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ORAL PRESENTATIONS

O1 The Epidermolysis bullosa Center Freiburg – patient care, diagnostics and research.
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The Epidermolysis bullosa (EB) Center Freiburg is the coordination center of the German EB-Network and a national center of excellence for rare skin fragility disorders. It combines clinical activities with internationally competitive research and deals with molecular diagnostics, clinical management, elucidation of disease mechanisms, and development of evidence-based novel therapies (Figure 1). EB is a group of severe and socially relevant genetic skin diseases characterized by mechanically induced blistering and life-long fragility of the skin. EB has a highly negative personal, medical and socio-economic impact on the life of the patients and their families, and the unmet medical need is high. - The activities of the EB-Network build upon the combination of clinical and scientific expertise of the partners in Germany and neighboring countries (cross-border care), and upon the synergies generated in the past years.

The EB Center Freiburg performs molecular diagnostics, coordinates multidisciplinary care for patients and their families, advises general practitioners, medical specialists, nursing staff and therapists, and disseminates information to lay public and media. The office of the Center is available for enquiries for 24 hours and responds within 24 hours. The team includes a coordinator, physicians, nurses, a social worker, a documentary clerk, scientists and laboratory technicians with expertise in EB. The consultations are usually out-patient or day clinic appointments, but hospital admission is possible for severe cases requiring extensive medical treatments. Standardized clinical practice with a diagnostic algorithm and standardized patient documentation facilitates diagnostic processes, and a weekly EB-expert meeting evaluates all diagnoses as a quality assurance measure. Currently the EB-patient registry contains data of >1000 patients with molecular genetic diagnosis and has an associated biomaterial collection of skin biopsies, cells and blood samples. These serve as basis for research on epidemiology of EB and for clinical and laboratory investigations on novel causes, disease mechanisms, genotype-phenotype correlations and treatments for EB. - In addition to numerous international research collaborations, the EB Center is actively involved in larger structures for rare diseases. The Freiburg Center for Rare Diseases [http://www.uniklinik-freiburg.de/fzse.html] provides high-level scientific expertise, innovative diagnostics and interdisciplinary care for people with rare disorders of the skin, the musculoskeletal system, the kidney, the lung, the eye, the blood and the immune systems. Internationally, EB-Clinet [http://www.eb-clinet.org], a European network of EB Centers, and the Genodermatoses Network, an international network on rare skin diseases for professionals and patients [http://www.genodermatoses-network.org] aim at establishing a European Reference Network for genetic skin diseases.

O2 Perspective having a Centre of Expertise that covers more than one rare disease.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O2

The vast majority of rare diseases affect more than one organ of the body, and eighty-five percent of the patients have symptoms within the initial five years of life. In childhood, the medical specialty, i.e. pediatrics, is not confined to one organ, but by age. In adulthood, the medical specialties are defined by an organ (e.g. heart, eye, urinary system, etc). As rare diseases do not respect borders for either age or organ, the organizational approach of healthcare for rare diseases need to take that into consideration.

At the Centre for Rare Diseases at Aarhus University Hospital, Denmark we want to use that "cradle to grave" approach. At the Centre, we see more than 1200 different patients, distributed across more than 100 different diagnoses. The core-staff consists of three pediatricians who all have clinical, diagnostic, treatment and coordinating tasks, and who either see the patients alone or by having joint clinical consultations with a variety of organ-related specialists. A cooperative medical relationship for one specific diagnosis, for example, Tuberosus Sclerosis, can also be used taking care of patients having Neurofibromatosis or von Hippel Lindau disease. At a certain time, they all may need care from a neurosurgeon, an ophthalmologist, a dermatologist, etc.. We make sure that there are one or few dedicated people involved from each specialty, and in this way we manage to get a firmly close-knitted established team in which the personal from the different medical specialties know each other, and are tuned to take care of patients with different diseases having similar medical challenges. We think, that this approach gives a lot of synergy effects and "spin of", not only in the setting of treatment, but also as regard the diagnostic set up, and also as regard research.

Our setup provides us with significant challenges as well. It is difficult to be an expert regarding too many diagnoses, and as we continuously have to include new patients, and the patients cannot we processed to others, we have a great accumulation of patients. However, patients with rare diseases need treatment and care anyway, and we will try to meet this challenge with organizing ourselves scattered across the University Hospital in a Core Centre, primarily doing the diagnostic set-up, and with satellite centers, taking care of the treatment, placed at different organ-related highly specialized, but mutually coordinated, departments.
O3
Quality monitoring in the English National Health Service.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O3
Monitoring of services in the National Health Service in England is framed around clinical outcomes, safety and patient experience. A system of dashboards is being developed to provide monthly information about specialised services. The initial pilot has included a set of key information about services to patients with haemophilia and cystic fibrosis, for example the proportion of patients on home treatment (haemophilia) or the proportion admitted to a ward with specialist staff (cystic fibrosis). Data items were agreed by clinicians as relevant and important. The information is available from every provider. In the highly specialised services for very rare disease (prevalence less than 1 in 100,000) the dashboard runs annually, not monthly, and is based on long experience. Outcome monitoring is particularly well developed for sold organ transplant, with agreed protocols for investigating and responding to statistical outliers.
Quality of life measures are used in some services such as epidermolysis bullosa and neurofibromatosis type 2 [2], but there is not enough experience with these measures to compare different hospitals or to track trends.
Safety incidents such as ‘never’ events are rare; they are reported and investigated immediately.
Patient experience is monitored through surveys and close contact with patient organisations. A key mechanism for monitoring quality in the highly specialised services is an annual meeting. Attendance by all providers of the service is mandatory. Clinical outcome data is presented on all patients treated, and interesting or informative cases are discussed by the clinical teams. The meeting provides an excellent forum for peer review, exchange of clinical experience and learning.
References

O4
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O4
The first French National Rare Disease Plan allowed the establishment of 131 centres of expertise (CEs) from 2004 to 2007. The process of evaluation elaborated with the HAS (Haute Autorité de Santé) was based on a cycle of 5 years: three years after the certification, the CEs were asked for a document of auto-evaluation and at 5 years there was a visit on site to complete the evaluation. As the certification of CEs was done over a period of 4 years, all the CEs were not evaluated at the same time and it resulted in a complex scheme with heterogeneity of the evaluation according to the time point of the process. The items collected during autoevaluation consisted in general information regarding the composition of the team and of the steering committee, the methods used for the elaboration of the document and quantitative data concerning the activities (clinics, hospitalizations, geographical origin of the patients, proportion of children). Six specific missions of the CEs were also evaluated: expertise, referral, research, epidemiology, healthcare pathway and medicosocial organization. The documented ended with an action plan on which the experts relied for their evaluation during the visit on site at 5 years. This process demonstrated many positive aspects: constructive stimulation of the actors, commitment of institution direction and set up of a virtuous circle based on the fundamental three steps: anticipation, implementation and evaluation. However this process had many caveats: redundancy of some items that led to confusion in the responses, lack of support for the methodology mandatory to evaluate the impact of the CEs actions, heaviness of the organisation of the visit on site and most of all impossibility to retrieve essential information and to analyse them as the documents were elaborated on a word file with free text. The evaluation of the first plan by the high council of public health thus concluded it was necessary to simplify and to optimize the efficiency of the process. In addition, it has to take into account the new ambitions of the 2nd plan. A working group dedicated to this question collaborated with the HAS and elaborated a simplified document for certification. The process now includes an on-line simplified annual activity report based on quantitative and semi-quantitative data. These reports will be analysed each year by a permanent group – with adjustment of the financial support – together with a final report at 4 years based on the new certification document. Visit on site will be decided only if problems appear during this follow-up or on request of the centre.

O5
FindZebra - the search engine for difficult medical cases.
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Physicians as well as laypeople use both general purpose and specialised web-based search tools when confronted with medical questions. FindZebra.com is a tool for generating hypotheses about rare disease diagnosis. It uses freely available high quality curated information on rare diseases and open source information retrieval software (Apache Lucene Solr) tailored to the problem. FindZebra is intended primarily for physicians and other professionals concerned with diagnosis of rare diseases. Our benchmarking against several search tools (Google search, PubMed and http://omim.org)
shows that FindZebra has higher performance in retrieving the correct diagnosis when queried with symptoms [1,2]. Our findings indicate that the ranking algorithm used is the most important factor for the success.

References

O6 Towards a European platform for Rare Diseases Registries.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O6
The Joint Research Centre (JRC) is a Directorate-General (DG) of the European Commission (EC), It was established in 1957 and its mission is to provide independent, evidence-based scientific and technical support throughout the EU policy cycle. Health is a key European policy area and research on Rare Diseases (RD) is identified as a priority in both the Commission Communication on RD: Europe’s challenges COMM (2008) 679 final and the Council Recommendation on an action in the field of RD (2009/C 151/02).

O7 The French national registry for rare diseases: an integrated model from care to epidemiology and research.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O7
The first national plan for rare diseases (2005-2008) set the network for care and research in the rare diseases (RD) field across all French hospitals. The 131 RD centers of expertise (CE) initiated various IT projects to register electronically their RD patients. The CEMARA project [1] up to now registered 235,000 RD patients, from 62 RDCE (out of 131), 383 units of care and described over 4000 rare diseases. The identified limits of the CEMARA model were: i) data collection was not incorporated in the care setting, ii) exposed to data re-entry, iii) coping with data privacy new regulations and iv) gaining a wide national consensus on the data to collect for all RDs and from all CEs. To overcome these limits, the 2nd national plan for rare diseases (2010-2014) promoted the creation of a national data repository for all rare diseases (BNDMR) based on the CEMARA model with the following objectives: i) identifying RD patients within the health information systems in care setting, ii) describing the RD demand of care, and the adequacy of the supply and iii) identifying patients eligible for clinical trials or cohorts.

The proposed national architecture incorporates a national minimum data set for all rare diseases (F-MDS-RD) into hospital information care systems to enable electronic patient files re-use for epidemiological studies or research [2]. To ensure a full interoperability between local hospital information systems and the BNDMR, a national interoperability framework is defined. It is set on 3 pillars: i) defining a national patient ID for rare diseases that will help to identify patients across different health IS, ii) defining a common data format for all rare diseases, compatible with EHR standards such as HL7, and iii) setting the necessary technical data flows complying with strict security rules for data privacy [3] and security.

The minimum data set for rare diseases is now being implemented in several local systems, and connectors are being rolled out with several database suppliers. Data re-entry is nowadays a major concern for clinicians. Enabling data re-use is not only an interoperability problem; data must be structured, qualified, standardized [4] and suitable for research [5]. The structuration of the data collected is set on a variety of standard terminologies such as Orphanet or the Human Phenotype Ontology which requires to be accompanied with the necessary IT tools to help clinicians coding the data [6].

References

O8 National Rare Diseases Registries: overview from Spain.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O8

The Spanish Rare Diseases Registries Research Network (SpainRDR) is a project aimed to build the National Rare Diseases Registry in Spain based on the input of two different methods: patient outcome research registries and population-based registries. The project has been approved within the IRDIiRc framework and is co-funded by the Institute of Health Carlos III (ISCIII), the Health Departments of the Autonomous Communities (regions) and the Spanish Ministry of Health, Social Services and Equity (MSSEI) of Spain. The project addresses one of the main recommendations of the
National Rare Diseases Strategy and also collaborates with some other RD registering actions like GDRR-NIH, RD-CONNECT and EPIRARE. With the unprecedented collaboration and support of medical societies, researcher networks, patient organizations, Pharma industry and health policy makers, SpainRDR is running an effective and necessary way to develop knowledge and raise awareness of the rare diseases burden, which will contribute to design the provision of health and social services as well as the improvement of diagnosis, prognosis, treatment and quality of life of patients and families affected by RD.

The project is leading by the Institute of Rare Diseases research (IER, ISCIII) and it is organised in six work packages: WP1 Coordinating Management, WP2 Registering activity related methods, WP3 Data analysis and outcomes research, WP4 Quality Assessment and ELSI issues, WP5 Dissemination and impact, and WP6 Patient registries. A Manual of Procedures including a quality assurance plan, common data elements, coding and classifications criteria, standard operating procedures, ELSI rules, statistical analysis methods and the official website network are actions already carried out or being finalized. Specific CDE have been also consolidated for those patient registries already implemented at the central RD repository (alpha-1 antitrypsin deficiency, pulmonary histiocytosis, lymphangiomyomatosis, alveolar proteinosis, sarcoidosis, thraquea deficiency, pulmonary histiocytosis, lymphangiomyomatosis, stasis and familial spastic paraparesis). At the same time, some other patient registries’ CDE’s are currently being developed, such as.

Congenital Suprarenal Hyperplasia and Bradykinin linked angioedema. We are preparing also CDEs for cystinosis and congenital anemia. After the necessary pilot study developed during 2013, we are now collecting prevalence cases from 2012-2012 and the first preliminary results are already available using specific applications designed by SpainRDR.

Acknowledgements: SpainRDR network

OSSE – open source registry software solution.

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Project goal: OSSE (Open Source-Registersystem für Seltene Erkrankungen in der EU / Open Source Registry System for Rare Diseases in the EU) provides patient organizations, physicians and scientists with open-source software for the creation of patient registries. As a result, the national registry landscape is improved to comply with European principles regarding e.g. minimum data set and data quality, as summarized in the EUCERD recommendation on rare disease registries. Also, the necessary interoperability is achieved to facilitate federation of those registries on a national and international level.

Overall concept: The registry toolbox: OSSE primarily provides a registry toolbox that allows for the definition of forms for longitudinal and medical contact data and of the corresponding data schema by means of a registry editor. Common data elements, which can be chosen to build the forms, are defined within a metadata repository (MDR) following ISO/IEC 11179. This approach provides semantic interoperability and data quality. All harmonized data sets for rare diseases will be available through the MDR. Further items can be added at any time while building disease-specific registries and will be available for all OSSE-compliant registries. The OSSE registry provides plausibility checks regarding ranges defined in the MDR and field-specific dependencies, data versioning, workflow support, interfaces for configurable data import and export, and role-based access control.

Pseudonymization: To meet data protection requirements, OSSE supports pseudonymization of patient data: the part of the data allowing for the identification of patients is replaced by a pseudonym and stored separately in the patient list that should be controlled by a trusted third party. For pseudonymization we use the opensource software “Mainzelliste” [“http://www.mainzelliste.de”].

Distributed search: Interoperability between different OSSE registries is achieved by a distributed search infrastructure taking into account data ownership and privacy aspects. The central search broker allows specified search queries in all OSSE-compliant registries based on the existing MDR items. Results are presented to the person in charge of the data management for each registry; the exchange or dissemination of data remains in full control of the data owner.

Acknowledgements: There are two related projects currently underway at the University Medical Center in Mainz: se-atlas, an interactive map of relevant experts on rare diseases in Germany; and ZIPSE, a central information portal on rare diseases in Germany. OSSE is funded by the German Federal Ministry of Health as part of the “National Action Plan for Rare Diseases”. For more information see http://osse-register.de

O10

German approach of coding rare diseases with ICD-10-GM and Orpha numbers in routine settings.

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In Germany all physicians are compelled to code according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM), according to the Statutory Health Insurance. The classification is in use since 2004 in the same Version for inpatient and outpatient care. Special coding guidelines are to be used for inpatient care.

DIMDI provides an Index to the ICD-10-GM, which contains approx. 80,000 terms. For electronic use the index is published with a unique identifier (so called Alpha-ID). This enables electronic communication of diagnosis on a more granular level than the broad categories of ICD-10.

In the German project “Coding of Rare diseases” (July 2013 – June 2016) all rare diseases from Orphanet will be coded according to ICD-10-GM and missing terms will be added to the ICD-10-GM-Index-Database. On a regular basis an Alpha-ID file with all indexed diagnostic terms together with the relevant codes from both systems will be published. Coders in Rare diseases Centers in Germany will be encouraged to use the two coding systems by implementing the file in their IT-systems. An evaluation of possible additional use of the file in existing IT-systems will be performed at the end of the project. The file could e.g. help to enable easy access to Orphanet for Users at the time of diagnosis, treatment, or when advising patient/family or coding from routine IT-applications in all kinds of healthcare settings.

Two main goals are targeted with the project. First of all it is important to standardize coding of rare diseases in Germany by providing electronic files for easy implementation, which will result in standardized code pairs from the two systems. Selecting codes manually from the two different systems is a potential for errors in patient documentation and might lead to incorrect statistical evaluation of rare disease cases. Secondly the aim of DIMDI is to reduce the administrative burden on the health care system in Germany whenever possible. By providing two coding systems in one file the coder will have to perform the coding just once, a significant reduction of time.

Acknowledgements: The project is part of the “National Plan of Action for People with Rare Diseases” and is funded by the German Ministry of Health

O11

How to code rare diseases with international terminologies?.

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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O11

Having codes for each and every rare disease (RD) would help European and national health authorities obtain a better knowledge of healthcare pathways and of their impact on specialised health care services (centres of expertise for instance) and on budget. It would also allow having sound data on the epidemiology and natural history of RD, and provide data for clinical research which is critically needed in this field. Improved codification for rare diseases is cited as a priority in the Council
Recommendation on an action in the field of rare diseases (2009). Currently, only a small fraction of rare diseases have codes in international nomenclatures, making it impossible to trace patients with rare diseases in health information systems on a national and international level. Most European countries use ICD 10 or 9 in their health information systems, some (UK, Belgium, Spain) have decided to adopt SNOMED CT. The number of rare diseases which have a specific code in these two nomenclatures is limited: 466 in ICD10 and 2 883 in SNOMED-CT. In order to provide a common nomenclature specific for rare diseases, Orphanet has established, with the support the European Commission, a nomenclature and classification of RD. The nomenclature and classification are based on scientific publications and on expert advice. It is aligned with every medical terminology in use both in the clinical than in research settings, allowing for interoperability between different coding systems. Terms in the Orphanet nomenclature were introduced in the next ICD11 which is expected by 2017, and will be integrated into SNOMED CT thanks to a partnership between Orphanet and IHTSDO. The Orphanet nomenclature offers possibilities to be downloaded from www.orpha.net in seven languages (Dutch, English, French, German, Italian, Portuguese, Spanish), and is released twice a year as a PDF document downloadable at http://www.orpha.net [2].

References
2. [http://www.orpha.net/conso/cgi-bin/Education_Home.php?lng=EN#REPORT_RARE_DISEASES].

O12

The importance of helplines in National Plans.
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In the last years, the Internet has attracted a considerable attention as a means to provide health-related information. Rare disease patients have been described as active internet users, accessing the web both for searching activities and for communication purposes [1]. Despite the great opportunities offered by health 1.0 and health 2.0 applications, some concerns arise as well, particularly regarding the following aspects: the accuracy and reliability of the information provided, a reported increase in feelings of anxiety and protection of personal information. Furthermore, the use of the internet in the health domain is linked to inequalities issues. E-health literacy [2] has been reported to be lower in patients and caregivers experiencing a high disease burden, as the one caused by many rare conditions. The analysis of the activities of 11 help-lines, operating in 7 European countries and part of the European Network of Rare Disease Help-lines, outlines that the phone still represents a valuable source of information that could trigger important developments for all stakeholders.

Background: Generation and dissemination of information has been a crucial area for actions in the field of rare diseases. In this context, rare disease patients and their experience are recognised as a unique source of information that could trigger important developments for all stakeholders. The European Network of Rare Disease Help Lines (ENRDHLs) is an initiative led by EURORDIS. ENRDHLs was created within the EU-funded Rapsody with the main aim of improving the quality of services provided by European helplines for rare diseases. In order to fulfill this objective, various rare diseases information services from across Europe came together to share expertise and propose ways in which the network could support other services in Europe.

Materials and methods: The Caller Profile Analysis is one of the mandatory commitments for the ENRDHLs members. It is a cross-sectional survey that describes the rare disease helpline services, provided by the participating partners for a specific month. The 2013 survey covered all enquires received from 1 to 30 October 2013.

Results: 12 rare disease helplines from 8 countries (France, Italy, Spain, Switzerland, Portugal, Romania, Bulgaria and Croatia) took part in the Caller Profile Analysis 2013, giving information on 1 672 enquiries. The results show a decreased number of enquires on specific rare disease patients and their experience are recognised as a unique source of information that could trigger important developments for all stakeholders.

Acknowledgements: The Caller Profile Analysis is a joint activity of the ENRDHLs and its members that is funded by the European Commission.
O14 RARE-Bestpractices: a platform for sharing best practices for the management of rare diseases

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O15 Emergency guidelines and emergency cards.

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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O15

O16 OrphanAnesthesia – anesthesia recommendations for patients suffering from rare diseases.

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Anesthesia is becoming safer over the past decades. This process was driven by the development of new anesthetics and the establishment of modern safety concepts. On the other hand anesthetists benefit from profound pathophysiological knowledge and the competence of translating patient specific conditions into individual perioperative risk. But in case of rare diseases this concept is often lacking specific knowledge about the patient conditions and its importance for anesthesia.

OrphanAnesthesia is a common project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine in cooperation with the European Society for Paediatric Anaesthesia. The aim of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases with the target of improving patients’ safety. When it comes to the management of rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists and make it available for physicians worldwide.

By the end of June 2012 NOS News got hold of a concept advice to the Minister of Health. It proposed to stop the reimbursement of the orphan
drug treatments targeting Pompe’s disease and Fabry disease. All three enzyme-therapies are very expensive. For Pompe-patients costs roughly between € 400,000 and € 700,000 a year, for Fabry-patients about € 220,000 a year. The main argument for stopping the compensation was the cost-ineffectiveness of the enzyme-therapy. In other words: too much money for too little result.

The concept advice was written by the CVZ, the main advisor of the Minister on the health-insurance. The Pompe and Fabry enzyme-therapies got insurance-coverage for a limited period of four years beginning 2009. The registration by the EMA was based on very limited evidence. The proposal to stop the reimbursement of Pompe and Fabry therapies – only babies with the classical form of Pompe would keep the compensation - , was the first ever of this kind. There is no alternative treatment available. And no patient can afford to pay hundreds of thousands of euros year after year.

We realised that this proposal crossed a unique line. Until 2012 CVZ refused the reimbursement of several drugs. In the field of chronic diseases, for example, not every new drug is automatically reimbursed. But there are always alternatives that are. Not in this case.

We tried to publish this story with all parties concerned: the patients and their organisations, the doctors specialized in Pompe and Fabry diseases, the CVZ, the Health Ministry. They all refused to comment. For five weeks we tried to convince them, before we published without their consent. At first the messenger was blamed for the bad news. In the end we were hailed for preventing this plan to become reality. From July 2012 until October 2013 we closely followed the decision making process. We attended hearings where everybody had the opportunity to try to convince the CVZ to change its views.

The CVZ refused to withdraw its proposal, but finally made a U-turn and advised the Minister to maintain the reimbursement of the therapies for all patients. The patients and their relatives were relieved. One could argue that common decency won.

But the real problem remains unsolved. Why are these enzyme-therapies so expensive? Why are they so mediocre? Is it true that the industry lacks incentives to come up with a better product since the limited one generates such a substantial amount of money?
Our software, Exomiser, is openly available to use at our website [http://www.sanger.ac.uk/resources/databases/exomiser/query](http://www.sanger.ac.uk/resources/databases/exomiser/query) and for download to perform local analysis. We are currently collaborating with the NIH Undiagnosed Disease Program to achieve diagnosis of problematic cases through exome analysis. In conclusion, our results clearly show the value of collecting comprehensive clinical phenotype data for translational bioinformatics and future work will focus on producing a robust solution for clinical diagnostics.

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**References**


**O20**

The experience of a charity in translating the results of basic research to therapies for patients.

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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O20

Rare diseases represent a relevant societal challenge that calls different players into action, with the aim of providing a diagnosis to patients, understanding the disease pathophysiology and, most importantly, developing treatments and therapies to effectively improve life quality and expectancy.

Biomedical research charities play an important role in the fight against rare diseases, as they are driven by a strong patient need and are focused on diseases otherwise poorly supported by public or private funders. Since 1990, the Telethon Foundation has supported research on genetic diseases, most of which are rare, through intramural and extramural investments in Italy based on strict, excellence-driven fund allocation criteria.

Although Telethon-funded research still relies on a strong base of fundamental studies aimed at disclosing the pathophysiology of genetic diseases, it has progressively shifted towards preclinical and clinical studies, today standing at 50% of Telethon’s investments. In particular, the considerable expertise on gene therapy built at the Telethon Institute for Gene Therapy (TIGET), a joint initiative with the San Raffaele Hospital in Milan, has led to the first safe and effective gene therapy for a genetic disease, the severe immunodeficiency ADA-SCID [1]. This goal was achieved with continued support by the charity, which included creating a dedicated clinical trial office for regulatory support and training of specialized staff and bearing the cost and risks of the production of the therapeutic vector according to good manufacturing practices.

Finally, making this therapy available to patients required the skills and resources of a pharmaceutical company; dealing with a ultra-rare disease such as ADA-SCID presented a challenge that was met by GlaxoSmithKline (GSK). In 2010, Telethon/San Raffaele signed an agreement with GSK, including a license for the development of the ADA-SCID retroviral gene therapy and a collaboration program for six more genetic diseases based on a lentiviral gene therapy platform. TIGET has recently obtained clinical proof of concept for the first two diseases in the pipeline: metachromatic leukodystrophy and Wiskott-Aldrich syndrome [33,41]. Meanwhile, GSK is progressing towards registration of the ADA-SCID therapy, a process still entailing Telethon’s direct involvement, besides close collaboration with TIGET.

The partnership between Telethon and GSK illustrates a novel collaborative model whereby a charity fulfills its traditional role as a funder and also acts as a driver for translating research results into the clinic and promoting transition to the industrial development, to the final benefit of patients.

**References**


**O21**

Health care cost-containment measures in the context of the economic crisis: impact analysis.

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Aims: As a response to the economic and financial crisis that hit Europe and the rest of the world in 2008, most health authorities adopted series of measures to contain or to reduce the healthcare expenditure. In 2010-2011, some 116 health reforms were adopted or planned in the European Union (EU)/European Economic Area (EEA). Some measures can potentially severely impact public health. This analysis explores the impact of such measures for patients with rare diseases (RD).

**Methods:** A literature search was done, in addition to the collection of information from RD patients’ organisations. Press articles as well as reports from international organisations (OECD, EC, WHO) were analysed.
Proceedings from conferences on the impact of the economic crisis on the health of citizens were used. There are important limits when analysing measures taken and the impact we observe: no causal relation can be made.

Results: In many countries, the most frequent measures adopted to reduce the health consisted in price reduction of pharmaceuticals (15 price reductions in 11 countries), change in co-payment (13 measures in 9), reimbursement (8 countries), reference price system (10 countries) and INN prescribing made mandatory. Other health budgets were also affected (public health, care...).

Information on the consequences for citizens or patients is limited: increased incidence of suicides in the UK, of HIV infection cases in IV drug users in Greece, with also an increase of stillbirths. For RD, according to one survey among 403 Greek patients, those with a RD were more likely to report a medicine shortage than patients with a chronic disease (37/96 versus 23/207). In France, reimbursement of transport to centres of expertise can be refused. In Romania, a list of 101 medicines for which a reimbursement decision has been postponed for 5 years includes 21 medicines for RD. In Spain, a list of 43 medicines that can be obtained at the hospital but now with co-payment includes 13 products for RD. In the UK, the fund for new treatments for RD was suppressed. In Germany, the price negotiation for most orphan medicinal products (OMP) lasts for more than 15 months. A systematic review of articles on payer assessment for OMP showed that in average 1.4 articles were published by year between 2000 and 2008 and in average 8.8 between 2008 and 2013, indicating more acute difficulties with OMPs since the onset of the economic crisis.

Conclusions: Our analysis certainly reveals increased access to care difficulties, with some indications of moderately severe issues but no global “catastrophe”. Facts and testimonies from literature search and patients are few, and the health impact of the measures can hardly be estimated. Our next action will consist of a questionnaire sent directly to patients with RD in Europe to document on the difficulties they are facing.

O22

Understanding off-label use and the new challenges.

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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O22

As there are several thousands of rare disorders and only some tens of orphan drugs authorized in Europe, off-label use of medicinal products occurs frequently in the diagnosis, prevention and treatment of rare diseases.

Off-label use is the use of a medicinal product for another indication, another patient group, another dose or by another route of administration as indicated in the package insert. This so-called off-label use is suggested by a similar mode of action or a similar pathology. The competent authorities complain about this therapeutic usage because there is no evidence of their safety and efficacy. Payers hesitate to reimburse this non-validated use. The only responsible person for this use is the prescriber. Sometimes there will be asked to sign an informed consent. Normalization of this off-label use can only be done by the sponsor not by the medical profession or the patient organization. Pharmaceutical companies are not allowed to mention the off-label use to the medical profession: recently settlements are reached against companies to resolve allegations of off-label promotion of their orphan pharmaceutical products (Tobi, Trisenox, Xyrem). Some pharmaceutical companies bring the old substance on the market as a so-called new “repurposed” or “rediscovered” medicinal product with a higher price (Litak, Quenobilan, Savene, Xenlibox). When the medicinal product is taken from the market (deflazacort, mexiletine) the off-label uses lose their only treatment.

At the faculty of pharmacy of the University in Leuven, a group of students performed in-depth interviews to all the stakeholders in this process and identified the main obstacles to regularization. The Belgian Health Care Knowledge Center [https://kie.fgov.be/] will further explore these recommendations and give advice to the public authorities to take further actions. The Belgian Minister of Health already proposed a Royal Decree to reimburse some off-label use under restricted circumstances such as “unmet medical need”. EURORDIS has launched an off-label questionnaire within their members to explore the impact of this off-label prescribing for patients with rare diseases: http://www.ataxia.org.uk/news.php/234/off-label-use-of-medicines-information-needed-from-people-with-ataxia.

O23

Findacure – the Fundamental Diseases Partnership.

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Findacure is building a movement to promote the search and development of treatments and cures for fundamental diseases, on behalf of patients and those who care for them.

Fundamental diseases are extreme and rare genetic disorders that offer a unique opportunity to better understand other diseases, including many common conditions. For instance, study of the LDL-receptor in familial hypercholesterolemia led to the development of statins for the prevention of heart disease. Research into the articular damage in alkaptonuria, a rare genetic disorder, has led to be a better understanding of osteoarthritis.

Findacure empowers patient groups to evolve into effective advocates for change. Findacure also campaigns for a receptive research environment and facilitates patient groups to drive the development of treatments.

If a patient group exists, it’s often run privately and part-time by patients or patients’ family members. They generally have little scientific background, few contacts in academia, no knowledge of drug development, and limited experience of fundraising. That’s why Findacure is organising a series of workshops with expert speakers covering key issues for new patient groups, such as how to participate in clinical trials, how to interact with industry and academia, and how to manage a small patient group effectively.

On the drug development side, a good example of Findacure’s partnership model is the DevelopAKeure programme. The main objective of DevelopAKeure is to study the efficacy and safety of an orphan designated drug, nitisinone, in order to obtain its marketing authorisation for the treatment of patients with alkaptonuria, for which there is no licensed treatment.

The DevelopAKeure consortium brings together a pharma company, a biotech, academia, clinicians and two patient groups in a new model of collaboration. It applied for funding from the European Commission in order to implement phase 2 and 3 clinical trials. To do so, it had to overcome a number of regulatory, scientific and logistical hurdles – many of which are faced by other patient groups trying to develop treatments.

Learnings from Findacure’s experience and its wider network will be published in a forthcoming handbook for rare disease patient groups early next year.

O24

Early access to medicinal products: potential and limits.

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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O24

On average it takes 12 years and a billion euros to develop a new medicinal product from first discovery to availability for patients. Especially in the later stages of development, when promising phase 2 data are available it is difficult to accept for patients there is no general access. In order to make medicines available at an earlier stage and to optimise their development, new ways of taking medicines through the assessment procedures for registration and reimbursement are highly needed.

A new pilot, called adaptive [1,2] will start soon under responsibility of the European Medicines Agency. The idea behind is to give promising products an early access to medicinal products: potential and limits.
studies) will give a better idea of the optimal use of the product in that daily setting. However, there are some downsides as well: what if a product after registration turns out not to be as good as we thought? Might this lead to stop of reimbursement or even withdrawal of the product and what would that mean for patients who are benefiting from the treatment? Secondly, we do already see now that reimbursement agencies and payers are not always convinced of the added value of newly registered products and decide not to reimburse. What would happen if products come to the market in a less mature stage? Would industry be prepared to launch their product at a lower price, since there is less robust evidence collected on their products? Would there be even more unequal access between European member states, reimbursement in some but not all?

The current system is no longer sustainable, so we need to start with these pilots. But we need to do it carefully, evaluating the pitfalls along the way, involving patients and physicians from the start as well as reimbursement agencies and payers. And we need to open and honestly discuss the risks as mentioned above as well.

References

O25
Are we ready? What is missing and what is needed? A regulator's perspective.
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*Orphanet Journal of Rare Diseases* 2014, 9(Suppl 1):O25

Background: The lack of clinical data for orphan drugs and the development of "precision medicines" or advanced therapies have required a new regulatory approach to guarantee a marketing authorization for new and innovative medicines.

What is actually changing in the scenario is the way Agencies are managing the regulatory procedures to ensure a rapid access to treatment for patients with unmet medical needs.

In the last few years EMA and National Agencies have provided a lot of scientific advices (SA) to companies and applicants about orphan designation, Cts design, marketing authorisation procedures and HTA evaluations.

Currently the global scenario is already changing as we are issuing licenses for marketing authorization under exceptional circumstances and conditional marketing authorizations. The legislative framework is also changing with the new Pharmacovigilance Directive and the new Regulation on Clinical Trials entering into force progressively by 2015.

Materials and methods: The new Pharmacovigilance Legislation supports a Progressive Patient Access Scheme (PPAS, or "Adaptive Licensing") approach by expanding EMA authority to request mandatorily to Applicants a post-marketing evaluation of effectiveness in addition to safety.

The basic principles of PPAS approaches are facilitating early access to an early medicine approval, by acknowledging and managing uncertainty about favourable and unfavourable effects. The result will be achieved through the conduction of optimised RCTs, the monitoring of risk-based SA and the harmonisation of RCTs platforms.

Lots of effort is needed by everyone through a new level of cooperation, in particular regulators, companies and the CRQs need to go down to patient level in order to evaluate how the trial is proceeding and by avoiding complex policies. Moreover, patients have to accept a certain level of uncertainty as the clinical studies are not completed and Clinical Trials investigators need a continuous talking to patients during the drug development to ensure the higher level of achievable safety.

Results and conclusions: A successful PPAS pathway depends on the willingness of patients, regulators, health-care providers and payers to accept a greater level of uncertainty using the new medicine in the expectation of an improved benefit risk profile. Furthermore, PPAS approach could facilitate a more open and timely strong scientific dialogue and significant cooperation among stakeholders and a time reduction to full market approval resulting into a possible impact reduction on the overall cost of development.

O26
A company experience of the first MoCA pilot project.
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*Orphanet Journal of Rare Diseases* 2014, 9(Suppl 1):O26

Background: Pricing and reimbursement authorities often lack sufficient information to decide about Orphan Medicinal Products (OMPs), because of pricing, high levels of uncertainty and small datasets, amongst others. EU Member States share similar challenges as they seek to include OMPs appropriately in their healthcare systems.

The "Process on Corporate Responsibility in the field of Pharmaceuticals", launched in 2010 under the Belgium EU Presidency, included a project on a "Mechanism of Coordinated Access to Orphan Drugs" (MoCA), to explore whether a collaborative approach could create opportunities for more timely, sustainable and equitable access to OMPs. Twelve EU Member States, industry, patients' representatives and other stakeholders developed a potential mechanism for such cooperation in the MoCA Recommendations. EU Member States adopted these as part of the formal conclusions of the Process on Corporate Responsibility on 17 April 2013.

The Recommendations identified points where voluntary cooperation could smooth the process of evaluation, by sharing information and data along a coordinated, dialogue-based pathway; as well as a first draft "Transparent Value Framework" (TVF) to provide a possible structure for national pricing and reimbursement discussions.

From theory to practice: the MoCA pilot projects: The Medicines Evaluation Committee of the European Social Insurance Platform (MEDEV) initiated pilot projects in July 2013. Companies were invited to participate with OMPs at any stage of development, with the objective of testing the different elements in the Recommendations. Sobi signalled its interest to participate.

Seven EU Member States volunteered to join the collaboration, together with European Organisation for Rare Diseases (EURORDIS) and two patient groups representing the therapeutic area. The participants agreed potential areas for collaboration, created a timeline of meeting and topics for shared discussion (Figure 2), also including other stakeholders.

Sobi's experience of participating in the MoCA pilot project: The May 2014 evaluation provided opportunities to review the MoCA dialogue's ability to deliver on its objectives and where more work needs to be done. Sobi experienced the MoCA as an important and highly relevant forum, providing the opportunity for managed, prospective, multi-stakeholder, trust-based dialogue, which progressively reduces uncertainty and allows sponsors to "design-in" payer-driven elements into development programmes and

![Figure 1(abstract O26)](http://www.ojrd.com/supplements/9/S1)
availability. It is based on voluntary participation of all participants so is highly flexible. It gives national payer bodies information to help them in their national providing and reimbursement decisions.

**Conclusions:** The first pilot was a success in testing the practical elements of a collaborative dialogue. Further projects will further test the Recommendations and the MoCA’s ability to contribute to access to OMPs timely, equitably and sustainably. The participants in the MoCA pilot are planning to write up their experiences with an aim to publish their joint findings to date.

**O27**

**Managed entry agreements.**
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O27

**Background:** New scientific progress in the “precision medicine” direction and a better diagnosis of rare diseases have led Regulators and Payers to focus their vigilance towards the real life setting. Although Regulators and Payers are taking into consideration patient pressures for rapid access to treatment, nevertheless they must balance the difficulties of taking significant decision coping with uncertainties when deciding on pricing and reimbursement processes.

**Materials and methods:** A large number of mechanisms (Managed Entry Agreements) have been developed to limit the reimbursement of medicines to those subpopulations that are most likely to benefit from treatment. MEA are playing a key role in bridging the possible gap by the management of uncertainty in knowledge relating to pricing and reimbursement of new medicines. Furthermore, monitoring registries represent one of the most advanced experience through all developed MEA tools. The aim of these registries is to define patient eligibility to a treatment by ensuring the proper use of the medicinal product according to the approved indications and concerning decision taken on reimbursement.

According to the variety of mechanisms and the way they are structured, MEAs offer a wide flexibility ability to deal with different types of uncertainties at the same time through the monitoring and combination of financial and performance-based agreements (e.g. budget impact, weakness in clinical evidence, etc). A taxonomy has been developed within the European project “Capacity building on managed entry agreements for innovative medicines” in order to enable the provision of a solid guide in the process of identifying the most appropriate scheme to be adopted in each specific situation.

Regarding the objective of the MoCA project to identify the pathway, that may facilitate the access of OMP to the market, it was very hard to find agreements among all participants on how to facilitate the access of orphan drugs in the real life setting, given the high cost and the lack of evidence of these products.

**Results:** Hence the use of MEAs representing a significant tool for the management of a sustainable pharmaceutical expenditure and also for the generation of further clinical evidences by registries’ adoption, they can be considered the key element to overcome this concern.

**O28**

**Differential pricing: solidarity at times of financial crisis.**
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O28

The financial crisis which has hit Europe (and beyond) in 2008 has been described as a "health system shock" by the WHO which has urged EU Member States to ensure that the national healthcare systems would continue to promote universal access to health services by increasing efficiency in the health sector. The challenge for Member States is to ensure access to innovative medicines for unmet medical needs, while at the same time meeting cost containment objectives and rewarding innovation.

The need for improving sustainability of EU health systems has led to thorough analysis of different pricing models in Europe which showed substantial support of a wide range of stakeholders (including research-based industry, patients and payers) in favour of a differential pricing system as a reimbursement policy measure for new and cost-intensive medicinal products, which is the case for most orphan medicinal products (OMPs).

One way to reduce the impact of OMPs on national healthcare budgets is to differentiate prices according to different levels of Gross Domestic Products (GDPs) and introduce some sense of proportionality between a country’s ability to pay and a fair level of reward for innovation.

The idea for this differential pricing system would therefore be to introduce a price differentiation not country by country but by “clusters of countries”: High, Medium and Low income countries, knowing that in Europe the GDP per capita varies from 1 to 6, with Luxembourg being the highest and Bulgaria the lowest.

In a first phase, differential pricing would be limited to medicinal products responding to high unmet medical need: a price would be agreed on the basis of a value-based pricing system, with the value being assessed with the EU Transparent Value Framework delivered by the MoCA (Mechanism of Coordinated Access) process. Then variations by cluster would apply within a range from minus to plus 10%.

Two main obstacles to the introduction of a differential pricing system have been identified as being the External Reference Pricing and the practice of parallel imports.

The reflection process is still on-going at EU level on differential pricing as a way to address the three following main policy objectives: timely and equitable access to medicinal products for all patients, control of health expenditures linked to medicines and reward for innovation. There is an overall need for political support from Member States and industry.

**O29**

**Identifying specific social challenges of rare diseases: current challenges and issues.**
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**Background:** EURORDIS Care Survey program conducted with over 12000 patients in 23 countries (2002-2008) has concluded that «social security systems are usually designed around common diseases and are not flexible enough to take into consideration unprecedented health needs» [1] and has provided a few insights into rare diseases (RD) patients and families social challenges. Further data collection and literature review is needed in order to assess more accurately these social challenges.

**Objective:** To compile information on social challenges of RD patients and their families.
Method: The identification of challenges is performed based on a literature review of:
- Communication from the Commission on Rare Diseases: Europe’s Challenges (2008) [2];
- Council Recommendation on an Action in the Field of Rare Diseases (2005) [3];
- EUROLPLAN Report on 15 National Conferences (2010-2011) [5];
- EURORDISCare Survey Programme (2002-2008);
- Rare Diseases: Addressing the Need for Specialised Social Services and Social Policies [6].

Results: Main social challenges identified:
- Lack of long term, funded and sustainable policies and structures at national level for the integration of patients with RD into social services and policies;
- Weak coordination between health and psychosocial complementary care, between central and regional/local infrastructures, leading to a consequent lack of multidisciplinary holistic approach;
- Lack of systems to accurately evaluate patients’ disability degree and consequent lack of adequate compensation measures;
- Lack of information and understanding of patients’ disabilities and corresponding implications in patients’/families’ daily lives;
- Lack of training of social sector professionals to deal with rare, complex cases, resulting in unprepared services/structures and insufficient sharing of best practices;
- Scarcity of social services and social policies/benefits. Difficulties in accessing services;
- Lack of case managers guiding patients/families to access the different types of care and structures;
- Lack of personalised/flexible measures and policies;
- Lack of measures to remove burden from family in daily care;
- Lack of systems to deal with transition from adulthood to childhood and ageing.

Conclusion: To improve the access from RD patients/families to adequate and high quality social policies and services there is a need to address these current social challenges by shaping national policies and implementing solutions at MS level. Guiding principles to address some of these challenges are currently being compiled within the European Committee of Experts on Rare Diseases Joint Action Work Package 6.

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The first strategic Plan in the world with a comprehensive approach for rare diseases was implemented in France from 2005 to 2008, followed by a second Plan in 2011 [1]. The 1st Plan had one objective: ensuring equity in the access to diagnosis, treatment and provision of care. The Second Plan aims at improving patient’s and carers’ health and social care, as well as developing research and European and international cooperation.

Among the major achievements of the 1st Plan was the designation and support of 131 National centres of expertise in University hospitals, coordinating networks of 500 centres of competence at regional level. One of the missions of those centres is the coordination with primary care, medical and social care. In the framework of the 1st Plan, pilot networks were created by two centres together with patient organisations and local professionals, and funded by the Regional Health Agencies of Pays de la Loire and Languedoc-Roussillon.

It is now understood that the interface of centres of expertise with social services is essential, when taking care of severely disabling and rare diseases, to facilitate clinical research and clinical trials, prevent the burn-out of medical teams and the explosion of medical costs. Highly specialised hospital care is inefficient if patients do not access adapted schooling, employment, housing and social services at home. Without adapted support, they soon return to the hospital. Moreover, specialised social care is much cheaper than hospital care, and people have a better quality of life. Today the reorganising of existing centres of expertise, diagnosis and research laboratories, patient associations, social professionals and care networks is encouraged to share resources and tools and cover all rare diseases and patients with unclear diagnosis in the long term. Following a call for proposals in 2013, 20 to 25 disease networks are being identified and supported. Disease networks and clusters of centres of reference at regional level are encouraged to establish links with the local authorities in charge of the compensation of disabilities “Maisons Départementales des Personnes Handicapées (MDPH)”, participate in workshops to improve the use of medical certificates, develop a common language and common evaluation tools. Following the creation of international codes for rare diseases, Orphanet is now assessing consequences of rare diseases on disabilities in daily life using WHO ICF-CY 2007, and developing disease specific fact sheets [2].

All rare diseases are not associated to rare disabilities [3]. However 65% of rare diseases are associated to multiple disabilities. People with complex dependency needs do not find adequate support in existing social services: they require pluridisciplinary evaluations, collaboration of different local services, existing centres of expertise and resource centres, and complex cases managers if available. Coordination and good will are not enough. Integration of all available health and social services is needed to support inclusive and continuous life trajectories.

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O31 Rare diseases and disabilities: improving the information available with three Orphanet projects.
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There is currently very little information available about the disabilities encountered by rare disease (RD) patients. Orphanet [http://www.orpha.net], the international database and portal on RDs and orphan drugs, has designed various projects to improve the knowledge and visibility of disabilities associated with RDs, and to provide tools to help the stakeholders. First, we have added content to the texts of the Orphanet Encyclopaedia for the General Public (133 texts) about the daily difficulties associated with the disease and its management. This information is provided through three questions: “What disabilities result from the disease?”, “What resources are available to limit and prevent the disability?” and
"Living with: the disability on a daily basis". These texts are validated by medical experts, disability specialists and patient support groups. Secondly, we have created a specialised collection of texts dedicated to professionals and social service providers, the Orphanet Disability Encyclopaedia. It focuses on the disabilities associated with a specific RD. These disability factsheets provide a brief overview of the medical aspects of the disease, validated by medical experts, and include a description of the disabilities experienced by patients and their management. Fifteen texts are currently available in French.

Finally, with the Orphanet Disability Project, we index the functional consequences of each RD with the Orphanet Functioning Thesaurus, adapted from the “Activities and participation” and “Environmental factors” domains of the International Classification of Functioning, Disability and Health-Children & Youth version (ICF-CY [1]), as well as additional terms to describe cognitive abilities, sleep, temperament and behaviour. Through a questionnaire sent to medical experts, disability specialists and patient organisations, we collect data for each RD: the activity limitations and participation restrictions, their temporality during the course of the disease (permanent or transient difficulty, delay, loss of abilities), their severity and respective frequency in the patient population with current standard management, and important environmental factors. The collected data is analysed and standardised to constitute the Orphanet Functioning Database study already indexed in 857 RDs are already indexed and 540 more are in progress thanks to the contribution of hundreds of people and organisations from 43 countries. These RD disability core sets, which can be integrated into information systems, will be freely available in 7 languages. In addition, we will map the “Body structures” and the “Body functions” domains of the ICF-CY to the Human Phenotype Ontology [2], enabling us to list the anatomical structures and physiological functions impaired for each RD. This information will increase knowledge and aid in better evaluating and managing the daily difficulties and needs experienced by RD patients. It can also help social agencies in distributing appropriate disability compensation measures with equity and equality. Finally, it will enable decision makers to assess the social burden of RDs and can be utilised in the set-up of measures that will allow for the better social integration of disabled people with RDs.

Acknowledgments: These projects are funded by the Caisse Nationale de Solidarité pour l’Autonomie.

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O32 Social profiles project - only the strong survive.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O32

Introduction: Rare Diseases Denmark has developed a tool, Social Profiles, to promote the dialogue between the rare disease patients and their social workers. This is more necessary than ever - an interview study during the fall 2013 shows substantial problems in the interaction between the families and the health care sector and social services.

Method: The Social Profiles was developed with the involvement of volunteers from the member associations of Rare Diseases Denmark. The interview study included parents, adolescents and adults as well as adults with rare diseases were interviewed. The interviews were semi-structured, and analyzed on the basis of grounded theory.

Results from interview study: The interviews showed that you must be resourceful to be able to navigate the welfare systems, as one mother said: ‘only the strong survive’. The core problems in the health care sector were described as challenges not being taken seriously, difficulties in being diagnosed and referred to the right specialists. Lack of coordination and overview are key problems for adult patients, who are not affiliated to the national centers of rare diseases.

One of the main problems for the rare disease patients meeting the social service sector is the startup phase. Many families discovered until late the opportunity to receive social support. Furthermore families are experiencing a lack of transparency in the case-management. The rarity leads to increased documentation requirements, which can be difficult because of the lack of knowledge of rare diseases and because the standard procedures are inadequate. The rare families encounter distrust among caseworkers because of the lack of knowledge of the diagnosis. Therefore they feel distrusted and experience a cumbersome system with slow processing of applications and numerous appeals.

Initiatives – Social Profiles: Rare Diseases Denmark has developed a tool, Social Profiles, to promote the dialogue between the rare disease patients and their social workers. The Social Profiles bring the professionals up to speed on their knowledge about the diagnosis, its symptoms, treatment, prognosis and variation. These characteristics are verified by a physician. The Social Profiles also provide a checklist with special needs, which differ according to the age of the rare disease patient. It also offers references to patient societies and patient associations.

The Social Profiles are developed by the patient associations and hosted on the website: http://www.sjaeldenborger.dk.

O33 Patient innovation under rare diseases and chronic needs.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O33

Background: The patients afflicted by more than 7000 rare diseases are in “orphan” markets. They can expect little help from producers in the form of specialized products, and they have strong incentives to develop, or adopt solutions developed by peers, to help them cope with the diseases. We don’t know the extent to which patients and caregivers respond to these incentives and innovate, how they perceive impact of their solutions, and how they share their solutions with others.

The objectives of this work are: to measure frequency of patient innovation in a population of rare diseases patients; to measure efforts by patients to share their solutions with others; to explore which factors drive patients to come-up with solutions and share them with others.

Material and methods: We developed a questionnaire comprised of 67 questions grounded in user innovation theory and adjusted to the rare diseases context. After validation, we applied the questionnaire over phone in a consecutive sample of 500 rare disease patients/caregivers. Subjects were selected from the list of individuals who contacted the helpline of an association of rare diseases patients from 2009 to 2012. The solutions reported by patients were validated for their novelty by two medical professionals. Additional data about diseases were collected from databases on rare diseases. We develop multivariate regression models to test relationships between our key variables and patient innovation and solution sharing.

Results: 263 (52.6%) of the respondents reported having a solution. 46 (9.2%) individuals reported solutions that they personally find valuable, and that are also evaluated as novel by expert medical evaluators. We find that the likelihood of patient innovation increases as education level increases, and with increase in perception of limitations imposed by the disease. 84 individuals shared their solutions, and the most common mode of sharing is patient-to-patient, reported by 74 individuals. There is a positive relationship between the impact of a solution on the respondents’ overall quality of life and likelihood of patients sharing their solutions, and inverted U relationship between age and the solution sharing.

Conclusion: If anything like this fraction of innovators holds for the overall population of hundreds of millions of people worldwide estimated to be afflicted by rare diseases, patients and their caregivers who innovate to solve their own needs and improve their personal conditions may be a tremendous potential resource of information to improve management and care for many who are similarly afflicted.
O34
Can people living with a rare disease be independent? Inspiring personal stories.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):O34

The Hungarian Williams Syndrome Association successfully organised the “Wing-Test” project supported by the Norwegian Fund and assisted by FRAMBU, the Resource Centre for Rare Disorders of Norway. In this presentation we first would like to present our innovative good practices from the perspective of the Participants and their families and summarize the results and effects on the life quality of these people and society.

What was this project about? The goal of the program was to prepare young adults (and their families) living with some kind of rare disease and disability to have their own independent life and work. Another goal was to form partnerships of strategic importance between the participants’ local services for better care. Therefore we organised two camps, one week each, as the first step to create the conditions of a long-lasting home. The target group of the project was 23 young people (14-35 years old) living with Williams syndrome or other similar disability, who are still living with their families, but they’ve already left school, or just having their last school years; and their families. During the one week program the youth with the help of the volunteers and the professionals could try themselves in different kind of work: gardening, forestry, tending to farm animals, housework, creative activities etc., while we were going to turn our attention to develop their abilities to become more independent. An important part of the program was to get in touch with local people, too.

Conclusions: The Empowerment Weekends for young adults show how important it is that especially patients with a rare disease understand their malformation, take over responsibility, and care for themselves. Medical reports should be given to the parents and patients, and the diagnosis should be explained to them in detail. The project is transferable to other rare diseases. It is crucial to involve patient organizations in the organization of those projects.

POSTER PRESENTATIONS

P1
Se-atlas-cartographic representation of experts for rare diseases.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):P1

Motivation: Numerous highly specialized facilities for the diagnosis and treatment of rare diseases exist in Germany, but it is challenging to present them adequately. Searching in the internet is a common way for patients to find medical information or appropriate clinical experts [1]. Existing services and databases such as Orphanet already offer good contact information to expert centers. A core challenge is to keep the data up to date and to ensure the expertise of the listed centers.

Aim of the project: The project’s aim is to visualize and present the known expert centers in an innovative way and to help completing existing data bases. The representation is realized in an interactive map and in a list format. Stakeholders of the information system are patients and their relatives, doctors, non-medical personnel and the general public.

The basis for the underlying data set of the eligible facilities is provided by the project partner Orphanet Germany. The project’s primary goals are to consistently increase the data set and to ensure its quality.

Conception: In se-atlas general information about the expert centers like name, address, special consultation hours, etc. are stored. To find the relevant centers, they are tagged additionally with the treated diagnoses (by using the Orphanet classification and ICD-10). The decision which centers will be listed or not will be made by an editorial team based on the so-called NAMSE criteria proposed in the German national plan by the Joint Declaration and Agreement on the Establishment of the National Action League for People with Rare Diseases (NAMSE). Both, centers for rare diseases and patient organizations will be allowed to grant affirmations of quality. The conception allows for individual views of the cartographic visualization to be included on other web pages, e.g. those of patient organizations.

Realization and test: At present, the system is implemented in a prototypical way and accessible for registered persons only. The core functions are realized and the Orphanet classification is included. The next steps are to include the Orphanet data base of expert centers and contact the centers for rare diseases for including them.

Schedule: Se-atlas started in June 2013 and is scheduled to run for two years. The public release of the official version is planned for January 2015.

Reference
P2
Setting up strategies: patient inclusion in biobank and genomics research in Europe.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):P2

Rare disease patient organisations have a tendency to be deeply involved in research development and infrastructures, and are practiced at founding strategic alliances with clinical and research networks [1]. In building an integrated platform for rare disease databases, registries, biobanks and bioinformatics through the RD Connect project, we wanted to explore explicitly and in detail, the inclusion of rare disease patients and their advocates in RD Connect’s core activities.

RD Connect collaborates closely with two related research projects EURenomics (rare kidney disease) and Neuromics (rare neuromuscular/neurodegenerative disease) both of which utilise genomic technologies to improve care and therapies for specific disease groups. A workshop of 45 clinicians, scientists and patients/advocates from RD Connect, EURenomics and Neuromics, identified two areas of concern. The first were procedural, around the inclusion of patients in governance including: on-going dialogue between researchers and patients; mutual education; and reporting and dissemination. The second set were contemporary ethical, legal and social issues (ELSI), around privacy, informed consent, data sharing, return of results and incidental findings. A review of the literature found that rare disease patients’ views on these contemporary issues are rarely documented.

To explore these two areas we have parallel initiatives designed to include patients through membership of boards and committees at the highest levels and via a specific research strand investigating ELSI. Through including patients in governance, RD Connect fulfills the top level of Arinstein’s ladder of participation, that of citizen control, whereby those who the governance structure serves are represented in decision making [2]. Among other things, a Patient Advisory Committee works to discuss and build consensus on issues affecting patients and a Patient and Ethics Council promotes dialogue on ELSI between patients/advocates and researchers within RD Connect, Neuromics and EURenomics.

In our research strand we are exploring patient hopes, expectations, concerns and fears for the creation of an integrated platform for rare disease databases, registries and biobanks in a series of focus groups and a Delphi exercise. Using the notion of communities of practice, which encourage collective learning through shared endeavour, we aim to use the findings from this research to inform discussion and education activities which will enable patient perspectives to be embedded into the work of RD Connect, EURenomics and Neuromics [3]. Bearing in mind that patient organisations and scientific groups may have different decision making mechanisms, we will experiment with creating spaces to allow meaningful, on-going dialogue between patients/advocates and researchers [4].

Acknowledgements: This work has been supported by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement 305444 (RD-Connect)

References

P3
Preserving the owner’s autonomy in networks of patient registries and biobanks.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):P3

Background: To achieve statistical significance in rare disease research, bio- or data samples taken from one patient registry or biobank may need to be complemented by those of other institutions [1,2]. While a first overview of potential research partners can be obtained using public catalogues as established by BBMRI [3] or Orphanet [4], this article focuses on mediation services, which provide deeper insight on available material using criteria-based search on fine-grained, non-aggregated datasets. Until now, these datasets were provided either beforehand via regular uploads (central search, e.g. CRIP [5] and the NCI’s specimen resource locator [6]) or on-demand via distributed queries (federated search, e.g. i2b2 SHRINE [7] and EHR4CR [8]). However, both ways give third parties whom the data or sample owners may neither know nor trust insight into their databases. The requirement for self-disclosure places owners in a dilemma: On the one hand, they want to contribute to promising collaborative research projects. On the other hand, they ‘frequently hold proprietary views on their data’ [9] and want to carefully consider with whom to share their assets collected over years without facing pressure of justification for rejecting a proposal.

Results: We propose a method to search distributed databases, yet fully keep their owner’s data sovereignty: The decentral search exploits distributed, heterogeneous, highly sensitive datasets from equally heterogeneous systems for overarching research questions. Similar to other federated searches, the decentral search detects matching material in distributed data stocks. However, their query mechanism is replaced by a novel request mechanism that involves the owner with a high degree of control, who can (decentrally using their own registry or biobank systems) decide if and what to answer based on a specific project proposal. As no datasets ever leave their institution, they can reject projects without risking their good standing as a cooperative scientist. While the decentral search sacrifices real-time answers, it leads to several beneficial side effects: improved data protection due to data parsimony, tolerance for incomplete data schema mappings, flexibility with regard to patient consents and decreased effort when the network is initially joined.

Conclusion: The decentral search allows to exploit bio- or data samples while fully preserving their owners’ data sovereignty. It is employed in the Consortium for Translational Cancer Research, one of the six German Centres for Health Research comprised of eleven university hospitals. The decentral search also marks the centrepiece of the OSSE national registry of rare diseases.

Acknowledgements: The German Consortium for Translational Cancer Research is funded by the German Federal Ministry of Education and Research. For more information, see http://www.unimedizin-mainz.de/dktk. OSSE is funded by the German Federal Ministry of Health as part of the “National Action Plan for Rare Diseases”. For more information see http://osse-register.de

References


### P4

**Characterization and classification of Rare Disease Registries by exploratory data analyses.**

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**Orphanet Journal of Rare Diseases** 2014, 9(Suppl 1):P4

European Commission and Patients Associations identify Registries as strategic instruments to improve knowledge in the field of Rare Diseases [1-2]. Interoperability between Rare Diseases Patient Registries (RDPR) is especially needed to support research activities, to validate therapeutic treatments and to plan public health actions. Because of the extreme variety of RDPR, a uniform and standardized way of collecting data and the identification of specific levels of connection between RDPR with similar aims is needed.

In this study, exploratory data analyses were applied to the EPIRARE (European Platform for Rare Diseases Registries) Registry Survey in order to generate a macro-classification and characterization of RDPR and to deepen different informative patterns.

At first, a Multiple Correspondence Analysis (MCA) suggested associations between selected variables characterizing the structure of RDPR (Figure 1). Then, a Cluster analysis (CA) was developed using the declared “Aims” of each RDPR. CA confirmed the variable associations emerged by MCA and identified three groups defined as: Public Health (PHR), Clinical-Genetic Research (CGRR), and Treatment Registries (TR). Finally, the random forest (RF) method was applied to the Survey data, leading to six classification models endowed of good predictive power and thus confirming the reliability of considering three groups of RDPR. RF also identified several informative variables which allowed the characterization of the three categories of RDPR, defined by data of different nature and by different levels of diffusion (Table 1).

These results, identifying different profiles of RDPR and specific informative needs, represent an informative support aimed at addressing the activities for the design of an European platform of Rare Diseases. Identification of informative cores could address the activities of a platform able to enhance the sharing of information between RDPR with common aims, but also to facilitate a coherent dialogue between RDPR with different profiles.

Guide to interpretation: the arrows indicate the directions of association among the aims; the dimension of the circles represents the frequency of the variable. The higher are the coordinate and the frequency of the variable, the more it contributes to the interpretation of the factorial axis; variables placed on the same direction are correlated.

**Acknowledgements:** This work is part of the activities of EPIRARE, a 3-year project started on April 15, 2011 (grant 2010 12 02) and co-funded by the European Commission within the EU Programme on Health

### P5

**National rare diseases registry in Spain: pilot study of the Spanish Rare Diseases Registries Research Network (SpainRDR).**

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**Table 1 (abstract P4) Main characteristics of Clinical-Genetic Research, Treatment, and Public Health Registries according to the most informative variables emerged after the random forest method.** Variables reported in the table characterize most of the registries of each class

<table>
<thead>
<tr>
<th>Variables</th>
<th>Public Health Registries</th>
<th>Treatment Registries</th>
<th>Clinical-Genetic research Registries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aims</strong></td>
<td>- epidemiologic research</td>
<td>- treatment evaluation</td>
<td>- clinical research</td>
</tr>
<tr>
<td></td>
<td>- disease surveillance</td>
<td>- treatment monitoring</td>
<td>- genetic</td>
</tr>
<tr>
<td></td>
<td>- healthcare services planning</td>
<td></td>
<td>- natural history of the disease</td>
</tr>
<tr>
<td><strong>Collected data</strong></td>
<td>socio-demographic</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Coding system</strong></td>
<td>ICD</td>
<td>No coding system or own code</td>
<td>No coding system or own code</td>
</tr>
<tr>
<td><strong>Services requested to a EU platform</strong></td>
<td>&quot;Quality control systems&quot;</td>
<td>&quot;Facilitated access to useful data sources&quot;</td>
<td>&quot;Model documents&quot;</td>
</tr>
</tbody>
</table>

This table is adapted from a broader context. For full references, please refer to the original source.
Data representing 80.2% of the Spanish population have been included in the pilot study. CDEs mainly comprise variables relevant to personal identification data and RD definition. RD patient information was collected from regional health databases corresponding to 2010 and 2011: electronic hospital records (discharges basic minimum dataset), mortality registry, health insurance card databases, electronic primary care clinical records, chronic renal diseases registry, orphan drugs registry, newborn screening registry and tumor registry, among others.

Results: Data representing 80.2% of the Spanish population have been initially communicated to the central data repository during the pilot study (Figure 1). A total of 824,399 RD cases have been detected. As an example, RD show 26% congenital anomalies; 19% endocrine, nutritional and metabolic diseases; 13% blood and blood-forming organs and certain disorders involving the immune system (Figure 2). Practical problems detected in the pilot study have been discussed and fixed. Final patient recruitment has already started and it will include RD cases detected from 2010 to 2012.

Conclusion: In summary, National Institute of Rare Diseases (RD) Research and Population-based registries addressed to epidemiologic research, health and social planning [1]. The pilot study aims to detect the difficulties of developing the national and population-based RD registry.

Material and methods: Both comprehensive RD lists and common data elements (CDE) have been defined and harmonized with other international strategies (EPIRARE, RD-CONNECT, NIH). CDEs mainly comprise variables related to personal identification data and RD definition. RD patient information was collected from regional health databases corresponding to 2010 and 2011: electronic hospital records (discharges basic minimum dataset), mortality registry, health insurance card databases, electronic primary care clinical records, chronic renal diseases registry, orphan drugs registry, newborn screening registry and tumor registry, among others.

Results: Data representing 80.2% of the Spanish population have been initially communicated to the central data repository during the pilot study (Figure 1). A total of 824,399 RD cases have been detected. As an example, RD show 26% congenital anomalies; 19% endocrine, nutritional and metabolic diseases; 13% blood and blood-forming organs and certain disorders involving the immune mechanism; 10% diseases of the circulatory system (Figure 2). Practical problems detected in the pilot study have been discussed and fixed. Final patient recruitment has already started and it will include RD cases detected from 2010 to 2012.

Conclusion: In summary, National Institute of Rare Diseases Research and Regional Health Departments of Spain are working together towards a harmonized RD patient registration. The Spanish experience could be a model for other countries with complex political and administrative structures which, in order to carry out a national RD registry, will require the standardization of criteria, data harmonization and coordination between regions.

Acknowledgements: On behalf SpainRDR group. Financial agency: Instituto de Salud Carlos III - International Rare Diseases Research Consortium (IRDiRC). Grant no. IR11-RDR

Reference
1. The Spanish Rare Diseases Registries Research Network [https://spainrdr.isciii.es/en/].
The United Kingdom (UK) Facioscapulohumeral Dystrophy (FSHD) Patient Registry launched in May 2013. Funded by the Muscular Dystrophy Campaign and supported by the TREAT-NMD Alliance. This patient driven registry collects the internationally agreed core dataset, an outcome of an ENMC Workshop held in 2010 [1], through a novel online portal (http://www.fshd-registry.org/uk). Genetic details are added by a nominated neuromuscular specialist. In addition questionnaires about pain, quality of life and scapular fixation are included.

In the 12 months between May 2013 and May 2014 over 400 people registered, 92% with a diagnosis of FSHD1. Similar proportions of patients registered from both sexes and 59% of patients were between 40 and 70 years old (mean 47.39). Muscle weakness was widely reported with periscapular shoulder weakness occurring most frequently (89%) followed by weakness of the hip girdle (73%), facial muscles (72%) and foot dorsiflexor (71%). The onset of facial weakness was reported significantly earlier than weakness in other areas with 66% experiencing facial weakness before 20 years old.

Full time wheelchair use was reported in 18% of cases, 62% having lost ambulation between 31 and 60 years old (mean 41.61). Use of a wheelchair or other assistive device part time was reported in 44% of cases. A small proportion of patients report hearing loss (18%), retinal vascular disease (2%) and using ventilation (7%). Additional questionnaires on pain were completed by 350 patients during this time and the majority reporting at least some pain, most often described as tiring or aching. Persistent pain (experienced for at least 3 months in a year) was reported by 92% with 53% of people describing this pain as distressing, horrible or excruciating. The location of the pain is variable but most often reported on the shoulder.

A broad spectrum of patients has registered providing a new insight into the FSHD population in the UK. The Registry aims to help facilitate and accelerate clinical research and trials, sharing a common dataset with a growing number of FSHD registries around the world will allow the registry to achieve this locally and internationally. The registry is well placed to inform future clinical research and help develop of standards of care.

Reference

P7 Sanfilippo syndrome registry project and natural history studies: an example of patients, parents and researchers collaborating for a cure.

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In the past 5 years two clinical trials for Sanfilippo type A have been conducted, namely Shire’s enzyme replacement therapy and Lysogene’s gene therapy. Nationwide Children’s Hospital is aiming to start gene-therapy clinical trials for types A & B in 2014. For other Sanfilippo types C and D the research is at preclinical stages including gene-therapy (Type C) and developing and characterizing a knock-out mouse model (Type D). These recent scientific advancements towards treatments for Sanfilippo Syndrome indicate that it is time for us to collect and analyze information on Sanfilippo patients in a single centralized registry as part of the PatientCrossroadsCONNECT website (https://connect.patientcrossroads.org/?org=SanfilippoRegistry) In addition it is important we understand how the disease progresses and what differences there may be between the different types of Sanfilippo Syndrome. This requires natural history studies (NHS) which can help us in determining the clinical outcome measures, identify potential surrogate endpoints via defined assessments including standardized clinical, biochemical, neurocognitive, behavioral, developmental, and imaging measures. From our experiences such data collected from NHS studies are generally not shared between researchers except when published as scientific papers at a much later date. Sanfilippo Syndrome has a very small patient population and the participation in multiple NHS (which may be occurring simultaneously) places an unrealistic burden on patients and families. Sanfilippo Syndrome is also ultra—rare and patients are geographically diverse. Providing patients and families with an outlet to find pertinent information pertaining to Sanfilippo, such as where Natural History Studies and clinical trials are taking place, or making themselves known by participating in a centralized registry, is essential. With the use of RareConnect platform (http://www.rareconnect.org/en/community/sanfilippo-syndrome) we hope to bring families from around the world closer together and give them access to information that they may not have access to otherwise.

We describe how the data collected from the NHS studies for Types A and B performed at Nationwide Children’s Hospital and for Type C at The Children’s Hospital at Montefiore will be available to other qualified institutions to prevent repetition. Such NHS studies and registries can also help in identifying participants for future clinical trials. We illustrate through this work how close collaborations between parent/patients led disease organizations and clinical researchers, is essential to ensure our limited funding and time is well spent as we try to identify treatments as quickly as possible.

P8 The RE(Act) Initiative and the use of an online community to enhance research on rare diseases.

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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):P8

There is a striking need for increased international cooperation in scientific research on rare diseases (RDs). Existing research efforts are in fact still scattered and fragmented research is being performed with little coordination between research laboratories. This lack of coordination is particularly detrimental to the increase of knowledge and to the delivery of new therapies for RDs because the resources are very limited and the patient population is small for each disease. Moreover, traditional funding...
P9 New e-health services for the European Network for Rare and Congenital Anaemias (e-ENERCA).
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1)P9
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Rare Anaemias (RA) are a group of Rare Diseases (RD) with prevalence, in Europe, less than 5 per 10,000 individuals. Major forms of RDs require red blood cell transfusions, iron chelation, splenectomy, and/or in very severe cases, bone marrow transplantation, as main therapeutic options. Beta-thalassaemia major is predominant in Italy and Cyprus, and sickle cell disease (SCD) in African population. During the last 30 years, SCD is increasing in Europe due to African immigration, leading to an important impact on healthcare burden in several countries. Preventive programs, aiming to epidemiological control, and improvement of diagnosis and clinical management of major RA, are crucial for decreasing the affected birth rate and achieving an efficient balance between morbidity and patient’s life expectancy. Since 2003, the European Network for Rare and Congenital Anaemias (ENERCA) has taken an active role for improving this situation by the following actions: a) the identification of Centres of Expertise on RAs in Europe according to the recommendations of ENERCA White Book b) the promotion of best clinical and laboratory practices by the publication of ENERCA recommendations c) the improving of continuous medical education, by organising topic-specific training courses, workshops and symposia, e) the empowerment of patients, by cooperation with Patient’s Associations, and co-organizing a bi-annual European Symposium on RAs with interactive patients-health professionals sessions. In September 2013, a new phase of the project called e-ENERCA has started with the aim to provide, patients and professionals with e-Health tools for assure the same access to health services in RAs across Europe, independently from the country of practise and origin of the patients. e-Health services will be developed through the set-up of three different e-platforms endorsed by ENERCA website (http://www.enerca.org) : 1) e-Registry, a Pan European registry of RAs for gathering patient’s data necessary to achieve the required sample size for epidemiological surveillance and clinical research 2) e-Learning, a teaching platform for the dissemination of knowledge, continuous medical education, and best practices awareness and promotion through Internet, and 3) e-Medicine, a platform to provide, at distance, expertise (teleexpertise) and diagnostic facilities (telediagnosis), avoiding, when possible, the need of travelling. Finally, e-ENERCA will also promote the recognition of the previously identified Centres of Expertise in RAs (White Book) by the national health authorities, a mandatory condition for ENERCA final recognition as European Reference Network in Rare Anaemias (RA-ERN).
Acknowledgements: On behalf ENERCA consortium

P10 Prenatal therapy in developmental disorders: drug targeting via intra-amniotic injection to treat X-linked hypohidrotic ectodermal dysplasia.
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Orphanet Journal of Rare Diseases 2014, 9(Suppl 1):P10
Background: Disorders that irreversibly affect fetuses make early stage therapies desirable. X-linked hypohidrotic ectodermal dysplasia (XLHED), the most common inherited disorder of ectodermal development affecting the skin and its appendages, glands, and teeth, is caused by a lack of the signaling molecule ectodysplasin A1 (EDA1). In the Tobby XLHED mouse model, repeated intravenous administration of EDA1 to pregnant mice has been shown to correct the developmental abnormalities in the offspring. Maternal drug administration, however, exposes mothers to potential drug toxicity and is limited by thevariability in transplacental drug delivery. Alternative approaches to fetal treatment should entail low risk drug delivery with reproducible pharmacokinetics. We hypothesized that a single injection of an EDA1 replacement molecule into the amniotic fluid could allow sustained drug exposure at levels sufficient for correction of XLHED.
Materials and methods: A human IgG1:EDA1 fusion protein, EDI200, was tested for its stability in human amniotic fluid using a receptor-binding ELISA. It was injected into amniotic sacs of wild-type mice to evaluate fetal drug uptake and pharmacokinetics, and administered to Tobby mouse fetuses at doses between 1 and 100 µg/g fetal weight. Phenotypic correction was assessed.
Results: EDI200 was demonstrated to be stable in amniotic fluid at 37°C for at least one week. Intra-amniotic administration of the highest dose resulted in substantial fetal uptake with mean serum levels of 9.0 and 1.2 µg/ml at 6 and 96 hours, respectively. Maternal serum levels remained <0.1 µg/ml. In Tobby mice, a single intra-amniotic EDI200 injection at day 15 of gestation restored normal ectodermal development in a dose-dependent manner. Doses of 10 µg/g fetal weight or above led to complete phenotypic correction of skin appendages, eccrine sweat glands, eye lids, and teeth. No adverse effects of the treatment were detected during an observation period of one year.
Conclusions: Intra-amniotic protein application may lead to rapid and continuous fetal uptake, sustained serum levels, and therapeutic efficacy comparable with repeated maternal injection. It allows prenatal drug targeting with minimal maternal exposure and may, thus, represent a novel paradigm for treatment of disorders in early human development.

P11 Integration of Rare Diseases into Social Services.
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3Romanian Prader-Willi Association, Zalau, Romania;
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Background: Social Services are instrumental to the empowerment of people living with rare diseases and to the improvement of their well-being and health. However, these services are still scarce and often not adapted to the needs of people living with rare diseases. Access to these services remains a challenge for patients and families affected by rare diseases.

Objective: The European Committee of Experts on Rare Diseases Joint Action Work Package 6 - “Specialised Social Services and Integration of RDs into social services and policies” (enabled by EC Co-funding 20112201) - aims at giving more visibility to existing Specialised Social Services and good practices as well as advocating for the integration of people living with rare diseases in services not specific/exclusive to rare diseases, by working on training of social services providers.

Method: In order to achieve the objectives above, the following methods have been used: mapping of Specialised Social Services available in Europe via a collection of contacts among EURORDIS members and network; collecting guiding principles for Specialised Social Services and for the Training of social services providers through the organisation multi-stakeholder workshops; compiling case study documents on expert existing services by organising country visits to expert services and applying a detailed questionnaire; advocating for these services via policy fact sheets.

Results: The following results have been obtained: map of Specialised Social Services (Figure 1) and creation of EURODIS website section; Documents on ‘Guiding Principles for Specialised Social Services’ and ‘Training for Social Services Providers’; Case study documents on Agrenska (Sweden), Frambu (Norway), Bátor Tábor (Hungary) and Group Homes for Prader-Willi Syndrome (Denmark); policy fact sheets on Therapeutic Recreation Programmes, Respite Care Services, Adapted Housing Services, Resource Centres.

Conclusion: European Committee of Experts on Rare Diseases Join Action Work Package 6 has now made available a set of information on specialised social services and on consensual good practices essential to the improvement of holistic care of people living with rare diseases. As the leader of this Joint Action Work Package, EURORDIS encourages decision-makers, patient representatives, national authorities, patients and families to use these tools to move forward in integrating people living with rare diseases into social services, in coordination with the national plans and strategies for rare diseases.

P12
E-learning course for Norwegian caregivers.
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Objectives: Frambu Resource Centre for Rare Disorders in Norway has registered 140 persons with Prader-Willi Syndrome (PWS), and often receives inquiries on telephone and e-mail about different aspects concerning this group. Frambu offer local guidance and courses at Frambu, but with limited time resources for local guidance, as well as limited possibilities for local caregivers to participate in courses at
Frambu, we found it necessary to distend our competence services for this group. The aim was to provide essential education about PWS to caregivers that work in group homes all over Norway to ensure better and closer follow-up for people with PWS. Our goal was to develop an electronic course to caregivers, as a new competence service from Frambu that will supplement our traditional services.

Methods: A group of five professionals from Frambu was in the project group. Through workshops and meetings we have developed learning goals for eight different themes, concerning different aspects of daily life of a person with PWS. The Norwegian Prader-Willi association, caregivers and other professionals with competence on PWS have participated in this work.

Results: The e-learning course was accessible in Norwegian on the internet in December 2012. The content of the e-learning course appears through videos and photos of people with PWS, interactive tasks, case examples and written information.

Conclusions: Frambu Resource Centre for Rare Disorders has developed a new education tool for caregivers. By August 2014 255 caregivers have finished the course, and the response and feedback is very positive. The evaluation shows that the participants found the content of the course useful, that they became motivated to change their practise at work, and that the course was a good alternative to physical course gatherings. In conclusion we can say that e-learning is an effective tool for teaching caregivers about rare disorders.

P13

Evolution of national and European policies in the field of rare diseases and their impact over the past five years.

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The 2009 Council Recommendation on an Action in the Field of Rare Diseases (2009/C 151/02) [1] encouraged Member States to elaborate a national plan or strategy for rare diseases before the end of 2013. One of the principal tasks of the European Union Committee of Experts on Rare Diseases (EUCERD) [2], through its Scientific Secretariat, was to analyse the results of the actions cited in the Recommendation, notably through the production of the annual report on the ‘State of the Art of Rare Disease Activities in Europe’ [3]. The 2014 edition of the report considers the impact of European policy and national plans/strategies (Figure 1) on the organisation of health care and services for patients with rare diseases, including access to diagnosis and treatment, as well as considering progress in the field of registries, rare disease research initiatives, the genetic testing offer, access to information on rare diseases, patient organisations, and specialised social services. In terms of national plans and strategies for rare diseases, by end 2013, the deadline to elaborate national plans/strategies for rare diseases fixed by the Council Recommendation, most EU Member States had submitted a plan/strategy to their national authorities and sixteen countries have adopted a plan/strategy (Figure 2). France and Spain have implemented and assessed their first plan. As their number one priority, most countries plan to identify and design centres of expertise for rare diseases. Many of these plans/strategies, however, have no dedicated budget for their actions, a result of the unfavourable economic context which may hinder the implementation of defined measures. The next challenge for EU Member States will be to effectively implement and assess these plans, which the new Commission Expert Group on Rare Diseases [4] will follow closely. Research in the field of rare diseases has been boosted in recent years due to European and international initiatives, such as European research projects funded via the DG Research and Innovation framework programmes and the E-Rare ERA-NET [5] as well as the creation of the International Rare Disease Research Consortium (IRDIRC) [6]. The Orphanet database [7] continues to expand and provides data collected in 37 European and surrounding countries with partner teams in Canada and Australia and negotiations ongoing in other world regions. Nearly all countries now have a national alliance for rare diseases ensuring that the voice of rare diseases, carried by Eurordis [8] at the European level, is heard.

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References


2. European Union Committee of Experts on Rare Diseases [http://www.eucerd.eu].

Figure 1(abstract P13) Emergence of concepts and initiatives surrounding rare diseases in Europe (December 2013)


5. E-Rare [http://www.erare.eu].


Figure 2(abstract P13) Stages of development of national plans or strategies for rare diseases in EU MS in December 2013.