+41483/mm after 28 months of ERT. Splenomegaly decreased from a mean of 14.512+7.87 to 4.60+3.05 of normal value for weight and hepatomegaly improved from 1.42+0,43 to 1.06 of normal value for weight.

Conclusions: Enzyme replacement therapy (ERT) administered for 28 months in Romanian patients with Gaucher disease type 1 led to a marked improvement in haematological parameters and an important regression of hepato- and splenomegaly.
Access to diagnosis and prophylaxis for patients with Sanfilippo Romania

Author: Dr Mirela Crisan, Dr Paula Grigorescu-Sido, Dr Victoria Cret - First paediatric Clinic Cluj Napoca, Romania

Keywords: SanFillippo, diagnosis, prophylaxis

Summary:
Sanfilippo syndrome or mucopolysaccharidosis type III is characterised by severe neuropsychic impairment. In the absence of any efficient treatment, prenatal diagnosis remains the only option available to families with a risk of transmitting the disease.

Text:
Access to diagnosis and prophylaxis for patients with Sanfilippo syndrome in Romania. Sanfilippo syndrome or mucopolysaccharidosis type III is characterised by severe neuropsychic impairment secondary to the excessive accumulation of acid mucopolysaccharides, consecutive to a deficiency of lysosomal enzymes: heparan N-sulfatase (type A); alpha-N-acetylglucosaminidase (type B); glucosaminide acetyltransferase (type C); and N-acetylgalactosamine-6-sulfatase (type D). The authors present the clinical observation of 4 children (three girls and a boy, of which two siblings), aged between 3 and 8 years, followed up by the Centre of Genetic Pathology Cluj, with the diagnosis of MPZ type III B. The work methods included: a) patient history, clinical examination, and specialized examinations (neurological, ophthalmologic, ENT); b) measurement of lysosomal enzymes; c) radiological and ultrasonographic examinations. The diagnostic evaluation showed: a positive family history for 2 of the 4 children (the siblings under study); onset of the disease after the age of 2 years by progressive severe neuropsychic involvement; presence of craniofacial dysmorphism (coarse features, thick eyebrows, synophrys, prominent supraorbital arches, wide nasal pyramid, anteriorly oriented nares, macrostomia, hypertrophic dental arches); visceromegaly (hepatosplenomegaly and cardiomegaly in 2 children, 1 child, respectively); specific radiological changes (shortening of long bone diaphyses and patchy osteoporosis) in 3 patients; alpha-N-acetylglucosaminidase deficiency (values ranging between 0 and 0.17 nmol/h/ml plasma). No functional biochemical or haematological changes were found. Death occurred in one patient (boy) at the age of 10 years, secondary to severe neurological complications. In the absence of any efficient treatment, prenatal diagnosis remains the only option available to families with a risk of transmitting the disease. Performed in the presence of a new pregnancy in the family with the two affected children, it allowed the exclusion of the disease and the birth of a healthy child.
Outcome of genetic Counselling Italy: the experience of a single centre in Italy

Authors: Dr Sofia Douzgou, Dr Chiara Palka, Dr Rita Mingarelli - CSS-Mendel Institute, Viale Regina Margherita 261, Rome 00198, Italy

Keywords: outcome, genetic counselling

Summary:
We re-evaluated 1020 sessions held by the same team of clinical geneticists through a homogeneous procedure, in an attempt to provide some insight into quality assessment of the genetic counseling service.

Text:
We assessed the genetic counselling sessions held in the CSS-Mendel Institute in Rome, by the same team of clinical geneticists, using a homogeneous procedure including collection and storage of genetic data with the SHIRE® software. Topics and questions discussed with the consultants during genetic counselling have been widely debated and the information provided was incorporated in a conclusive letter. We have re-evaluated 1020 cases consecutively referred throughout a period of 30 months, in three different settings: 254 prenatal, 463 postnatal and 303 reproductive. The 70% of cases were concluded at the end of the first session and the 30% after two or more sessions. “New” information was provided in the 85% of cases. In 220 cases the counselling was integrated with a genetic test, including 10% of them sent to external laboratories. In addition, in the 7% of cases, external expert advice was requested to support a clinical hypothesis. The 30% of patients referred were from an outside region, witnessing the Institute’s attractive power. In the 254 prenatal cases referred for a foetal risk of pathology, a questionnaire was administered to the couples, following genetic counselling, to weigh the impact of received information onto family planning and reproductive choices. The 52% of couples returned the filled-in questionnaire. The percentage of pregnancies reaching the term was lower in couples with more than 15% of risk, but was not related to counselling efficacy as measured according to the consultants’ perception. Aged mothers (over 35 years) with no children had fewer propensities to terminate pregnancies in respect to those with one or more children. This study should provide some insight into quality assessment of the genetic counselling service.

Figures 66:
Participants in ECRD 2007
DYSCERNE - A European Network of Centres of Expertise for Dysmorphology

Authors: Ms Pam Griffiths, Prof Dian Donnai, Dr Bronwyn Kerr, University of Manchester, Nowgen Centre, Manchester, United Kingdom

Keywords: Dysmorphology, Centres of Expertise, Centres of Reference, diagnosis, networks

Text:
Over 2,500 rare and difficult to diagnose conditions presenting with patterns of birth defects have been identified. The rarity of these dysmorphic conditions means that even in Centres of Expertise, experience may be limited and a diagnosis might be delayed or not made at all. Making a correct diagnosis is the cornerstone of patient management, enabling clinicians to locate other patients with the same condition, share clinical experience, and increase individual and collective knowledge about rare conditions. For patients and their families, the importance of having a diagnosis cannot be over-emphasised. It can help them come to terms with the condition, reassure them that they are receiving appropriate care, and may facilitate making contact with other affected individuals and families for support and advice.

DYSCERNE aims to raise current standards for the diagnosis, management, and information dissemination of rare dysmorphic syndromes by forming a network of Centres of Expertise in dysmorphology. The Network is funded by the European Commission, Directorate General for Health and Consumer Protection. The main partners in DYSCERNE are six designated Centres of Expertise for Dysmorphology (UK, Belgium, France, Italy, The Netherlands and Poland). The University Of Manchester, UK, is lead partner and coordinating and managing centre for DYSCERNE. To facilitate the project aims, a web-based diagnostic system (DDS) will be established, enabling clinicians to submit difficult to diagnose cases electronically for expert review. Access to the DDS will be via designated ‘nodes’. There will be at least one ‘node’ in every EU Member State, and an on-line training course will be provided for clinicians using the service. Project members will also develop management guidelines for selected multi-system disorders which will be piloted and disseminated widely throughout the clinical genetics community. DYSCERNE will also serve as a demonstration project for future EU Networks.
Controlling Sickle-Cell syndromes in Portuguese-speaking sub-Saharan African populations: Role of the Portuguese health system in a trans-continental patient mobility context

Author: João Lavinha - Organisation INSA Min Saude, Portugal
Keywords: Sickle-cell, sub-Saharan Africa, prenatal diagnosis, mobility.

Text:
Sickle-cell disease (SCD; OMIM 603903) is a rare autosomal recessive condition characterised by haemoglobin (Hb) S production, leading to haemolysis (anaemia), vascular disease (thrombophilia) and immunodeficiency (infection). SCD affects predominantly populations of sub-Saharan African and Asian Indian origin and their descendants in Europe and the New World. It displays marked clinical heterogeneity with a wide severity range, possibly in result of a complex gene-gene and gene-environment interplay. Due to the lack of reliable severity predictors and an effective affordable cure, many at-risk couples choose to participate in prevention programmes based on carrier screening, nondirective genetic counselling, prenatal diagnosis and termination of affected pregnancies. Successful programmes have been running for the last two decades in the USA, Latin America and Europe. However, in the most affected regions this kind of control has not been a priority, despite the fact that thousands of new patients are born every year. Following its long-standing relationship with African populations, Portugal has issued an official guideline opening its national haemoglobinopathy control programme to families coming from African Portuguese-speaking countries. As a result, since 1990 sixty-seven such families have been referred to our centre by various hospital services (e.g. haematology, medical genetics, obstetrics and paediatrics) and primary health care centres. So far, this activity, positively sought after by the families, allowed (through an informed choice) the prevention of eleven new SCD cases and the detection of a large number of asymptomatic HbS carriers. The data presented here are a successful illustration of the concept that the provision of genetic services should be adapted to the population’s needs, socio-cultural background, history and demography, respecting differences, while being equitable and accessible to all. To fully achieve this goal a comprehensive collaborative endeavour is underway aiming to replicate this intervention model in a large African Portuguese-speaking country.
Genetics of red blood cell enzyme deficiencies in Portugal: mutation profile on PK, G6PD, P5’N and TPI deficiencies

Author: Prof Licinio Manco - University of Coimbra, Coimbra, Portugal
Keywords: red blood cell enzyme deficiencies; PK, G6PD, P5’N and TPI deficiencies; gene mutations

Summary: We performed the molecular characterization of 101 unrelated Portuguese patients with PK, G6PD, P5’N-I and TPI deficiencies. Gene mutations were identified establishing genetic profiles in Portugal and improving the knowledge of red blood cell enzyme deficiencies.

Text: Red blood cell (RBC) enzymes sustain an active metabolism in erythrocytes to maintain the integrity and flexibility of membrane and to preserve the haemoglobin function. Losing nucleus, mitochondria and ribosomes, erythrocytes use glycolysis to produce ATP, the pentose shunt to generate NADPH and other enzymes to nucleotide degradation. Mutations leading to RBC enzyme deficiencies result in varied clinical manifestations including haemolysis and neurological or developmental abnormalities. For diagnosis, carriers screening and prenatal diagnosis purposes we performed the molecular characterization of 101 unrelated Portuguese patients with PK, G6PD, P5’N-I and TPI deficiencies. Standard methodology for molecular studies was used.

Among 23 PK deficient patients 9 different PKLR mutations were found, 7 of them for the first time: 1010G>A(337Arg>Gln), 1435C>T(479Arg>Cys), 1670G>C(557Gly>Ala) and 1706G>A(569Arg>Cys); two splice donor site (GT) mutations [IVS8(+2)T>G] and [IVS10(+1)G>C]; -72A>G in the R-type promoter; del109-130, a 22 bp deletion in exon 3. The most common PK mutation in Southern Europe 1456C>T(486Arg>Trp), and 993C>A(331Asp>Glu) were also found.

Molecular study of 71 G6PD-deficient individuals revealed 14 different mutations. The most commons were A-(376G/202A) (0.62) and Betica (376G/968C) (0.14). We found 7 new G6PD variants: Mira d’Aire 1048G>A(350Asp>His), Anadia 1193A>G(398Glu>Gly), Açores 595A>G(199Ile>Val), Covão-do-Lobo 1205C>A(402Thr>Asn), Figueira-da-Foz 1366G>A(456Asp>His), Coimbra 592C>T(198Arg>Cys) and Tondela del1076-1094(p.360-365del). Other known G6PD variants identified were Seattle, Chatham, Santa-Maria, Kamiube and Canton. In
5 patients with P5’N deficient anaemia, we identified 3 new P5’N-I gene mutations: 502G>C(168Gly>Arg), 773T>C(258Ile>Thr), and the insertion of an Alu element within exon 9. The previously described mutation 425T>C(142Leu>Pro) was also found.

The molecular basis of TPI deficiency was established in two patients with a very severe phenotype. The most frequent TPI mutation 315G>C(104Glu>Asp) was found in 3 alleles. The second mutation, 188C>A(62Ala>Asp), was not previously described.

In conclusion, the knowledge of RBC enzyme deficiencies was improved with the molecular characterizations of Portuguese patients with associated clinical phenotypes.

**European network of rare bleeding disorders. En-rbd.**

**Author:** Prof Flora Peyvandi, Internal Medicine Department, University of Milan, Italy

**Keywords:** rare diseases – bleeding - network

**Summary:**
Rare Bleeding Disorders (RBDs), representing 3-5% of all the inherited coagulation deficiencies, are autosomal recessive diseases leading to lifelong bleeding. Despite the existence of RBDs databases, data are not yet sufficient to indicate which course of action is needed to improve diagnosis and treatment. This lacuna could be made up by the collection and organization of clinical, laboratory and treatment data and their statistical analysis using a unique and homogenous model. In this frame a project was funded by PHEA. Each of the 10 participating Centre will insert and manage patients’ data through a protected access area on the www.rbdd.eu web-site, following the same data collection scheme. Queries and reports are deemed to be fundamental for the research and interrogation of the database. The final goal will be the creation of a unique on-line tool available to all Centres dealing with RBDs.

**Text:**
Rare Bleeding Disorders (RBDs), representing 3-5% of all the inherited coagulation deficiencies, are autosomal recessive diseases leading to lifelong bleeding, relatively neglected by health care providers and drug manufacturers. Based on a decade-long research, an International Registry on 400 patients from 19 countries, was compiled (www.rbdd.org). Major cohorts were
from Iran (155) and Italy (154); remaining patients were spread worldwide. According to coagulant activity, 41% of patients were severe, 20% moderate and 39% mild; 77% of patients was fully characterized for 165 different mutations (70% novel) increasing knowledge on RBDs genetics by 15%. Despite the existence of this and other RBDs databases, data are not yet sufficient to indicate which course of action is needed to improve diagnosis and treatment. This lacuna could be made up by the collection and organization of clinical, laboratory and treatment data and their statistical analysis using a unique and homogenous model. As the most readily available data come from Europe, we chose to create a network among 10 European Centres in order to develop a novel communication tool for managing, editing and viewing collected information. This project was submitted and funded in the frame of PHEA. Each Centre will insert and manage patients’ data through a protected access area on the www.rbdd.eu web-site, following the same data collection scheme. Queries and reports are deemed to be fundamental for the research and interrogation of the database. The final goal will be the creation of a unique on-line tool available to all Centres dealing with RBDs. Statistical results derived by all the clinical, therapeutic and genetic information will be available to clinicians and patients, as well as National and Supranational organizations and regulatory agencies (FDA, EMEA). Moreover, data obtained on distribution and treatment of patients could stimulate the interest of pharmaceutical industries in developing new products.

**Italian network for Primary Immunodeficiencies (IPINET) : an useful operative model for rare diseases**

**Authors** : Dr Annarosa Soresina - Dept. of Paediatrics, University of Brescia, Spedali Civili di Brescia, Italy

**Keywords** : immunodeficiency multicentre network; web based system; quality of care

**Summary** :
The IPINET web-based system is an interesting operative model applied for rare diseases research and clinical care. It is a national network of Centres of expertise and non-specialised centres that produces, shares and updates disease-specific diagnostic and therapeutic protocols, improving the quality of care and the quality of life for patients with Primary Immunodeficiency

**Text** :
The management of Primary Immunodeficiency Diseases(PIDs),rare diseases due to defects of the immune system, presents difficulties concerning
assistance organization, clinical care and research. To overcome that, the IPINET, established in 1999 within the Italian Association of Paediatric Haematology and Oncology and with the support of the Italian patients’ Association of Primary Immunodeficiencies (AIP), aims to: - assure a definitive molecular diagnosis to all cases with clinically diagnosed or suspected PIDds by means of highly qualified referral laboratories; - decrease health migration and its related individual and social costs by means of a network of Centres of expertise and non-specialised centres, that produces, shares and updates disease-specific diagnostic and therapeutic protocols; - build a centralized system for PIDds data collection to evaluate both patient accrual and the long-term efficacy and late-effects of previously and currently adopted treatments; - share knowledge and experience between centres participating in the web network program. Fifty-nine Centres have jointly formulated and adopted common protocols for diagnosis and treatment of children and adults with X-linked and Autosomal recessive Agammaglobulinemia, Chronic Granulomatous Disease, Common Variable Immunodeficiency, Transient Hypogammaglobulinemia, Wiskott Aldrich syndrome, Deletion 22 syndrome and Ataxia Teleangiectasia, available on Italian website www.aieop.org; an English version is available linked to the ESID website, www.esid.org/links. The IPINET identified referral laboratories for molecular diagnosis and utilized a web-based centralized system for data collection and analysis of the PIDds at the Italian Interuniversity Computing Centre. The system allows management of the whole informative flow with consultation of protocols and exchange of information across forum. Each centre enters patients’ information by electronic forms of registration, diagnosis, therapy, side effects, annual follow-up. From 1999 to the present day, the IPINET obtained the enrolment of large series of cases (123 XLA, 30 AAR, 68 CGD, 303 CVID, 85 THI, 59 WAS, 103 DEL22), has assured a large amount of high quality data, optimized operator work, improved the ability of physicians to manage such a rare diseases and has lead to a quality of care improvement of PIDds children and adults.

Perspectives, difficulties and achievements of RESOCANAUX, the six-year-old collaborative french network dedicated to diagnosis and research about skeletal muscle channelopathies

Authors: Dr Damien STERNBERG - Hospital Practitioner, Assistance Publique Hôpitaux de Paris, France

Keywords: channelopathy, periodic paralysis, myotonia congenita, paramyotonia, Andersen-Tawil syndrome, electromyography, therapeutic trial, diagnostic test
Summary:
The six year activity of RESOCANAUX network has enabled to set up and make a extensive use of high-quality electromyography and genetic diagnostic tools that will be the basis of the evaluation and stratification of future therapeutic trials.

Text:
Skeletal muscle channelopathies are diseases of muscle membrane excitability. They result in periodic paralysis or in transient or permanent, effort-dependent or temperature-dependent stiffness (myotonia and paramyotonia). They result in a various degree of handicap for patient activity, although they are rarely life-threatening. Causal genes were identified from 1991 to 2001 as ion channel genes. Different potential pharmacological treatments exist, but their posology and the exact indications according to genetic defect or clinical presentation, are not defined.

The French collaborative (“RESOCANAUX”) network was initiated in 2001 (i) to improve genetic and electromyography diagnostic tools for those under-recognized diseases; (ii) to gain a better comprehension of the pathophysiological mechanisms; (iii) to set-up stratification and evaluation tools to make therapeutic trials interpretable. This network involved all University Hospitals and some other Hospitals in France, as well as some other European countries. Participants sent clinical data and a sample for genetic diagnosis. Over 850 independent cases or families suspected with skeletal muscle channelopathy were referred. The diagnosis was confirmed and characterized at the molecular level in 560 of them, in whom the wide mutational spectrum of those diseases has been extensively characterized. Reproducible and reliable EMG tests specific for skeletal muscle channelopathies were set up with the help of molecular genetic results. These tests have been published and are routinely available in clinical practice. A French Reference Centre dedicated for Skeletal Muscle Channelopathies, with clinical and electromyography expertise, was created in 2005, and a therapeutic trial for periodic paralysis is beginning in collaboration with a NIH-funded American network.

Original mutant channels associated either with periodic paralysis or myotonia have been studied extensively, for their clinical correlates, as well as their biophysical properties.

Retrospective as well as prospective analysis of clinical data focusing on handicap and response to treatment are on the way.
ENERCA - European Network for Rare and Congenital Anaemias

Authors: Prof Joan-Luis Vives Corrons - Head Red Cell Pathology, Hospital Clinic i Provincial, Barcelona, Spain

Keywords: Centres of Expertise, Reference Networks, Rare Anaemias

Summary:
The European Commission, through their Directorate for General Health and Consumer Protection, is funding the ENERCA Project. Each of its members has been individually chosen to provide expert experience and advice. The main objective is to improve the communication between specialists and to establish a support network for them. This is done through:

ENERCA WEBSITE: To provide patients and their families with a reliable information source in their language so they are better equipped to understand their condition.

Text:
The European Network for Rare and Congenital Anaemias, ENERCA, has entered into the second phase after having been approved for granting by the Public Health Directorate of the European Commission. The first part of the project started in October 2002 and finished in April 2004 and it aimed at facilitating specific information about rare anaemias for patients as well as for doctors, scientists and other professionals dealing with these diseases. The ENERCA web page was created during that period and provides specific information aimed at two target groups; the public part for patients and the extranet with restricted access for professionals. A further objective was to promote cross-border cooperation between experts in Europe in order to establish the basis for implementing the ambitious aims of the second phase. ENERCA II started in September 2005 and will run for 36 months. 12 experts from 7 European countries have already consolidated the international cooperation. The main objective is to contribute to the improvement of awareness on rare anaemias by measures in:

1. Health information. Referral laboratories and experts are identified in order to provide best professional assistance throughout Europe. Information that is easy to understand by patients is available. The medical alert card MAC for patients is promoted. There is an on-line forum for professionals where exchange of information can take place.

2. Epidemiological surveillance. Available data on rare anaemias in Europe will be evaluated and systematic screening will be encouraged.
3. Establishing harmonized European training. This is planned for professionals in order to improve their understanding of molecular and genetic mechanisms in rare anaemias.


5. Keeping the web site updated. The web page is under constant revision in order to complete information in both the public part and the extranet.

The Spanish hereditary haemorrhagic telangiectasia (hht) unit

Authors: Dr ROBERTO ZARRABEITIA - HHT UNIT COORDINATOR, HOSPITAL SIERRALLANA, TORRELAVEGA (CANTABRIA), SPAIN

Keywords: Hereditary Haemorrhagic Telangiectasia (HHT), Rendu Osler Weber

Summary:
The Spanish HHT Unit begun to work in 2002. It offers clinical approach, genetic test, molecular research and it is supported by the Spanish Association of HHT patients. The aim is to offer the widest attention for HHT patients. New projects on quality and cooperation networks are been held.

Text:
Hereditary Haemorrhagic Telangiectasia (HHT) or Rendu Osler Weber (OMIM 187300/600376/601011/610655) is a rare disease with autosomal dominant inheritance causing vascular dysplasia leading to telangiectasias and arterio-venous malformations. Clinical criteria to diagnose HHT are based on the presence of epistaxis, telangiectasias, internal organ involvement and familiar history (Shovlin et al. Am J Med Genet 2000;91:66-7).

Several HHT centres have been created worldwide sponsored by the HHT International Foundation. In 2002, the Spanish HHT Unit began to work based on three structures:

1. Reference Hospital (Hospital Sierrallana. Torrelavega. Cantabria): we offer HHT screening procedure (blood tests, X Ray, abdominal ultrasound, thoracoabdominal multisliced CT, brain angioMRI, contrast Ecocardio, capilaroscopy, QOL survey and evaluation by ENT, Ophtalmology, Neumology, Gastroenterology and Rheumathology). We provide specific treatments (including interventional radiology), and follow up. Genetic test, counselling and embryonic preimplantation selection are available.
2. Molecular Research (Centro Investigaciones Biológicas. CSIC, Madrid) : we perform investigation on molecular basis, models with blood outgrowth endothelial cells and genetic therapy using mice, supported with grants from the Sanitary Investigation Funds, National Investigation Program and Ramón Areces Foundation. Members of CIBERER (Spanish network of groups studying rare diseases).

3. Spanish Patient’s Association and its web site www.asociacionhht.org : providing update of information and resources for families in Spanish and Portuguese, yearly meeting, promotion of collaboration with European associations. Member of FEDER (Spanish Federation of Rare Disease Associations). Projects in course :

   a) Certification in ISO 9001 as a method to improve standards of quality in clinical care and as a previous phase to get the nomination as a national reference centre for HHT (Spanish Health Ministry law 1302/2006).

   b) Development of a European network of HHT Units : VIIth European framework program (Public Health/Health Program) 2nd call.

Summing up, our aim is to offer the widest possibilities of diagnosis, treatment and prevention for HHT patients.

**European Research Networks**

**Ocular manifestations of rare metabolic diseases**

**Authors** : Dr Pedro Alves-Faria, Porto, Portugal

**Keywords** : metabolic diseases

**Summary** :
Although an accurate biochemical diagnosis is essential for the diagnosis of this group of diseases, systemic and ophthalmic findings are necessary to make us suspect their existence. The wide range of ocular findings shows how difficult it is to diagnose this group of diseases.

**Text** :
Introduction : Metabolic disorders are usually inherited autosomal recessive diseases in which there are an abnormal function of several enzymes in the
cellular metabolic pathways, which are critical to normal cellular function, growth, and development. Ophthalmic manifestations sometimes are characteristic of the underlying metabolic disease and its detection is important for the correct diagnosis. Diseases associated with lipid metabolism have several types and subtypes with a very different clinical presentation. Methods: The authors studied eleven patients with gangliosidosis, Krabbe disease and mannosidosis, who were referred to the Ophthalmology Department of Hospital São Joao. The possible existence of ocular manifestations was examined by means of biomicroscopic and fundoscopic examinations, OCT and electrophysiological examinations. Results: These patients have a very wide spectrum of visual impairment and different degrees of neurological involvement. Even within the same disease there were differences in the clinical presentation. Fundoscopic examination ranges from normal to showing typical alterations with diffuse pallor. Electrophysiological alterations were detected in all patients. There was a case of congenital cataract.

Conclusions:
This is a very rare group of diseases with distinct clinical presentation, usually associated with decreased visual acuity. Although an accurate biochemical diagnosis is essential for the diagnosis of this group of diseases, systemic and ophthalmic findings are necessary to make us suspect their existence. The wide range of ocular findings shows how difficult it is to diagnose this group of diseases.

Epidemiology of Cornelia de Lange Syndrome in Europe – Population based data

Authors: Prof Ingeborg Barisic, Dr Visnja Tokic, Dr Maria Loane,
Department of Paediatrics, Children's University Hospital Zagreb, Croatia
Keywords: Cornelia de Lange syndrome

Summary:
Descriptive epidemiological population-based data on Cornelia de Lange Syndrome from 33 EUROCAT congenital anomaly registries (16 European Countries)

Text:
Cornelia de Lange syndrome (CdLS) is a rare genetic syndrome characterized by the specific facial dysmorphism, hypertrichosis, upper limb deficiency, intrauterine growth retardation, developmental delay and a variety of associated malformations. The particular clinical features make severe
forms of the syndrome easily recognizable. We have analysed the population-based data extracted from the database of EUROCAT (European Surveillance of Congenital Anomalies), a large European network of birth defect registries that use the same epidemiological methodologies. The study is based on the 23-year (1980-2002) monitoring covering 8,558,346 births from 16 European countries. We found the prevalence of the classical form of CdLS to be 1.24/100 000 births and estimated the overall CdLS prevalence at 1.6-2.2/100 000 or 1:80,645 births. There were 91.5% (97/106) live born infants with high first week survival (91.4%). Termination of pregnancy following prenatal diagnosis was performed in 5.7% (6/106) cases, and 2.8 % (3/106) were foetal deaths. Prenatal detection rate of abnormalities in CdLS cases was 32.1% in the last eleven years. The most frequent associated congenital malformations were limb defects (73.1%), congenital heart defects (45.6%), central nervous system malformations (40.2%) and cleft palate (21.7%). Almost 70% of infants, born after the 37th week of gestation, weighed ≤ 2500 g. Low birth weight correlates with a more severe phenotype. All patients were sporadic. Maternal and paternal ages do not seem to be risk factors for CdLS and no evidence of exposure to consistent teratogenic agents was noted.

The GITER group and the treatment of rare diseases in Spain

Authors: Francesc Bonet Clols, Investigador, Barcelona, Spain

Keywords: Orphan drugs

Summary:
The group GITER focuses on the research of rare diseases therapeutics and have found information about the treatment of 59 diseases and 899 patients, with the collaboration of hospital pharmacies and through surveys for patients. GITER also develops other activities.

Text:
Objective
Introducing the activities of GITER (Rare Diseases Therapeutics Research Group) included in REPiER (Epidemiological Network on Rare Diseases research) that looks for a greater knowledge of rare diseases pharmacological treatment.

Results
The group GITER has focused its research on the study of the treatment of Rare Diseases in paediatrics, with the collaboration of different hospital
pharmacies placed in various Autonomous Communities, paying special attention to the pharmaco-economic aspects of treatments. Simultaneously, a study on therapeutic needs for rare diseases has been carried out through surveys for patients of different rare diseases, in cooperation with the Spanish Alliance for Rare Diseases (FEDER) and other nodes of REPiER. Part of these results allows complementing the pharmaco-therapeutic and pharmaco-economical study of treatment costs carried out with pharmacy hospitals, especially in the case of diseases treated in out-patient departments. We have obtained information on the treatment and costs of 59 diseases, mainly metabolic, with a total of 899 patients, although the number of cases of most diseases has been very few. The study allows knowing the importance of orphan drugs in Spain and their economic impact in the cost of rare diseases. When an orphan drug is used represents an average of 84% of pharmacological treatment cost. The actions of GITER also include the assessment to the Institute of Research on Rare Diseases (IIER) on orphan drugs, including the participation of members of the group in various books about rare diseases. A webpage on legislation of orphan drugs has been developed and GITER also collaborates on the webpage of REPiER with the elaboration of a database on orphan drugs and their situation in Spain. Finally, GITER collaborates in the elaboration of the EuOrphan webpage providing information on medicinal products for rare diseases.

Figures 67: Participants in ECRD 2007
**Major variations in the prevalence of autosomal recessive disorders: lessons from Bradford.**

**Authors:** Dr Peter Corry - Bradford Teaching Hospitals
NHS Foundation Trust, Bradford, United Kingdom

**Keywords:** Autosomal recessive, ethnic variation, resources, research.

**Summary:**
Very high rates of autosomal recessive disorders have been identified in British Pakistani communities. Increases are likely in other minority community groups in Europe. Health authorities must recognise that prevalence varies considerably and target resources at areas of need. Appropriate and sensitive measures for prevention should be considered. However, there are opportunities to target both clinical and genetic research.

**Text:**
Background. Carrier rates for autosomal recessive conditions vary in different communities. Cystic fibrosis gene carriage is common in Europeans while genes for thalassaemia are common in Mediterranean and Middle Eastern peoples. The actual prevalence of disease is also influenced by marriage patterns, particularly consanguinity and endogamy.

Settings. Bradford is a city of about 370,000 inhabitants in Northern England. In recent decades there has been significant immigration from Pakistan. This is a young population and now accounts for nearly half of births. A majority of Pakistani marriages are consanguineous, with first cousin unions being favoured. However, this is against a background of cousin marriages in previous generations and a preference for marriages within the biraderi or clan (endogamy).

Findings. It is thought that autosomal recessive disorders are more than 10 times more prevalent in Bradford’s Pakistani children. Nearly 150 of these conditions have been identified in our population. Inborn errors of metabolism, deafness, primary microcephaly, platelet and coagulation disorders all show large increases. A British study of neurodegenerative disorders notes that 8% of UK cases are from Bradford. However health service funding often fails to reflect these numbers.

Clustering of otherwise very rare conditions enables clinical and genetic research. For instance, major advances in the understanding of human brain development have followed local research into the causes of primary microcephaly.
Summary. Very high rates of autosomal recessive disorders have been identified in British Pakistani communities. Similar increases are likely in other minority ethnic groups in Europe. Health authorities must recognize that prevalence varies considerably and target resources at areas of need. Appropriate and sensitive measures for prevention should be considered. However, there are opportunities to target both clinical and genetic research.

**Mutational and multimeric study in patients with types 2 von Willebrand’s Disease (vWD2)**

Authors: Teresa Fidalgo - Centro hospitalar Coimbra-Departamento de Hematologia, Coimbra, Portugal

Keywords: Von Willebrand Disease type 2

Summary:
Functional, multimeric and molecular characterization of 10 unrelated patients with vWD2 attending to Centro Hospitalar Coimbra Haemophilia Centre.

Text:
VWD2 has the subtypes: 2N- defective binding of vWF to factor VIII and low FVIII/FvWAg ratio with mutations in the FVIII-binding domain (D), (D/D’-D3); 2A, 2B and 2M - discrepancy between the level of vWF :Ag and the vWF :Act or vWF :CBA. vWD2A have no high molecular weight vWF multimers (HMWM) and mutations in D/A1-A2. vWD2B is associated a thrombocytopenia, caused by gain-function mutations within D/ A1. vWD2M is defined by a low platelet-dependent function with normal HMWM and mutations in D/A1. Aim- Functional and molecular characterization of 10 unrelated patients with vWD2 attending our Haemophilia Centre. Methods- The vWF function was studied by ELISA; RIPA; multimeric structure of VWF SDS-agarose electrophoresis with automatic densitometry. vWF gene, exons 18-25 and 28 were studied by direct sequence of PCR fragments. Results- 4 vWD2N have FVIII :C/binding site mutations: 3 homozygous (Hmz) R854Q and 1 heterozygous (Htz) R816W. Among the 6 patients with a VWF :RCo/VWF :Ag ratio < 0.7 and absence of HMWM, 5 mutations were identified in exon 28, in the Htz state: 2A S1506L, I1628T and C1272F (not previously be described); 2B R1306W; 2M F1369I and S1378F. Discussion- 2N patients, R854Q, have a moderate phenotype; one was originally diagnosed as mild haemophilia A. In 2N R816W the Htz does not explain reduced FVIII levels and the absence of vWF :VIIIB. The absence of other mutations suggests a null allele. The new 2A C1272F muta-
tion, located in the first cysteine of C1272-C1458 loop, probably .2A mutations S1506L, disrupt an important interaction region vWF/GPIb I1628T at D/A2 have multimer pattern according to the vicinity of ADAMTS13 Y1605/M1606. In 2M the abnormal multimer pattern is most probably due to mutation S1378F. In our experience, multimer analysis is very useful to draw the strategy for the vWF molecular studies in order to differentiate the VWD subtypes.

**Assessment of Thyroid Function in Multi-Transfused Thalassemia Patients**

**Authors**: Farideh Jalali Farahani - Iranian Blood Transfusion Research Centre, Tehran, Iran

**Keywords**: Thalassemia Major-Ferritin-Subclinical Hypothyroidism-Primary Hypothyroidism-Thyroid Function-

**Summary**: The main objective of this study was to estimate the prevalence of thyroid dysfunction in patients including both thalassemia major and thalassemia intermedia. The following items were recorded in their questionnaire: sex, age, kind of thalassemia (major or intermedia), dose of received deferoxamine, serum thyroid hormones, and ferritin Levels. Then correlation of thyroid functional status with age, serum ferritin level, and dose of received deferoxamine, was evaluated. We had 178(91.3%) thalassemia major and 17(8.7%) thalassemia intermedia. 162 (83.1%) patients were Euthyroid, and 27 (13.8%) had subclinical hypothyroidism (Confidence interval= 9-18.6%), and 6(3.1%) were primary hypothyroid (Confidence interval =0.7-5.5%). Mean ferritin levels in the above groups were for Euthyroid group= 1923 +/- 1470 ng/ml, subclinical hypothyroidism = 1723 +/- 1346 ng/ml, primary hypothyroidism= 1569 +/- 734 ng/ml respectively. Mean dose of received deferoxamine was 21.9 +/- 13.5 mg/kg/day in Euthyroid patients, and 19.2 +/- 10.6 mg/kg/day in subclinical hypothyroidism, and 21.6 +/- 8.7 mg/kg/day in primary hypothyroidism. No significant correlation was found between abnormal thyroid function and serum ferritin levels (p=0.55), deferioxamine dose (p=0.33) and age (p=0.11).

**Text**

Objectives: Despite improved haematological care, multiendocrine dysfunction is a common complication in thalassemia patients. The main objective of this study was to estimate the prevalence of thyroid dysfunction in
patients including both thalassemia major and thalassemia intermedia. Method: A questionnaire was designed for 195 referral patients from the thalassemia clinic. The following items were brought up in the questionnaire: sex, age, kind of thalassemia (major or intermedia), dose of received deferoxamine, serum thyroid hormones, and ferritin levels. Patients were divided into 3 groups based on serum thyroid hormones levels: Euthyroid, Subclinical hypothyroid and Primary hypothyroid. Then, the correlation of thyroid functional status with age, serum ferritin level, and dose of received deferoxamine, was evaluated. Results: We had 178 (91.3%) α thalassemia major (50.6% male, 49.4% female) and 17 (8.7%) thalassemia intermedia (23.5% male & 76.5% female). 162 (83.1%) patients were Euthyroid, and 27 (13.8%) had subclinical hypothyroidism (Confidence interval = 9-18.6%), and 6 (3.1%) were primary hypothyroid (Confidence interval = 0.7-5.5%). Mean ferritin levels in the above groups were for Euthyroid group = 1923 +/- 1470 ng/ml, subclinical hypothyroidism = 1723 +/- 1346 ng/ml, primary hypothyroidism = 1569 +/- 734 ng/ml respectively. Mean dose of received deferoxamine was 21.9 +/- 13.5 mg/kg/day in Euthyroid patients, and 19.2 +/- 10.6 mg/kg/day in subclinical hypothyroidism, and 21.6 +/- 8.7 mg/kg/day in primary hypothyroidism. No significant correlation was found between abnormal thyroid function (subclinical and primary hypothyroid) and serum ferritin levels (p=0.55), deferoxamine dose (p=0.33), age (p=0.11). Conclusions: Although no significant correlation between thyroid functional status and serum ferritin level was found, further studies in larger sample size of thalassemia patients and evaluation of the other factors associated with thyroid functional are recommended.

Rare Bleeding disorders: database and security issues

Authors: Mr Paolo Lanzi - Alekos Scarl, Milan, Italy

Keywords: European network for rare bleeding disorders database

Summary:
Database application and security for the EN-RBD Project

Text:
The aim of the EN-RBD application is to give out a tool to collect information on Rare Bleeding Disorders patients, by editing and viewing patients’ data, and performing data extraction through a query system, thus giving particular care to data security and privacy, through authentication, authorization and tracking.
We are using a web client-server technology: a database server (MySQL, a free RDBMS) and a web server to run the application (Apache, with PHP scripting, SSL encryption and authentication certificates), in order to enable any browser on any platform as a client. The application has a navigation style based on the web standard, and a contextual on-line help manual can be used at any point in the application.

Application data are aimed on the patient, but, according to European privacy laws, the main form contains limited personal data (city of origin, date of birth and an ID number), in order not to allow a direct identification of the patient. Other linked tables contain specific data about deficiency type, phenotype analysis, genetic analysis, samples collection, a template for calculating the “Bleeding Score”, bleeding symptoms, surgery management, and other diseases. To update or insert new data, the user is required to perform an action (by clicking on a webpage button), in order to avoid accidental data modifications. Some caption tables support these data, by listing the available choices. Some caption tables can be expanded by adding options to these lists.

Administration data are managed by the database administrator and contains users' and operators' data, password management, queries management, and contextual on-line help guide editing.

To view and extract data, a list of queries is available to the user. According to the user's need, the administrator can create new specific queries.

Possibilities of evolution in distal renal tubular acidosis – observation of two patients in a family

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Keywords: renal acidosis, evolution

Summary
Distal renal tubular acidosis is a rare genetic disease with the possibility of a favourable outcome.

Text
Introduction. Distal renal tubular acidosis is a rare genetic disease, inherited in a predominantly autosomal recessive manner, but the autosomal domi-
nant inheritance is also possible, with a potential evolution towards severe complications or an infaust evolution in the absence of therapy. Clinical observation. In a family, two children, a boy and a girl, were diagnosed with distal renal tubular acidosis. Diagnosis was made at the age of 18 months, 8 months, respectively. Both children had polyuria and growth delay. Diagnosis was established based on the following criteria: clinical (polyuria, bone deformities, statural retardation), bio-humoral (metabolic acidosis, dyselectrolytemia: hypopotassemia, hypophosphatemia, hyperpotassiuia, hyperphosphaturia, high alkaline phosphatase), and imaging (bone mineralization disorders, nephrocalcinosis). The evolution of the two cases was different: in the case of the boy, inconsistent treatment caused renal failure, resulting in death at the age of 11 years. In the case of the girl, treatment (consisting in the preparation of sodium bicarbonate, potassium chloride, disodium phosphate, and vitamin D) although was accepted only at the age of 9 ½ years, when some of the disease complications: (nephrocalcinosis, hypophosphatemic rickets, and short stature) were already present, the results were satisfactory (resumption of statural growth, weight gain, clear improvement in Astrup parameters and normalization of the ionogram).

Conclusions: The observation presented emphasizes the possibility of a favourable outcome in a severe genetic disease.

Rare diseases in Norway: registering incidence and prevalence

Authors: Mr Mitchell Loeb, Ms Lisbet Grut - SINTEF Health Research, Oslo, Norway

Keywords: incidence, prevalence, register data, ICD-10, Norway

Summary:
In this project several national data registers are used to provide estimates of register-incidence and register-prevalence of 28 selected rare diseases in Norway over a period from 1999 - 2004.

Text:
This project aims at providing increased knowledge and understanding on incidence and prevalence of selected rare diagnoses in Norway through the use of national data registers.

Norway is in the rather unique position of having extensive database registers for the entire population. Among these are the national Birth Register, the national Death Register, and a national register that records recipients from The National Insurance organisation. Each of these registers includes
an individual’s unique Personal Identification Number (allowing for record linkage) and diagnosis information through the use of the ICD-10 classification system.

In addition a National Patient Register records all admissions to all hospitals in the country. This register also includes ICD-10 information but does not allow for patient identification or record linkage.

Making use of expertise in the field of rare disorders and the ICD-10, 28 diagnoses were selected for inclusion in this project. Each of these was identified by one or more ICD-10 codes.

Record linkage allowed us to provide estimates of incidence and prevalence based on cases registered in one or more of the above national registration systems. We describe the ‘register-incidence’ and ‘register-prevalence’ of these 28 rare diseases in Norway during the period 1999 - 2004. We present the challenges to undertaking a registration exercise based on register data, in particular the need for consistency and precision in registering rare diseases – the fewer the cases the greater the precision required; as well as the strengths and weakness inherent in using the ICD-10 for classifying rare diseases.

Translational Research in Europe - Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD)

Authors: Dr Stephen Lynn, Prof Volker Straub, Prof Kate Bushby
- TREAT-NMD, Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne, United Kingdom

Keywords: Network of Excellence

Summary:
TREAT-NMD is a European neuromuscular network addressing the fragmentation currently hindering translational research for cutting edge therapies in rare neuromuscular diseases.

Text:
The TREAT-NMD (Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases) network of excellence is an FP6-funded project that aims to address the fragmentation across Europe that currently hinders translational research for new cutting-edge therapies in rare inherited neuromuscular disease. The network brings together academics, clinicians, and industry representatives from 11 European coun-
tries, in partnership with patient organisations, to deliver new treatments for patients with these devastating disorders. Currently, TREAT-NMD is the only disease-specific EU-funded Network of Excellence in rare disease and commenced in January 2007. Initially, muscular dystrophies and spinal muscular atrophy will be specifically targeted. There are a number of barriers and challenges facing the neuromuscular community and the aims of TREAT-NMD are to bring cutting edge therapies into the clinic by addressing the lack of standardised protocols for preclinical animal studies, molecular diagnoses and patient assessment and management. The TREAT-NMD objectives are to:

1) Integrate tools, methods and knowledge for adapted and efficient NMD treatment. This will include creating a Coordination Centre to oversee research, communication and management of the network. The Coordination Centre will be the hub for all the Centres of Excellence and associated technological platforms and will assist in the translation of new drugs into practice.

2) Accelerate and optimise research outcomes for NMD treatment. This will include toxicology and safety assessment for production of clinical grade materials for clinical trials. Developing standards of care and diagnosis and defining outcome measures for clinical assessment.

3) Ensure the spread of excellence both across Europe and globally, through implementing a dedicated communication platform to address training and education needs, and to promote the participation of Eastern European countries.

All the objectives for TREAT-NMD will be established within the 5-year duration of the network, and will be sustained through the Coordination Centre, which will be a permanent and self-sustaining structure for the European neuromuscular community.
DEFI: A French National Network on Adults with Primary Hypogammaglobulinemia

Authors: Dr Eric Oksenhendler - Hopital Saint-Louis, Paris, France
Keywords: Primary Immune Deficiency; Hypogammaglobulinemia; CVID

Text
DEFI is a national prospective study on primary hypogammaglobulinemia in adults.

The main initial objectives were to promote a national network of clinical centres, immunological and clinical studies, diagnosis in families and genetic screening.

From April 2004 to May 2007, 341 patients and 336 first degree relatives were included in 37 clinical centres. Standardized clinical and immunological data are centralized in a computerized database. Serum, PBMCs and DNA from patients and relatives are stored in a duplicate Biological Resource Bank.

CVID represents the most important diagnostic group: 252 pts (110 M / 142 F): 200 sporadic and 52 familial cases. Most patients were of European Caucasian ancestry.

Initial symptoms: Median age was 19 y. (0-77) and URTI were the most prevalent symptoms: bronchitis 38%, sinusitis 36%, pneumonia 20%. Autoimmune cytopenia 10%, adenopathy and/or splenomegaly 6%. Diarrhoea 7%.

Symptoms at diagnosis: Median age was 34 y. (0-77) and URTI were still the most prevalent symptoms: bronchitis 28%, sinusitis 21%, pneumonia 31%, bronchiectasis 14%. Autoimmune cytopenia 9%, adenopathy and/or splenomegaly 8%. Diarrhoea 7%.

The median delay for diagnosis was 6.9 years. In 28% of the patients, the symptoms had started before the age of 15y while the diagnosis of Primary Immune Deficiency (PID) was established during childhood in only 12%.

Genetic studies: PID usually observed in children were detected or confirmed in 14 XLA, 2 XLP and 4 HIGM. TACI gene sequencing revealed homozygous mutations in 7 patients and a high frequency (27 patients) of heterozygous mutants.
CVID is the most frequent PID with hypogammaglobulinemia in adults. Symptoms often started during childhood but the diagnosis was often delayed to the third decade of life. DEFI is a large national network that provides, standardized, prospectively collected, data and material for clinical and research studies on PID in adults.

**THAOS - Transthyretin-Associated Amyloidoses Outcomes Survey, A New Global, Web-Based Registry**

**Authors**: Dr Ole B. Suhr - Umeå University Hospital, Umeå, Sweden

**Keywords**: Transthyretin, Transthyretin-associated amyloidosis

**Summary**
THAOS is a new global, multi-centre, longitudinal observational survey (registry) designed to characterize the variability, progression, and natural disease history, regional differences in disease expression, and the genotypic-phenotypic relationship in TTR amyloidosis.

**Text**
Available data suggest variability in the natural history of TTR-amyloidosis (ATTR), particularly between genotypes and geographic locations. TTR amyloidosis is caused by dissociation of the TTR tetramer into monomers that misfold due to genetic mutations or aging, and ultimately form amyloid deposits in various organs. There are over 80 known mutations of TTR, which result in variable phenotypic expressions of amyloidosis that commonly affect the peripheral nerves, heart, kidney, or vitreous.

The hereditary forms of TTR amyloidosis (ATTR) are autosomal dominantly inherited diseases with variable penetrance. Symptom onset varies but is usually in the third to fifth decade of life, and consists most commonly of peripheral and autonomic neuropathy and/or a restrictive cardiomyopathy. Survival for most mutations is 9-13 years after onset. Currently, the only disease-modifying therapy for ATTR is orthotopic liver transplantation. Wild-type TTR amyloidosis is characterized primarily by a restrictive cardiomyopathy that predominantly affects elderly males (>70 years of age). TTR amyloidoses are rare diseases, though the ATTR-V122I-mutation that is associated with restrictive cardiomyopathy is found in approximately 4% of the African-American population.

THAOS is a new global, multi-centre, longitudinal observational survey (registry) designed to characterize the variability, progression, and natu-
ral disease history, regional differences in disease expression, and the geno-
typic-phenotypic relationship in TTR amyloidosis. The ultimate goal is
to better understand, manage and treat patients with TTR amyloidosis.
This registry will collect data for up to 10 years on the most relevant ex-
pressions of TTR amyloidosis, including medical and transplant history.
The physical assessment will include cardiac and neurological examina-
tions and renal/bladder function. Quality of life will be assessed by EQ-
5D and Norfolk-QOL-DN questionnaires. Hospitalizations and medica-
tion use will also be recorded. The registry is web-based, with ongoing
data analysis and publications coordinated by an international group of
amyloid experts.

Screening of subtle copy number changes in Aicardi syndrome
patients with a high resolution X-chromosome array-CGH

Authors: Saliha Yilmaz, Hervé Fontaine, Karène Brochet - Nancy-
Université, Laboratoire de Génétique, EA4002-IFR111, CHU
de Nancy-Brabois, Vandoeuvre les Nancy, France
Keywords: Aicardi syndrome, array-CGH, X chromosome

Summary
This study reports for the first time the use of a full coverage X-chromosome
array to screen for imbalances in 18 Aicardi syndrome patients.

Text
Aicardi syndrome is an uncommon neurodevelopment disorder affecting
almost exclusively females. Chief features include infantile spasms, corpus
callosal agenesis, and chorioretinal abnormalities. Aicardi syndrome is a
sporadic disorder and hypothesized to be caused by heterozygous muta-
tions in an X linked-gene but up to now without any defined candidate
region on the X chromosome. Array based comparative genomic hybridi-
sation (Array-CGH) has become the method of choice for the detection of
micro deletions and micro duplications at high resolution. In this study, for
the first time, 18 Aicardi syndrome patients were analyzed with a full cover-
age X-chromosomal BAC arrays at a theoretical resolution of 82 kb. Copy
number changes were validated by real time quantitation (qPCR). Copy
number polymorphisms were noticed but no disease-associated aberra-
tions were identified. For such conditions as Aicardi syndrome, in which
there are no familial cases, additional patients should be studied in order
to identify rare cases with sub microscopic abnormalities, and to pursue a
positional candidate gene approach.
Information Services

Orphanet: achievements and new challenges

Authors: Dr Ségolène Aymé, Dr Ana Rath, Dr Valérie Thibaudeau, Dr Matthieu Levi-Strauss, Bruno Urbero, Marc Hanauer, Orphanet, Paris

Keywords: Orphanet, orphan drugs, rare diseases, database, clinical trials, specialised clinics, directory of services, encyclopaedia, OrphaNews, prevalence, research projects, diagnostic laboratories

Summary
Orphanet is a freely accessible database dedicated to information on rare diseases and orphan drugs with the aim of improving the diagnosis, care, and treatment of patients with rare diseases.

Text
Orphanet is a freely accessible database dedicated to information on rare diseases and orphan drugs with the aim of improving the diagnosis, care, and treatment of patients with rare diseases. Run by a consortium of 35 partners and managed by the Orphanet France team in Paris, France, all partners adhere to a common quality charter to provide patients and health professionals with the highest quality of products. An expert-authored, peer-reviewed Encyclopaedia covers over 5,000 diseases. All articles are written in English and abstracts are progressively translated into the 6 languages of the website: English, French, Italian, Spanish, German and Portuguese. The 35 national teams are in charge of collecting rare disease service information at the country level to produce a Directory of Services which includes information on specialised clinics, clinical laboratories, research activities and support groups. For the benefit of health professionals, the website offers a clinical sign search tool to assist in the diagnosis of rare diseases. A clinical trial registration tool allows patients to register as volunteers to participate in research projects. This service aims at speeding up the enrolment of patients in clinical research. The Orphanet France team also manages The Orphanet Journal of Rare Diseases and publishes a newsletter, OrphaNews Europe, which serves as the electronic newsletter of the European Commission’s Rare Diseases Task Force for over 7,000 readers. The Orphanet website is accessed by over 25,000 distinct users every day, half of which are health professionals and one third of which are patients and their families. Other end-users include teachers, students, journalists, industry managers or interested people. To better serve its audience, Orphanet has recently established new services in the field of documentation which will be presented.
Involving Patients in the process of producing information material: the Rikshospitalet hospital experience in Norway

Authors: Ms Birgitte Bjerkely, Mr Mads Bjerke - Rikshospitalet University Hospital, Oslo, Norway

Keywords: Patient participation, Information material

Summary
This poster presentation will illustrate the way in which this patient participation and influence takes place throughout the process of producing information material.

Text
Patient participation on different levels in the Norwegian health care system has been a major issue for the government over the last 15 years. The legislation states that the patient’s voice is a key element in developing health care services for the public.

Both individuals and patient’s organizations have the opportunity to influence on the services they can rightfully claim, using their experiences and opinions.

Centre for Rare Disorders at Rikshospitalet University Hospital is a national interdisciplinary resource centre which offers assistance to anyone, both patients and their health- and support network, affected by one of the 50 rare diagnoses that are assigned to us by the health care government.

The Centre cooperates methodically with patients and their families towards a systematic collection of patient insight. We use this important tool to reach the best possible solutions for both individuals and groups of patients.

Producing, developing and distributing information concerning the diagnoses in question is one of the Centres main objectives. Centre for Rare Disorders has developed a model for this kind of patient participation in the making of information material, where the patient’s involvement in the project from start to finish is one of the main targets. The patients play a major role in this respect, contributing with their experience and ways of making the material useful for both other patients and their health- and support network. The production phase starts with an initial brainstorming, attended by a widely composed reference group, followed by several quality assurances.
The ORPHANET Directory of Services: Activities Related to Rare Diseases Across the United Kingdom

Authors: Emma Gillaspy - Nowgen, University of Manchester, Manchester, United Kingdom

Keywords: Orphanet

Summary
This publication presents the data on rare disease-related activities that has been collected to date from across the United Kingdom. This data has been added to the Orphanet website which is the European portal of rare diseases.

Text
Orphanet (www.orpha.net) is the EC-funded online resource for rare diseases and orphan drugs. Orphanet aims to contribute to the improvement of the diagnosis, treatment and management of patients through a website which features a rare diseases listing and a directory of services alongside other specialised products. The website, now the largest of its kind in the world, is accessed daily by 25,000 users from 170 countries. The Orphanet consortium consists of partners from 35 countries including the UK. Each partner is responsible for gathering information from their respective countries for the online directory of services. To date, in excess of 25,000 activities related to rare diseases from the 35 countries have been added to the directory. The Orphanet UK team have so far collected more than 1800 UK activities for the directory comprising:

- 245 specialised outpatient clinics covering the possible treatment of 2889 rare diseases
- 888 diagnostic tests for 485 different rare diseases
- 224 patient organisations supporting families affected by up to 1392 rare diseases
- 305 research projects investigating 438 rare diseases
- 57 research projects investigating 71 rare diseases
- 84 professional networks covering 872 rare diseases
- 20 disease registries covering 200 rare diseases
- 84 professional networks

In summary, activities from 865 people operating from 957 UK locations have been added to the Orphanet directory of services. This represents good coverage of the ongoing UK activities which are related to rare diseases. The directory is a vital part of the service Orphanet provides. It aids health professionals and patients by providing information on currently available clinical and laboratory diagnostic services. It also facilitates collaboration in the research and development of future treatments for rare diseases. Finally, it allows patients and their families to feel less isolated by providing the means to find relevant support organisations.
The Swedish Rare Disease Information Database and The Swedish Information Center for Rare Diseases

Authors: Christina Greek Winald, Birgitta Gustafsson, Lisbeth Högvik - The Swedish Information Center for Rare Diseases, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden

Keywords: rare disease information database patient families professionals researchers helpline organisations awareness

Summary
Summary The Swedish Rare Disease Information Database contains full text documents of 220 very rare diseases. New texts constantly being produced. The texts are also published in English. Cooperation with patient and parent organisations. The Centre also serves as a helpline and source of guidance. The centre is funded by the Swedish National Board of Health and welfare.

Text
The Swedish Rare Disease Information Database contains full text documents of 220 very rare diseases and new texts are constantly being produced. The texts are also published in English. At present there are more than 45,000 visitors to the site each month and the number of visitors is steadily increasing. The database is available on-line at www.sos.se/smkh

The aim is to increase awareness and understanding of rare diseases by offering detailed descriptions not only regarding medical information but also psychological, social and educational aspects. The information is produced in close cooperation with the most prominent experts in Sweden on the diagnoses. Patient and parent organizations supplement this information. A scientific advisory board reviews all information texts before they are published. The texts are continually updated and revised.
The Swedish Information Center for Rare Diseases is commissioned by the Swedish National Board of Health and Welfare to be responsible for the production of information material in the database and to provide assistance with information searching and retrieval. The centre also serves as a helpline and a source of guidance regarding rare diseases. Access to the database and the services provided by the centre are free for people with rare diseases and their families as well as for parent and patient organizations, professionals, researchers and public authorities.

The Swedish Information Center for Rare Diseases is run under the auspices of the Sahlgrenska Academy at Göteborg University and is funded by the Swedish National Board of Health and Welfare.

**The Adult programme at Agrenska a Centre of Competence for Rare Diseases**

**Authors**: Robert Hejdenberg, President Agrenska, Sweden

**Text**

Agrenska is a national centre of competence for rare diseases our aim is to build not only knowledge but to build competence among our target groups. By being a progressive and creative meeting place between needs and knowledge we contribute to spreading information to our target groups children, adults and families as well as to professionals. By our method of working in several dimensions:

- Knowledge transfer from experts in a number of fields concerned
- Exchange of experiences
- Reflections

The ambition with our programmes is to build competence/capability for life.

Since 1989 Agrenska has developed programmes for children and adults with rare diseases, their families and professionals concerned. We want to contribute and provide knowledge to the families to enhance the coping process. Agrenska strives to both develop and make proper tools available to patients suffering from any rare disease, in order to improve their everyday life.

The Adult programme

We run the Adult programmes since 2005 as a project (financed partly by The Swedish Inheritance Fund). During three to four days we run a development programme for adults with the same rare disease. The adult’s learn
about the medical, social, educational, and psychological aspects of their situation, we run 6 programmes per year.

During the programme an editor is documenting all lectures and the discussions. During a session we collect information of the everyday life consequences of having a rare disease, which we document and make available on our webpage. The target groups are people with rare diseases their relative’s professionals concerned and other interested.

Our experiences show that these unique programmes meet the needs for these groups, and they get empowered and better prepared to handle their everyday lives.

**Psychosocial (re)habilitation**

**Authors**: Monto M., Streng H., Suosalmi M. - Finnish Association of People with Mobility Disabilities, Lahti, Finland

**Keywords**: habilitation, rehabilitation, psychosocial rehabilitation, rare disabilities, mobility disabilities, empowerment, peer support, identity, interaction, family

**Summary**

Our presentation will report on the goals, contents and methods of psychosocial (re)habilitation. Also the significance for participants of courses organised during the period of July-October 2007 will be reported. Primary elements to be assessed are identity, empowerment, close personal relationships and interaction, peer activities and functional everyday life.

**Text**

Psychosocial (re)habilitation

For a family with a member with a rare disease or disability, proper examinations, diagnosing, therapies and medications are essential. These are basic requisites for the growth and development of the individual but only part of the total picture. In order to become empowered and find their own place in the family and society, a disabled/chronically ill person also needs psychosocial support and (re)habilitation. This gives him/her the possibility to develop as a person with solid self-esteem interacting with the environment and managing his/her own life. Also abilities and skills to use services are needed to make their everyday life functional.

Psychosocial (re)habilitation supports a person’s self-respect and overall wellbeing. Essential is to give him/her measures for empowering and
to advance and exercise social skills. Typical methods of psychosocial (re)habilitation are group discussions and activities, support by peers having experienced similar life situations, learning by doing, sharing of information and implementing it in one’s everyday life.

A resource centre for people with rare mobility disabilities and diseases is operating at the Lahti Rehabilitation Centre. One sector of activities is psychosocial (re)habilitation. Extensive know-how and know-why have accumulated over 18 years. Courses are usually for families, but also for youngsters and adults with without their families. Some courses have concentrated on the question of rareness and any person with a rare disability/illness may participate in these. On the other hand courses are also arranged for various diagnostic groups. The focus in these courses is the specific features of the diagnose.

Our presentation will report on the goals, contents and methods of psychosocial (re)habilitation. Also the significance for participants of courses organised during the period of July-October 2007 will be reported. Primary elements to be assessed are identity, empowerment, close personal relationships and interaction, peer activities and functional everyday life.

**Web-enabled System Design for Managing Clinical Information in Hemophilia Care**

**Authors** : Prof Leonor Teixeira - Universidade de Aveiro, Aveiro, Portugal  
**Keywords** : Haemophilia; Patient Treatment; Patient Registry; Home Therapy; Shared Care; Web Application; Design of Information System.

**Summary**
Nowadays, Information Systems combined with the Internet, have a significant role in data storage, as in the efficiency and promptness of data transfer and can offer a large contribute in managing and manipulating the information resulting from treatment and attendance of chronic patients, as haemophiliacs. On the other hand, the Internet also created the opportunity of patients to insert data concerning home treatments.

This paper briefly describes the design process of a Web-based information system to help the management of inherited bleeding disorders integrating, diffusing and archiving large sets of information from heterogeneous sources in scope of the haemophilia care at the Haematology Service of Coimbra Hospital Center, in Portugal.
Text

Healthcare is characterized by a highly complex environment where the process of patient care requires an unusual amount of communication between different health care professionals (HCPs). For a better patient care, the various HCPs have to cooperate, a processed often called shared care (Garde & Knaup, 2006; Schabetsberger et al., 2006). Nowadays, there is an increasing incorporation of a heterogeneous set of Information Systems - paper-based and computer-based - on the daily work of HCPs, in order to retrieve information about patients (Coiera, 2003; Van-Bemmel & Musen, 1997). The complexity of the patient care process combined with the heterogeneity of the information resources leads to a paradigm of data redundancy in the healthcare services in general, and haemophilia care in particular.

Haemophilia is a chronic disease that affects about 400,000 people worldwide; however, most of these people do not have access to adequate treatment (Evatt, 2005). A system for patient registry is a critical tool for monitoring, identification and diagnosis of these patients; furthermore, it serves as an essential tool for managing their treatment. A registry is a database or a collection of records of people identified as having haemophilia or inherited bleeding disorders. The purpose of a registry is to define the population demographics and collect observational data on specific haemophilia health concerns such as the prevalence of viral infections, factor inhibitors, and implementation of prophylaxis for children or different product usage (Baker, Laurenson, Winter & Pritchard, 2004).

Portugal, in spite of having about 1000 patients with haemophilia, doesn’t have a haemophilia national patient registry and most haemophilia treatment centres don’t have a specific system to store and manage information concerning this pathology.

In order to help the management of this information at the Haematology Service of Coimbra Hospital Center (in Portugal), as well as to facilitate communication between HCPs and patients and improve the utility and quality of clinical data and treatment information, a Web-based Information System under study is briefly presented in this work.
Innovating action proposed by Tous Chercheurs and the French-speaking Federation of DNA Schools: Practical training in biology and genetics for rare disease associations

Authors: Dr Marion MATHIEU - Tous Chercheurs, Marseille, France

Keywords: Tous Chercheurs, Federation of DNA schools, practical training in molecular biology and genetics, rare disease associations, researcher work, research specificities

Summary
In May 2004, the association Tous Chercheurs (initially named DNA school in Marseilles) developed innovative practical training for rare disease associations. These trainings help patients to acquire a good knowledge in biology and genetics, understand time scale and specificities of research, see research progress on their pathology. Between 2004 and 2006, Tous Chercheurs formed 130 patients from 13 different associations, highlighting that such an approach is meeting a crucial need and desire from patient associations. Since 2007, these sessions have been expanded to a national scale (France). Acting as initiator and catalyser of this type of training of patient associations, we look forward to extend this successful story to a Europe-wide level.

Text
Rare diseases associations have an essential role in informing patients about the scientific and medical implications of their disease. Moreover, they are increasingly interested in research, from which they hope to gain better knowledge and prevention of their disease. Because the time scales of research and patients waiting for treatments intrinsically differ, it is essential to train members of disease associations with the various aspects of research, in order to contribute to a closer relationship between the scientific community and these associations.

Accordingly, for the last 3 years, the association DNA school in Marseilles (renamed Tous Chercheurs since July 2007) has developed practical training in molecular biology and genetics for orphan genetic disease associations. These 3-days sessions take place in a laboratory where the trainees work “as” a researcher, together with tutors who are experienced research fellows. They learn to observe, formulate hypotheses, propose protocols and carry out experiments. In addition to the practical work, every session includes discussions with researchers specialized in the pathology under the scope of training. The trainees thus understand concretely how researchers work and their constraints.
Between 2004 and 2006, Tous Chercheurs formed 130 patients from 13 different associations, highlighting that such an approach is meeting a crucial need and desire from patient associations. At the same time, more and more associations want to benefit from these training sessions. To achieve this, and to make access easier for associations from all over France, it was essential to expand these sessions to a national scale. This was possible in 2007 thanks to the French-speaking Federation of DNA Schools, built around 6 members distributed throughout France, to whom we transferred our competences. Acting as initiator and catalyster of this type of training of patient associations, we look forward to extend this successful story to a Europe-wide level.

Centre for Rare Diseases in Bulgaria: a model for an integrated approach

Authors: Prof Rumen Stefanov - Information Centre for Rare Diseases and Orphan Drugs, Plovdiv, Bulgaria

Keywords: rare diseases policy, information centre, rare diseases awareness

Summary
The Centre for rare diseases in Bulgaria is presented as a successful model for integral rare disease approach that can be adapted and applied also in other countries.

Text
Healthcare systems in EU member states (MS) differ to great extent among countries in respect to their structure, organization and funding. What is common, that they are not ready to face the specific problems and needs of people with rare diseases for prevention, diagnosis, treatment and rehabilitation. Bulgaria is an example of a new MS with a substantial work and activities in the area of rare disease policy and organization, achieved in a very short time. At the end of 2004, the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) started as a project of a non-government non-profit organization (www.raredis.org). This Centre highlights the importance of working simultaneously in 6 main directions – information, education, awareness, support, networking and lobbying. Currently, a National health plan for rare diseases is in the process of review and approval. We present our Centre for rare diseases as a successful model for integral rare disease approach that can be adapted and applied also in other countries. To our opinion, MS health policy initiatives for rare diseases must be stimulated by the European commission, should germinate by initiative groups within the country and work in the suggested 6 directions.
New Treatment
and Orphan Drug Development

Access to the diagnosis
and treatment of patients with
mucopolysaccharidosis type I in Romania

Authors: Dr Camelia Al-Khzouz, Prof Paula Grigoresco-Sido - First Pediatric Clinic, Univ. of Medicine and Pharmacy Cluj, Cluj-Napoca, Romania

Keywords: MPZ tip I, ERT,

Text

Work hypothesis. Mucopolysaccharidosis type I (MPZ type I, Hurler disease) is a monogenic autosomal recessive disease, induced by a deficiency of the enzyme α-L-iduronidase, whose main characteristics are craniofacial dysmorphism, severe somatic retardation, organomegaly, progressive mental retardation that can develop into dementia, osteoarthropathy with flexion contracture, and corneal opacities.

Material. The authors present the clinical evolution of two siblings, V.P., female, aged 9, and R.P., male, aged 4, with the diagnosis of MPZ type I, who have received enzyme replacement therapy for 18 months.

Work method:
The diagnosis of MPZ type I suggested by the characteristic clinical picture was specifically confirmed by the dosage of leukocyte alpha-L-iduronidase. Treatment with Aldurazyme in a dose of 1 mg/kgc/dose was administered in i.v. perfusion at one week interval. The following parameters of the two children were monitored initially and at 6 months: clinical examination, somatometry, imaging examinations (radiological and ultrasonographic), biochemical tests, functional respiratory tests, ophthalmologic, neurological, and psychological examination.

Results:
The complete evaluation showed the following:
a) an improvement in craniofacial dysmorphism;
b) a reduction in the flexion contracture of the joints of limbs with a better joint mobility;
c) hepatic volume measured by imaging decreased from 2.04xN to 1.28xN in R.P., and from 1.82xN to 1.08xN in V.P.; spleen volume diminished from 6.9xN to 5xN in the boy and from 6.19xN to 3.2xN in the girl;
d) statural growth was resumed in the girl (6.5 cm/18 months) and became normal in the boy (9 cm/18 months); a weight gain of 4 kg, 6 kg, respectively, was found;
e) bone impairment was maintained at the same level in both children;
f) degenerative keratopathy was maintained constant in V.P. and improved in R.P.;
g) moderate psycho-intellectual retardation in the girl, mild retardation in the boy did not progress. The quality of life of the two siblings improved significantly.

Conclusions:
Enzyme replacement therapy with Aldurazyme, which has recently become available to patients with MP type I, has a favourable influence on the evolution and prognosis of these patients.

Treatment with biphosphonates in osteogenesis imperfecta. Experience of the 1st paediatric clinic Cluj

Authors: Dr Simona Bucerzan, Prof Paula Grigorescu-Sido - Ist Pediatric Clinic, Cluj-Napoca, Romania

Keywords: osteogenesis imperfecta, biphosphonates, children

Summary
In osteogenesis imperfecta, on pamidronate treatment clinical symptoms and occupational score improved, no more fractures occurred.

Text
Hypothesis and aims. Mutations of genes which encode type I collagen, cause bone fragility in osteogenesis imperfecta, different severity of clinical findings being explained by imperfect genotype-phenotype correlations. Recent research has contributed to a better understanding of pathogenesis but no efficient therapy is yet available. Theoretically, blocking osteoclastic bone resorption and enhancing osteoblastic bone formation can result in growth of bone tissue. Because treatment with aminobiphosphonates, which act by osteoclastic blockage, was recently introduced, the authors enrolled osteogenesis imperfecta patients from the records of the clinic in a therapeutic trial with pamidronate. Patients and methods. The study group included 5 patients (2 girls and 3 boys), aged between 6 – 16 years, recorded by the Center of Genetic Diseases of the 1st Pediatric Clinic as osteogenesis imperfecta patients. Study method consisted in physical examination, biohumoral assays regarding bone mineralization process, radiograms, osteodensitometry, assessment of
occupational score. Results. Between 4 and 13 cycles of pamidronate (preparation Aredia) treatment were administered, doses ranging between 0.75 – 0.89 mg/kg/day, provided by IV infusion, in 3 subsequent days, every 4 months. The drug was well tolerated, mild fever after the 2nd dose in 2 patients, was the only side effect recorded. Biohumoral parameters of phospho-calcic metabolism remained within normal limits, excepting not dosable alkaline phosphatase in a female patient who also associated hypophosphatasia tarda. Bone pain subsided and Z score improved. Conclusions. On pamidronate treatment clinical symptoms and occupational score improved, no more fractures occur.

Safety And Efficacy of Orally Administered Fx-1006A in Patients with Familial Amyloid Polyneuropathy (FAP): A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study

Authors: Dr Teresa Coelho - Serviço de Neurofisiologia, Porto, Portugal

Keywords: Transthyretin, Transthyretin-associated amyloidosis, Familial Amyloid Polyneuropathy, Fx-1006A

Summary
The safety and efficacy of orally administered Fx-1006A, a novel and selective stabilizer of both variant and wild-type transthyretin, are being evaluated for the treatment of Familial Amyloid Polyneuropathy in a Phase II/III clinical study, Fx-005.

Text
FAP is a rare, autosomal dominant sensory-motor and autonomic neuropathy caused by variant TTR deposition. Symptom onset is usually in the third or fourth decade of life, and death usually occurs within 9-11 years after onset. Currently, the only disease-modifying therapy for FAP is orthotopic liver transplantation. Fx-1006A is a novel, selective and potent stabilizer of both wild-type and variant TTR, with no NSAID activity. Fx-1006A, which is anticipated to provide disease modification and halt disease progression, is being evaluated in a Phase II/III study (Fx-005) in FAP patients.

Fx-005 is a randomized, double-blind, placebo-controlled, multimember, study evaluating the safety and efficacy of once-daily oral Fx-1006A versus placebo in V30M FAP patients (the most common amyloidogenic TTR mutation). A total of 120 patients will be randomized in a 1:1 ratio to receive Fx-1006A 20 mg or matched placebo once daily for 18 months. As there are no validated clinical endpoints for FAP, endpoints
validated for a neuropathy also affecting sensory, motor and autonomic nerve fib bers (i.e. diabetic neuropathy) are being utilized. The co-primary endpoints are categorical response in the Neuropathy Impairment Score-Lower Limb (i.e. stabilization/improvement vs worsening), and change from baseline in total quality of life score in Norfolk QOL-DN at 18 months, with the study powered to detect clinically meaningful differences between treatment groups. Secondary assessments include quantitative sensory testing, nerve conduction, heart rate response to breathing, and modified body mass index. TTR stabilization will be measured as a biochemical surrogate marker of efficacy, using a validated immunoturbidimetric assay. Pharmacokinetic sampling will allow description of population pharmacokinetics, with dose selection confirmed via a PK/PD sub study. Safety assessments include vital signs, laboratory tests, electrocardiograms, echocardiography, physical and eye examinations, and adverse event monitoring.

Enrolment is expected to complete in 2007, with data availability in 2009.

Skeletal Pathology in Gaucher disease on Enzyme Replacement Therapy

Authors: Dr Carmencita-Lucia Denes, Prof Paula Grigorescu
Sido - Ist Pediatric Clinic, Cluj-Napoca, Romania

Keywords: Bone Disease, Gaucher Disease

Summary
There is a significant improvement in the clinical symptoms of the osteopa thy in Gaucher Disease during ERT, while the imaging changes showed no relevant improvement with ERT.

Text
Introduction:
Gaucher Disease Osteopathy is considered the most severe complication of the disease. Without treatment it evolves to irreversible changes and even disability. Enzyme Replacement Therapy (ERT) is trying to decrease and even eliminate bone pain, to prevent bone crisis and avascular necrosis and to increase the mineral density.

Objective:
To establish the severity of bone disease at the time of initial diagnosis and the evolution of skeletal pathology in patients receiving ERT.
Patients and Method:
44 Type I Gaucher patients were assessed in the Hospital for Genetic Diseases, Cluj-Napoca, Romania. 31 patients were on treatment with ERT. Bone Disease was assessed by clinical symptoms (bone pain, bone crisis, fractures and ankylosis) and by imaging (X-ray, MRI, DEXA). Results: Bone pain was recorded in all patients, 9% had bone crisis, 11.36% had fractures and 13.63% ankylosis. All patients were imaged by X-ray, using the Hermann Staging Criteria: 50% presented with Hermann stage II, 13.69% with Hermann stage V, the most severe one. Out of the 30 patients examined by MRI, using both Dusseldorf and Terk Criteria, 23.33% had the most severe score 8-3b. Out of the 37 patients examined with DEXA, 18.92% had severe bone disease (Z score < -2.5) and 48.64% mild/absent disease (Z score < -1).

Monitoring the ERT receiving patients revealed the following aspects. There were no new bone crisis or fractures and bone pain improved significantly. The X-Ray, MRI and DEXA aspects showed no changes in over 50% of patients and improvement in only 6.45% of the patients. Conclusions: There is a significant improvement in the clinical symptoms of the osteopathy in Gaucher Disease during ERT, while the imaging changes showed no relevant improvement with ERT.

**Splice Switching Oligonucleotide Therapy for Duchenne Muscular Dystrophy, ß-Thalassemia, and Cystic Fibrosis**

**Authors:** Ryszard Kole - University of North Carolina, USA

**Keywords:** Ercole Biotech, alternative splicing, Duchenne Muscular Dystrophy, ß-Thalassemia, Cystic Fibrosis, orphan drug, oligonucleotide therapy, clinical trial

**Summary**
Ercole Biotech’s platform splice switching technology is applicable to a wide range of human disorders, including several rare and genetic diseases such as Duchenne Muscular Dystrophy, ß-Thalassemia, and Cystic Fibrosis.

**Text**
Most human proteins are produced through alternative mRNA splicing, a process that results in the creation of multiple mRNA and protein isoforms from a single gene. As such, Ercole Biotech’s platform splice switching technology is applicable to a wide range of human disorders, including several rare and genetic diseases. Ercole Biotech and its academic collaborators have demonstrated the feasibility of correcting splicing to treat Duchenne...
Muscular Dystrophy (DMD) and ß-Thalassemia in animal models and Cystic Fibrosis (CF) in cell culture models. DMD is caused by mutations in the dystrophin gene, which codes for a protein essential to the structure and function of muscle cells. ß-Thalassemia is caused by mutations in the ß-globin gene, which encodes the critical blood protein ß-globin. CF is caused by mutations in the CFTR gene, a cellular protein that controls proper fluid secretion, especially in lungs. Currently, no treatment for DMD exists while treatment for patients with severe ß-Thalassemia is limited to blood transfusions, iron chelation therapy, and bone marrow transplants. Treatment to control the symptoms of CF includes airway clearance, digestive enzyme therapy, and vaccinations. Ercole Biotech’s patented Splice Switching Oligonucleotide (SSOs) therapies, based on the research of Professor Ryszard Kole and his colleagues at the University of North Carolina at Chapel Hill, work through the mechanism of SSO binding to a targeted splicing element in pre-mRNA thereby blocking the disease related pathways and promoting the production of desirable proteins. Clinical trials of SSOs are expected to begin in 2007 for DMD in Great Britain and USA and in 2008 for ß Thalassemia in Thailand.

Hypereosinophilic syndrome and its treatment

**Authors** : Florence Roufosse - Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Belgium

**Key words** : Orphan drug—Hypereosinophilic syndrome—Mepolizumab—Clinical trial

**Text**

Drug development for rare diseases is challenging. Diagnostic tools are often inadequate, knowledge about epidemiology and pathogenesis is poor, endpoint selection to show statistical significance in small numbers of patients with diverse symptoms can be problematic, and standardised treatments or randomised clinical trials for comparison may be lacking. Hypereosinophilic syndrome (HES) is a heterogeneous group of rare disorders characterised by sustained blood and tissue eosinophilia. Clinical manifestations vary from non-specific symptoms to life-threatening, end-organ dysfunction attributed to eosinophil-mediated tissue damage. Long-term maintenance therapy is needed to reduce eosinophil levels and prevent disease progression. A subgroup of patients with a FIP1L1-PDGFRA gene rearrangement responds to imatinib. However, for the majority of patients, systemic corticosteroids are first-line therapy, although they lead to significant morbidity due to numerous dose-related side-effects. Mepolizumab is
a monoclonal antibody that binds to and blocks the action of interleukin-5, a cytokine crucial for eosinophil maturation, growth and survival. An international, randomised, double-blind, placebo-controlled trial evaluated mepolizumab for the treatment of FIP1L1-PDGFRA–negative HES. Patients (controlled on prednisone 20–60 mg/day) received intravenous mepolizumab 750 mg (n=43) or placebo (n=42) every 4 weeks for 36 weeks, and their prednisone dose was tapered according to eosinophil counts and HES clinical activity. Significantly more mepolizumab-treated (84%) than placebo-treated (43%) patients achieved the primary endpoint (≤10 mg/day prednisone for ≥8 consecutive weeks) (P<0.001; odds ratio, 8.0 [95% CI, 2.7–23.8]). Eosinophils decreased to <600/µL for ≥8 consecutive weeks in significantly more mepolizumab (95%) than placebo (45%) patients (P<0.001; odds ratio, 18.9 [95% CI, 4.7–75.2]). Mepolizumab was generally well tolerated. In conclusion, HES is a heterogeneous disease with variable symptoms and treatments. To reflect this, a trial design to standardise disease control with steroid monotherapy was implemented, allowing powered efficacy determinations based upon steroid endpoints in a relatively small number of patients.

Patient Driven Innovative Projects for Rare Diseases

Family Route Maps - a patient driven project to develop a tool to help access information and services for families with six genetic conditions.

Authors : Ms Anna Allford, Ms Melissa Hillier - Genetic Interest Group, London, United Kingdom

Keywords : Rare genetic diseases, Focus Groups, information, access to services

Summary
An early finding from the Family Route Map project indicates that patients with rare genetic conditions want a Centre of Excellence with a lead clinician to co-ordinate their care.

Text
Together with Patient Support Groups and their members representing six rare genetic disorders, the charity Genetic Interest Group explored information
and services currently available to families in the UK as the first stage in the development of Family Route Maps designed to signpost information and guide patients, families and carers through the available appropriate healthcare and other services. In addition to providing future practical guidance to people with the six specific disorders, the project will produce a generic Route Map template which can be used for other genetic conditions. Focus Groups and supplemental interviews with patients belonging to Support Groups as well as interviews with health professionals who specialise in these conditions were used to gain their views and experiences. An online patient questionnaire was also available to widen patient participation. Common themes were identified and seven categories emerged: Information; Communication; Education of Healthcare professionals; Diagnosis of rare genetic disorders; Empowering patients and parents/carers; Ethical, Legal and Social issues; and, Treatment & Surveillance of patients and families with rare genetic disorders. Findings suggest that patients with rare genetic disorders are not given sufficient information about their condition, services are considered ‘patchy’ and some families are still not aware of, or accessing, NHS Clinical Genetic Services. Additionally, many feel they receive sub-optimal treatment/surveillance for their condition and would prefer to have a Centre of Excellence responsible for their care with one lead Clinician acting in a co-ordinating role. Awareness amongst clinicians of the necessity for clear care pathways to help patients living with rare and sometimes life-threatening conditions, with the aim of a protocol for support, monitoring and treatment is required to ensure all health and care personnel have the necessary information to care for these patients and families. Could European Networks of Expertise fulfil this urgently needed role?

**Structured multidisciplinary clinics for Alström syndrome families led by Alström Syndrome UK support group**

**Authors**: Dr Catherine Carey, Dr Richard Paisey, Prof Tim Barrett - Torbay Hospital, Torquay, Devon, United Kingdom

**Keywords**: Alström

**Summary**
Patient-led development of a national specialist service for Alström syndrome, a complex multisystem disorder. Integrating clinical review, life management, research and peer support.

**Text**
Life with a rare disorder is challenging and exacerbated by difficulties accessing clinical care and social support. Complex, multisystem medical issues require
lifelong specialist input. However, healthcare delivery is usually fragmented - typically multiple appointments with a range of providers, often geographically spread. Smooth transition from paediatric to adult care is rare. Patients and families feel frustrated and isolated, while clinical expertise is restricted.

Alström syndrome is a rare, autosomal recessive disorder due to a mutation in ALMS 1 gene. Cone rod dystrophy resulting in early blindness, hearing loss and insulin resistant diabetes are characteristic. Multi-organ involvement is frequent, unpredictable and complex, affecting renal, hepatic, pulmonary, gastro-oesophageal, pancreatic, bladder and endocrine systems. About 60% patients develop cardiomyopathy, the commonest cause of early death. Long term clinical monitoring is critical.

Alström Syndrome UK (ASUK) patient support group initiated annual meetings in 1997 and invited professionals to hold informal clinical and life management workshops. Patients and families shared experiences, gained understanding of the issues they faced and enabled the professionals to develop expertise through working with them. ASUK successfully championed this model of patient-led care which received formal recognition and funding in 2006 from the National Service Advisory Group (NSCAG) who commission for highly specialised services in England.

The service is accessible by anyone in the UK with Alstr m syndrome and is designed to complement local provision, providing diagnostic testing, multidisciplinary clinical review, peer support and expert sessions on life consequences e.g. education. Although the centres for children/young people and adults are separate, ASUK and the multidisciplinary team attend both sites to ensure continuity of care.

Conclusion:
This innovative approach allows families to interact and share concerns with professional teams over two days of discussion, exercise, medical review and affords the opportunity to explore new investigations and treatments.

Collaborative Experience of the Romanian Prader Willi Association

Authors: Ms Dorica Dan - Romanian Prader Willi Association, Zalau, Romania

Keywords: Rare Diseases, genetic counseling, NGO collaboration
Summary
Developing awareness about the needs of children with Rare Diseases and engaging public in a shared strategy for the development of genetic services, will ensure a collaborative international approach in sharing of expertise and experience.

Text
In the absence of a national governmental strategy for Rare Diseases in Romania, the collaboration of local and national NGOs for patients and medical specialists is essential.

The aim of our paper is to focus on the encouragement of a collaborative effort between RPWA, Higher Education Medical Universities, medical specialists, and NGOs serving beneficiaries in the rare diseases sector through a multidisciplinary approach.

Families have interacted with medical specialists and benefited by becoming more assertive and by achieving more developmental milestones.

APWR has established contacts with a Genetic Lab in Bucharest and renewed the contact with Mauro Baschirotto Institute for Rare Diseases (Italy) and established new relationships with genetics specialist which helped us to diagnosed the patients in important genetics Institute and laboratories: Institute of Medical Genetics from Zuerich (Switzerland), Institute of Human Genetics- Wuerzburg (Germany), Institute of Clinical Genetics, Olgahospital-Stuttgart (Germany), Genetic Lab- Bucharest.

Organised training courses for parents, genetic evaluating for children with mental handicap, psychological, social and genetic counseling with the help of professional volunteers from Timisoara and Oradea;

Organised a training course in genetics for family doctors at the request of Doctors Collegium and RPWA under auspicious of the Medicine University from Timisoara;

Organised and attending common activities with professional organization: OAMMR, Doctors’ Collegium, establishing the Romanian National Alliance for Rare Diseases.
Living with a Rare Disease: a Study of Living Conditions for Persons with Rare Disorders.

Authors: Mr Jonas Bo Hansen - Centre for Rare Diseases and Disabilities, Copenhagen, Denmark

Keywords: Living conditions, rare disorders, questionnaires

Summary
Living Conditions for people suffering from rare disorders are far from well described! In a unique Danish study of families suffering from thirteen different rare diseases individuals and families and their living conditions from birth to adulthood are subject to a thorough investigation. The mapping of living conditions is based on answers from totally 891 questionnaires and a number of group interviews. All in all it is possible both to detect the living conditions for the special rare disease in question and for a variety of rare diseases - the differences as well as the similarities.

Text
Living Conditions for people suffering from rare disorders are far from well described! In a unique Danish study of families suffering from thirteen different rare diseases individuals and families and their living conditions from birth to adulthood are subject to a thorough investigation. The mapping of living conditions is based on answers from nearly 900 answered questionnaires and a number of group interviews.

The mapping is carried out by the Danish National Centre for Rare Diseases and Disabilities but is patient driven in the sense that the patient associations have been a leading force in formulating, distributing and gathering the questionnaires to the members/families. Also the patient associations have drawn attention to topics of particular relevance to their patient group.

All in all it is possible both to detect the living conditions for the special rare disease in question and for a variety of rare diseases - the differences as well as the similarities.

For example the investigation shows several indications of what is really the rare about having a rare disease: how it inflicts life that nobody knows about the disease and the implications of the lack of knowledge to the support you can get from family and authorities.

Also it is possible to tell the differences between living with a visible versus an invisible rare disease: what the implications are when family and carers
show suspicion to you and you always have to explain the pain and tiredness and other symptoms.

The importance of knowledge of the disease and of coordination between the various sectors involved in support and care is well recognized but the implication of lack of coordination is shown with great strength in the mappings.

An important topic in all the mappings is the importance of patient associations and the support each individual and family can obtain from the patient association.

The above topics will be thoroughly described and elaborated on in the poster presentation.

Living conditions have been investigated for - among others: Spielmeyer-Vogt/Batten, Ehlers Danlos Syndrome, Marfan Syndrome, Crouzon Syndrome, Soto Syndrome, Galaktosaemia Syndrome and Angelman Syndrome.

A Pilot Project for a European Network for Congenital Limb-reduction Deficiency

Authors: Dr Martin Johnson - The Thalidomide Trust, St Neots, United Kingdom

Keywords: Congenital Limb-reduction Deficiency, Electronic Patient Records, On-line Patient Registry

Summary
This paper describes a pilot project developed by the Thalidomide Trust to create a Health Support Service capable of being expanded to support all CLD patients within the EU.

Text
This paper describes a pilot project developed by the Thalidomide Trust to create a Health Support Service capable of being expanded to support all Congenital Limb-reduction Deficiency (CLD) patients within the EU. The Thalidomide Trust is a member of the European Forum for Congenital Limb-reduction Disability, together with the Föreningen för de Neurosedynskadade and the Bundesverband Contergangeshäditger. These three organisations support 25-30% of the 15,000 people estimated to be affected by CLD within the EU.
The planning parameters of the project included: worldwide availability
of the service, identifying relevant clinical specialists, gathering available
recorded information (published and unpublished) relevant to the support
of CLD, and identifying gaps in the capability of primary care provision to
prevent duplicating existing services.

The intended outcomes of the project include: improved quality of life for
CLD patients, establishing the range of CLD-specific health problems and
reducing the incidence of these problems. It also expects to identify appro-
priate areas for research, and increase the awareness of CLD-specific health
issues among primary care providers and patients. The problems associated
with identifying and evaluating Centres of Excellence are discussed.

Technology issues include: AAA website accessibility standards, electronic
patient records, and an on-line patient registry. It also reviews the devel-
opment and use of an on-line Instant Medical History tool, for improved
diagnosis.

The progress of this project at the end of the first 3 years is reported, in-
cluding 9 months of a clinical evaluation involving some 60 (UK) patients.
Delays, costs, frustrations among the patient group, and pressures to change
methods are discussed, as well as the next steps for expanding the network
into other national groups.

Breaking the Silence about Immune
Deficiencies: a Consensus Conference

Authors: Mrs Bianca Pizzera Piantanida - IPOPI - International
Patient Organisation for Primary Immunodeficiencies, Arona, Italy

Keywords: Primary Immunodeficiencies

Summary
In 2006 IPOPI obtained a European Commission grant to provide a Eu-
ropewide Consensus Conference on the Diagnosis and Management of
Primary Immunodeficiencies (PIDs) in the EU. This has provided a model
for Europe but also for the rest of the world - and indeed for rare diseases
other than PIDs

Text
Primary Immunodeficiencies (PIDs) are a group of more than 100 rare
diseases of the immune system. They are genetic conditions that range in
severity and bare the clinical hallmarks of persistent, recurring infections. Left un/misdiagnosed, PIDs lead to a lifetime of chronic illness, permanent organ damage, disability or even death.

Treatments in the form of antibody replacement therapies (immunoglobulin) are available, and have a long history of proven efficacy, leading to reductions in illness and burden on healthcare provider resources.

The core issue with PIDs is therefore one of chronic under diagnosis, with symptoms often not recognised by doctors, sufferers or their families.

With funding from the European Commission’s 2005 Public Health Programme, the International Patient Organisation for Primary Immunodeficiencies (IPOPI), the European Society for Immunodeficiencies (ESID), the International Nurses Group for Immunodeficiencies (INGID) and the European Federation for Immunological Societies (EFIS) held an EU PID Consensus Conference in June 2006. The aim of which was to increase recognition of PIDs as a public health issue, and create a forum for experts to discuss and propose a consensual public health approach to PIDs.

The European PID Consensus Conference successfully brought together clinicians, patients, policy makers, regulators and manufacturers, and is an outstanding example of how the EU Public Health Programme can enable cooperation among organisations that play different roles in supporting improved care for a rare disease.

The presentation at the 2007 European Rare Disease Conference will cover the development and execution of this project, and will include evidence of the success this project has had in communicating:

- The negative impact PIDs have on healthcare systems and undiagnosed patients,
- The disparities of care and treatment across the EU,
- Actions and initiatives that can be taken to reduce the burden of PIDs.
Working with Patient Organisations – an excellent experience for professionals

Authors: Dr Maria Puiu, Dr Alina Tarniceru, Dorica Dan - Romanian Prader-Willi Association, Timisoara, Romania

Keywords: Patient Organisations, rare diseases, professionals

Summary
The experience of collaboration between professionals and Patient Associations is extremely useful equally for professionals (knowing and understanding rare diseases, correct and quick diagnosis, adequate treatment and monitoring, counselling and support, involvement in the adjustment of health care policy for rare diseases) and also for patients and their families who benefit from proper medical education, understanding and trust in professionals.

Text
The Department of Medical Genetics from the University of Medicine and Pharmacy “Victor Babes” Timisoara and the Genetic Division of “Louis Turcanu“ Emergency Hospital for Children have started few years ago a project to bring together the genetics and the community.

The collaboration with Patient Organizations and particularly with Romanian Prader Willi Association converted this initiative to an innovating associative project with great efficiency in medical education concerning rare genetic diseases.

There were organised numerous lectures, workshops and meetings for specialists (of various specialties: family doctors, paediatricians, neonatologists, cardiologists, neuropsychiatrists), students, medical personnel, active members of Patient Associations, parents and patients. These discussions permitted the understanding of the main problems for different actors that come in contact with rare diseases. Most of these problems are in relation with the multidisciplinary approach of the patient to establish the correct and early diagnosis, the treatment and best possible monitoring.

The psychological and bioethical aspects are extremely important in the equation professional – patient – family, but frequently neglected in our health care system. The presence of professionals during the meetings of the Patient Associations members have increased the confidence of patients and facilitated the communication between doctor and patient. The professional could overhear aspects of the diseases that specialty literature can’t always present clearly enough. He understood exactly the multiple prob-
lems concerning education, counselling, support, medical attendance of the patients with rare diseases. He especially understood the remarkable role of Patient Associations and the importance of cooperation with these associations to increase the quality of life for these patients and to encourage the health care system to support them. Equally the professionals and Patient Organizations militate for: adequate local and regional health care policy for rare diseases, the creation of some national expertise centres for rare diseases, the adhesion to European research programs for rare diseases.

Working with Patient Organisations is very useful for professional and fighting for equity and better chances for our patients generates a profound feeling of professional contentment.

A quality of life study as a tool for the patient organisation

Authors: Dr Balthasar Schaap - ADCA vereniging Nederland, Hoogwoud, The Netherlands
Keywords: Quality of life, patient driven research, organisation empowerment

Summary
Patients’ organisations can strengthen their capacity by organising a quality of life study. The results of such a study that can be done by the patient organisation with little help or a handbook provide data that are useful to analyse the problems of the individual patients and their solutions to the limitations. It is recommended to encourage patients’ organisations to carry out such studies and compare results with other patient organisations.

Text
A quality of life study as a tool for patients’ organisations. Much money and effort is spent on getting financial support for basic research on rare diseases. A quality of life study among the patients’ organisation members can provide figures that give an insight in the daily life limitations caused by the disease concerned. It also provides you with the solutions that have been found by the individual members. The data can be used as a base level study, to measure the influence of certain interventions on the quality of life. The study can be carried out by the patients’ organisations with little support or even with the help of a simple handbook.

The study I carried out with a student was financed by the patients’ organisation at a cost of about € 3200.-
IBEA - The Italian Bank for Alternating Hemiplegia, a tool for the promotion of the research on a rare disease.

Authors: Maria Rosaria Vavassori - A.I.S.EA Onlus, Verderio Superiore, Italy

Keywords: Open Bank, Bio-Bank, Clinical Registry, Patients Rights, research, research projects, patient association,

Summary
The Italian Bank for Alternating Hemiplegia IBEA is an open repository containing the clinical data and the blood samples of the Italian patients affected by Alternating Hemiplegia (AHC), a very rare neurological disease.

The Bank is directly managed by A.I.S.EA the Italian Patient Association for AHC and safeguards the patients’ rights to the privacy and the information about the results of the research projects using the Bank.

Text
Alternating Hemiplegia (AHC) is a very rare disorder characterized by early onset, recurrent episodes of hemiplegia affecting alternatively both sides of the body, occurrence of paroxysmal phenomena such as tonic and dystonic attacks, oculomotor and autonomic disturbances.

It is a highly chronically debilitating suffering with deleterious effects on the quality of life of the affected patients.

AISEA, the Italian Patient Association for AHC, was created in 1999 with the main goals to support the families, spread the knowledge about the disorder, promote and support the research.

Since the beginning, we realized that the best way to achieve this last goal was to provide the research groups with an easy, non exclusive access to the clinical data and blood samples of as many AHC cases as possible.

At the same time, as patients, we wanted to safeguard our rights to the privacy and to the information about the results of the research projects using our data and samples.

Therefore we created the Italian Bank for AHC, IBEA, a project coordinated by AISEA, in collaboration with its Scientific Committee.
By means of a rigorous protocol and through the direct management of the association, the Bank can safeguard the patients’ rights and, at the same time, offer impartiality, transparency and ease of access for any kind of research on AHC.

At present, the Bank contains the complete clinical documentation and the biological samples of more than 30 Italian patients. Three clinical studies and two genetic researches are currently using the Bank. AISEA also agreed with their managers that the results will be delivered to the patients, kept in the Bank and shared with the scientific community through publications.

The Bank is linked to the European Registry for AHC, under the management of ENRAH, the European Network for the Research on AHC.

**Pollicino (Tom-Thumb) Project: rare disorders patients finding their way**

**Authors**: Dr Teresa Sellan - Veneto Region Register for Rare Disorders-Padua University-Italy  
**Keywords**: information, advocacy, web, patients’ Associations

**Summary**

Pollicino is a communication project aimed at spreading information on rare disorders at different levels. The created web-site collects information especially on practical aspects of daily-living, care opportunities and benefits provided by the Italian Law, paying particular attention on patient advocacy and empowerment.

**Text**

Pollicino (Tom-Thumb) is a communication project oriented to rare diseases’ patients, their relatives and the health professionals involved in the diagnosis, care and cure of these patients. The project is promoted by Uniamo, the Italian Alliance of patients’ associations, funded by the Ministry of the Social Solidarity, and realized with the support of the Veneto Region Register for Rare Disorders.

Aim of the project is to realize a database supporting a web-site containing information on RD and related issues. In particular attention will be focused on patient advocacy and practical information on aspects of daily living, i.e. school inclusion programmes, equal job opportunities, accessibility, free-time, sports, etc. The project develops through several steps. Firstly, a listening phase in order to identify information needs expressed by the patients. Self-adminis-
tered validated questionnaires were distributed to all the 82 Uniamo Associa-
tions in order to collect information on critical issues the patients want to be covered within the project. An analysis of the questionnaires and of the Italian RD scenario outlined the difficulty of getting useful and validated information often dispersed across different sources. Data collection on legislation, care networks, existing facilities, research and successful experiences of patients prise en charge lead to the creation of an Oracle Database supporting a web-browse application. Personal login and passwords have to be used to access restricted areas of the web-site. While some information is common to all RD, other data are specific for single disease. The website contains links to other Associations websites in order to guarantee the expansion of the available information.

The project represents an experience aimed at disseminating simple and accurate information on all aspects of patient care, not only strictly medical ones, and to advocate patient empowerment.

Policy Implementation : European, Regional, State and Local Policy

**Services for people with rare disorders and disabilities in Norway – an overview**

**Authors** : Mr Stein Are Aksnes - Directorate for Health and Social Affairs, Oslo, Norway

**Keywords** : Organisation, Resource centres, services, “to live with” - perspective, rare disorders

**Summary**
The Norwegian services for people with rare disorders are based on national Resource centres. These centres give services to persons with needs which
will not be met by standard procedures or the ordinary health care and social services, with a focus on the “to live with”-perspective. Rehabilitation and rare disorders department at the Directorate of health and social affairs has the overview of the services for persons with rare disorders in Norway.

Text
The demography and geography in Norway cause special challenges for people with rare disorders. The population counts around 5 million inhabitants, spread in a country with a distance of 2518 km from south to north. Norway is divided in 4 health care regions and 431 municipalities.

Today we have 16 different state financed Resource centres for persons with rare disorders in Norway, 6 of these for persons with dual sensory impairment. 3 of the centres give services to persons with a specific diagnosis/group of disorders, while the rest works with several diagnoses. One of the centres works with oral health for all rare disorders.

We define rare disorders as less than 500 known cases at a national level (1/10,000). To establish a service for persons with a rare disorder at one of the centres, the dysfunction has to be congenital and complex/compound, and there must be a need for multidisciplinary and cross-institutional services. Such services are established for more than 300 different rare diagnoses.

The Resource centres shall see to that persons with rare disorders are given the same opportunities as everyone else, and they are expected to meet the need for support, which is not met by standard procedures. They give services to people of all ages and their family members in a “to live with”-perspective, to help them to manage their everyday lives.

The Directorate of health and social affairs co-operates with the Resource centres to ensure optimal use of resources. Furthermore the directorate provides an overview of the incidence of congenital and rare diseases and syndromes and provides an overview of the living conditions of the groups in question. The directorate advises users, family members and service providers, and is involved in international cooperation, e.g. Nordic collaboration to develop the database www.rarelink.eu.
Piedmonte Registry of Rare Diseases: an example of Regional Based Registry for the support of Rare Diseases Health Policy

Authors: Dr Simone Baldovino, Dr Maria Maspoli - Centro Multidisciplinare di Immunopatologia e Documentazione su Malattie Rare – Centro di Coordinamento della Rete Regionale Piemontese per le Malattie Rare, Torino, Italy

Keywords: rare diseases registry, rare diseases policy

Summary
The Piedmont Regional Registry of Rare Diseases is part of a larger project, i.e., the Regional Network for Rare Diseases. The aim of the project is to collect data on the prevalence of a great deal of rare diseases so as to allow for the rational distribution of funds, to develop shared diagnostic and therapeutic protocols, and to provide patients, associations, and health and social workers with information about rare diseases.

Text
Objectives:
The Registry was developed to collect data on about 700 diseases. The collected data allow us to estimate the prevalence (and in the future also incidence), diagnostic criteria, therapeutic approaches and costs related to each disease. These data are important in order to develop a public health policy aimed to answer to the needs of patients affected by rare diseases.

Methods:
The first phase lasted 6 months and involved 6 Experimental Centres. Data concerning 832 cases were recorded according to the form provided by the Italian National Institute of Health (Istituto Superiore di Sanità).

The second phase, which started in January 2006, and is currently ongoing, is an attempt to involve every Public Health facility in Piedmont in the collection of data. A database for data collection and processing was developed by the Regional Agency of Informatics (CSI) and is available through a regional intranet (named RUPAR). Each participating hospital sends its data to the coordinating centre located in Turin.

Results:
During the first 18 months of activity about 2500 files on patients affected by a rare diseases were collected. Careful evaluation led us to exclude 402 forms from validation due to missing mandatory information.
Conclusions and Proposals:
Data collected by the Piedmont regional Registry of Rare Diseases will also be cross-referenced with other Regional Databases, such as the Hospital Discharge Form (Scheda di Dimissione Ospedaliera) or the Regional Registry of Disability Challenged Patients (Passaporto delle Abilità). The aim of this data mining process is to estimate more specific epidemiological and financial indicators.

**Lysosomal Storage Disorder Management in Romania: an Overview**

**Authors:** Dr Katalin Csep - University of Medicine and Pharmacy, Tg Mures, Romania

**Keywords:** lysosomal storage disorders, treatment, diagnosis, information, research

**Summary**
The structure, the possibilities, results and difficulties of lysosomal storage disorder management in Romania will be presented.

**Text**
Lysosomal storage disorders, a group of more than 40 inherited diseases, were described beginning with the XIXth century. Biotechnology opened a new era, and enzyme replacement therapy, the standard care for Gaucher, Fabry, Pompe disease and some MPS forms, changed the natural course of these otherwise incurable diseases. The emergence of new drugs created new possibilities but also new tasks. Romania joined the EU on January 1, 2007. The possibility of treatment requested pioneering work under difficult circumstances and the major challenges we experienced were the lack of knowledge, interest and financial resources. When it comes to rare disorders and orphan drugs with a high price you often hear the argument that several other cases could be solved with the same amount of money necessary for only one patient. However, this attitude is changing and education and information is essential for this process. The collaboration of patient associations, health care professionals, the drug company and policy makers shows results. In 1997, specific diagnosis became available at the Biochemistry Department of the University of Medicine and Pharmacy and the National Centre for these disorders was created at the 1st Paediatric Clinic in Cluj where diagnosis, treatment and regular monitoring of the constantly growing number of patients are coordinated, in collaboration with treating physicians.
from all over the country. Therapy entails a financial effort, and, in the present, treatment is assured by the national insurance house or compassionate use programs. A national program for Gaucher disease has been launched, and local experts have created the guidelines of optimal care based on international practice and the national experience. From the EU membership, we expect easier access to treatment, faster drug registration and better collaboration of all parties involved, pivotal for finding the best comprehensive management in such rare and heterogeneous disorders.

**Estimating the impact of Rare Disorders on population health : an Italian experience**

**Authors**: Dr Monica Mazzucato, Veneto Region Register for Rare Disorders-Padua University, Italy  
**Keywords**: Register, Hospital Discharge Records, ICD codes, prevalence  

**Summary**  
The study estimates the impact of RD on population’s health comparing two independent sources of data monitoring the same population. ICD-based current statistics can be used to roughly estimate the number of affected patients in a defined area.

**Text**  
To estimate the impact of RD on population’s health we have compared two independent sources of data monitoring the same population: Veneto Region Register for Rare Disorders (VRRRD) and Hospital Discharge Records Register.

VRRRD, established in 2002, covers a population of 4.5 million inhabitants and is based on an informative system connecting all the Reference Centres, all the Health Districts and Pharmaceutical Services. 11,000 patients are enrolled: the most represented rare diseases are haematological ones (16%), followed by congenital malformations (15%) and neurological disorders.

To analyze HDR database, both ICD9-CM and ICD-10 codes were assigned to each disease included in the Italian reference list, issued in 2001. The list includes 581 names, corresponding to 2138 diseases. A total amount of 344 ICD9-CM and 490 ICD-10 corresponding codes were identified. Congenital malformations and rare metabolic diseases are better described in the ICD-10, if compared to ICD-9 CM. Specific codes, coding single entities or
different diseases, still rare, represent 74% of all the selected codes. Hospital Discharge Records of Veneto Region for the 4-year period 2002-2005 were analyzed. All the records containing at least one of the identified codes were selected. We obtained 114,000 discharges corresponding to 81,000 patients. Among these, those with a specific RD code are nearly 22,000, leading to an estimated overall crude prevalence of RD calculated for the specific codes of 5 per 1,000 inhabitants.

Comparing the two data sources, nearly 70% of the patients enrolled in the Register can be traced by HDR. No bias in the distribution of diseases groups among registered and non-registered patients was observed.

ICD-based current statistics can be used to roughly estimate the number of affected patients, but show some limits in tracing patients affected by rare disorders described by non univocal and non-specific codes in the classification systems.

**New Italian initiatives for addressing rare diseases**

**Authors**: Dr Domenica Taruscio - Centro Nazionale Malattie Rare (National Centre Rare Diseases), Istituto Superiore Sanità, Rome, Italy

**Keywords**: Rare diseases, policy, Italy, orphan drugs, research

**Summary**

The abstract provides an overview of how Italy is addressing rare diseases focusing on 5 major pillars: definition of clear policy guidelines, availability of a network for the provision of care, implementation of a surveillance system, identification of innovative schemes for support the research and promotion of patient’s engagement.

**Text**

Institutional framework. The Italian Government promulgated a Regulation on Rare Diseases (RDs) (Ministerial Decree 279/2001, «Institution of the national network of rare diseases»). The Decree identifies approximately 500 RDs for which patients are diagnosed and treated completely free of charge, lists the criteria for the establishment of the centres designated to manage RDs patients and establishes the National Register of RDs at the National Institute of Health (Istituto Superiore di Sanità – ISS).

Provision of care. Regional centres have been identified in the entire national territory. A permanent inter-regional technical group including Regional
Representatives, the Ministry of Health (MoH) and the ISS was established to optimise the function of the regional networks.

Surveillance. The national register of RDs was established at the National Centre Rare Diseases (ISS) in order to contribute to the national and regional health planning and to ensure the surveillance of RDs.

The National registry of Orphan Drugs was established at the ISS with the aim of establishing a post marketing surveillance system of orphan drugs available in Italy in order to get more information on the number of patients treated and the appropriate use of the drugs.

Research. The Low 326/2003 requires to the Italian pharmaceutical companies to donate 5% of their promotional expenditure to a specific fund established within the Italian National Medicines Agency (AIFA).

The AIFA used the fund to launch 2 calls for proposal (in 2005 and 2006) including orphan drugs among the priorities. The MoH and the ISS launched two national calls for proposals (in 2004-2006 and 2006-2008) on RDs and in 2007 contributed to support the first trans-national call for European projects on RDs (E-Rare project).

Patient engagement. The Italian Minister of Health has formally established a “Consulta” of RDs patients’ organisations in order to provide a forum for strengthening the dialogue between patients’ organisations and MoH.

Rare diseases in Catalonia: perception of needs and action proposals (A regional experience in Spain).

Authors: Maria Mena, Katia Bones Rocha, Margarita Pla and Josep Torrent-Farnell - Fundació Doctor Robert, Barcelona, Spain

Keywords: rare diseases, health and social systems, attention and assistance, expressed needs.

Text
Introduction:
Rare diseases are a challenge both for health and social systems as well as health professionals. Although these systems have started to develop actions to improve attention and assistance to this type of patients, people who suffer rare diseases continue living situations of exclusion and social marginalisation.
Objective:
The objectives of this study are as follows:

1. Identifying needs and problems that this segment of the population suffers in order to propose solutions to establish feasible projects in the Catalan health system. (Catalonia is an autonomous region of eight million in habitants with full competences in budgeting and planning related to health and social care).

2. Searching consensus with the different agents (affected people, caregivers, health professionals and patients’ associations) to identify main needs and actions to be taken.

Methods and participants:
The methodology used in this study was qualitative: 8 individual in-depth interviews, 1 triangular group, 2 discussion groups and 48 Delphi questionnaires. The participants were health professionals, affected people, caregivers and association members, being 70 people in total.

Results:
The results obtained can be summarized in five main points which have been considered by the health and social system to improve the quality of the assistance offered. These aspects refer to: 1) the lack of information as well as the lack of accessible and organised information systems, 2) the difficulties to detect rare diseases, access to health and social attention and the model of it, 3) the absence of economic and social funding, 4) the lack of basic, clinical, epidemiological, and social research and 5) promote the empowerment and full participation of patient’s associations in the decision making process.

Conclusions:
The mentioned results, the enormous quantity of needs detected and the current situation underline the urgency of beginning to establish strategy lines in this region. Results are full consistent with those detected in Spain as well as in other EU Members States. Rare Diseases’ main problems are the lack of proper funding and human resources and patients are still facing with a huge fragmentation of both health and social services. In this current environment equity access can not be guaranteed and a new integrated health-social model needs to be considered. Positive experiences already gained in other UE countries such the integrated approach in France, can be used to model national and regional models in other countries.
Orphan drugs: the challenges of availability and sustainability in Veneto Region

Authors: Dr Oliviana Gelasio - Veneto Region Register for Rare Disorders-Padua University, Italy

Keywords: orphan drug, designation, cost monitoring, sustainability

Summary
Prevalence data from the monitoring system established in Veneto Region, Italy, since 2002 allow a rough estimation of the costs related to orphan medical products for rare disorders patients. The impact on the regional and national system is not negligible due to the high costs of these treatments and to the increasing number of patients eligible to therapy. A challenge concerning sustainability of this system in the near future is arising.

Text
In recent years, in the US and Europe, incentives provided by orphan drug legislation have resulted in the development of innovative therapies for a number of rare diseases. In the EU, a drug will receive orphan status designation if it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting less than 5 persons per 10,000. This definition can be extended to more frequently occurring diseases if they are life-threatening, seriously debilitating or if the return on the marketing would not be expected to justify the investment in development.

The number of orphan applications at COMP has increased steadily; 382 orphan designations have been granted until October 2006, covering 319 different medicinal products proposed for 192 different conditions. 70 out of 382 (18%) orphan designations have been approved for RD reported in the Italian reference list, issued in 2001. In Italy OMP are reimbursed by the National Health System. Using prevalence data provided by the monitoring system established in Veneto Region, 4,5 million inhabitants, we estimate the impact of OMP expense on the regional health system. For our Region we estimated a global expense of 58 million euros in the last year. As an example, 16 patients affected by Fabry disease are enrolled in the Regional Register, 3 were excluded due to too recent registration. Considering that the annual average cost for ERT is 185,000 euros person/year, we estimate a global expense at enlarged EU level of 318 million euros/year.

Some critical points emerge in the process of designation: prevalence-slicing effect, lack of precise information on number of eligible patients, widening of indication after availability on the market. The potential effect
on health care systems due to high cost treatments and increasing number of eligible patients needs to be evaluated in terms of sustainability.

Initiatives for Persons with Haemophilia in Europe

Authors: Dr Hubert K Hartl – EHC, Gablitz, Austria
Keywords: Haemophilia, Initiatives, Advocacy

Summary
The EHC is a European Patients’ umbrella organisation which developed from a small central European initiative to a influential advocacy and lobbying organisation.

The enlargement as well as the ongoing professionalism enabled the national member organisation to improve the situation of chronically ill persons not only by their own efforts, as they can rely on a supportive and effective governing body.

Text
The European Haemophilia Consortium (EHC) was established in 1986 by nine Haemophilia Societies, all members of the World Federation of Haemophilia. It is a voluntary umbrella organisation of 44 National Haemophilia Associations and Societies (NMOs) in Europe (as defined by WHO-Europe). These organisations represent about 30,000 members (PwH) out of the estimated 80,000 PwH in the NMO- countries.

The Steering Committee (SC), representing the NMOs, consists out of four elected representatives of the NMOs and two co-opted members.

In 2002/2003 a switch of the political interest of EHC’s Steering Committee happened. A feasibility-study was carried out and the newly elected SC of 2003 started to develop and to work on several new core issues.

Nevertheless the mission statement of the organisation remained the same: To improve the quality of life for people with haemophilia in Europe.

• Improve the strength and national such as European influence of the organisation in becoming a legal entity, develop a new Corporate Identity, Constitution, Transparency Guidelines and Codes of Conduct.
• Develop suitable methods of fundraising to provide independent financing for EHC-activities.
• Settle an agreement (MoU) with the World Federation of Haemophilia about future cooperation and exclusiveness of certain activities.
• Establish a Medical Advisory Board (MAB)
• Improve lobbying in developing European countries to support the establishment of Comprehensive Haemophilia Care, increase of factor-usage and availability as well as state-of-the-art-treatment.
• Develop surveys amongst the NMOs on a regular basis to update on needs and expectations within the different health care systems.
• Work on EU-level to carefully follow and try to influence European developments; especially in the fields of Blood Safety, availability and affordability of factor concentrates, Public Health and Patient Mobility.
• Raise awareness for patients with bleeding disorders amongst the new, enlarged European Parliament.
• Establish close, regular cooperation with the relevant directorates of the European Commission and the Council of Europe, especially concerning Rare Disorders.
• Steadily improve information exchange and cooperation within the NMOs and with third parties, such as EMEA, EC, Patient and Industry representatives and other stakeholders.

Four years experience of the French nationwide cystic fibrosis (CF) newborn screening (NBS): strategy and results on more than 2 million births.

Authors: Dr Michel Roussey, Dr Anne Munck - Association Française pour le Dépistage et la Prévention des Handicaps de l’Enfant (AFDPHE), Paris, France
Keywords: Cystic fibrosis. Newborn screening. CF centre;

Summary
Organisation and results of a national CF newborn screening in France

Text
CF NBS started in France on a routine basis from 2002. Methods: At D3 on dry blood spot samples were performed an immunoreactive trypsinogen assay (IRT) and a CFTR genotyping analysis (Kit Elucigene CF 30) for IRT specimens over the cut-off level (aim: 0.5% selected NB; 60 µg/l raised to 65 µg/l) if parental informed consent was signed at birth. Either neonates with 1/2 mutations or the ones with no mutation (by 2005: only if D3-IRT > 100 µg/l) / no DNA analysis but a persistent IRT increase (30 µg/l raised to 40 µg/l) were referred to a CF centre for a sweat test. Results: 2,718,000
babies have been screened. 18.610 NB had an elevated IRT D3 and the CFTR analysis has been carried out in 97.7%. 3.437 infants were sent to CF centres and 612 CF were identified through NS and 23 false negatives were clinically recognized (frequency = 1/4280 with important regional variations). 443/612 had 2 mutations, 141 only one mutation and 28 no mutation or no DNA analysis. 43% of CF babies were F508del/F508del and 85% had at least one F508del. 83/612 (13.5%) were mild variant of CF. The CF Kit 30 detected 87% of the patients’ mutations, the median age at initial consultation was 34 days, and 54% were already symptomatic (66 with a meconium ileus). Most of the difficulties encountered were due to DNA testing. A protocol combining IRT and PAP (pancreatitis associated protein) measurements was tested in 200.000 babies in order to avoid DNA analysis. This IRT/PAP protocol showed that it was feasible, cheaper, and at least as efficient as the IRT/DNA protocol. Conclusion: CF NBS is feasible routinely all over a nation with a unique procedure but needs a strong organisation. NBS is a huge hope for these very early diagnosed patients.
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List of participants as of November 20th 2007  
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