Two years ago, at the ECRD in Krakow, we were celebrating the recommendation of the Council of Ministers on an action in the field of rare diseases: this recommendation requests that Member States define and implement a plan or a strategy for rare diseases by the end of 2013 and asks the European Commission to establish a EU Committee of Experts in the field of Rare Diseases (EUCERD) as a forum of stakeholders to propose action points at EU level. Two years on, there is enough evidence to judge the outcome of Recommendation which can be qualified as positive despite the economic crisis. The dynamic of action is still impressive (Figure 1). The EUCERD has been established and fulfills its mission as expected. The publication of the EUCERD annual report on the state of art of rare disease activities in Europe testifies the many achievements [1]. The EUCERD adopted a set of quality criteria for the designation of centres of expertise.
for rare diseases at national level. This work served as a basis for the working
group on centres of expertise in the framework of the Cross Border
Healthcare Directive. All countries are now engaged in the process of
elaborating a plan or a strategy for rare diseases (Figure 2). The recent
developments in genomics now translate into more diagnostic tests for rare
diseases. So far over 1,800 rare diseases can be tested in one EU country.
Targeted funding for rare diseases has also produced its effects, with more
transnational cooperation which translated into the important decision to
establish an International Consortium to fund research: the IRDiRC. The
Consortium will allow more ambitious goals to be set and achieved faster
and it will ease the mobilisation of the critical mass of expertise and
resources whilst avoiding overlaps in research. The Regulation on Orphan
Medicinal Products is still producing positive effects with currently over 70
products with a marketing authorisation in the EU and many more in
development. The Orphanet database became a Joint Action between all
Member States, showing the great degree of willingness to provide unified,
high-quality information to all EU citizens. Last but not least, patient
organisations are increasingly better organised to make their voice heard.
Not only is EURORDIS the voice of patients in Europe, but umbrella
organisations have been established in most countries (Figure 3).

Reference
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A2
State of the art of rare disease activities around the world: overview of
the non-European landscape
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A2

With support from patient associations, political frameworks for rare
diseases have been established throughout the world albeit with varying
definitions for rare diseases.
In the USA, the National Organization for Rare Disorders was instrumental
in passing the 1983 Orphan Drug Act and the 2002 Rare Disease Act,
which includes medical devices and dietary products as orphan products. In 2011, the House passed bills supporting research for undiagnosed diseases and preserving regulatory fee exceptions for orphan drugs.

In 2012, the Canadian government awarded five-year rare disease research grants. With advocacy from the Canadian Organization for Rare Disorders, Health Canada concluded consultations on an orphan drug regulatory framework. Several provinces have implemented orphan drug access programs and expanded newborn screening.

In Argentina, the Geiser Foundation led advocacy resulting in the 2011 Rare Disease Law, obliging health and social systems to provide assistance. A central committee, including patients, will coordinate activities like neonatal screening and patient registries. In 2010, Colombia passed the Orphan Disease Law and hosted the 2nd National Forum of Orphan Diseases. In 2011, Peru passed legislation promoting treatment and a national strategy including diagnosis, surveillance, prevention, care, and rehabilitation.

Through the 1972 Medical Care Program for Specific Diseases, Japan provides medical cost subsidy to patients affected by "56 rare and intractable diseases." The 1993 Orphan Drug Law supports research and development. In 2008, Supporting Organizations for Patients with Rare Diseases was formed.

Since 1991, Singapore’s Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. The Taiwan Foundation for Rare Disorders helped secure the Rare Disease and Orphan Drugs Act in 2000. Diseases affecting fewer than 1 in 10,000 that are officially recognized are eligible for medical coverage. In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000. The Genetics and Rare Disease Centre supports national reference centres and research.

In China, in 2011, medical professionals called for legislation to support healthcare, research, orphan drug development, and epidemiological studies for diseases affecting fewer than 1 in 10,000. Australia’s 1987 Orphan Drugs Policy makes available rare disease drugs, based on US regulatory information. In 2010, consultation for a national strategy was posted online. In 2012, Rare Voices Australia was formed.


A3
National plans: case study Belgium
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In October 2011 the Belgian Fund for Rare Diseases and Orphan Drugs, a consortium of stakeholders supported by the King Baudouin Foundation, handed over the recommendations and proposed measures for a Belgian Plan for Rare Diseases. In follow-up of the EU recommendations to issue national plans by 2013, the Minister of Public Health and Social Affairs
Rare diseases are very complex and require comprehensive strategic planning. Because health and social services were not well adapted to the needs of those most vulnerable patients, a first National Plan for Rare Diseases has been implemented in France between 2009 and 2010, acknowledging the specificities of rare diseases. Information was developed for patients, professionals and the general public (in Orphanet database and Maladies Rares Info Service helpline), access to high quality care and treatment was facilitated with the designation of 131 centres of reference at National level, and 502 centres of competence at regional level, and the coordination and funding of research was improved, with a 200 million Euros budget overall.

After a thorough evaluation, the second French Plan consolidates previous achievements, and reinforces European and international cooperation. The aim is to diagnose and cover each and every disease and patient. 20 university laboratories of genetics have been equipped with Next Generation Sequencing technology for clinical use. Research, public health and social authorities, health agencies, patients associations, experts, scientific societies are working together to improve the evaluation of the needs of those most vulnerable patients, a first National Plan for Rare Diseases in Member States (2009/C 151/02) (8 June 2009) and most recently in the Directive on the application of patients’ rights in cross-border healthcare (2011/24/EU) (9 March 2011) as a means of organising care for thousands of heterogeneous RD affecting scattered patient populations across Europe. The European Union Committee of Experts on Rare Diseases (EUCERD) http://www.eucerd.eu issued a set of Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States [1] to guide Member States (MS) in this area.

The scope of CE in terms of disease coverage is an important issue as the expectation is to provide CE for all RD patients’ needs at national level. CE were grouped by medical area. Three or more MS have designated centres for: juvenile arthritis/pediatric rheumatological diseases, developmental anomalies and malformations/dysmorphology, hereditary cardiac diseases, dermatological diseases, epidermolysis bullosa,editary diseases, haemophilia/constitutional bleeding disorders, mastocytosis, hereditary diseases of the metabolism, porphyrias, epilepsies, neuromuscular diseases, amyotrophic lateral sclerosis, pulmonary diseases, severe pulmonary hypertension, cystic fibrosis, hereditary immune deficiencies, ophthalmological diseases, genetic kidney disease, cranofacial anomalies, neurofibromatosis, Rendu-Osler disease.

On the basis of this experience, a consensus can be thus identified that centres are required for around 12 groups of RD, 30 subgroups, and 26 individual diseases where centres currently exist in two or more countries. Most of these groups of RD fit into the traditional organisation of healthcare by medical area. However some grouping outside of traditional medical specialities is necessary, e.g. diseases of connective tissue, rare bone diseases, neurofibromatosis, multimalformation syndromes with intellectual disability, mitochondrial diseases, any multi-systemic complex disease, etc. This analysis could be of use for MS currently considering the organisation of CE for RD. This work was carried out by the EUCERD Scientific Secretariat with the support of EC Joint Action N°20082291.

Reference
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European Reference Networks: developing a EUCERD opinion
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The establishment of European Reference Networks as laid out under the Cross Border Health Care Directive (CBHCD) is a major opportunity for the rare disease community. There have been many successful networks for rare disease groups, but their establishment has been ad hoc and funding streams variable. Sustainability has been a major challenge. Although the assessment of the quality of these networks has not been systematic, nonetheless networks have succeeded in establishing important infrastructure including disease specific registries, shared tools such as tele-expertise and the production of disease specific guidelines and training pathways. Within the CBHCD it is envisaged that European Reference networks will be established, and these will not only relate to rare diseases. These networks will primarily link nationally designated centres of expertise. Within the EUCERD a process is being followed to inform the CBHCD committee on the specific issues relating to ERNs for rare diseases. These recommendations relate to areas of designation and governance, capacity building and resources to support ERNs and quality assurance.

Scope of centres of expertise for rare diseases in European countries where they exist
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The development of centres of expertise (CE) and European Reference Networks (ERN) in the field of rare diseases (RD) is encouraged in the Council Recommendation on an Action in the Field of RD (2009/C 151/02) (8 June 2009) and most recently in the Directive on the application of patients’ rights in cross-border healthcare (2011/24/EU) (9 March 2011) as a means of organising care for thousands of heterogeneous RD affecting scattered patient populations across Europe. The European Union Committee of Experts on Rare Diseases (EUCERD) http://www.eucerd.eu issued a set of Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States [1] to guide Member States (MS) in this area.
The recommendations will be discussed in a series of meetings in 2012, with the aim of producing a EU-CERD recommendation on ERNs for rare diseases by the end of the year in line with the timeline of the cross border health care directive.

A7
Can the cross-borders directive improve the quality of genetic testing in the future?
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A survey of a series of genetic centers in Europe [1] showed that today a substantial number of samples from patients are being sent abroad for DNA analysis to laboratories in Europe, the US or elsewhere in the world. 66% of the 233 laboratories, which replied to the questionnaire, received samples from other countries and 47% sent samples to other countries. In absolute numbers this would mean that about 1/4 of all samples cross borders today. This traffic will only further increase when the European cross-border directive 2011/24 [2] will be activated. This directive states that “Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 25 October 2013”. The focus of these regulations and provisions should be on the quality of the services wherever the patients or their samples are being examined [3]. The quality management of the facilities i.e. evidence that they follow international guidelines, e.g. those published in 2007 by the OECD [4] or are accredited under the ISO 15189; that appropriate pre- and post-testing counseling is guaranteed; particularly when whole genome or exome sequencing is considered; and that patient representatives are involved in the implementation of these processes, should become compulsory. The Direct to Consumer (DTC) testing facilities, available through internet, have forced geneticists to reconsider the way genetic services are provided. A positive aspect of this development is that issues, such as information for prospective consumers, counseling and support, consent, data protection, interpretation of results, and others have received much more attention than in the past. The EuroGentest Network of Excellence (NoE), supported by DG Research (2005 – 2010) and its successor as Coordination Action (2011-2013), together with the European Society of Human Genetics, have worked very hard on the improvement of the quality of the genetic services in Europe. Nevertheless, such efforts by ’volunteers’, will not suffice once the new Directive is in place. To guarantee quality services to the consumers we will need harmonisation of the services, which can only be achieved at the European level through the existing facilities of the commission. There is a need for a regulatory framework for Quality Assurance (ISO accreditation), for test development and use, harmonised legal, regulatory and healthcare policies for pharmacogenetics as well as a the finalization of the revision of the IVD directive, preferably in harmony with the ‘Global Health Task Force’.

References

A8
Transition from childhood to adulthood in Duchenne muscular dystrophy (DMD)
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A8

Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy, affecting 1 in 3500 live male births. Mutations in the X chromosome result in an absence of dystrophin, causing progressive muscle degeneration and loss of ambulation by the early teens with respiratory, orthopaedic and cardiac complications. Without intervention these complications lead to death at a mean age of 19 years. However, the natural history of DMD is well-known and can be changed with proactive multidisciplinary management to address predictable complications [1]. Better care has led to a growing adult DMD population, challenging the notion of DMD as a “paediatric” disease. This population faces particular challenges, not only medical (e.g. associated with long-term steroid usage, orthopaedic, ventilation, and cardiac, gastrointestinal or genitourinary problems), but those associated with wider issues of transition. These include medical transfer from paediatric to adult services, and social transition to independent living and full societal inclusion. Transition arrangements to adult facilities, which vary considerably between clinics and countries, are usually needed due to regulations governing access to paediatric services. As DMD requires co-ordinated care, this move from cohesive paediatric clinics to disjointed adult services is often problematic, and a successful transfer should be the culmination of a period of planned transition. Wider social transition, enabling independent living and further education/employment, is also very important(2). However, as with many other disabilities, adults with DMD face obstacles to full participation. Planning is crucial, and preparation for adulthood should be considered in partnership with families as part of a comprehensive package of psychosocial care from diagnosis. Recent research suggests that despite legal and health frameworks, DMD transition care in the UK is highly diverse and sometimes lacking[3]. Positive experiences were characterised by forward planning and long-standing relationships between the family and healthcare professionals. In Denmark an integrated model of care is provided by the National Rehabilitation Centre for NMDs (RCfM), which supports families from diagnosis with a comprehensive programme of courses and interventions at significant life milestones [4]. Patient advocacy groups also play a very important role in transition, particularly through programmes such as the MDA Transitions Center. Although there is no one-size-fits-all model for DMD transition care, some features seem particularly important to successful transitions. These include continuity and stability in care; the integration of wider social issues; the involvement of the young man and his family in decision-making; and the support of patient advocacy groups.


References

A9
Developing a national plan for rare diseases in Germany through concerted action: the national action league for people with rare diseases
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Introduction: To improve health and well-being of people with rare diseases and to implement the Council Recommendation of the European Union on rare diseases the German Federal Ministry of Health, in cooperation with the Federal Ministry of Education and Research and the National Alliance of Patient Groups for Rare Diseases, has initiated a national action league for people with rare diseases - Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE). NAMSE brings together all key bodies and organisations of the German health care system (27 in total) to enable concerted action based on the adoption of a joint declaration. In four working groups on “Information, Diagnosis, Care/ Centres/Networks and Research” of NAMSE recommendations are being developed.

Results: The process of identifying and later labelling national centres of expertise and their participation in European Reference Networks is of central importance. Three types of centres have already been defined on the basis of specific criteria (Figure 1). These can be differentiated in disease/disease-group specific medical care functions or structures and non-disease specific activities (important for all rare diseases). To guide patients and health care professionals through the health care system a common, quality assured information platform, pooling the existing information services, is discussed.

NAMSE pursues a patient-centred approach respecting the patients and their concerns. Therefore seamless care pathways are a recurrent theme throughout the planned measures. They are considered to accelerate the diagnosis and are of central importance for patient without diagnosis.

Conclusions: Each working group of NAMSE has developed a set of advices. For all special indicators with targets and a timeline are being developed to evaluate their effectiveness after their implementation. Therefore an evaluation board comments all indicators proposed for the different advices. All advices have to be prioritised based on their probability of implementation by a consensus conference. The draft of German National Action Plan will be assigned to the Federal Ministry of Health in 2013.

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Classification and coding of rare diseases: overview of where we stand, rationale, why it matters and what it can change

Carl Linnaeus published one of the most important early disease classifications in 1759, classifying a total of 325 diseases into 11 classes and 37 orders. This work, Genera morborum, provided a source of inspiration for a number of other classifications which paved the way for the classification of Bertillon in 1891 that subsequently became the first edition of the International Classification of Diseases (ICD). The latest edition of the ICD (ICD-10), includes nearly 500 rare diseases, only about 240 of which have a specific ICD code. With roughly 8000 named RDs and at least 100 new RDs characterized yearly, this means that less than 3% of RDs have codes in the ICD-10. Correspondingly, rare diseases have been largely invisible in national mortality and morbidity statistics, and policy makers have tended to allocate much fewer resources for research and clinical care in the field of rare diseases than might be expected given their overall prevalence of at least 5% of the population.

The new edition of the ICD (ICD-11, which is due by 2015) offers an opportunity to address these shortcomings. A Topic Advisory Group on Rare Diseases chaired by Ségolène Aymé has been coordinating efforts to create a comprehensive classification (nosology) of rare diseases for the new ICD. The classification is to follow a primarily clinical approach, and a polyhierarchy approach is used to include rare diseases affecting several body systems are included in each relevant chapter.

Phenotype ontologies such as the Human Phenotype Ontology complement disease classifications by providing a tool to describe and analyze the spectrum of signs, symptoms, and other abnormalities that people with the disease in question may display. A large number of different vocabularies and ontologies for human phenotype have been developed for different goals and users, but it will be essential to improve interoperability between
these terminologies in the future to in order to make maximum use of all available resources.

Classifications, ontologies, and other computational resources for human disease and phenotype will allow more accurate statistics about prevalence of rare diseases, better allocation of health care resources, and an improved ability to perform computational analysis of human disease manifestations for differential diagnosis and clinical decision support systems. Additionally, they will provide a basis for deep phenotype analysis to characterize the natural history of rare diseases and to discover clinically actionable complications and risks.

A11 Speeding up research with the Semantic Web

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Data for Rare Diseases are often distributed. Ideally, we can combine relevant data and biological insights from any place in the world and use it directly in our own computational analysis. However, too often data is poorly described making it hard to find, hard to assess its quality, and hard to integrate with other data. A valid question is: ‘Why can’t we analyse it as if it came from one global database?’ Here we introduce the Semantic Web as an enabling technology for making data interoperable and thereby expediting biological insight.

The Semantic Web ‘language’ is RDF: the Resource Description Framework. It uses the ‘hyperlink’ mechanism known from the internet to refer to data instead of web pages. Meaningful relations are specified as triples: subject, predicate, object. For example, ‘CAPN3’, ‘interacts with’, ‘ParV8’. Written in RDF:

http://www.uniprot.org/uniprot/P20807
http://www.conceptwiki.org/index.php?concept=adfd604e-5c2b-11df-b0cb-001517ac506c
http://biozfdrf.org/geneid/29780

While RDF is meant for computers, we see that: (i) RDF triples convey meaning; (ii) hyperlinks specify the location of data, which might be different databases (even within a triple); (iii) data items are also references to other RDF documents with more triples (e.g. try http://www.uniprot.org/uniprot/Q13547 in a browser). A hyperlink can be in any number of triples, effectively creating the world wide database of meaningfully linked data that is needed in the study of Rare Diseases. Ontologies can also be encoded in RDF, thereby extending the functionality to a global knowledge base. New experiments and discoveries can continually add information to this knowledge base.

For example, the Semantic Web can help us to find drug targets for Rare Diseases. For this purpose, OpenPhacts [1] is integrating compounds from Chemsperid [http://chemspider.com], proteins from UniProt [http://uniprot.org], pathways from WikiPathways [http://wiki.pathways.org], and documents from PubMed [http://www.ncbi.nlm.nih.gov/pubmed]. We also make DNA sequence variations from the Leiden Open Variation Database [LOVD [http://www.lovd.nl]) available in RDF, and visualised via the UCSC genome browser.

However, a number of barriers must be overcome. First, databases pre-dating the Semantic Web are used abundantly and must be integrated. This is usually an expensive and tedious task. Secondly, building a scientific reputation often conflicts with data sharing. Therefore, we have developed a data publishing framework called Nanopublication: an application of RDF that links authorship to individual datum (tribution). This creates a transparent and equitable incentive for data sharing. Nano publications also provide incentives for the exposure of legacy data.

In conclusion, Nano publications and Semantic Web technology makes data easier to find and directly applicable to integrative analyses.

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Reference

A12 Professional clinical guidelines for rare diseases: methodology

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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A12

Guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances[1]. They concern often complex diagnostic or therapeutic strategies with several possible interventions at each step, where each intervention has to be assessed and compared with other possible interventions at short and long term for efficacy, effectiveness, efficiency (optional), side effects, quality of life, acceptability, benefits/risk ratio. For common diseases, the methodology and the different steps of the guidelines development process have been established and apply the principles of evidence-based-medicine. Developing guidelines for rare diseases (RD) is more difficult, because of the lack of sound evidence, surveys of clinical practices, data about patients’ opinion and ethical reflexions [2].

During the 1st French national plan for rare diseases, HAS (French National Authority for Health) was mandated to define a method to develop guidelines for RD - which are called PNDS (National Diagnostic and Treatment Protocols) in France - and coordinate their writing with the RD centres of reference [3]. A PNDS constitutes a best practice reference document for healthcare professionals in charge of rare disease patients. Based on it, HAS drawn up a ‘List of Procedures and Services’ (LAP), which includes all of the diagnostic tests, drugs, medical devices and services that appear justified in providing care to a patient. From 2005 to now, only 47 PNDS were published and 8 are on-going, because the development method is complex and expertise is scarce; 135 new PNDS projects are pending. In the 2nd French plan for rare diseases it was proposed to define a simplified method for developing the PNDSs, in order to speed up their production, by using the protocols already developed by the RD reference centres, incorporating and adapting recommendations devised by foreign groups of experts when appropriate; and setting criteria for prioritisation of the PNDS production. This process is on its way.

Orphanet has launched the production of emergency guidelines, written by centres of reference in collaboration with emergency department practitioners, patient organisations, and validated by a special reading group, with members of emergency medicine learned societies. They include a short description of the disease, recommendations for immediate care, transport and orientation, before getting to the emergency ward, recommendations for the emergency ward (complications to be looked for, diagnostic and therapeutic particularities, drugs interactions, anaesthesia), recommendations for patient’s and family’s comfort, list of contacts 24h/24 [4].

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A13 The involvement of patients in developing clinical guidelines

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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A13
My two children were diagnosed with Alström Syndrome when aged 15 and 18 after a long battle to get their multiple medical conditions recognised as a syndrome. After diagnosis it was apparent that there were no experts in the condition in the UK and little information. To address this I founded the charity AS UK to bring together the 7 known cases with the doctors who had worked with my children. Their experience of the disease increased overnight primary through talking with parents and patients who were the only experts in the disease. The first meetings were held in a hotel, later we moved to Torbay hospital using equipment at the weekend when no one else was using it. The ethos of listening to patients and parents as experts was fundamental to the development of the clinics. In 2006 we were successful in getting the NHS National Specialised Commissioning Group to recognise the importance of the clinics and they now fund children’s clinics at the Birmingham Children’s Hospital and adult’s clinics at the Queen Elizabeth Hospital Birmingham. AS UK was the first charity to be funded as an equal partner with the two hospitals. Today 55 patients are seen at the two clinics and expertise continues to grow. In 2009 AS UK was successful in gaining Big Lottery Medical and Scientific Funding and research has started. A database has been set up and tissue bank begun. In 2010 AS UK became a partner in an EU wide project with two other rare conditions EURO-WASB (Wolfgram, Alström and Bardet Biedl) The overall aim is for this register to be a key instrument to increase knowledge on these rare diseases, improve the lives of affected people through better management, and to develop clinical research. In 2011 AS UK started an Asian mentoring scheme in response to the high number of Asian patients in families whose culture practice consanguinity. From the initial 3 Asian patients known to us we now know of 24 patients most are related. This is an area we are developing further. From small beginnings this patient led initiative has shown how an ultra-rare condition can go from obscurity to gaining NHS specialised clinical services, National and European research projects, medical handbooks, patient information, clinical guidelines and improved quality of life for patients.

A14

How reference networks develop, implement, and monitor guidelines
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Rare diseases pose many challenges. A paucity of randomised controlled trials for most conditions means that best-practice care guidelines are often non-existent or poorly developed. Where they exist, healthcare professionals may be unaware of them. Furthermore, evaluation of guidelines is difficult, as traditional methods of health-care research (such as hospital admissions and mortality statistics with ICD codes) are not applicable to rare diseases. The CARE-NMD project to improve care for Duchenne muscular dystrophy (DMD) provides an example of how Reference Networks may develop, implement and monitor rare disease guidelines.

The development of the DMD care guidelines was facilitated by the US Centers for Disease Control, and led by patient organisations, translational research networks, and health agencies. In the absence of overwhelming clinical trial evidence, 84 international experts used the RAND/UCLA Appropriateness Method (RAM) to generate consensus on the necessity and appropriateness of clinical interventions and assessments. Yet despite the guidelines, many DMD patients do not receive the treatment they describe. CARE-NMD has established a Reference Network of care centres for DMD in Europe, to develop the guidelines in clinical practice and identify reasons for non-compliance, and assess guideline impact on quality of life. Dissemination, via professional and patient networks, has addressed the problem of a lack of awareness of guidelines for this rare disease. Strategies have included presentations at meetings, journal and website publications, media interviews, and professional training courses tailored to local needs in East European partner countries. The ‘Family Guide’, a more accessible version of the care guidelines, is now available in over 20 languages and has been very well received. To monitor implementation, the project has conducted the largest ever cross-sectional study of DMD patients and their families (n=1677, response rate 66%) across 7 European countries. This assessed – via process and outcome indicators – whether the care they receive aligns with the consensus guidelines, and reported quality of life. In addition, a survey of healthcare professionals has been distributed to care sites in these countries via the Care and Trial Site Registry (CTSR), an online self-registration platform for neuromuscular centres developed by the TREAT-NMD network of excellence. This now includes information on patient care, care settings, research activities and clinical trial capabilities of more than 200 sites. A Reference Network such as CARE-NMD enables implementation, assessment and monitoring of care guidelines for rare diseases. The data it gathers will be crucial in further developing and refining guidelines.

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A15

Training medical students on rare disorders
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A significant challenge faced by families and patients affected by rare diseases is the general lack of awareness among medical professionals of the sheer number of rare diseases that exist and the sometimes devastating impact a rare disease can have on all aspects of a person’s life. Many doctors believe that they are unlikely to come across a rare disease in their professional careers and simply do not realise that it is not rare to have a rare disease. The School of Medicine and Medical Science in University College Dublin has developed an innovative educational module that aims to increase awareness of rare diseases among medical students.

We have developed an elective module with contributions from patient organisations, clinicians, academic staff, research scientists and pharmaceutical industry. The module is offered to undergraduate medical students in the final year of their pre-clinical training. The module was designated a grade neutral module which makes no impact on the student’s overall grade that academic year. The method of assessment had to reflect the overall aim of the module, which was to increase awareness of rare diseases among medical students and not examine the level of scientific knowledge of a host of rare disorders. Assessment of the module had two distinct components. The first was a reflective learning journal that had to be completed by the student at regular intervals during the semester. Students also had to prepare an information pamphlet suitable for a medical professional detailing genetic basis, symptoms and treatment of the disorder chosen, as well as resources for further information. Feedback from the module has been extremely positive. All contributors were very enthusiastic about the module and very keen to be involved. Feedback from the students was exceptionally complimentary. Many students commended the multidisciplinary approach taken. The highlights of the module were the talks given either directly by the patients themselves, or by representatives of patient support organisations. These accounted for approximately 30% of the lectures. There is no doubt that these sessions proved both inspirational and memorable for the students. Entries to the reflective journal described how the module and in particular the experiences described by the patients prompted many students to research particular disorders in more depth and made a lasting impact on them. The feedback from the module has been overwhelmingly positive and shows the advantage of using a multidisciplinary approach where the student can hear directly from the patient, learn about the importance of research and advances in treatment of rare disorders and identify resources that will be useful in their future professional careers.

Acknowledgements: The author would like to acknowledge the contribution made by IPPSO in facilitating this initiative.
A16
The Italian project to increase health professionals’ training and awareness on rare diseases
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Background: The scarce knowledge of rare diseases among family pediatricians and general practitioners who operate at local level and in frequent contact with rare disease patients is seen in Italy as one of the causes leading to delay in diagnosis and to the lack of reference to a centre of competence.

A project aimed at the training of these health professionals was started in February 2009 by the Italian Federation of Rare Diseases UNIAMO with the societies and federations of family paediatricians and general practitioners with the support of FARMINDUSTRIA, Association of Pharmacists.

The main aims are to train participants to develop a new diagnostic sensitivity but also in the high complexity care of the RD patient (child or adult), to lay the groundwork for the establishment of a handover protocol which allows the RD patients and their family to benefit from a real continuity of care from pediatric to adult age, being this shift of competence now completely random and to create trainers able to transfer this knowledge and these messages in different contexts, at first regional and then provincial, through the organisation of local educational courses as part of the required upgrading of the different health professionals.

Method: The format of the courses is developed in two parallel sessions and two plenary sessions. The outset is focused on the concept of network. It is thereafter presented.

Results: As for January 2012 11 courses took place in 11 different regions with a total of 619 participants. In the current year 6 courses are to be held in other regions.

Conclusions: The increased knowledge among family doctors and pediatricians will better the quality of life of rare disease patients.

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1 Italian Federation of Family Doctors FIMMMG 2 Italian Federation of Paediatricians FIMP.
3 Society of Pediatrics SIP Italian Society of Genetic Pediatric Diseases and Congenital Disability SIMGePeD.
4 Italian Society of General Medicine SIMG 5 Italian Society of Human Genetics SIGU.

A18
Spina Bifida and primary prevention
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Spina Bifida is a neural tube defect (NTD), which occurs within the first 25 days of pregnancy and affects around 1 in 1000 pregnancies in Europe. It cannot be cured, although improved medical interventions mean that many people with Spina Bifida live into old age and have a good quality of life. However lifelong follow-up is required. IF is an umbrella organisation of national organisations of persons with Spina Bifida and focuses on primary prevention, access to health and the right to life. Around 70% of Spina Bifida can be prevented by a daily intake of Folic Acid two months prior to conception and two after. With Folic Acid the same child is born without Spina Bifida. Access to life-saving treatment of new-borns with Spina Bifida is in discussion. IF strives for the right of treatment of all new-borns with Spina Bifida. Spina Bifida became a rare disease because of prenatal detection and terminations of pregnancies and not because of primary prevention. Several hospitals closed their coordinated care units for Spina Bifida. Research decreased and Spina Bifida is perceived by many professionals as a solved problem. Prevention of most of the birth defects starts before conception. That’s why IF co-organised in October 2010 a European Preconception Care conference in Brussels. When a couple plans their pregnancy they should take all measures to prevent possible problems: not drinking alcohol, not smoking, not taking drugs and taking Folic Acid. IF advocates for fortification of staple food with Folic Acid and set up a
European awareness campaign. Most women do not know about the risk of having a baby affected by an NTDS. This is even truer among women of lower socio-economic status where the incidence is higher. IF produced two reports on Prevention of NTDS’s in Europe and organised a hearing in the European Parliament. To improve peri-conceptional folic acid levels women of childbearing age can only be reached by a combination of counselling, intake of Folic Acid, fortified staple food and further investment in monitoring and research. Persons with Spina Bifida make the need for prevention visible and IF believes that it should be integrated in National Plans for rare diseases. In Belgium we had a first success. A crucial orphan drug in the care for the neurogenic bladder is taken for approval.

A19

Finding new medicines to fight CF: multiple steps of a success story
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Background: Cystic fibrosis (CF) is a major life-limiting genetic disease leading to severe respiratory symptoms caused by mutations in CF transmembrane conductance regulator (CFTR), a chloride channel expressed at the apical membrane of epithelial cells. Absence of functional CFTR from the surface of respiratory cells reduces mucociliary clearance, promoting airways obstruction, chronic infection and ultimately lung failure [1]. Despite major advances treating the symptoms, which pushed survival beyond the second decade (~25 years in Europe), CF is still a life-limiting condition [2]. However, to further increase CF patients life expectancy, CF needs to be treated beyond its symptoms, i.e., through treatments addressing the basic defect associated with CFTR gene mutations [3]. So far ~1,900 CFTR mutations were reported [4], but one single mutation, F508del remains the most common one, as it occurs in ~90% of CF patients in at least one allele [5] and is associated with a severe clinical phenotype. Despite that most efforts are focused on correcting the F508del-CFTR which causes intracellular retention of the mutant channel at the endoplasmic reticulum (ER), several additional strategies are emerging to rescue other (rarer mutations) which, in some populations, also have high prevalence. To this end, CFTR mutations are usually grouped into functional classes, towards a “mutation-specific” therapeutic approach by which mutations within the same functional class can be corrected by the same therapeutic strategy towards a “personalized medicine” approach [6].

Materials and methods/results: To apply such strategy CFTR mutations are thus classified into six main functional categories [7,8], namely: a) class I mutations (e.g., mutations generating premature stop codons, e.g., R1162X) prevent protein production; b) class II mutations (includes F508del) cause intracellular retention and premature degradation, thus preventing mutant CFTR from reaching the cell surface; c) class III mutations (e.g., G551D) cause impairment in the channel gating (i.e., decreased open probability); d) class IV mutants have substantially reduced flow of Cl- ions through the CFTR channel (e.g., R334W); e) class V mutants include mostly alternative splicing mutants (e.g., 3272-26A>G) which allow synthesis of some normal CFTR mRNA (and protein), albeit at very low levels; and v) class VI mutants (e.g., c.120del32 [9] or membrane- rescued F508del) impair the plasma membrane stability of CFTR.

Conclusions: Several therapeutic strategies adopting this “mutation-specific” approach are currently under experimental testing or clinical trial [3,6]. Based on the current “drug pipeline”, these are expected to rise in numbers very soon.


References

A20

Exon skipping for DMD
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Duchenne muscular dystrophy (DMD) is a severe, progressive muscle-wasting disorder, while Becker muscular dystrophy (BMD) is milder muscle disease [1]. Both are caused by mutations in dystrophin, a protein, which stabilizes muscle fibers during contraction by linking muscle actin to the extracellular matrix. In DMD patients mutations disrupt the open reading frame, generating prematurely truncated, nonfunctional dystrophins [2]. In BMD patients, mutations maintain the reading frame allowing production of internally deleted, partly functional dystrophins. The exon skipping approach uses antisense oligonucleotides (AONs) to induce skipping of targeted exons during pre-mRNA splicing, with the aim of reading frame restoration, converting of the severe DMD into the milder BMD phenotype [3]. This approach is mutation specific. However, as mutations cluster in a few hotspots, skipping of some exons applies to larger groups of patients (e.g. exon 51 skipping applies to 13% [4]). After promising results in cultured cells and animal models where AON treatment allowed in dystrophin restoration (reviewed in [3]), a first clinical trial was performed by LUMC and Prosensa Therapeutics, where four DMD patients where intramuscularly injected with an exon 51 (GSK2402968/ PRO051, a 2-O-methyl phosphorothioate (2OMePS) AON) [5]. Exon skipping and dystrophin restoration was observed for each patient in muscle biopsies taken 4 weeks after the injection.

Towards systemic application, studies in animal models revealed that dystrophic muscles facilitated uptake of 2OMePS AONs and that subcutaneous delivery was feasible [6]. In a subsequent clinical trial, patients were subcutaneously injected with 2OMePS AONs targeting exon 51 [7]. Dystrophin was restored in a dose-dependent manner at levels up to 15%. All patients were enrolled in an open label extension study and have received subcutaneous AON injections at 6 mg/kg for over 2.5 years. A pivotal, double-blind, placebo-controlled multicenter trial for exon 51 skipping is currently ongoing (coordinated by GlaxoSmithKline).

In parallel, preclinical studies to further optimise treatment regimes are in progress as well as clinical trials for additional exons for exon 44 skipping (PRO044, applicable to 6% of patients). Trials are planned for exon 45 and 53 skipping (PRO045 and PRO053, both applicable to 8% of patients). The mutation specificity of the approach poses challenges to drug development regulations. A concerted effort of academic researchers, industry, regulators and patients is needed to adapt regulations to enable application of these personalised medicine approaches to rare diseases.

References
The EPIRARE project[1] aims to build consensus and synergies for the development of an EU platform for rare disease registries and to address relevant regulatory, ethical and technical issues associated with the registration of rare disease patients. To this aim, a survey was carried out among existing rare disease registries and databases to get information on their objectives, needs, governance mechanisms, sustainability, and measures for the compliance with regulatory and ethical requirements and for quality assurance, as well as expectations from and opinions on a registry platform. Responses were received from 255 registries, of which 220 active registries were selected based on the completeness of the response. Among responding registries, 18, 61, 17 and 3% were international, national, regional or local. The fraction of registries population based, hospital based and following case series or cohorts was, respectively 56, 23 and 20%. Epidemiological and clinical researches were the most declared scopes (respectively 71, 61% in a multiple answer question) and characterized two clearly different clusters of registries. Treatment efficacy and safety was the scope indicated by 45% registries. A wide heterogeneity is found regarding the disease coding system used, with 62% using their own or no code. Twenty-seven percent registries are established by law or to comply with regulatory requirements, while 73% as part of research projects or as an autonomous decision of clinicians or patients. Half of the registries shares data with other registries and 33% with centres of expertise, while 30% do not exchange data neither with them or with bio banks. Registries were established with no initial funding (21%) or with funding by public authorities (37%), industries and foundations (21%), research institutes and hospitals (25%), patients associations (16%) and the European Commission (15%). After the initial phase, more registries (25%) are run without specific funding; frequency of funding sources remains stable but for the European Commission, which decreases to 6%. Different procedures are applied for quality assessment, but each of them is applied by 46-58% registries. A main governing body is not present in 34% registries and 48% registries have no policy to ensure long-term sustainability. Main needs expressed are financial support, improved communication strategies and more extended geographical coverage, data sources and registry networking. The vast majority of respondents (80%) is favourable to a platform for registries and 60% submit that new legislation can facilitate registration. Popularity of expected platform services are technological tools, specific expert advice and resources.

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clinical trials in rare diseases is often more expensive on a per patient basis. R&D investment must therefore be recovered with lower volume of sales, leading to higher prices for OMPs than other medicines. Scientific advances offer new perspectives by making treatable and curable new important diseases. Policy makers must reward innovation based upon unmet need and patient outcome. Technology platforms, franchises and global reach are three potential levers at company level to sustain profitable development of OMPs. New and innovative pricing models based on rational value assessment and realized by contractual agreements could address the issue of affordability while taking into account country differences.

While there are strategic choices that manufacturers can make to overcome barriers to contribute to public health goals, there are many other factors that inhibit effective or optimal access to new treatments that are beyond industry’s control or influence. Social, ethical, political considerations must guide improved access so that all patients can access OMPs in an equitable manner. Political will is needed to allocate the necessary funding within health budgets and support a solid rare diseases public health policy.

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A24

Mechanism of coordinated access to orphan drugs

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Context: Although the EU Council stated(1) that “all health systems in the EU aim to make provision, which is patient-centered and responsive to individual need”, numerous sources show important and unacceptable differences in access to orphan drugs in the Member States of the European Union (EU COM(2), EURORDIS(3,4), BE EU Presidency(5,8), EU Council(6)). With this regard, in the context of the 2010 Belgian EU presidency initiative on ‘Innovation and Solidarity’ and within the framework of the process on corporate responsibility in the field of pharmaceuticals(7), EU Commissioner Tajani launched the project Mechanism of Coordinated Access to Orphan Drugs.

Objectives: Design a concrete operational mechanism of coordinated access to orphan drugs for patients, stakeholders and Member States. Through coordination and cooperation between stakeholders and Member States at EU level, real access is to be provided to orphan medicinal products for patients with unmet medical needs and for whom these solutions would otherwise be out of reach – in an affordable and sustainable way (‘real life access’).

Methodology: The project is managed by Belgium (NIHDI), supported by the European Commission (ENTR, SANCO, COMP, MARKET) and Eminet. Thirteen other Member States (Austria, Estonia, Finland, France, Greece, Hungary, Italy, Malta, Netherlands, Poland, Portugal, , Spain, Sweden) are participating, together with the different stakeholders (AIM, EPF, ESIP, EURORDIS, CPME, EFPIA, EGA, EuroPaBio, GIP). Three work packages (WP) cover the three different aspects of granting effective access to medicines (WP1: Identifying and assessing a relevant orphan drug , WP2: Selection of the target population and mechanisms of funding , WP3: Treatment ). In each WP operational steps and implementing activities were identified. Feasibility at present and opportunities for near future development of desirable coordinated activities were studied, and no-go solutions were documented and rejected. Integrating the three WP will lead to the development of implementable scenarios for pilot projects and result in policy recommendations.

Discussion: Guaranteeing an added value for all stakeholders and especially from a patient’s perspective through cooperation and coordination is the main objective of the project. Although coordinated access at an European level will be organised on a voluntary basis, at some point in time, some sort of commitment from the participating partners is required. Moreover, it is crucial that the subsidiarity principle is not compromised in any way. Duplication of efforts will be avoided and previously made investments – in terms of financial and human resources, expertise and experience - (ex. by ElNet HTA, EMA COMP, EUCERD, CAVOD) will be valorised.

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A25

A coordinated EU approach to informed access decisions: CAVOD process proposals – the possibility to turn concept into reality?

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Background: The European orphan legislative framework has been successful in delivering approved new treatments since its establishment in 2000. But the data needed to reach a positive risk-benefit analysis for regulatory approval often falls short of that needed by Member States to justify reimbursed availability to patients. This gap leads to differences in availability of new orphan medicines. The CAVOD proposals build on more than 12 years of formal collaborative approaches to European orphan drug policy, which have consistently agreed on the need to gather and share information at a European level. They would establish a process for the exchange of knowledge from the earliest stage in a drug’s development, through to in-life outcomes after a treatment is available to patients, with the objective of bundling fragmented know-how to allow the timely production of well-informed decisions on national pricing and reimbursement, while respecting existing roles, responsibilities and competences.

Methodology and context: The approach intends to optimise processes, notably at four key time points. All activities should be based on existing and planned roles, responsibilities and legislative frameworks, and in collaboration between all parties involved at Member State and EU level, including regulators, HTA bodies, payers, patients and the sponsor. Early dialogue between the EMA, regulators and HTA bodies should be instigated at the time of orphan designation and the assumption of significant benefit. This should continue through protocol assistance to the Marketing
Authorisation and confirmation of the significant benefit. Between the CHMP opinion and the granting of the Marketing Authorisation, the available information on a drug should be gathered in a useable form and additional information requirements defined, together with a plan for development to be undertaken by the Marketing Authorisation Holder. This will give HTA bodies access to the widest pool of in-use data on a pan-European basis, although the appropriate methodological tools to evaluate orphan drugs will need to be developed.

Proposed results: It is intended that the collaboration at European level on the clinical added value of an orphan medicinal product will bridge the gap of data generation and availability between what is needed to reach a positive risk-benefit analysis and what is needed to facilitate understanding of the appropriate positioning of a product in the therapeutic arsenal for a given rare condition within national healthcare systems. This should be a voluntary process carried out on a case-by-case basis. Uptake will be a key measure of success, because use of the system will largely depend on its ability to deliver a more streamlined approach. Implementation could start already where the elements are in place, while additional required elements are being developed.

A26
Market access of orphan drugs and the role of multi-criteria decision making
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A26

Background: A number of factors play a role in market access of orphan drugs, such as the extent to which an orphan drug meets a medical need; existence of alternative health technologies; disease prevalence; number of orphan drug indications; and added clinical benefit of the orphan drug. How can these factors be taken into account in market access decisions given that there is uncertainty over which factors matter and given that not all orphan drugs meet these criteria to the same degree [1]? Materials and methods: Multi-criteria decision analysis is a technique which enables decision makers to consider multiple criteria in market access decisions. This technique brings together an expert panel which identifies the relevant decision-making criteria and their relative importance. The panel then quantifies the extent to which an orphan drug attains each criterion. The scores of the orphan drug on the different criteria are weighted according to their relative importance and an overall score for the orphan drug is computed. Drugs are ranked according to their score and resources are allocated based on this ranking until the budget is exhausted.

Results: To the best of the author’s knowledge, no multi-criteria decision analysis has in practice been carried out for orphan drugs. However, the following paragraphs illustrate this technique by proposing and justifying three criteria that could be considered in orphan drug market access decisions, i.e. disease prevalence, existence of alternative health technologies, and repurposing. With respect to prevalence, an economic rationale suggests that prices of orphan drugs used for rare diseases with higher prevalence should be lower than prices of orphan drugs used for rare diseases with lower prevalence. Similarly, the price of orphan drugs should reflect the combined prevalence across its indications. The existence of alternative health technologies is a second criterion to consider in market access decisions in the light of the impact of competitive pressures on orphan drug pricing. Finally, orphan drugs which were originally developed for a common disease, but later repurposed for a rare disease are likely to have incurred lower costs of research and development and, therefore, should claim a lower price than an orphan drug which has been developed uniquely to treat a rare disease.

Conclusions: The use of multi-criteria decision analysis would enhance objectivity and transparency of market access decisions for orphan drugs by taking into account societal preferences about orphan drugs for rare diseases.

Reference

A27
Leveraging existing opportunities for improved Orphan Drug approval in the EU
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A27

The EU regulatory framework provides opportunities for increased flexibility and speed for Orphan Medicinal Product (OMP) marketing authorisations, nevertheless the yearly rate of OMP approvals is not increasing [1] and available tools and procedures are used infrequently. According to a review of approval timelines from 2001-2010 [2], FDA median total review time for OMPs (235 days) was almost 5 months faster than the median EMA review time (381 days). Furthermore, FDA approves OMPs 87 days faster than novel therapies overall, whereas EMA takes 15 days longer. One driver for this striking difference between FDA and EMA review time for OMPs seems to be FDAs granting of a Priority Review which was the case for 78% of orphan product applications between 2006 and 2010 [3]. An Accelerated Review at EMA was granted only for ~3% of approved OMPs since 2001 [4]. Conditional Marketing Authorisation (CMA) is another tool that could help shorten time to availability of new OMPs, unfortunately only ~5% of approved OMPs have benefited so far [4].

Early dialogue and agreement between the applicant and EMA scientific bodies on required data would allow more timely alignment and predictability, thus supporting increased use of Accelerated Review and CMA. Coupled with more flexibility on study design for OMPs, e.g., greater acceptance of surrogate endpoints, single well-controlled trials, and data packages supplemented with post-marketing and compassionate-use data, this would create a more favourable environment for OMP approvals in the EU. Other approaches for speedier OMP approval should be explored, including a ‘rolling application’ that would allow initiating review of parts of the dossier prior to validating the entire application. Additionally, increased collaboration between EMA’s scientific bodies could help streamline the various regulatory procedures between orphan designation and approval, e.g., parallel discussions with the Paediatric Committee, the Committee for Advanced Therapies and the Scientific Advise Working Party. The success of such measures will require a close dialogue between the applicant and EMA. Applicants for any procedures regarding orphan drugs would benefit from a continuous support from EMA’s orphan drug sector as they have an in-depth understanding of the special challenges OMP developers face. Taking an OMP through all regulatory hurdles until approval in a more timely manner requires increased regulatory flexibility and predictability. Although regulatory procedures in the EU are working well, improvement could be achieved by increasing the use of existing tools and more creative thinking on conditions for approval of OMPs in the EU.

References

A28
Compassionate use programmes for rare diseases: proposals for actions
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The voluntary process carried out on a case-by-case basis. Uptake will be a key measure of success, because use of the system will largely depend on its ability to deliver a more streamlined approach. Implementation could start already where the elements are in place, while additional required elements are being developed.

A26
Market access of orphan drugs and the role of multi-criteria decision making
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A26

Background: A number of factors play a role in market access of orphan drugs, such as the extent to which an orphan drug meets a medical need; existence of alternative health technologies; disease prevalence; number of orphan drug indications; and added clinical benefit of the orphan drug. How can these factors be taken into account in market access decisions given that there is uncertainty over which factors matter and given that not all orphan drugs meet these criteria to the same degree [1]? Materials and methods: Multi-criteria decision analysis is a technique which enables decision makers to consider multiple criteria in market access decisions. This technique brings together an expert panel which identifies the relevant decision-making criteria and their relative importance. The panel then quantifies the extent to which an orphan drug attains each criterion. The scores of the orphan drug on the different criteria are weighted according to their relative importance and an overall score for the orphan drug is computed. Drugs are ranked according to their score and resources are allocated based on this ranking until the budget is exhausted.

Results: To the best of the author’s knowledge, no multi-criteria decision analysis has in practice been carried out for orphan drugs. However, the following paragraphs illustrate this technique by proposing and justifying three criteria that could be considered in orphan drug market access decisions, i.e. disease prevalence, existence of alternative health technologies, and repurposing. With respect to prevalence, an economic rationale suggests that prices of orphan drugs used for rare diseases with higher prevalence should be lower than prices of orphan drugs used for rare diseases with lower prevalence. Similarly, the price of orphan drugs should reflect the combined prevalence across its indications. The existence of alternative health technologies is a second criterion to consider in market access decisions in the light of the impact of competitive pressures on orphan drug pricing. Finally, orphan drugs which were originally developed for a common disease, but later repurposed for a rare disease are likely to have incurred lower costs of research and development and, therefore, should claim a lower price than an orphan drug which has been developed uniquely to treat a rare disease.

Conclusions: The use of multi-criteria decision analysis would enhance objectivity and transparency of market access decisions for orphan drugs by taking into account societal preferences about orphan drugs for rare diseases.

Reference
Aims: Patients’ advocates, regulators and doctors have the constant objective to make the best treatments quickly available to patients. Compassionate use programmes (CUP) as defined by the EU Regulation (EC) № 726/2004 article 83.2 are designed to provide early access before the marketing authorisation (MA) of a medicine. It is necessary to evaluate the achievements of the present legislations on CUP in Europe in order to propose actions that could integrate CUP into an improved orphan drug development model.

Rationale: The European legislation is not applied on the same way in the Member States (MS) even if in almost all MS a scheme for CUP exists. The experience of the European Medicines Agency, MS and companies is that this lack of harmonisation makes difficult the early access to important new medicines particularly for rare diseases.

Methods: Series of workshops with all stakeholders and a survey conducted by EURODIS in 2010-2011 via a questionnaire to 64 holders of a marketing authorisation for an orphan medicinal product helped analysing current practices across Europe, experience at the European Medicines Agency’s (EMA) level, and how CUPs are inserted in the general development of an orphan medicinal product.

Results: The survey showed the obstacles in the implementation of such programmes, and also their benefits. By enlarging the number of patients exposed to a new product, CUPs can expand the number of exposed patients in safety databases by 20%–90%. Nine products with a CUP were reviewed, some programmes starting early in the development of safety databases. In other cases, only recently. Only France could provide all 9 products on a compassionate basis, while 3 countries could provide a programme for 5-6 products, 5 countries for 3-4 products, 23 countries to 1-2 products, and 10 did not provide any product on a compassionate basis.

The French Temporary Use Authorisation system (A.T.U) illustrates the benefits for public health. CUPs can represent: coupled in providing early access to drugs for patients, control close by the competent authority of the use of new drugs and appropriate information of stakeholders. France could provide 75% of the 64 authorised orphan medicinal products on a compassionate basis in average 35 months prior to the MA.

Main conclusions: This work led to an initiative to improve information and transparency about CUPs in Europe, and also to propose good practices in this domain. In order to improve the situation it is proposed to pursue the dialogue with MS and companies and to set up a “Facilitation group” between MS in order to exchange information and to build up on common experiences.

From rationing to rationality: an n-of-one trial service for off-label medicines for rare (neuromuscular) diseases

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Aims: To provide an evidence-based n-of-one trial service for off-label medicines in the Netherlands, especially for neuromuscular diseases, for patients, caregivers, and health care professionals. Aims and methods: Consensus building on drug approval and reimbursement, best-off-labelling, and reimbursement rules. The first n-of-one trial service in the Netherlands started with the approval of the EMA and reimbursement of Zavesca (Atadexa; Genzyme) for Gaucher’s disease (GLA). Other studies are ongoing for B-thalassaemia and sickle cell disease[6,7].

Background: Systematic evaluation of outcomes is essential for clinical trial research, yet outcomes often neglect the voice of the child and parent, particularly within paediatric orphan diseases. While guidance for the development and validation of Patient Reported Outcomes (PROs) and Observer Reported Outcomes (ObsRO) measures are available from EMA and FDA, little attention has focused on paediatric and orphan disease PRO/ObsRO development methods[1,2].

Methods: We summarize considerations for the development, validation and use of paediatric measures and provide examples of their successful use.

Results: Table 1 provides the recommended steps for PRO/ObsRO development, as well as the challenges and potential solutions in PRO/ObsRO development in paediatrics and orphan diseases. When developing paediatric measures, it is critical to use developmentally appropriate language and techniques to ensure measures have content validity and will be reliable and valid.

Concept elicitation (using qualitative research) and psychometric validation require samples sizes within narrow age bands (0–2, 3–5, 6–8, 9–11, 12–14, 15–17), but also need to consider rates of development within the context of the condition being studied. From 0–5 years, parents are asked about child behaviours they observe that are indicative of symptoms or impact. For 6–11 years, the child and parent should be asked though simple questions, with images attached to responses, should be used for the child. For 12–17 years, more adult language (without jargon) can be used. Pooling data across ages can only be considered if different age versions are shown to be conceptually equivalent.

PROs have been used to aid decision making for regulatory approval (as in the case of icatibant for the treatment of Hereditary Angioedema) [3–5] and reimbursement (as in the case of Exjade for the treatment of iron overload for β-thalassaemia and sickle cell disease)[6,7].

Conclusions: Strong paediatric PRO/ObsRO research is needed to ensure ‘fit for purpose’ outcomes are used in paediatric trials to collect robust evidence regarding the safety and efficacy of drugs for children who have orphan diseases. When successfully implemented, all stakeholders benefit: regulators, payers, doctors, parents and most importantly, the children themselves.
Table 1 (abstract A30) Challenges and potential solutions for PRO/ObsRO development and implementation in paediatrics and orphan indications

<table>
<thead>
<tr>
<th>Steps to PRO/ObsRO development</th>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature Review/Desk Research</td>
<td>Literature often limited</td>
<td>Consider grey literature (blogs, dissertations)</td>
</tr>
<tr>
<td></td>
<td>Broad age ranges covered</td>
<td>Conduct interviews with expert clinicians, nurses and patient advocacy groups</td>
</tr>
<tr>
<td>Concept Elicitation</td>
<td>Limitations in memory, cognitive ability, language by age/condition</td>
<td>Carefully guided interview guides and well trained interviewers</td>
</tr>
<tr>
<td></td>
<td>Children can be shy</td>
<td>Creative interview techniques, toys and drawings</td>
</tr>
<tr>
<td></td>
<td>Rarity of condition makes recruitment/saturation hard to achieve</td>
<td>Collapse age groups where appropriate</td>
</tr>
<tr>
<td></td>
<td>Parents unable to report some symptoms/domains not known to them</td>
<td>Must achieve saturation within each narrow age range – can this be relaxed for orphan indications? Get FDA feedback early</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider other respondents (teachers, nanny etc)</td>
</tr>
<tr>
<td>Selection/ development of a measure</td>
<td>Few disease specific measures exist in paediatrics and orphan diseases</td>
<td>Think about PRO selection early</td>
</tr>
<tr>
<td></td>
<td>Existing instruments don’t meet FDA/EMA guidance</td>
<td>Talk to patient advocacy groups</td>
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<tr>
<td></td>
<td>Who is the best respondent?</td>
<td>Engage FDA early</td>
</tr>
<tr>
<td></td>
<td>How should you administer the questionnaire?</td>
<td>Consider EPRO vs pen/paper vs IVRS in context of condition and age of child</td>
</tr>
<tr>
<td></td>
<td>How should the questionnaire be worded?</td>
<td>Questions/responses should be clear and simply worded</td>
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<tr>
<td></td>
<td>Child can’t remember without a concrete event to recall to</td>
<td>Short recall period required</td>
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<tr>
<td></td>
<td>Parent items must be observable… but they may not be with the child all day</td>
<td>Consider all types of respondents (parent, teacher, nurse, child, dr)</td>
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<tr>
<td></td>
<td></td>
<td>Consider ‘child told me’ questions</td>
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<tr>
<td>Cognitive debriefing/ content validity testing</td>
<td>Hypothetical situations don’t work with children</td>
<td>Allow child to complete diaries at home for a few days prior</td>
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<td></td>
<td>Children give you answers they think you want to hear</td>
<td>Use carefully worded interview guides and well trained interviewers</td>
</tr>
<tr>
<td></td>
<td>Small sample sizes in rare conditions</td>
<td>Questioning should not be too repetitive nor lengthy</td>
</tr>
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<td></td>
<td></td>
<td>When analysing, check for consistency between behaviour and responses</td>
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<tr>
<td></td>
<td></td>
<td>Collapse age groups as appropriate</td>
</tr>
<tr>
<td>Psychometric validation</td>
<td>Sample should be stratified by age group, but small samples in orphan indications</td>
<td>Consider validating as part of trial and/or include data from cognitive debriefing (move forward at risk)</td>
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<tr>
<td></td>
<td></td>
<td>Consider collapsing across age groups</td>
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<tr>
<td></td>
<td></td>
<td>Consult regulatory early</td>
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<tr>
<td></td>
<td></td>
<td>Utilize psychometrics done in other diseases if adapting a measure</td>
</tr>
</tbody>
</table>

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A31

The psychological processes involved in patient empowerment

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Patient empowerment is widely accepted as a process by which people are helped to use autonomous decision making in order to better self-manage their condition, gain control over their health and remain socially integrated [1]. Prevalent definitions of empowerment are therefore mainly based on the view that autonomy is recognised in people’s self-determination, and that empowerment is a procedural process of giving (provider to patient) and taking (patient from provider) power. Such definitions tend to minimise the uncontrollability which is inherent to living with severe health conditions. In such contexts, autonomy may be alternatively regarded as feeling secure in caring relationships [2], and having ‘ownership’ for one’s decision might be just as appropriate and empowering as participating in ‘shared decision-making’ [3]. This points the need to consider other approaches to patient empowerment. Living with a chronic health condition, particularly if the condition is progressive and disabling, implies that patients and families embrace three equally important challenges: managing illness work, managing everyday tasks, and coping with the need to maintain (or reconstruct) a continuous and valuable sense of self [4]. The third challenge is not sufficiently addressed in prevalent definitions of empowerment. Patient empowerment needs to
be seen as a dynamic and creative process that is shaped by the individual’s own activity and yet acknowledges the individual’s dependence on others. As such, it is closer to the logic of care than the logic of choice [5]. In the logic of care, patient empowerment depends on not only the need to develop a sense of choice and control, but also the need to: i) feel secure and connected and; ii) develop a sense of meaning and coherence [6,7]. Patients’ need for competence and control is generally well addressed in self-management support interventions that promote cognitive and behavioural efforts to enhance self-efficacy and performance. By contrast, patients’ need for coherence and meaningfulness, which involves relinquishing control when challenges are perceived as being uncontrollable, is insufficiently acknowledged. Taking and relinquishing control should be seen as two interdependent aspects of a single dynamic process, rather than two opposites on a continuum from disempowerment to empowerment. As far as the need for security and connectedness is concerned, recent theoretical developments point to the importance of looking at how people’s attachment styles, shaped through previous experience of dependent relationships, might influence the patient-provider relationship [8]. Research is needed to understand how adaptive interventions may be built into health-care systems to more comprehensively support the complex psychological processes that underpin patient empowerment.

References

A32
The emergence of the cause of rare diseases and rare disease patients’ movement
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A32

Three features of the cause of rare diseases may be important for the future of the movement:
1. The category of rare diseases was originally created to remedy the problem caused by orphan drugs in the USA. The 1962 Kefauver-Harris amendments to the Food, Drug and Cosmetic Act required the company wanting to market a drug to prove its efficacy. Each drug had to be (retroactively) tested. Drugs that had not been tested however remained in hospital pharmacies, and were called “homeless” or “orphan”. Meanwhile, some U.S. patients were forced to discontinue their treatment. In the 1970s, these two phenomena pushed the FDA to try and find a status for the drugs that, although they had been developed, were not available for the patients. Defining these drugs as drugs for rare diseases appeared as the solution. This was the beginning of the rare diseases movement.
2. Facing a rare disease, the patients and their families often feel isolated. A series of interviews with 29 French patients and 15 relatives who were affected by one of 6 rare disorders suggests that, once illness has become an important aspect in the life of a person with a rare disease, or a of person related to one with a rare disease, this person will try to meet other people in the same situation.
3. Rare disease organizations are issue-based (people gather to struggle with common problems that they want to solve together) while coalitions of such organisations tend to be rarity-based (organizations come together because their members address rare disorders). A series of 61 interviews with patients, relatives, volunteers and employees in 8 French associations identified three solidarity principles for these coalitions: (1) the “one for all” principle, where any advancement for one disorder will benefit many others; (2) the “every man for himself” principle, where one should support their own rare disorder organisation; (3) the “all for one” principle, where solidarity is moral. None of these principles is satisfying. Gathering people with/or related to rare disorders with others addressing the same issues, i.e. an issue-based approach in ad-hoc coalitions, has the potential to be strong and cohesive. E.g.: coalitions of rare disease associations with Aids or cancer associations for access to insurance or credit.

A33
The political empowerment of rare disease patient advocates both at EU and national level
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A33

Thirty years ago, the patients were left with many uncertainties, no networks and no access. The rarity of the disease made it difficult to identify specialists, little information could be found. Most of the patients were engaged in a longstanding process of obtaining the right diagnosis and treatments when these were available. Significant inequity was the only standard amongst European countries.

In this context, the patients, their parents and relatives have formed clusters, reached out to other families and established patient organisations for their own diseases. The scarcity and scattered expertise on rare diseases have led patient organisations in Europe, since the early 1980s to become the link between patients and experts so to support the emergence of specific medical communities, to raise awareness and advocate for patients’ needs. Gradually, National Alliances of Rare Diseases were created to promote their rights at the national level. In March 1997, the European Organisation for Rare Diseases (EURORDIS) was established to build a strong pan-European community and critical mass to voice patients’ common needs and expectations, the European level being the most relevant to develop meaningful solutions.

People Living with Rare Diseases have shaped the concept of rare diseases as a public health policy issue: very heterogeneous diseases linked together around the specificity of rarity. Commonalities are: low prevalence, chronic, severe and often life threatening disease, limited scientific and medical knowledge base, lack of investments, winding road to diagnosis and treatment, social exclusion. Rare disease patients’ organisations are advocating across all rare diseases and all European countries. In the 1990s, new catalysing factors included scientific breakthroughs such as the mapping of the human genome and biotech therapies, and the emergence of internet as a powerful tool for information sharing.

The Committee for Orphan Medicinal Products constitutes a corner stone in developing treatments for rare diseases as much as to prompt patients’ participation in the decision making processes. Driven by a common agenda, rare disease patients promote innovative approaches to design research and healthcare policies, from medical intervention to quality of life, adapted to small populations.

Today, Rare Diseases are high on the European political agenda. European Member States are in the process of adopting national plans for rare diseases integrated within a coherent European policy framework. The active role of patients’ representatives is now recognised as a major contribution to innovation and as catalyzing cooperation and sustainable development.
A34

Rare family days: a family empowerment programme

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Having a seriously ill child is intrusive for the entire family. Still, knowledge about how to manage family life for these families is limited, especially when the diagnosis is rare. To offer tools to cope with their situation, Rare Disorders Denmark (RDD) developed Rare Family Days (RFD). RFD is an empowerment programme targeted families with children carrying a rare disease. The programme purpose is to empower families in their everyday life by offering an opportunity to create supportive networks, a forum for exchange of experience-based knowledge, knowledge of social and legal affairs, knowledge of psychological aspects of family life and tools for conflict management and goal setting.
RFD consists of:
- a weekend course for the entire family
- a one-day follow-up for parents
- access for parents to a closed internet forum with information, links and an opportunity to keep in contact
The programme alternates between network-creating activities for the entire family, activities for children, activities for parents with professional presentations, presentations and discussions by volunteering patient representatives who engage throughout the programme as mentors for the families, group discussions and problem solving.

Evaluation and effects: To document the effects, RFD was tested and evaluated based on a randomized controlled trial (RCT) supplemented with interviews with selected parents. Two groups of eight families completed the programme in 2011. The RCT was based on questionnaires for parents at baseline, after the weekend and after six months for the intervention group and a wait-list control.
As a proxy for empowerment, the parents’ knowledge of the child’s disease, the social welfare system and legal aspects were tested along benefits from networking and experience-based knowledge sharing.
Final results have not yet been reported. A full-length article is under preparation with expected submission deadline in December 2012.
Preliminary results show that participants increased their knowledge in different areas, benefitted from creating network with each other and benefitted from sharing experience-based knowledge. The qualitative evaluation showed that families during experienced cohesion and unity.
The physical meeting enabled them to learn from each other and from the instructors’ professional knowledge. Participation in RFD created drive and hope for the future.

Acknowledgements: Thanks to the advisory board, Steen Bengtsson and Christoffer Svennusson Sonne-Schmidt from The Danish National Centre for Social Research for invaluable feedback.

A36

Climb’s black and ethnic minority information project (BEMIS)
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A36

Our unique three year project enabled us to film and catalogue a library of 110 DVDs covering many inherited metabolic diseases, diagnosis, symptoms, treatment, research and prognosis. This information was then transcribed into written format and translated into various languages. This innovative project grew out of a need identified during a 2 year research project for information covering metabolic diseases. Our work with families from an ethnic minority background in the West Midlands of England showed that there was an identifiable gap in our service provision and in order to meet this need we would have to change the way we worked and the information that we provided to families, adults and professionals. Our information needed to be clear, simple and easily accessible. Unfortunately, the rareness of these conditions meant that Climb’s existing information in English, was hard to access for many families, communities and people who did not read English as their first language. Following on from our research project and our work with minority communities and travellers, we identified diseases, languages and formats needed for our project. We chose 110 metabolic conditions and two languages to translate the information into. We also produced a variety of leaflets and posters to convey this information. Many specialists agreed to be filmed. The aim was to produce disease specific information on a DVD initially into two languages Urdu and Punjabi, which would cover many important aspects of inherited metabolic diseases including:
Symptoms - Long term effects - Treatment - Diagnosis - Dietary requirements.
Care - Long term treatment options - Specialist treatment - Research - Prognosis.
Inheritance factors - Genetics.
Initial translations and DVDs led to requests for more leaflets in more languages. Our final list of languages used was Arabic, English, Cantonese, French, Danish, Greek, Hebrew, Japanese, Persian, Portuguese, Punjabi, Russian, Spanish, Urdu, Welsh.
On occasion, Climb was able to meet service users who had been through the AKU Society’s, RLUH and UoL funded four-year programme. The AKU Society and RLUH in parallel launched a global campaign to identify AKU patients, starting with three patients in the UK and reaching more than 1,000 patients globally by 2012. AKU patients and their families set up formal AKU Societies in the UK, France, Germany, the Netherlands, Italy, the USA and Canada in order to build the patient movement. A study was carried out to find out the average cost of an AKU patient to the National Health Service: £100,000 a year. This was used to build a case to the NHS for funding the National Alkaptonuria Society at RLUH and launching it in June 2012. The AKU Society, RLUH and UoL led the creation of an international consortium including 15 pharma companies, biotechs, universities, clinical trial centres, patient groups and contract research organisations in eight countries across Europe and North America. Thanks to funding from the European Commission, this consortium will launch in late 2012 a five-and-a-half year clinical development programme to develop and obtain marketing authorisation for nitisinone, a small molecule that inhibits the accumulation of homogentisic acid. Further AKU research centres have also been established in Jordan and South India.

References

A38
Is more involvement needed in the clinical trial design & endpoints?
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Orphanet Journal of Rare Diseases 2012, 7(Suppl 2):A38

Duchenne muscular dystrophy (DMD) is a recessive X-linked form of muscular dystrophy, affecting around 1 in 3,600 boys, which results in muscle degeneration and eventual death. Long before any promising drug was at the horizon Duchenne parents came forward to organise research meetings where they made it clear they were willing to shoulder responsibility and contribute towards advancing treatments and a cure. They became funders of peer reviewed research and advocated for government support. Some organisations started their own research institutes others invested in extramural research, clinical centers and industry to develop viable treatments for DMD and BMD. Currently several potential drugs are in phase 3 trials.

Through this experience Duchenne parents have learned including Patient Organisations in trial design and selection of endpoints can make drug development more efficient. Patients participate in clinical trials and will ultimately be the ones to decide whether the tested drugs are beneficial to them to an extent that EMA and FDA allow these drugs. Hence patient input and advice is essential to develop a clinically meaningful endpoint. A clinical meaningful endpoint is an endpoint that directly measures how a patient feels (symptoms), functions (the ability to perform activities in daily life), or survives. Therefore, a primary endpoint should be a direct measure of one of these. A primary endpoint should generally not be a measure of something that is not important to the patient [1]. Who knows better than the patients what is important to them? It is remarkable that clinicians and industry often don’t discuss the choice of primary outcome measures with patient organisations in an early phase, but only after they have already collected the data and are at the point to discuss outcomes with regulators.

Regarding trial design, ethic committees mostly decide about the burden and risk of participation in relation to a certain trial design without asking the patients or patients’ organisations for their opinion. That is remarkable because they are the ones who have to deal with the burden and take the risk. Often researchers and regulators only look at the burden of the medical intervention, where for many patients other factors add much more to the total burden of participation in a trial.

Care revolves around the people with a disease. Without them there would be no need for research and drug development. It is important that the needs of these groups are the starting point for initiatives concerning them. Patients know what it means to have this condition. It means they will bring their questions and needs are based on their own experience, interests and vision. There is a lot to gain from well utilised experience and expertise.

Reference

A39
Patient perspective on CT Involvement: are they listening to my needs?
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Introduction: Patient involvement is a key factor in the development of treatment, hence in (pre) clinical trial design, choice of primary and secondary endpoints, protocol set-up etc. Including patient representatives in drug and treatment development from A to Z as equal partners would lead to a better and longer life for the patient.

Benefits: Patient involvement in clinical trial guarantees that the drug or treatment tackles issues and problems patients experience. The study design is patient centered, which means closer to real life, better recruitment and less CT drop out. Taking into account the burden CT’s put on "normal life" for a person with a rare condition during study set up and
CT execution, improves the representativeness of the study and ensures that once the drug or treatment is available to the patient “in real life”, adherence is maximized. The result is a more effective and efficient drug and treatment for the patient and society.

**Methods:** Patients should be asked which drugs or treatment would “by priority” benefit them, before the CT design is determined and what their needs are (for ex. Eurocare CF) in general but also for every drug or treatment development. Structured and systematic involvement of patients in drug and CT development is required. Using different tools (questionnaires, interviews, focus groups) on a regular basis could help develop a structured, patients’ representatives view on their needs. Patients have a say in defining for example what kind of care is needed; what will improve their QOL, outcome and life expectancy; what type of molecule, drug or treatment will do the trick; what kind of trial(s) we need; which population is targeted: adult and/or pediatric population; and what type of administration of the molecule/drug is possible, comfortable, can be fitted in daily life?

**Conclusion:** It is possible and necessary to involve patient representatives in drug and treatment development, especially clinical trials, on a European level. It should be considered “good clinical practice” in design and implementation of clinical trials to imbed the patients’ point of view (by patient representatives) structurally, making it a legal obligation if desired, in policy decisions regarding drugs and treatment; in clinical trial networks; in pharmaceutical companies wanting to develop a drug or treatment; and others.

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### A40
**A route map for the patients journey**
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*Orphanet Journal of Rare Diseases* 2012, 7(Suppl 2):A40

**Background:** The Route Map for Adrenoleukodystrophy (ALD) and Adrenomyeloneuropathy (AMN) is a user led research project to create a repository of information and knowledge about two specific rare diseases. This Route Map provides a comprehensive resource to be used by patients, families and health and social care professionals.

From our survey we know that more than 60% of our patients with ALD or AMN are not receiving enough information and often the information they receive is not in an easy and patient friendly language. We also know that this situation is quite common across rare diseases.

**The aims and the approach:** The aims of the Route Map (RM) have been:
- Improving the quality of care for patients with ALD and AMN
- Empowering patients and their families, expressing the potential contribution they can give to the NHS system
- Improving the quality of the relationship between patients and specialists
- Improving awareness of the conditions

We have developed the RM using a patient centred approach. This has meant that patients have been involved since the beginning and in different phases of the project to co-design the RM. NHS professionals have also been involved in the design process.

We have talked with patients to develop the questionnaires to make sure that we were asking the right questions; involved patients in focus groups to discuss openly and collectively about some general and some more specific issue; explored things from a different angle starting from the patient experience perspective of the care they have received.

This has made possible to derive knowledge and create deep understanding of complex processes; starting from personal stories we have been able to design the patient’ journey map.

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### A41
**First German Academy for Further Medical Training on Rare Diseases (FAKSE, http://www.fakse.info)**
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**Orphanet Journal of Rare Diseases** 2012, 7(Suppl 2):A41

**Problem:** On average it will take up to seven years to be diagnosed with an orphan disease. During this time, patients will have seen several doctors, received a large number of changing diagnoses, consulted the internet various times and will have undergone many forms of treatment. Since the majority of rare disorders affect more than one organ system, it is almost impossible for physicians not specialising in rare disorders or working in this area on a daily basis to diagnose an orphan disease.

**Approach:** The Centre for Rare Diseases Tuebingen (University Hospital Tuebingen) opened the first German Academy for Further Medical Training on Rare Diseases (FAKSE) in April 2011. The goals of the academy are (i) educate practice-based physicians and clinicians on the matter of rare diseases in an interdisciplinary and illustrative fashion, (ii) raise awareness for these disorders and provide physicians with methodologies and “Red Flags” for better recognition of RD and (iii) to bring physicians in contact with relevant experts and patient organisations.

**Methodology:** FAKSE offers practitioners and clinicians the possibility to receive first-hand information on orphan diseases from interdisciplinary experts. Each training course focuses on a group of related RD such as rare storage disorders and comprises high standard video based lectures, presentation of specific ‘Red Flags’ (symptoms one should think of a rare disorder), and meet-the-experts workshops to discuss unclear cases.

Throughout its first year, FAKSE organised four training courses and has already trained 250 physicians.

By date, training included courses on rare neurological diseases, rare storage disorders, rare female genital malformations, rare skin disorders, rare infantile malformations of the maxillofacial region and rare eye disorders. In 2012, two more courses on rare auto inflammatory diseases, rare storage disorders, rare tumours will be held. Further courses for 2013 are already being planned.

Since December 2011, FAKSE collaborates with Germany’s umbrella association for patient organisations (ACHSE).

Cite abstracts in this supplement using the relevant abstract number, e.g.: Giehl et al: First German Academy for Further Medical Training on Rare Diseases (FAKSE, http://www.fakse.info), *Orphanet Journal of Rare Diseases* 2012, 7(Suppl 2):A41