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Proceedings from the IX International Conference on Rare Diseases and Orphan Drugs (ICORD). Ede (The Netherlands), October 7-9, 2014

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PROCEEDINGS FROM THE IX INTERNATIONAL CONFERENCE ON RARE DISEASES AND ORPHAN DRUGS (ICORD).

Ede (The Netherlands), October 7-9, 2014

The Societal value of Prevention, Diagnosis and Treatment of Rare Diseases

Invitation from the President

On behalf of the Organizing Committee, I am pleased to invite you to the IXth International Conference on Rare Diseases and Orphan Drugs (ICORD), which will take place in the Netherlands, October 7-9, 2014.

We are very delighted to be able to host you in the charming city of Ede and to be back in the European Union since our last meeting in Rome 2009. The recent ICORD annual meetings in South America, Asia-Pacific and Eastern Europe have enriched ICORD as an organization. The past events have contributed to the globalization of ICORD, an increased understanding of world-wide needs as well as enlarging the visions and contacts of our members. Indeed, rare diseases and orphan drugs are undoubtedly global matters, which in ICORD find a unique and transparent forum for discussions, presentations of ideas and collaboration.

In parallel, our recent group editions of ICORD's position (Acta Pediatrica, 2012) and the Proceedings of the past meeting in Russia (RARE Diseases and Orphan Drugs, 2014) offer space where all stake holders within Rare Diseases can advocate their concepts, achievements and ideas.

The ICORD Working Groups sessions provide opportunities for researchers, regulatory, industry and patient organization groups to express their special needs and develop joint activities.

This year the ICORD conference will take place in conjunction with the FIGON Dutch Medicine Days (FIGON DMD), and is locally supported by ZonMw, providing more opportunities of interactions. Therefore, we wish to welcome you to this year's ICORD meeting and hope to see you in the Netherlands.

Virginia Llera, MD.
ICORD President; GEISER Foundation President

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The ICORD annual meeting will take place in conjunction with the FIGON Dutch Medicine Days and interactive sessions with ZonMw and the Dutch Clinical Trial Foundation will be organized in addition to separate ICORD sessions.

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Future ICORD meetings

X ICORD, in associations with the Mexican Federation of Rare Diseases FEMEXER, will take place in México FD (México) October 15-17, 2015. The event will be preceeded by the 5th Latin American meeting of Rare Diseases ER2015LA (GEISER Foundation and FEMEXER), October 12, 2015; and the World Congress of Discoveries and Innovations in Orphan Diagnoses and Drugs, October 13-14, 2015. The events will be developed in a coordinated format incorporating all the main topics of interest for rare diseases and orphan drugs. For proposals or more information contact the local Secretariat at FEMEXER proyecto.pideundeseo.mexico@gmail.com, GEISER info@fundaciongeiser.org, icord@karolinska.se.

*Any members of **ICORD** can suggest the inclusion of topics and/or speakers in the programs of the annual meetings. The respective Strategic and Planning Committee will consider it. Deadline for proposals will close 6 months before the meeting date (Check **ICORD** web-site). Submitted abstracts will be rated and the abstracts with the highest score will be proposed for oral presentations in the official program. Remaining abstracts will be suggested for poster presentations.*

For more information, or becoming a member, see http://www.ICORD.se, or contact the ICORD Secretariat E-mail: icord@karolinska.se, desiree.gavhed@ki.se

Abstracts from the IX ICORD annual meeting: OP = Oral presentations; PPa = Academic poster presentations; PPi = Institutional poster presentations.

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OP-01. Mitochondrial Drug Development: from bench to bedside.

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The development of new drugs finally leading to clinically relevant improvement for mitochondrial disease is a challenging, time-consuming, sometimes frustrating and expensive process involving many different stakeholders. The foundation for developing such drugs lies in a detailed understanding of the biological processes of normal and hampered energy metabolism at the different levels of complexity. In executing such a mitochondrial drug development program we came across several, first to be solved issues, including the development and validation of relevant clinical outcome measures for the mitochondrial disease group. In this lecture I will present the state of the art of our public-private drug development program, with a focus on different classes of new chemical entities, and discuss the various unsolved issues enabling so far a proper judgement of the clinical relevance of mitochondrial disease intervention strategies in general the field is facing.

OP-02. The Biopontis Alliance for Rare Diseases (BARD) – a non-profit partner to the community of rare disease organizations in early stage development of cures candidates

Barbara L. Handelin*, Ph.D., Richard A. Basile, Marlene E. Haffner^, M.D., MPH., Erik T. Tambuyzer^^, Ph.D.**

* BARD, Philadelphia, PA, USA, ** BARD, Raleigh, NC, USA, ^ BARD Board of Directors, USA, ^^ BARD Board of Directors, Belgium, erik@tambuyzer.be

The field of rare diseases is an excellent example for personalized healthcare, with patients in a central role in the discovery and development processes of treatments for their disease. Collaborative partnerships are needed to move development of rare disease therapies forward in early stages as no stakeholder alone has all knowledge, resources and expertise.

The newly founded BioPontis Alliance for Rare Diseases (BARD) presents a scientific and economic partnership model to work on cures for serious and rare diseases. The founders have developed an innovation joint venture model with a business and scientific development structure able to fill the gap between discovery science and the pharmaceutical and biotech industry. We build bridges across the discovery/preclinical development translational gap bringing the required "expertise pillars": scientific and technical, legal (patenting), regulatory and commercial transactional skills and negotiation. BARD operates as a partner with academic inventor groups and/or patient organizations to develop therapy candidates, as co-owners of the process and the outcomes. Recognizing the need to harness and align all sources of funding for rare disease therapies, the non-profit corporation is structured to create financial bridges between philanthropic resources and the commercial sector.

The network of contract research companies and academic institutes that has been created can conduct the development work needed for each initiative, which is being guided and led by central project management and industry experienced managers within the core of the entity. The founders have worked with academic institutions to co-develop transformative licensing agreements which are fairness based, providing the originators a pro rata share of revenues that are generated from the full intellectual property estate. Master license agreements are in place with an initial group of academic institutions (others to be added over time) which remove the need to renegotiate the terms of licensing and sponsored research agreements for each project, and this same process will be gone through with patient organization partners. This promotes focusing on the goal of creating potential treatments rather than reinventing licensing terms and benefits.

BARD is currently prepared for the launch of its operations and is seeking donations and scientific collaborators. Operating for a global patient community and market, it will favorably embrace partners from across the globe bringing financial, scientific and patient organization skill sets.

OP-03. International school of public health for rare diseases

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The Italian National Centre for Rare Diseases (CNMR, www.iss.it/cnmr), established in 2008, is the result of a strategic approach, which the National Institute of Health has developed for more than 10 years to deal with the public health challenges associated with rare diseases (RD). The CNMR mission is to promote and develop experimental research and public health actions on RD and orphan drugs, as well as to represent the national focal point for information and communication.

Every year, the CNMR organises a number of education and training activities on RD addressed to various stakeholders (physicians, healthcare operators, researchers, patient organisations, etc.) at national and international level, including e-learning. In particular, the CNMR organizes a yearly programme of international initiatives.

a) Summer School on "Health care guidelines for rare diseases" (http://www.iss.it/cnmr/appu/cont.php?id=2412&lang=1&tipo=56). The CNMR has organised this Summer School since 2012 in order to improve knowledge and adoption of RD guidelines. The one-week intensive course intends to provide participants with the methodological basis for the development of RD guidelines. It also gives an introduction of the commonly used standards for the assessment of existing guidelines. The international team of trainers facilitates an informal and interactive learning environment, by offering insights for discussion and stimulating the exchange of experiences across disciplines and different countries.

b) Summer School on RD and orphan drug Registries. The first edition has been in October 2013 and the second edition takes place on September 15-19, 2014 (www.iss.it/cnmr/news/cont.php?id=2327&lang=1&tipo=3).The course takes the participants through the main concepts and practical steps that must be undertaken in the establishment and management of a RD registry to ensure its usefulness, soundness and sustainability.

c) Capacity building (CB) activities started in the framework of the EUROPLAN project (www.europlanproject.eu). CB is a process beginning with the definition of needs and the obstacles that hinder progress in achieving the results. It encompasses all those policy actions that allow achieving specific objectives and maintaining the results over the time and include the training of human resources. The experience in capacity building gained in EUROPLAN will be useful for other sectors of the CNMR's areas of interest.

d) The CNMR carries out a number of courses addressed to patient organisations, aiming at empowering RD patients and their families in the daily management of their condition.

The past activities included the "Implementation and evaluation of a training programme on orphan drugs targeting patient associations and families of patients with rare diseases" and the "Parent Training on Prader-Willi syndrome".

Based on the experience and achievements built up in these years, we are organizing a EUROPLAN School of Public Health on Rare Diseases addressed to worldwide attendees in order to train stakeholders on the specific issues concerning RD, support the development of centres of expertise and Reference Networks, as well as strengthen international co-operation.

OP-04. An integrative model of rare diseases management in a tertiary hospital: from basic research to clinical practice and beyond

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The field of rare diseases (RD) is an emerging field of high interest from the research, commercial, clinical and societal points of view. Given its inherent fragmented nature, the available knowledge on RD needs to be structured and integrated at different levels. At Vall d'Hebron University Hospital (HUVH) we have been working on the implementation of a model that integrates the already existing clinical and research information that a complicated, tertiary reference hospital like ours has on RD. In this talk, we will present the model we have developed , on the one hand, to manage our internal expertise on RD and to improve the way we do research and apply it to the clinical practice and, on the other hand, to set our strategic lines on RD for the future. This model is based on the basic research we perform on RD and links it to the clinical practice and the hospital's patient care strategies. In doing so, we have been able to create a map of research on RD and to identify those RD where HUVH can become a strong, competitive, international reference and therefore those areas of rare diseases study and patient care which will become strategic for the future development of the hospital.

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OP-05. The Folic Acid supplementation/fortification policy paradigm from a multidisciplinary point of view

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The incidence of Neural Tube Defects (NTDs), which comprise spina bifida, anencephaly and encephalocele, vary across the world (0.5 – 6/1000 births). Most of these congenital malformations - which cause significant emotional, social and financial costs - can be prevented through public health measures. There is scientific evidence that optimal pre-conceptional serum and RBC folate levels, maintained throughout the first few weeks of pregnancy, significantly reduces the incidence of both occurrence and recurrence of NTDs. The fact that as much as 50% of the total pregnancies may be unplanned poses serious policy problems. Despite having access to the same epidemiological evidence, policy-makers around the world are recommending different interventions to increase the target group's Folic Acid (FA) intake. Since the early 1990s, national authorities worldwide have been interested in the potential of mandatory FA fortification as a policy response to the scientific evidence of the relationship between FA intake and the reduced risk of NTDs. As of June 2014, 79 countries have introduced fortification of wheat flour produced in industrial mills with at least iron and folic acid, except Australia which does not include iron and Congo, Venezuela, the United Kingdom, and the Philippines which do not include folic acid. However, mandatory fortification also raises scientific, ethical, technical and economic challenges. From a policy perspective, the issue is complex and controversial and has preoccupied policy makers, researchers, social scientists, and the population for some time and no clear, standardised solution for evidence-based and ethically accepted policy-making has been yet found. The policy options currently considered comprise: (1) Promotion of folic acid supplements to target group, (2) Mandatory folic acid fortification, (3) Voluntary folic acid fortification, (4) Increasing public awareness and nutrition education of target group and of population, and (5) No specific action. Each of these options entails risks and benefits as well as ethical and equity issues and financial and societal costs. When confronted with such a complex decision, a number of questions arise. What tools are available to policy makers to weigh the potential benefits against the real and theoretical risks of FA overload and guide them towards the adoption of the most effective and ethically acceptable choice? How can research evidence translate into effective and efficient policy decisions, balancing benefits and risks globally, resulting in policy determinations acceptable to all stakeholders? Are traditional decisions making tools useful to policy makers for choosing the most appropriate strategy regarding improved FA intake? In 2005, UNESCO's General Assembly signed the Declaration on Bioethics that offers a cohesive and unified structure for ethical decision making by Member States. Can this provide an effective framework integrating other available tools for the decision-making process regarding the current debate in FA policies? The main objective here is to keep alive the dialogue for a better decision-making process regarding improved FA intake to reduce NTDs, proposing a multidisciplinary approach to offer concrete advice to policy makers for policies that take into account the interests of all stakeholders.

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OP-06. Folate and prevention of neural tube defects: Tracking red blood cell concentrations will help guide policy decisions about fortification.

Clarke R.

University of Oxford. UK

Studies in China and Ireland have reported an inverse dose-response association of neural tube defect risks with RBC folate concentrations with a threshold for optimal RBC folate concentrations for prevention of neural tube defects of 1000 nmol/L. Applying the risk model developed from the Chinese data to population RBC folate concentrations in the United States, before and after fortification, it has been shown that the predicted estimates for the prevalence of neural tube defects were concordant with the observed prevalence before and after fortification. Taken together, the Chinese, Irish, and US data indicate that RBC folate concentrations of about 1000 nmol/L or greater should be the population target for preventing neural tube defects that should guide the choice of population fortification strategies.

Voluntary folic acid fortification causes extreme variation in folate status within populations (with low intakes in lower socioeconomic and ethnic minority groups and high intakes in users of high dose supplements). Consequently, the Scientific Advisory Committee on Nutrition has called for mandatory fortification in the United Kingdom to replace voluntary fortification, together with guidance on high dose folic acid supplements, to increase the population folate concentrations while avoiding excessive intakes of folic acid. Large trials of folic acid supplements at doses 10 times higher than the average extra intake after fortification provide reassurance that such a policy is likely to be safe. Population surveys of RBC folate concentrations, along with the optimum threshold confirmed by recent studies, will help to guide policy decisions to prevent neural tube defects.

OP-07. Could folic acid supplementation bridge the gap of the results of fortification? State of the art in Europe and future perspectives

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The effectiveness of folic acid mandatory fortification in increasing serum folate and reducing the occurrence of reducing Neural Tube Defects (NTDs) and congenital heart defects has been proven by many studies.

However despite the success in prevention of some congenital anomalies, mandatory fortification has been the object of animated debate over its potential *"side effects"* in the long term: high doses of synthetic folic acid can mask vitamin B12 deficiency with an increased risk of cognitive decline and promote an "acceleration phenomenon" in malignant neoplasm.

For these reasons, European countries have not yet adopted mandatory fortification and chose the promotion of folic acid supplementation as a *"precautionary approach"*.

Each country decide its own national official recommendation for folic acid supplementation.

Despite numerous campaigns promoted in Europe in the last years, prevalence of women taking folic acid supplements to reduce NTDs is still low: a systematic literature review shows that periconceptional folic acid use ranged from 5.7% to 55.5% in Europe. Furthermore, from data analysis emerged that a high percentage of women uses folic acid supplement the wrong way and with wrong dosage. This is probably due to the fact that among European women and their health care providers there is neither enough awareness and knowledge about the folic acid supplementation before pregnancy both in timing and dose.

Folic acid supplementation strategy has two weakness. Firstly, folic acid supplementation doesn't led to significant results in reaching a wider number of women of childbearing age: it does not include the ones who choose not to plan their pregnancy and therefore do not worry about supplementing their diet with extra folic acid. Secondly, disadvantaged women with a poor diet likely do not benefit from supplementation.

To make folic acid supplementation an effective strategy in primary prevention and increase its compliance, some actions should be undertaken in the future.

Training programmes and medical educational courses should be proposed to health care professionals to educate towards the beneficial effects of folic acid supplementation before pregnancy.

European countries should promote folic acid supplementation to all women of childbearing age: starting folic acid supplementation some months before pregnancy is perhaps too late to start an efficient periconcentional prevention of NTD's. Folic acid supplementation among all women in childbearing age should guarantee to everybody a decreased risks to have unhealthy babies.

Another promising strategy is providing free folic acid supplements to women in order to facilitate their folic acid intake mostly among low –income and disadvantaged women.

At last promoting folic acid supplementation along with healthy lifestyle and control of the health status among women in childbearing age can reduce the overall risk of adverse reproductive outcomes such as birth defects, infertility, pregnancy complications, intrauterine growth restriction and premature births.

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OP-08. Novel business models for orphan drug development

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There is a need for a new approach to (Orphan) drug development.

The orphan drug act is working to a certain extent, but the average prices are (very) high, even after patents have expired. These high prices form an increasing societal burden. Very few drugs for orphan disease have been developed in the last 10 years. The extent of its use is different in the different countries mostly related to reimbursement policies. Some drugs with orphan drug protection are clearly too expensive and the protection is sometimes even mis-or abused. With the rise of personalised medicine there will be a tsunami of new orphan drug designations and the question is can we afford such expensive drugs as a society or do we need another approach.

Drug development knows a 'classic' approach.

After fruitfull research (often academic, thus funded by public money) a patent is obtained and licenced to a pharmaceutical company. All the risks and costs are upon the company and all other participants i.e. patients, M.D's, medical institutions etc are paid for their contribution. There is no shared responsibility, nor shared financial benefit. In addition, drug prices are not transparant and for orphan drugs the prices are mostly around 200,000-300,000 EUR per patient per year. It is in my opinion clear that a pharmaceutical crisis is looming, just like the financial-bank crises of 2008, because the classic business model is still believing in and counting on double digit profits and no other models have been initiated.

New business models and approaches are needed; Fair Medicine.

In the new approach not one entity is solely responsible for the drug development but there is the need to form a coalition of all important participants in the chain of drug development. Bring these participants together on day one on the basis of trust and common goals with shared responsibility, shared financial input and shared profit returns. In this social enterprise investors should be primarily focussed on societal needs and not on shareholder value. Prices of the drugs developed are transparant and based on cost of goods with a societal acceptable profit margin for all the participants. We need new drugs but we should know the real costs and benefits. This a societal responsibility and than we can discuss if these drugs are really expensive or not.

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OP-09. Evaluation of orphan drugs: ways forward

Carla E.M. Hollak[1], M. Biegstraaten[1], M. G.W.Dijkgraaf[1], R. Hagendijk[2]

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Topic: Orphan medical products and their effectiveness

Introduction: Through the orphan drug regulation, enacted in 2000, development of orphan medicinal products (OMP's) has been stimulated. Although for most of newly developed OMP's, randomized controlled trials are mandated by the European Medicines Agency (EMA), evidence for efficacy can be scant. The patients enrolled in the trials are often limited in number and represent a selected sub-group of patients. Clinical and surrogate endpoints used may not be applicable to the broader "real-world" population. Patients with lysosomal storage disorders have invariably a wide variation in phenotypes, which makes effectiveness of a new treatment difficult to predict. The EMA may in these situations approve OMP's under "exceptional circumstances", implicating that it is unlikely for comprehensive data from clinical trials to become available. The pharmaceutical company (PC) is asked for additional data, often through the set-up of a Registry. Because of the high costs and uncertain clinical outcomes, regulators from EU member states request additional studies to address long-term (cost-)effectiveness and budget impact. Several problems have risen following this situation, exemplified by the evaluation of effectiveness for treatments of Fabry disease.

Example: Fabry disease is an X-linked multisystem disease caused by deficiency of the enzyme alfa-galactosidase A. Storage of glycosphingolipids causes small fiber neuropathy, progressive renal failure, heart failure, stroke and early death. Two enzyme replacement therapies (ERT's) have been authorized in 2001, agalsidase alfa and agalsidase beta, manufactured by two different PC's in different trials with different endpoints at different doses. Both products were authorized by the EMA under exceptional circumstances. The PC's launched two separate Registries. These proved of insufficient value for a robust effectiveness analysis in subgroups of patients: children, females, non-classical patients, those with early or advanced disease etcetera, primarily because of a lack of natural history data and incomplete datasets. In the Netherlands, a cost-effectiveness analysis was requested as part of the national reimbursement policy. We developed a lifetime state-transition model of the disease, showing modest effectiveness at a very high cost per QALY. However, the dataset was too small to use the model for subgroups of patients. Up to this day, PC's do not share their data and EU member states negotiate separately with PC's and healthcare professionals on reimbursement strategies. As a consequence national governments may come to different decisions with respect to their appraisal of OMP's which results in inequity throughout Europe.

The future: Initiatives have been launched to coordinate post-marketing authorisation research activities and further evidence generation in the EU, such as the Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA-OMP). However, this mechanism is voluntary and pilots are awaited. We propose that more effort is put in convincing PC's and regulators to adopt a different strategy of evaluation, by early launch of a Registry that aims to collect all relevant patient data and is supervised by an independent board. Such Registry should be disease-centered with active roles for healthcare professionals, patient organizations and regulators. Ideally, data are collected from PC initiated natural history and treatment studies as well as from expert centers and data entry becomes mandatory after authorization. Regulators should agree with EMA on important outcomes that can be used within member states for reimbursement. Such public-private partnership is urgently needed. The launch of EU reference networks for rare diseases may stimulate the development of such partnerships.

This study was funded by ZonMW, the Netherlands Organisation for Health Research and Development.

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OP-10. Novel developments in HTA methodology

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Objectives: Specific Legislation increased the number of orphan drugs substantially. Although the budget impact of a particular orphan drug might be small, the total of orphan drugs account for an increasing share of total pharmaceutical spending. This is due to the increasing number of orphan drugs on the market combined with high prices of these drugs. We assessed the differences between orphan drugs and non-orphan drugs with respect to the requirements for reimbursement dossiers. In addition, we assess whether different criteria were used for reimbursement decisions.

METHODS

Public available reimbursement dossiers were included, as well as two dossiers available to the researchers not yet been evaluated by CVZ. We evaluated whether the Dutch pharmacoeconomic guidelines and the ISPOR budget impact guidelines were applied. Additionally, we assessed whether the four pillars were used to appraise these drugs. Semi-structured interviews were conducted with people that were directly involved in the reimbursement process on orphan drugs.

RESULTS

Twelve persons were interviewed working in the field of orphan drug as respectively clinical expert, policymaker or researcher. Respondents indicated that, in principle, the level of evidence with respect to effectiveness should not necessarily be lower than for non-orphan drugs. They acknowledged that, the Dutch pharmacoeonomic guidelines are all valid to orphan drugs and should be applied. Respondents also identified additional aspects that play a role in the assessment of orphan drugs e.g. burden of disease, minimum level of effectiveness, budget impact, and availability of alternative treatment. A majority of the respondents indicated that a societal view should be represented in the process.

CONCLUSION AND DISCUSSION

Pharmacoeconomic guidelines are applicable in the field of orphan drugs and should not differ from non- orphan drugs. International collaboration in data collection could increase the level of the highest in attainable evidence. Timely debate between actors and decision makers about appropriate effectiveness measures and thresholds and appropriate timelines for dossier review would improve transparency of reimbursement process.

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OP-11. Beyond Orphan Drugs: Cooperation of a Biopharmaceutical Company with other Rare Diseases' Stakeholders.

Fernando Royo. Chairman, Fundación Genzyme (Spain)

The primary focus of any biopharmaceutical company is to provide safe and effective drugs to patients. However, its mission can -and desirably should- extend beyond this goal.

Rare diseases present a case where this extended cooperation is particularly needed and meaningful. Besides the scarcity of specific therapies, rare disease patients and their families must endure a myriad of challenges in their daily life: long and arduous diagnostic processes, haphazard disease management, administrative hurdles to access disability and other social benefits readily available to those with more prevalent diseases, and so forth.

Most of these issues can, however be traced to a couple of causes: insufficient medical knowledge and social awareness about the specific disease, and about the complexities of suffering a rare disease in general. Thus, these are obvious areas where a multi-stakeholder, cooperative approach can be most effective.

Genzyme pioneered many of these initiatives in the area of rare diseases, with various patient and family-oriented resources, as well as partnerships and support to patients associations. Some of its best known global activities include the "Expression of Hope" program and the Patient Advocacy Leadership (PAL) Awards.

At Fundación Genzyme –a Spanish non-for-profit entity- we focus our activities along three main axes:

- research support,
- continued medical education and
- patient empowerment & social awareness programs

In research, we've launched six annual open calls for grants. The proposals are evaluated by a jury led by reputable specialists in the field. Outside these periodic calls, direct institutional R&D support requests are assessed by the Foundation's Board supported, when necessary, by additional external experts.

Continued medical education is covered through various channels:

1) on-line courses, independently designed by leading specialists and certified by the competent academic board (CFCP-SCM) with 7,7 credits each (as a reference, university-level programs are generally awarded 1 credit/10h of presential lessons);

2) technical & financial support to specific courses, symposia, congresses, or other educational activities carried out by medical/scientific societies and/or academic institutions;

3) electronic media: a quarterly newsletter including medical & scientific news, bibliographic reviews, etc. For those less experienced, basic disease information is also hosted on our website, including relevant publications and pre-designed links to key public institutions (NIH's Clinicaltrials.gov and PubMed, Orphanet).

Finally, patient empowerment & social awareness programs are usually carried out in close cooperation with patients' associations, other NGO's and public institutions. An area of special attention has been the identification and removal of educational hurdles for children with rare diseases, aimed at achieving a wider and better awareness and support among their teachers and classmates.

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OP-12. The world of Spina Bifida and Hydrocephalus

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Objective: We aim to demonstrate the importance of mandatory folic acid fortification from the viewpoint of an international umbrella organisation for a preventable birth defect, Spina Bifida. The benefits of primary prevention by folic acid for the prevention of neural tube defects have been well established since the publication of the results of the Medical Research Council Vitamin Study in The Lancet in 1991. Since then many countries have introduced mandatory folic acid fortification and the incidence of Spina Bifida in these countries has been decreasing up to 70%. In Europe effective strategies for optimal prevention of Spina Bifida are still lacking. Even though the addition of vitamins to foods has been regulated since 2006, no country has made the decision to require mandatory fortification of a staple food with folic acid. Instead countries rely on voluntary fortification, sometimes public awareness campaigns, but mainly on a woman's own responsibility to take folic acid supplements. These strategies fail to reach those who are most at risk of a pregnancy affected by birth defects, namely women of low socioeconomic status. Additionally, 50% of all pregnancies are not planned. As a result, the incidence of Spina Bifida in Europe remains the same. Spina Bifida is one of the most serious birth defects and requires specialised surgery and lifelong care. It involves nerve damage, which can result in (partial) paralysis, clubfoot, scoliosis, incontinence issues, loss of sensation, and pressure sores. Many who are born with Spina Bifida also develop Hydrocephalus and can be faced with learning and developmental problems. Reduced mobility can lead to osteoporosis, obesity and diabetes. Due to the various health issues and the lack of coordinated, multidisciplinary care, people with Spina Bifida and Hydrocephalus are at an increased risk of premature death. Another issue is lack of knowledge about these conditions in certain countries, lack of resources for treatment and care, and negative stigma and superstition, which can lead to non-treatment and discrimination. The cost of mandatory folic acid fortification is minimal, especially when compared to the costs of healthcare for those born with Spina Bifida and the immeasurable impact on their lives and on their families.

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OP-13. The politics of rare diseases and orphan drugs

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Objective: Dutch and EU policies for orphan drugs and rare diseases will be analyzed from a macrosociological and political perspective drawing on insights from the field of science and technology studies (STS) and more in particular co-production analysis (CPA). This helps to identify 'lock-in' situations requiring broader institutional reconfigurations if we are to advance more adequately with respect to collective goals.

METHODS

The argument will be developed drawing on an empirical analysis of the Dutch Pompe and Fabry controversy 2012-2013 and recent European policy development with respect to policies for orphan drugs and rare diseases. As will be demonstrated public controversies that involve science and technology can be seen as vivo public technology assessment that complement more restricted forms of technology assessment (f.e. cost-efficiency analysis). Unfortunately they are seldom reflected upon that way. Yet, tensions between more restricted assessments and public controversy demarcate the political and regulatory space in which politicians and administrators seek to redefine the problem and politically more feasible ways of handling them. Especially over longer periods of policy development this may require institutional readjustments of the relations between market and state, and individual and collective responsibilities, and between national and transnational arrangements. This is usually accompanied or stimulated by shifting (applied) research agenda's and medical protocols and redefinition of professional, public and stakeholder responsibilities and rights.

RESULTS

The analysis of the Dutch controversy shows how a transnational approach to problems of selective use of therapy replaced a merely national one that was argued in terms of costs and effectiveness. The emerging EU policies reflect both European integration as well as advances in the biosciences and pharmaceutics. In combination this leads to agenda's for institutional and policy change that redefines both problems and ways to handle them at national and transnational levels. Yet, new scientific developments, including opportunities for big data analyses, changes in pharmaceutics, personalized medicine, intensified public-private collaboration, patient group participation and transnational collaboration and coordination, require political, legal and regulatory reform that will take decades to complete. In part they require technical and legal adjustments, but they also encompass political conflicts to be resolved.

CONCLUSION

With respect to the treatment of rare diseases and orphan drugs short term pragmatism are required but it should be explicitly aligned with agenda's to discuss further adjustments of institutional frameworks in European and national health care and research to deal with future opportunities and challenges.

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OP-14. International lessons from a Dutch reimbursement procedure on Pompe' and Fabry' disease

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In the summer of 2012 a large public debate took place in The Netherlands on the reimbursement of two expensive orphan drugs for Pompe' and Fabry' disease. On September 21, 2012 the appraisal committee (ACP) of the National Health Care Institute Package (ZIN) had to take a decision on this issue. Since its installation in 2008, I am a member of the ACP as the patient representative. In this presentation, I will first outline the main discussions in the ACP of the scientific assessment and the societal appraisal process. Secondly, I will add some learning points for the international patient community. The overall message is that right from the start patient groups should be involved in all stages of decision making concerning both registration and reimbursement. This would make decisions more appropriate for patients, for the general public and for the health care system. Concerning rare diseases, the importance of a single European reimbursement procedure is discussed.

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PPa-01. A methodological framework for phase III drug development in rare diseases

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Introduction: In rare diseases, there is a need to develop high quality, ethically investigated, and appropriately authorized medicines, without subjecting patients to unnecessary trials. In most cases however, the small number of available patients does not allow conducting adequately powered parallel group randomized controlled trials (RCTs).

AIMS AND OBJECTIVES

To develop generalizable framework for choosing the best-performing drug/endpoint/design combinations in orphan drug development. The two main objectives were (i) to provide a global strategy for each disease to identify the most relevant drugs to be evaluated in specific patients during phase III RCTs, (ii) and select the best design for each drug to be used in future RCTs.

METHODS

Data-analytical techniques, common multivariable statistical techniques, propensity score, instrumental variables for databases analysis. Mathematical modeling (pathophysiology and pharmacokinetic-pharmacodynamic relations) for drug effect and RCTs simulations.

RESULTS

Four main steps were identified : (i) the retrospective analysis of all available clinical databases in order to look for specific prognostic and predictive markers and to delineate the treatment that seems the most efficacious out of several potential treatments, (ii) the development of in silico (mathematical) models describing the disease, each treatment effect, (iii) the simulation of clinical trials in different patient populations and according to different study designs, (iv) the final analysis of results according to the drug efficacy (including the precision of the estimation of treatment effect), adverse events, trial power / number of patients needed, and the cost and duration for each trial design. Diseases considered were Dravet syndrome, cystic fibrosis and T-cell lymphoblastic lymphoma.

CONCLUSION

Such an approach will allow selection of the most attractive drug to be evaluated in a further phase III trial using the most appropriate experimental design.

PERSPECTIVES

Speed up the process of orphan drug development, develop new methods for translational research and personalized medicine, and contribute to European Medicines Agency guidelines.

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PPa-02. Mathematical model of T-cell lymphoblastic lymphoma: disease, treatment, cure or relapse of a virtual cohort of patients

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Introduction: T lymphoblastic lymphoma (T-LBL) represents around 25% of all Non-Hodgkin Lymphoma (NHL) in children and is considered as a rare disease. Most patients with T-LBL typically present with mediastinal tumor. T-LBL starts in the thymus and causes an increase in its volume. The thymus is an important organ in the development of the immune system in very young children. Its action becomes negligible in adults. The cells causing tumors possess genetic lesion that promotes their proliferation and blocks their differentiation.

AIMS AND OBJECTS

The aim of this study was to assess the possibility to reduce the treatment duration in order to reduce its toxicity, without increasing the number of relapses. This work focused on the development and the treatment of a T-LBL over a period of two years. This was the interval required to study the onset of the disease, the treatment of the acute phase and the maintenance treatment. Actually, the therapy of T-LBL is rather long with its total duration of 24 months in most protocols including induction, consolidation and maintenance therapy. After or during the treatment, patient can be cured or relapsed. Median time of relapse is one year after complete remission (range 0.2-5.9 years).

METHODS

The possible reduction was applied to pairs of virtual patients simulated with a mathematical model. One patient received chemotherapy with a short duration and another, a long duration. Multi-Scale hybrid model was used to simulate the ontogenesis of T cells, the disease at a cellular level and the action of medications. In this model, the fate of T cell was determined by system of ordinary differential equations (intracellular regulation) and reaction-diffusion equations (extracellular regulation). To model the individual behavior of patients, the cellular level and the whole patient must be simulated.

RESULTS

In the virtual population created by the model, we obtained different responses (cured or relapsed) of patients with the same dose of drug and the same duration of maintenance treatment. The number of relapses decreased (and number of healings increased) as a function of duration of "short" treatment.

CONCLUSION

This study suggests that the duration of treatment can be reduced without increasing the number of relapses. The population of virtual patients created by the modeling presented in this study could be included in a virtual clinical trial with different designs. Thus, development of a in silico modeling approach and of a clinical trial simulation tool can help to choose the most appropriate clinical trial in terms of drugs or therapeutic evaluation strategy/endpoint/study design.

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PPa-03. Modeling and simulation of experimental designs to optimize clinical trials for cystic fibrosis

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Introduction: The randomized controlled clinical trial is the „gold standard" to quantify the effect of a new treatment. However, in children, and more particularly in rare disease, small numbers of patients requires optimizing designs due to difficulties to drive sufficient powerful studies.

OBJECTIVES

The main of this study was to provide new approaches including modeling and simulation which could be implemented to help in the selection of the best design in the case of treatment of cystic fibrosis.

METHODS

Our multidisciplinary approach included (i) a mathematical model to describe the treatment effect of Dornase on muco ciliary clearance, (ii) generating population of virtual patients, (iii) the randomization of virtual patients in simulated clinical trials using different experimental designs previously modeled. The results obtained may help to choose the most efficient experimental design depending on the power of the study, the accuracy of the treatment effect and the time spent in the trial for a patient.

RESULTS

Different experimental designs were modeled: parallel, crossover, randomized withdrawal, early escape, n of 1, and adaptive randomization designs such as „play the winner" and „drop the loser." For each of these plans, results of 1000 simulations comparing cystic fibrosis patients treated with Dornase or placebo were used to estimate the treatment effect, the statistical power (measured as the number of significant trials observed) and number and average of time spent in the study for one patient.

CONCLUSION

This approach could reduce the number of patients to be included in clinical trials by selecting the most successful project in terms of time or cost. The addition of patient characteristics to the model could be used to better predict the effect of study treatment for a particular patient (personalized medicine). In general manner, this approach should accelerate the development of new treatments for rare diseases.

PPa-04. The Value of Whole-Exome Sequencing as a Diagnostic Tool for Rare Diseases – A Canadian Perspective

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Patients with rare diseases account for a disproportionate number of hospital admissions and costs. Often, these patients experience delays in diagnosis since they must see numerous doctors who have difficulty giving them a proper diagnosis. Current implementation of next generation sequencing (NGS), in particular whole-exome sequencing (WES), has greatly advanced the ability to rapidly identify disease genes; primarily for rare, single-gene disorders. Yet, before WES is incorporated into health care delivery for patients with rare diseases, there must be a clear understanding of its potential clinical utility, limitations and associated economic impact. This is particularly important given the amount of data generated using WES.

In this study, we investigate the challenges that rare disease patients face within the Canadian healthcare system and evaluate the value of WES diagnostic information on the lives of patients with rare diseases. This project proceeds through two distinct stakeholder groups: 1) patients and their families and 2) clinicians. In this study, we conducted focus groups with adult patients as well as parents of pediatric patients in different cities across Canada. We also conducted semi-structured interviews with clinicians, be they researchers or healthcare professionals. Our goal is to explore and understand the perceptions, expectations and preferences of patients, their families and clinicians regarding diagnostic testing of rare disorders.

Although centered on the Canadian context, the results will hopefully be useful for different research, clinical and policy communities. Exploring patients', parents' and experts' perceptions of diagnostic testing of rare disorders may enable a better understanding of how WES might best be used in a clinical setting as well as how WES might improve care for patients with rare diseases.

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PPa-05. Preferences for prioritizing patients with rare diseases: a survey of the general population in Sweden

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Incentives are offered to pharmaceutical companies in order to increase the number of treatments for patients with rare diseases. As a consequence, a number of new drugs have been introduced on the market—drugs that often fail to meet traditional cost-effectiveness criteria. This study aims to investigate if there are societal preferences for treating patients with rare diseases differently in priority setting situations compared with common diseases. Moreover, psychological mechanisms that potentially could explain such preferences are explored.

A postal questionnaire in three versions was sent out to a representative sample of the general Swedish population. Respondents were asked to choose to give treatment to a patient with a rare or a common disease in eight different scenarios. Rarity of the disease, different alternative costs, and group/individual level decisions was investigated. Psychological aspects in the presented scenaros that varied between subjects was related to proportion dominance, the identifiability of the patient, pseudo-inefficacy and if the scenario was expressed in priority or rationing terms.

Response rate was 41 % (n= 1239). For equal cost scenarios, 42.3 % were indifferent between the rare and the common group, 23.9 % chose to prioritize the rare disease and 33.4 % the common disease. When questions were framed to be on an individul as opposed to a group level repondents were significantly ($p<.001$) more likely to be indifferent. Proportion dominance increased individuals' preferences to prioritize rare diseases ($p<.001$). Identifiability and pseudo-inefficacy had no major effect on respondents' choices.

All else equal we see no strong support that a societal preference for rarity exists. However, we observe psychological effects influencing the judgments individuals make when setting priorities related to rare diseases. Whether or not these should be viewed as biases or an expression of true preferences is a matter for further discussion.

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PPa-06. Economic assessment of health technologies in rare diseases and orphan drugs: Expert opinions on priorities predominating in Hispano-American countries.

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Introduction: The relevance of health technology assessments (HTA) in rare diseases and orphan drugs programs is increasing in Latin American and Caribbean (LA&C) countries as evidence-based decisions will solve the natural difficulties and difference of interest between patients, payers, providers and government health priorities. A comprehensive methodological survey is being planned to be carried on in the continent; consequently some critical aspects were previously consulted in a group of 25 experts from five different LA&C countries and Spain (reference country with similar cultural profile but different environment). We hereby report the main results of such gathered opinions.

METHODS

Taking advantage of a National Rare Diaseases and Orphan Drugs meeting in Cuba, which was attended by latin-american experts, personal interviews were individually done at the site. Same followed non-structured procedures aiming to identify the major challenges and weak aspects for HTA studies in this field. Spontaneous argues were accepted. In addition, a literature survey was also conducted to complement the data. From a standard selection schedule (BIG6 mangement of information method by competence) a total of 75 papers were analysed and found useful, picking different opinions on HTA projects for rare diseases in the region.

RESULTS

The global outcome enlist a number of subjects typically impacting in countries of the region (i.e.: difficulties to solve the patient claims within a single country possibilities, lack of clinical studies with local population mainly when genetic is involved in the pathogenesis, isolation of experts and the lack of reference centres, huge geographic disparities, lack of experiences in HTA methods for rare diseases and orphan drugs, among others were the most frequently cited), but the assignation of health resources, which are indeed quite limited, will be lead by evidence of product efficiency and equity in accessibility according to a predominant opinion within the panel. The further literature survey supported many of the topics and priorities advised by the participant experts and showed similarities with the needs from other world countries but with different local priorities, which in turn may indicated that the local HTA studies should statically weight such priorities, and that data from different environments will not apply for local decisions.

CONCLUSION

this first opinion-approach suggest that the future survey should provide tools to answer those two mainly identified topics (therapeutic efficiency and equity in product accesibility) according to expert opinions from LA&C countries and from Spain as reference place. The survey should provide a rationale base for the assessments of the proper influence of the local priorities in the economic health evaluation. Further these studies will allow the achievement of autonomous decisions.

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PPa-07. Cost-effectiveness analysis of newborn screening for methylmalonic and propionic acidemias in Spain

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Introduction: The Spanish Ministry of Health, Social Services and Equality aims to reduce the inequalities in the newborn screening (NBS) programmes offered in the different regions of the country. For this purpose, several conditions are being evaluated attending to clinical effectiveness and cost-effectiveness criteria. Propionic acidemia (PA) and methylmalonic acidemia (MMA) are two classical organic acidurias that can cause severe neurocognitive deterioration or lead to early mortality. Although no evidence supports long-term benefits of NBS for these diseases, a decrease in early mortality has been observed.

OBJECTIVES

To evaluate the cost-effectiveness of incorporating PA and MMA to the national newborn screening panel in Spain, and to determine the budget impact of its implementation.

METHOD

We developed a cost-effectiveness model that compared two alternatives: to include PA and MMA to the panel of diseases screened in the national screening programme, and to detect these conditions by clinical diagnosis. The model takes into account the lifetime difference in quality-adjusted life years (QALYs) that may happen when these diseases are detected early enough as to prevent early mortality. The perspective of the analysis was that of the National Health Service in Spain, expressing the costs in 2013 euros. We estimated the cost related to the NBS programme including screening tests, confirmation tests, as well as treatment and follow up costs of those detected by the programme. These costs were compared with those related to the clinical diagnosis of the conditions. The differences in the costs were then compared with the difference on effectiveness. We estimated effectiveness by taking into account the different early survival rates among clinically-detected and screening-detected children, and by assigning literature-based utility values to the health states (mild-moderate mental retardation and chronic kidney disease) of the survivors. Health outcomes and costs were discounted at a 3% rate. We undertook a probabilistic sensitivity analysis using Monte Carlo simulation.

RESULTS

Adding NBS for PA and MMA to the Spanish screening panel is more costly and more effective than clinical detection. For a lifetime horizon, the incremental costs per newborn are 3.43 €, and the incremental QALYs per newborn are 0.00016, giving an incremental cost effectiveness ratio of 21,405.13 €/QALY. These results were found to be robust in the sensitivity analysis, estimating that NBS for PA and MMA is cost-effective with a probability of 80.5% and for a willingness to pay of 30,000 €/QALY. With respect to the budget impact, adding these diseases would cost an extra 0.76 €/newborn the first year, this amount increasing up to 1.34 €/newborn after ten years.

CONCLUSIONS

Adding PA and MMA to an ongoing NBS panel is cost-effective if a willingness to pay of 30,000 €/QALY is considered.

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PPa-08. Cost-effectiveness analysis of newborn screening for congenital adrenal hyperplasia in Spain

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Introduction: The Spanish Ministry of Health, Social Services and Equality aims to reduce the inequalities in the newborn screening (NBS) programmes offered in the different regions of the country. For this purpose, several conditions are being evaluated attending to effectiveness and cost-effectiveness criteria. Congenital adrenal hyperplasia (CAH) is a rare disease that comprises two classical forms: simple virilising (SV) and salt-wasting (SW). NBS can reduce the risk of early death in SW-CAH, and allow for a prompt detection and correct sex assignment.

OBJECTIVES

To evaluate the cost-effectiveness of incorporating CAH to the national NBS panel in Spain, and to determine the budget impact of its implementation.

METHOD

We developed a cost-effectiveness model that compared two options: to include CAH to the panel of diseases screened in the national NBS programme and to detect this condition by clinical diagnosis. The model takes into account the life expectancy of the newborns, capturing the long-term impact of the early detection. The perspective of the analysis was that of the Spanish National Health Service, expressing the costs in 2013 euros. We estimated the cost related to the NBS programme including screening tests, confirmation tests, as well as treatment and follow up costs of those detected by the programme.

These costs were compared with those related to the clinical diagnosis of the condition. The differences in the costs were then compared with the difference on the effectiveness. Effectiveness was measured using life expectancy, by taking into account early deaths avoided by screening, and expressed as life-years gained (LYG). We estimated the probability of early death from the literature as 0.70 % and 1.54 % for, respectively, screened and clinically detected SW-CAH; and the probabilities of clinical detection (clinical sensitivity) as 85% and 79% for, respectively, SW-CAH and SV-CAH. Health outcomes and costs were discounted at a 3% rate. We undertook a one-way sensitivity analysis on those parameters with the highest impact on the results and those surrounded by the highest uncertainty. We also carry out a probabilistic sensitivity analysis using Monte Carlo simulation.

RESULTS

Adding NBS for CAH to the Spanish NBS panel is more costly and more effective than clinical detection. For a lifetime horizon, the incremental costs per newborn are 1.71 €, and the incremental life years per newborn are 0.00022, giving an incremental cost effectiveness ratio of 7,899 €/LYG, which is below the usual threshold used in Spain, i.e. 30,000 €/LYG. The sensitivity analysis estimated that NBS for CAH is cost-effective with a probability of 88.5% and for a willingness to pay of 30,000 €/LYG. Nevertheless, there is a high uncertainty surrounding the sensitivity of the clinical detection (especially for SW-CAH cases). With respect to the budget impact, adding this disease would cost an extra 1.53 €/newborn the first year, this amount increasing up to 1.63€/newborn after ten years.

CONCLUSIONS

NBS for CAH is a cost-effective approach in the base case for a willingness to pay of 30,000 €/LYG, assuming a clinical sensitivity for SW-CAH of 85% when NBS is not available.

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PPa-09. Cost-effectiveness analysis of newborn screening for sickle-cell disease in Spain

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Introduction: The Spanish Ministry of Health, Social Services and Equality aims to reduce the inequalities in the newborn screening (NBS) programmes offered in the different regions of the country. For this purpose, several conditions are being evaluated attending to effectiveness and cost-effectiveness criteria. NBS for sickle cell disease (SCD) allows the introduction of prophylactic treatments to reduce the incidence and the morbi-mortality associated with the most severe complications of this disease. However, being a rare disease, the cost-effectiveness of this secondary prevention strategy should be carefully assessed.

OBJECTIVES

To evaluate the cost-effectiveness of incorporating SCD to the national NBS panel in Spain, and to explore the sensitivity of the results with respect to the cost of the screening test and the birth prevalence.

METHODS

A discrete event simulation model was developed that compared two alternatives: adding NBS for SCD to the national NBS panel; versus continuing with the clinical detection of this disease. The model followed a set of individually simulated newborns for 10 years, reflecting the impact of preventive treatments that can be established through early detection. We considered only those treatments with proven, evidence-based effectiveness, i.e., prophylactic penicillin for reducing or completely avoiding pneumococcal sepsis; parental education for the early detection of splenic sequestration; and prophylactic chronic transfusions to prevent a stroke episode. The perspective of the analysis was that of the National Health System, taking into account the direct healthcare costs, expressed as 2013 euros. We included the cost related to the NBS programme including screening tests, confirmation tests, as well as treatment and follow up costs of the affected children. The effectiveness of the intervention was measured by using life expectancy and health related quality of life related to the complications. Both the costs and effectiveness were discounted at 3%. We performed a probabilistic sensitivity analysis using 2nd order Monte Carlo simulations, which allowed the calculation of acceptability curves and the expected value of perfect information, and a two-way sensitivity analysis on the cost of the screening test and the birth prevalence.

RESULTS

Given the estimated birth prevalence in Spain (1:5908), NBS is more costly (1.30 €/child) and more effective (0.000049 QALYs/child) than clinical detection of SCD if a time horizon of 10 years is considered and the cost of the screening test is 2.5 €/newborn. The incremental cost per QALY gained is estimated to be 22,657.60 €/QALY, which is below the 30.000 €/QALY threshold commonly referred to in Spain. The sensitivity analysis shows that, if the cost of the test increases up to 4 €/child, NBS becomes not cost-effective, even for a relatively high birth prevalence (1:4,000). Contrarily, if the cost does not exceed 1.5 €/child, NBS is cost-effective, even for a low birth prevalence (1:10,000).

CONCLUSIONS

Although adding SCD to the Spanish national NBS panel is estimated to be cost-effective, this result is highly sensitive to the cost of the screening test and the birth prevalence.

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PPa-10. The italian external quality assessment in conventional cytogenetics of the national centre for rare diseases: state of the art and results of the 9th round (2013)

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The Italian External Quality Assessment in conventional cytogenetics, coordinated by the National Centre for Rare Diseases-Istituto Superiore di Sanità, started as a research activity in 2001. In 2009 the EQA was recognised as institutional activity and since 2010 laboratories pay a fee for each scheme (GU n.199-28th August 2009). Participation is open either to public and private laboratories.

The program covers prenatal, postnatal and oncological diagnosis with a retrospective format. In 2008 a web-utility, with restricted areas for participants and assessors, was developed; participants can send data through this system and assessors can look at all material sent by laboratories.

Assessment takes into account technical performance, analysis, interpretation and reporting. In 2013 a definition of poor performance was given for the first time.

Assessors are selected in collaboration with the Italian Society of Human Genetics and, at the end of the round; participants receive a report with marks and comments to improve the analysis. Until now nine EQA rounds have been completed; the 10th round (2014) is in progress. In 2013 (9th round) the total number of laboratories participating in the EQA program in cytogenetics was 77; in particular 53, 68 and 26 laboratories participated in the prenatal, postnatal and oncological scheme respectively.

In prenatal, postnatal and oncological diagnosis a satisfactory performance was assigned respectively to the 87%, 90% and 81% of participants. In prenatal diagnosis a poor performance was assigned to 7 labs out of 53 (i.e.13%); in particular two laboratories reported incorrectly the result of the analysis (i.e. ISCN and karyotype were not congruent with images), one lab reported a FISH ISCN formula not consistent with the result description and four laboratories made mistakes in at least two karyotype reconstructions. In postnatal diagnosis a poor performance was assigned to 7 laboratories out of 68 (i.e.10%); in particular two labs made mistakes in the two karyotype reconstructions belonging to one case, two labs made major errors in ISCN nomenclature, one lab sent images of both cases with a not sufficient banding quality, one lab reported in one case a not correct description of the result, one lab didn't describe at all the result in one case. In the oncological cytogenetics scheme a poor performance was assigned to 5 laboratories out of 26 (i.e.19%); in particular 2 labs described in a misleading way the cytogenetic result and 3 laboratories didn't carry out the analysis properly failing to set-up an appropriate culture in a multiple myeloma (2 labs) and in a chronic lymphocytic leukemia (1 lab) . In this work we will show the state of the art of the EQA in conventional cytogenetics and detailed results relative to the 9th round.

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PPa-11. Model of mucociliary clearance in cystic fibrosis lungs

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ntroduction: Mucus clearance is a primary innate defense mechanism for human airways. Cystic fibrosis (CF) is a genetic disease caused by mutations in the gene encoding the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. Cystic fibrosis is characterized by dehydration of airway surface and impaired mucociliary clearance. As a result, the removal of microorganisms from the airways is impaired, and patients experience recurrent pulmonary infections and chronic inflammation.

OBJECTIVES

The aim of this study was to develop a mathematical model of muco-ciliary transport and create a virtual population of cystic fibrosis patients in order to study mucus clearance under different conditions, such as disease severity, age of patients and location of the drug deposition (central or peripheral airways).

METHODS

A new physiology based mathematical model of muco-ciliary transport was developed, consisting of the two major components; (i) periciliary liquid layer (PCL) with cilia, positioned on the surface of the airway epithelial cells, and (ii) the mucus layer residing atop of PCL. In this model we studied mucus evacuation under normal conditions and in CF patients. We then investigated the effects of the inhaled medication dornase alfa, which reduces the viscosity of cystic fibrosis sputum by cleaving long DNA strands.

RESULTS

The results of the model simulations stress the potential relevance of the location of the drug deposition in the central or peripheral airways. Mucus evacuation was increased in case the drug was primarily deposited peripherally (i.e. in the lower airways).

CONCLUSION

The mathematical model and the created virtual population of patients could be used to study the effects of drugs in simulated clinical trials. This may help to efficiently optimize multiple aspects of a clinical trial (e.g. protocol of drug administration, medication dose, dosing interval, trail design, trial duration, sample size), before performing a clinical trial in real patients.

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PPa-12. Patients with rare diseases detected by primary care professionals in a small spanish autonomous community correspond mainly to ultra-rare entities

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Introduction: Primary Care (PC) professionals are the main actors in introducing patients into the Spanish National Health System (SNHS). Rare diseases (RD) patients represent a high % of the total population, but the system is not very proficient in managing them. Inquiries done among general practitioners points out that they need deeper knowledge in the RD field (mainly scientific, but also about resources, registries and social care facilities available for them and the patients). On the other hand, studies on RD patient needs points that their principal demand is the increase of empathy in the PC professionals. As a consequence, PC professionals are unable to identify their RD patients properly and they don't usually make use of PC.

OBJECTIVES

Our main goals were **i)** to evaluate RD knowledge in PC teams; **ii)** to sensitize them about the needs of patients; **iii)** to provide PC teams with the knowledge and tools to correctly detect, classify and register the RD patients in each Health Centre; **iv)** to estimate with how many RD patients is PC dealing with and **v)** to compare the diseases registered via PC with that registered by Specialized Care (SC).

METHODS

An intervention in all PC Health Centres in Cantabria (northern Spain) was made between January and May, 2014. It consisted of 35 sessions in which we conducted a RD knowledge test among participants. We also provided them with tools to improve their knowledge about RD and their ability to get to an accurate diagnose. Finally, we talked about the registries available for RD patients and professionals. Participants were encouraged to use their new abilities and the explained tools, to detect and register the RD patients in their patient's quota.

RESULTS

Previous knowledge in PC teams about RD is very limited: they only obtained 50.9% of correct answers in the test. A total of 17 different Health Centres participated in the locate-and-register activity, of a total of 35 facilities. PC teams found a total of 302 RD patients in their respective quotas, which is 4% of the total registered via SC. These patients suffer from a total of 126 different RD, 70 of which were only detected by PC teams. Of these 70 diseases, 35 are of unknown prevalence, 14 are considered rare (≤5 in 10,000) and the last 21, ultra-rare (≤5 in 100,000). There are 12 patients with two or more pathologies and 66 individuals that are relatives.

CONCLUSIONS

The low number of RD patients found indicates that these patients do not visit their PC team frequently and so, PC teams do not know them. The abundance of ultra-rare diseases declared indicates that PC teams wrongly identify exceptions to these pathologies. In conclusion, training programs and interventions as the one presented here, are needed to correct this trend.

PPa-13. BURQOL meter – development and future applications

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Objectives: The BURQOL-RD project was intended to develop a disease based model capable of quantifying the socio-economic burden and Health-Related Quality of Life (HRQOL) for patients with rare diseases (RD) and their caregivers in Europe. Its final product is an on-line interactive tool that can be used to measure the burden of different diseases in different countries. Its development and future applications are described here.

METHODS

An instrument to evaluate the burden of a rare disease, and the HRQOL of the patient and his/her carer, was developed in a pilot study that surveyed 10 rare diseases (RDs) in eight European countries (Spain, UK, France, Germany, Sweden, Italy, Hungary and Bulgaria). Adaptation to each RD was performed in every country with the collaboration of external experts, representatives from the Social Services and Patient Organisations (POs). Patients' outcomes were described through the scales of EQ-5D and Barthel Index, and carer's outcomes through EQ-5D and Zarit Scale. A bottom-up costing approach was used to estimate the total and average annual costs. Data on resources utilization were collected for each patient and to estimate resource utilization, the questionnaire requested information covering the 6-month period prior to the study. The data for the preceding 6 months were extrapolated to the entire year. Costs were divided in 4 categories: direct healthcare costs (drugs, medical visits, exams, and material), direct non-healthcare formal costs (professional caregivers, social services), direct non-healthcare informal costs (unpaid carers) and indirect costs (patient's and carer's productivity loss). Data was collected through an on-line questionnaire accessed by patients and their caregivers on Internet.

RESULTS

BURQOL Dynamic Outcomes is an on-line application that enables to visualize interactively the main results on demand for different groups of users (researchers, patients, POs, policy makers, etc.), applying different filters.

BURQOL Meter is based on BURQOL Dynamic Outcomes and it will permit to create new questionnaires in any language with adapted new databases, which means that the tool can be applied to measure the burden of any disease in any country. The required inputs from a user will be: patient's data on resource consumption, quality of life and the unit costs of the resources in the given country.

CONCLUSIONS

There is a clear interest in the future application of this tool in research projects focused on disease burden, and not necessarily that associated to RDs, enabling the outcomes obtained through very similar methods to be compared directly. In this way BURQOL Meter can help harmonise the measurement of the impact of new on socioeconomic and HRQOL issues in different EU countries, each with its own health and social care systems.

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PPa-14. Current situation of newborn screening in Spain: the role of cost-effectiveness analysis

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For many years, Spain has shown a heterogeneous picture where every region configured a different panel of disorders to be screened. While phenylketonuria (PKU) and congenital hypothyroidism (CH) are uniformly screened across the country, the coverage for other diseases is highly variable, as highlighted by the Spanish Association for Neonatal Screening (http://aecne.es/). Hence, 91.5% of newborns are screened for cystic fibrosis (CF), sickle-cell disease (SCD) covers 31.6%, congenital adrenal hyperplasia (CAH) 29.5%, biotinidase deficiency 8.6% and galactosemia 4.6%. Besides, 54% of newborns benefit from tandem-mass spectrometry but the panel of conditions screened with this technology differs from one region to another.

Recently, the Spanish Ministry of Health, Social Services and Equality has driven a set of measures aimed to reduce the inequalities in these newborn screening (NBS) programmes. These measures define the criteria used to guide the decision making processes with respect to the incorporation of new diseases to the national NBS panel, including providing evidence on the clinical effectiveness and the cost-effectiveness of the programme. Based on these criteria, five conditions have been added to the national NBS panel in addition to PKU and CH since 2013: CF, SCD, medium-chain acyl-CoA dehydrogenase deficiency (MCADD), long-chain acyl-CoA dehydrogenase deficiency (LCHADD) and glutaric aciduria type I (GA-I).

Cost-effectiveness models are widely used to support decision makers in a budget-constrained world. This kind of analysis allows for the costs and health outcomes of two or more interventions to be compared. NBS for inborn errors of metabolism is an intervention especially well-suited to a cost-effectiveness analysis, since it is applied to the whole newborn population but only a reduced number of children get a benefit (in terms of health outcomes) from it. Therefore, there is a delicate balance between the cost of the intervention and its benefits. Adding a new disease to an ongoing screening panel involves comparing the impact on cost and health outcomes of the early detection of a few cases, with those obtained when the same cases are detected only after the first disease signs or symptoms appear. However, this comparison requires robust data and methodological approaches to be correctly synthesised, and to increase the credibility of the results.

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PPa-15. IX round of italian national external quality assessment programme in molecular genetic testing: results (2013)

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In order to reach and maintain the quality in genetic testing laboratories in Italy, in 2001 the Italian National Centre for Rare Diseases at the Istituto Superiore di Sanità (ISS) established an external quality assurance programme for molecular genetic testing. It covers four molecular genetic tests for Cystic Fibrosis (CF), Beta Thalassemia (BT), Fragile X-Syndrome (FX) (pre-screening and full scheme) and Familial Adenomatous Polyposis Coli (APC).

The Italian EQA has primarily an educational role and its aim is to improve the quality of genetic tests used in clinical practice through recommendations, elaboration of guidelines and dissemination of methodological information. Since 2009 the activity has been regulated by governmental document (GU 199 28/8/2009) and participation is open both to public and private Italian laboratories.

In each scheme 4 DNA samples are validated and sent to participants together with mock clinical case description and technical information. Laboratories are asked to use their routine procedures and protocols to analyse samples and to report data. A panel of assessors reviews raw data and reports sent by laboratories. All data are managed through a web-utility.

Marking criteria were developed by the ISS in collaboration with assessors taking into account genotyping, interpretation and reporting, in line with European Quality Assessment programmes. For the first time the poor performance was assessed and penalized.

Individual report is sent to participants through the web utility; than results are discussed in a workshop organized by ISS.

In 2013 round the number of participants was 69: 54, 16, 12, 3 and 5 laboratories participated for CF, BT, FX full scheme and pre-screening and APC schemes respectively. In this round assessors reviewed 372 genetic testing analyses. Results showed complete and correct data in 87%, 87.5%, 92%, 100%, 100% of CF, BT, FX (full scheme and pre-screening), APC samples analyzed respectively. Problems occur in CF for interpretation in 5 samples, in BT for genotyping in 2 samples and in XF full scheme for genotyping in 1 sample. Lack of information/inaccuracy in reports was detected in all schemes.

Assessors have paid special attention to the interpretation of results, which was nor complete and accurate in some reports.

This work will show in detail all 2013 results and will present new strategies for future schemes.

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PPa-16. Italian cystic fibrosis patient registry: 2010 data

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Italian Cystic Fibrosis Patient Registry (ICFPR) was established in 1988. From 2009 the Registry is managed at the Istituto Superiore di Sanità by both the NCRD and the NCESHCP.

The ICFPR collects epidemiological, clinical and molecular data on CF patients from Regional CF Centers. The registry aims both at supporting and performing research on epidemiological, molecular and genotype/phenotype aspects, and at monitoring diagnostic and therapeutic approaches to improve patients care. Furthermore, comparison of CF clinical outcomes across Italy and, secondary, across Europe is addressed. All data included in the registry were entered by using a dedicated software (Camilla, Ibis Informatica) and Quality Controls have been established and performed to check the validity and accuracy of specific variables such as i) data completeness, ii) diagnosis, iii) nutritional and iv) pulmonary function status.

In 2010 twenty seven Italian CF Centers sent data to ICFPR and 4159 patients were registered (52% M vs 48% F). CF Italian prevalence has been estimated in 7.0x100.000. Five of the 27 Centers take care of more than 200 patients; 17 have 50 to 200 patients; 5 less than 50 patients. Interestingly, we estimated that the number of patients in charge of a specific Center is often significantly different from the number of patients living in the same Italian Region in which the CF Center is located, being this fact explainable by patient health care migration through different Italian regions.

Median age (yrs) of all patients included in the registry is 17; in particular, about 49% of all patients are more than 18 yrs old.

Regarding diagnosis it was estimated that median age (in months) at diagnosis was 6 vs 5 (M vs F) and that the number of new diagnosis in 2010 was 169. More than 87% of new CF patients were diagnosed by neonatal screening, indicating the efficacy and the importance of this program in the early identification of CF status.

More than 94% of patients were fully characterized from a genetic point of view; in particular, for 3956 out of 4159 patients, 2 different mutations were identified and for 32 patients the CF Centers also indicated the third mutation. Among the most frequent Italian CFTR mutations we mention F508del (44.41%), N1303K (5.25%) and G542X (4.93%). All the frequencies values of the mutations identified and reported in the ICFPR, are in accordance with European ones.

Regarding nutrition we calculated both the Weight for Length and the Length for Age (Z-score) for 0-2 yrs old patients, the BMI (Z-score) for 2-17 yrs patients and the BMI (Z-score) for >18 yrs old patients. In particular, according to Cystic Fibrosis Foundation criteria regarding patients >18 yrs old, a good nutritional status was observed in about 36% and 28% of patients (M vs F).

Finally, regarding mortality 34 patients died in 2010; we noticed that death still remain a rare event in CF patients. Respiratory insufficiency was the main cause of death (74% of patients).

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PPa-17. National rare diseases registry in Spain: pilot study of the spanish rare diseases registries research network (SPAINRDR)

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The development of a national Rare Diseases (RD) registry in Spain was launched in 2012 with the project SpainRDR, supported by the International Rare Diseases Research Consortium (IRDiRC). SpainRDR includes two different strategies: patient registries addressed to patient outcome research and population-based registries addressed to epidemiologic research, health and social planning. The pilot study aims to detect the difficulties of developing the national and population-based RD registry. 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. Data representing 80.2% of the Spanish population have been initially communicated to the central data repository during the pilot study. 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. 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. 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.

PPa-18. Spanish national rare disease biobank

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The mission of Spanish National Rare Disease Biobank (BioNER) is to support national and international research, collecting and storing biological samples of people affected by rare diseases, their relatives and controls. These samples are available for research on rare diseases, both etiologic and preventive aspects, as oriented to the search for new treatments and prognostic factors. The Institute of Health Carlos III is the holder of the BioNER, while the operational and functional responsibility lies with the Institute of Rare Diseases Research.

The BioNER is linked to the National Registry of Rare Diseases. Since 2010 belongs to the Spanish network of biobanks created by the Institute of Health Carlos III, RetBIOH. In addition, National Rare Disease Biobank is a founding partner of the consortium Eurobiobank, the first and unique European consortium of biobanks aimed at rare diseases. This European collaboration provides access to 440,000 biological samples from patients. It is also involved in SpainRDR, Spanish Rare Diseases Registries Research Network, an initiative of the International Rare Diseases Research Consortium (IRDiRC). It collaborates in the European project RD-Connect and the RD-HUB of the NIH in the United States, as well.

BioNER collect biological samples for over 120 different rare diseases. These samples are aliquoted DNA, plasma, serum and cells. The total amounts to 911 donors. 10% these donors are family controls with rare disease. In addition, the biobank includes biological samples from more than 3,000 donors affected by the toxic oil syndrome.

The biobank offers the following services: Processing of biological samples; Storage of samples and data associated with the National Registry of Rare Diseases; Storage of samples and data associated with the Registry of Autism Spectrum Disorders; Provision of samples for research projects by investigators; Access to sample collections of Eurobiobank; Access to sample collections of other European biobanks.

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PPa-19. Everyday consequences of rare diseases

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Background: Many rare diagnoses are syndromes that have complex consequences with a significant impact on the individuals´ everyday life. People with rare syndromes usually have multifaceted needs. Due to the rarity of the diagnose knowledge about consequences and needs is often scarce. Other aspects than the medical ones, such as educational, work related and social consequences are usually not known or not understood. This regards especially adults with rare diagnoses. Their experiences and needs are therefore important to explore.

OBJECTIVE

The aim of this study was to investigate how adults with four different diagnoses perceived their difficulties, needs and participation in everyday life.

METHOD

Individuals with four different diagnoses were interviewed in four focus groups: Artrogryposis Multiplex Congenita AMC (n=9), Dysmelia (n=11), 22q11deletion syndrome (n=10) and Klinefelter syndrome (n=8).

RESULTS AND CONCLUSION

The participants described complex and varying needs. Similar experiences, such as being discriminated, feeling disregarded in education and lack of coordination were common, although the individuals were affected by different rare diseases.

Lack of knowledge of the diagnoses and a limited holistic perspective in the health care and society support system have an impact on everyday life and lead to restrictions in participation.

CONTEXT

Ågrenska, situated in Gothenburg, Sweden, is a national centre and provides programs for people with rare diseases, families and professionals. One of the programs consists of a three days course for adults, aiming at empowering the participants to cope with everyday life and to gather information about everyday consequences of the diseases.

Ågrenska also spreads information about rare diseases and their consequences to different professionals and official service providers in order to contribute to enhanced competence in society at large.

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PPa-20. Ephedrine for myasthenia gravis and myasthenic syndromes: systematic review of an unlicensed treatment.

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Introduction: Myasthenia includes several rare conditions in which neuromuscular transmission is disturbed by antibodies (autoimmune myasthenia gravis, MG; and neonatal myasthenia gravis, NMG) or by defects in genes coding for neuromuscular junction proteins (congenital myasthenic syndromes; CMS). Most patients respond well to standard symptomatic or immunosuppressive therapies, but some require additional treatment. A clinically beneficial effect from treatment with ephedrine has been described, but its effects and adverse effects have not been systematically evaluated. Currently ephedrine is not licensed in the EU for any indication, and patients have to rely on import or preparation by local pharmacies. This entails a risk for availability and reimbursement. We present preliminary findings of a systematic review based on Cochrane protocol CD10028, submitted for publication to the Cochrane Neuromuscular Disease Group.

OBJECTIVE

To assess the effects and adverse effects of ephedrine in patients with autoimmune MG, transient NMG, and CMS.

METHODS

The Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL, MEDLINE and EMBASE were searched (31 March 2013), as well as reference lists of articles, proceedings of relevant conferences, and prospective trial registers. Furthermore, we contacted manufacturers and researchers in the field. The selection criteria were randomised controlled trials (RCTs) and quasi-RCTs comparing ephedrine as a single or add-on treatment with any other active treatment, placebo, or no treatment in adults or children with autoimmune MG, NMG, or CMS. Two authors independently assessed the design and quality of studies, and extracted data, including adverse effects. When necessary we contacted study authors for additional information.

RESULTS

No RCTs or quasi-RCTs describing the effect of ephedrine on MG, NMG and CMS were found. However, 53 non-randomised studies (before-after studies, case series and case reports) were found and described narratively. Thirty-seven were in patients with CMS, 5 in patients with MG, and in 11 the precise form of myasthenia was unknown. No studies were found for NMG. Although they provide low quality evidence, the results from these non-randomised studies suggest a possibly favourable effect of ephedrine on endurance, muscle strength and quality of life, which may depend on the type of myasthenia. Reported adverse effects included tachycardia, sleep disturbances, nervousness, and withdrawal symptoms.

CONCLUSIONS

Low quality evidence from non-randomised studies suggests a possibly favourable effect of ephedrine on muscle weakness and fatigability in myasthenia gravis and some congenital myasthenic syndromes, but adverse effects have also been reported. Research of better quality is needed. However, conducting parallel group RCTs is difficult due to the rarity of MG and CMS, the genetic diversity of CMS, and the fact that symptomatic treatment with ephedrine may be considered only in a small subset of patients Thus it may prove unfeasible to conduct these trials, even internationally. Alternative forms of prospective RCTs, such as aggregated n-of-one RCTs using appropriate and validated outcome measures, may be needed to obtain high quality evidence about treatment efficacy in small patient populations.

FUNDING

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PPa-21. Registries for rare diseases: the experience of a regional network.

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Rare diseases (RD) have been recognised as health care priority since 1998 when they were specifically mentioned in the National Health Plan. In 2001 a "National network for prevention, surveillance, diagnosis and treatment of RD" was established. This Network is based on a number of so called reference centers (most commonly university or tertiary level hospitals) and a Regional Coordination Center, one in each italian region. Among the tasks of the Regional Coordination Center there is the establshment and maintenance of a Regional Registry of RD, which ultimately can confere data to the National Registry based at the National Center for RD in Rome.

Lombardy: Region is the second largest, but the most popolous with approximately 9.700.000 people. Lombardy was one of first regions in Italy to establish a Regional Networkof RD, by designing 34 reference centers, a Coordinating Center (based at the Mario Negri Institute, in Bergamo) and a Regional Registry. The Registry collects demographic, administrative and clinical data on patients affected by 638 monitored RD, in addition to information about pharmacological therapies. Data are recorded by means of a web-based and smartcard-based software, that allows secure access, exchange and linkage of data. Case definition and data entry are within the competence of medical experts working at Reference Centers appointed by the regional health system. The Coordinating Centre of the RD network is in charge of validation and analysis of data, disseminates periodical reports and sends a shared dataset to the National Center for RD at Istituto Superiore di Sanità in Rome. The registry takes advantage from its link with census data obtained from administrative offices of Lombardy Regions.

As per June 30, 2013, 51.319 patients with RD have been identified, 47.905 of whom are alive. The prevalence is therefore 49.3/10.000, with a male to female ratio of 1:1.24. Linkage of data from several sources provides information not otherwise available, allowing valuable insights into RD epidemiology. Benefits of these linked data include the ability to investigate a broader range of public health questions than with a single dataset.

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PPa-22. The italian national rare diseases registry

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Objectives: A National Registry of rare diseases (RNMR) has been established in Italy in 2001 with the main objective of producing epidemiologic evidence on RD, of supporting policy making and health service planning and of monitoring exemptions from diagnosis and care costs. Here we describe the main steps of the RNMR implementation and its main achievements, in order to share this experience with scientists and policy makers in the field of RD.

METHODS

The RNMR structure is composed of clinical Centres dedicated to RD (primary source), regional/interregional registries (RR, intermediate source) and the central database situated at the National Centre for Rare Diseases, Istituto Superiore di Sanità. The design is cross-sectional and no longitudinal data are collected. Following the Italian regulation (D.M 279/2001) the registration includes a list of 331 single diseases or groups divided into 14 nosological categories, based on the ICD9-CM. These codes are functional to exemption procedures; the mapping to internationally used codes is now in progress. Quality control procedures are regularly carried out at regional and national level and assess the data completeness and consistency of procedures.

RESULTS

RNMR achieved full coverage of the national territory in 2011. The establishment of the RRs resulted in a significant increase of the cases communicated to the central database, which now contains 110841 valid records. All group codes are present and make up 58942 records. Diseases coded individually are 296 and make up 51899 records. About half of these records are represented by the following 15 most frequent diagnoses: Achalasia, Amyotrophic lateral sclerosis, Behçet disease, Bullous pemphigoid, Chronic inflammatory demyelinating polyneuropathy, Down syndrome, Hereditary hemorrhagic telangiectasia, Idiopathic central precocious puberty, Keratoconus, Klinefelter syndrome, Lambert-Eaton syndrome, Marfan syndrome, Mixed cryoglobulinemia, Pemphigus, Turner syndrome. Twenty-nine diseases were represented with one record only.

CONCLUSIONS

The quality assessment procedures are important in order to improve consistency of data collection and to allow the provision of sound results. We are not yet able to assess the completeness of case ascertainment for the production of sound epidemiological information.

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PPa-23. Fast-track management of neonatal erythroderma: A study description

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Introduction & objectives: Erythroderma in newborns is rare and a true challenge for the consulting clinician. Main causes are ichthysosis, infections, metabolic disorders, Netherton disease and primary immunodeficiencies. The final diagnosis is often made in a late phase. The purpose of this study is to investigate if following our proposed national (Dutch) multidisciplinary protocol combined with early genetic testing by next generation sequencing (NGS) will lead to a faster and more accurate diagnosis and prevention of possible complications and/or lethal outcomes of primary immunodeficiency's or metabolic disorders.

MATERIAL & METHODS

Based on a literature search a national multidisciplinairy protocol on the management of congenital and neonatal erythroderma has been developed. The protocol can be found on the website www.huidhuis.nl/afdeling/neonatale-erythrodermie. Information about this 2-year prospective cohort study (started 1 January 2014) will be sent electronically to all members of the Dutch Societies for Pediatrics and Neonatologists (NVK), General Practioners (LHV, NHG), Gynecology (NVOG), Dermatology (NVDV) and Youth Consultancies (NVJG, JGZ). Patients need to be referred to an academic medical centre for evaluation in a multidisciplinary setting where our protocol on the management of congenital and neonatal erythroderma (September 2012, update March 2014) will be followed. Importantly, the task force group on Pediatric Dermatology of the Dutch Society of Dermatology, the task force group of Pediatric Immunology of the Dutch Society of Pediatrics, and the task force group on Genodermatoses including the clinical genetics in the Netherlands are involved in further implementation of this project. NGS on known causes of neonatal erytroderma will be used (University Medical Centre Utrecht) to detect genetic defects followed by confirmation by Sanger sequencing. Furthermore, additional cellular tests and functional investigations will be performed to unequivocally demonstrate that the identified gene variants are indeed responsible for the erythrodermic phenotype. Genetic results will be expected within 8 weeks after initial presentation and will be linked to the clinical, laboratory and histological parameters. The usefulness of the protocol will be evaluated by comparing the time to diagnosis and patient outcome with that of a control group consisting of patients with neonatal erythroderma in the Netherlands registered in the PALGA system born before the start of this study.

RESULTS

The multidisciplinary protocol will be presented based on a literature review of the literature. No results can be given in this phase of the study. Inclusion has started in 2014.

CONCLUSION

We hereby introduce a 2-year prospective cohort study in which the usefulness and effectiveness of a newly introduced national protocol on the management of congenital and neonatal erythroderma will be studied. We hypothesize that in the majority of erythrodermic neonates a (faster) diagnosis can be made using this approach that prevents complications and mortality.

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PPa-24. Knowledge and perception about rare diseases among medical students in Romania

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Introduction: The development of research in the field of rare diseases and an adequate health care for this category of patients is possible only with a medical staff trained in this domain. The deficit of medical doctors able to diagnose rare diseases in Romania is a big problem, taking into consideration the fact that there are only 75 doctors specialized in genetics for 20 million people.

OBJECTIVES

The main purpose of this study is to evaluate the information regarding rare diseases among medicine students. The specific goals are 1) to evaluate the knowledge of the medicine student about rare diseases; 2) to analyze the training needs in this domain and 3) to identify the students' suggestions regarding the improvement of research and care of rare diseases.

METHODS

The cross-sectional survey was developed between October 1st 2013 and June 30th 2014, on a population of 893 senior medicine students from the University of Medicine and Pharmacy Carol Davila Bucharest. The tool used in this study was a self-administrated questionnaire with 24 items, divided in 4 parts (socio-demographic data, knowledge regarding rare diseases, training requirements in this field and strategies to improve the research and treatment of these diseases. The descriptive statistics was calculated with SPSS 17.0, and included proportions, cross-tabulation with intergroup comparisons (based on gender and the level of scientific activity).

RESULTS

Only 10% of the students knew the definition and the prevalence of rare diseases. Regarding the clinical aspects and treatment of rare diseases over 80% of the students answered correctly. The students involved in numerous scientific activities, had a higher number of correct answers (p=0,034). The female students pay more attention to the development of prenatal screening test (p=0,031). The importance of creating in Romania a rare disease registry have emphasized by 88% of the respondents. There were differences regarding the structure of this registry, because the female students wanted a national registry (p=0,007). About 2/3 of the students considered necessary the introduction of a course regarding rare diseases.

CONCLUSION

The level of knowledge about the prevalence of rare diseases among medical students is low but they have a high level of clinical knowledge in this field. It is necessary to organize training sessions during medical school and also after in order to gain a better understanding of this field. It is required to develop the screening in this field (prenatal diagnostic and genetic tests). We intend to launch a study in order to assess how much do the doctors, especially GPs, know about rare diseases and in what area do they want to develop their knowledge

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PPa-25. National program of rare diseases in Romania

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Introduction: The Associations of Patients with Rare Diseases in Romania estimate that there are over a million patients with rare diseases but the National Health Insurance House reports only a part of them. The rest of the patients are not correctly or completely diagnosed, and don't have the adequate treatment and care.

OBJECTIVES

The general objective of this study is to evaluate the development tendency of the National Program of Rare Diseases. The specific objectives are 1) to identify the evolution in the number of patients included in this program; 2) to evaluate the medium cost per patient in the program

METHODS

The study is an observational descriptive study over a period of three years (2011-2013) based on the public data of the Ministry of Health and National Health Insurance House.

RESULTS

The Romanian National Program for Diagnosis and Treatment of Rare Diseases started in 2007 with a number of 4 rare diseases. At present, it includes a number of 19 categories of rare diseases. The number of patients treated is increasing from 3165 in 2007, to 5385 in 2013. The number of children tested for phenylketonuria was 150,548 in 2011, 218,108 in 2012, 169,625 in 2013, but the allocated budget for every child increased from 1.51 euro in 2011 to 3.67 euros in 2013. Testing for phenylketonuria determined a growing of the number of children treated from 56 in 2011 to 108 in 2013. The medium cost per patient per year was 7727 euros in 2011, 8560 in 2012 and 8518 in 2013 for specific treatment. The highest medium cost per patient was recorded for Hunter syndrome (227010 euros in 2013). The presented costs don't include other medical and non-medical costs.

CONCLUSION

The number of patients with rare diseases receiving specific treatment is increasing and the access to new orphan drugs is growing. The national medical services for diagnosis, treatment and rehabilitation for rare diseases patients are different depending on the region. Most patients are diagnosed and treated in reference centers, and other patients have unequal access to specialized services and orphan medicines. For a better diagnostic of rare diseases and for an increase in the access to new generation treatment for a larger number of patients with rare diseases, it is necessary to develop a national registry for rare diseases, in order to facilitate the centralized report of the data. Thus the population and the state officials will be more informed, which will lead to an increase in the funding of these procedures and a better quality of life for the patients with rare disease and their families.

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PPa-26. Pilot program on neonatal screening for sickle cell anaemia in Catalonia

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Introduction: Catalonia is the region of Spain that has a higher number of births with parents coming from countries of Sub-Saharan Africa. In 2007 it was estimated that the neonatal prevalence of sickle cell anaemia in Catalonia was one in 4494 newborns. Early detection of sickle cell anaemia allows to establish preventive measures to reduce mortality from 8% to less than 1% and improves the quality of life of patients. In March 2013, from the Catalan network for the diagnosis and follow up of haemoglobinopathies and thalassemias – CATGLOBIN (www.catglobin.org) and in collaboration with the Public Health Agency of Catalonia, a pilot newborn screening program for sickle cell anaemia was started in order to assess its implementation in the official screening program.

MATERIAL AND METHODS

All newborns since March 1, 2013 from 15 hospitals in Catalonia that form the CATGLOBIN (see Table below) are included in the pilot program of neonatal screening for sickle cell anaemia. To perform the screening the same blood sample of the heel impregnated in standardized absorbent paper that is extracted in the neonatal screening program in Catalonia is used. The samples are analyzed by high performance liquid chromatography (HPLC) program Newborn Screening Program – BioRad®.

RESULTS

We have identified 10 cases of sickle cell anaemia, 234 cases of haemoglobin S in heterozygous state, 60 cases of haemoglobin C in heterozygous state, 6 case of haemoglobin D in heterozygous state, 8 cases of haemoglobin E in heterozygous state, 7 cases of alpha chain haemoglobinopathy in heterozygous state and 8 cases of beta chain haemoglobinopathy in heterozygous state. Preliminary results show a prevalence of one in 2697 newborns with sickle cell disease.

CONCLUSIONS

The preliminary results show a prevalence of sickle cell anaemia and the presence of haemoglobinopathies is higher than the autonomous communities where the neonatal screening for sickle cell anaemia is already included in the official screening programs as Madrid, Extremadura, Basque Country and Valencia Community. The data obtained so far confirms the need to include the sickle cell anaemia in the official program of neonatal screening in Catalonia.

15 CENTRES OF CATGLOBIN
Hospital Clínic de Barcelona
Hospital de la Santa Creu i Sant Pau
Hospital Infantil Sant Joan de Déu
Hospital de la Vall d'Hebron
Hospital Universitari Germans Trias i Pujol
Consorci sanitari de Mataró
Hospital de Granollers
Hospital St. Jaume d'Olot
Hospital Sant Jaume de Calella
H Arnau de Vilanova
Mútua de Terrassa
Hospital Joan XXIII de Tarragona
Hospital Verge de la Cinta
Hospital Parc Taulí de Sabadell
Hospital del Mar

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On behalf CATGLOBIN consortium

PPa-27. Professional views on newborn screening for pompe disease

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Objectives: Developments in enzyme replacement therapy have kindled discussions on adding Pompe disease, characterized by progressive muscle weakness and wasting, to neonatal screening. Pompe disease does not fit traditional screening criteria as it is a broad-spectrum phenotype disorder that may occur in lethal form in early infancy or manifest in less severe forms from infancy to late adulthood. Current screening tests cannot differentiate between these forms. Normally, expanding screening is discussed among experts in advisory bodies. While advisory reports usually mention the procedures and outcome of deliberations, little is known of the importance attached to different arguments and the actual weighing processes involved. In this research we aim to explore the views of a wide range of relevant professionals to gain more insight into the process of weighing pros and cons of neonatal screening for Pompe disease, as an example of the dilemmas involved in screening for broad-spectrum phenotype disorders.

METHODS

We conducted 24 semi-structured interviews with medical, lab, insurance and screening professionals, and executive staff of patient organisations. They were asked about their first reaction to neonatal screening for Pompe disease, after which benefits and harms and requirements for screening were explored in more detail.

RESULTS

Advantages included health gain by timely intervention, avoiding a diagnostic quest, having a reproductive choice and gaining more knowledge about the natural course and treatment. Being prepared was mentioned as an advantage for the later manifesting cases. Disadvantages included treatment costs and uncertainties about its effect, the timing of treatment in later manifesting cases, the psychological burden for the patient-in-waiting and the family. Also the downsides of having prior knowledge as well as having to consider a reproductive option were mentioned as disadvantages.

CONCLUSION

When weighing pros and cons, interviewees attach different importance to different arguments, based on personal and professional views. Professionals expect benefits from neonatal screening for Pompe disease, especially for early-onset cases. Some interviewees valued screening in later manifesting cases as well, while stressing the need for adequate support of pre-symptomatic patients and their families. Others considered the psychological burden and uncertainties regarding treatment as reasons not to screen.

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[1] This abstract forms part of an upcoming publication: Van El CG, Rigter T, Reuser AJJ, Van der Ploeg AT, Weinreich SS, Cornel MC. Newborn screening for Pompe disease? Exploring professional views. BMC Pediatrics 2014.

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PPa-28. Use of mini dental implants in ectodemal dysplasia children: up to 4 years follow-up of clinical cases

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Introduction: Ectodermal dysplasia is a hereditary genodermatosis characterized by a congenital defect of ectodermal structures, causing tooth malformations and anomalies. Implantology has become accepted in these subjects. However, cases are often complicated by a reduction in the size of the alveolar process, making the insertion of conventional implants difficult without bone grafting. The reduced diameter of mini-implants and their ease of insertion provide an interesting solution in supporting removable or fixed prosthesis. The ideal time and location of implant placement in young patients has fuelled significant research mainly due to the influence of craniofacial growth on the implant's behavior. Despite this, the literature still does not offer a consensus regarding the ideal time for implant placement. It is now accepted that the use of implants before the completion of the oro-facial growth is only recommended in cases of severe hypodontia and particularly in the case of anhidrotic ectodermal dysplasia syndrome. For some authors, it is even recommended that implant treatment is complete before the age of puberty to ensure aesthetics, as well as optimal functional and psychosocial development. These children generally have low oral health-related quality of life, and have been shown to suffer from psychosocial depression especially around the age of nine, as they begin to realize that their condition is quite different from that of other children.

The purpose of this presentation is to show five clinical cases and to report the follow-up of three of them in children (11-12 year- old) with ectodermal dysplasia in which mini-implants were used to support the prostheses.

We used two different types of mini implants (3M- ESPE – MDI -O- - Ball - Prosthetic Head- Collared -Standard- 1-8 and 2-4 x -10mm) and (3M - ESPE -MDI – Square- Prosthetic Head - Collared -MAX -2-4 -x- 13mm) according to the thickness of the bone crest in the mandible or in the maxilla. Among the advantages of using mini implants in children with AED, we noted the following points:

- A single, small surgical intervention is necessary and the insertion will be complete by the self-cutting and self-advancement of the implant.
- There is no need for a submerged healing period; additionally, prosthetic reconstruction can be performed immediately.

CASE REPORTS

In the first case, two mini-implants were inserted into the anterior part of the mandible for stabilizing a removable denture (2 years follow-up). In the other two cases, mini-implants were inserted in the maxilla and mandible to replace missing front teeth with fixed prostheses. Patients were called for follow-up every 6 months: in the second case follow-up lasted 4 years in the mandible and 2 years in the maxilla; in the third case, 2 years in the maxilla and 1 year in the mandible. The last fourth and fifth cases illustrate a full mouth restoration using these mini-implants.

CONCLUSION

The use of mini-implants in children with ectodermal dysplasia can enhance aesthetics, functional and psychosocial development.

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PPa-29. Overcoming barriers to developing, testing, and disseminating psychosocial and rehabilitation interventions in a rare disease context: the scleroderma patient-centered intervention network (SPIN)

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Introduction: Internationally, National Plans for Rare Diseases have emphasized the need for the development and delivery of programs that support patients and their families in coping with rare diseases. The National Plans emphasize the emotional, physical, and management challenges that people living with a rare disease face, and the dramatic lack of resources to support effective coping. Effective strategies that are readily disseminated to patients with rare diseases and their families must be based on research that prioritizes patient and caregiver input and provides an infrastructure for development and testing so that invested resources lead to tangible benefit. There are major obstacles, however, to developing, evaluating, and disseminating supportive care interventions for people with rare diseases. In scleroderma, a rare autoimmune disease, the Canadian Institutes for Health Research funded the Scleroderma Patient-centered Intervention Network (SPIN) to develop a research framework for overcoming barriers and developing and testing high-quality resources that help patients cope with their disease. By bringing together a collaborative network of people living with scleroderma, researchers, and health care providers from over 30 sites and 8 countries, SPIN collects important data on challenges faced by people with scleroderma and is developing a series of support tools. Currently, 4 online support tools are being developed for testing and dissemination to people with scleroderma from around the globe. All of these tools, once tested, will be made accessible to patients free of charge through patient organizations. Beyond scleroderma, the same innovative model used by SPIN can be used to help facilitate research and dissemination of patient-oriented health management tools for other rare diseases as well.

METHODS

SPIN utilizes the novel cohort multiple RCT (cmRCT) design to collect longitudinal data related to problems experienced by scleroderma patients and as a framework for developing, evaluating, and delivering eHealth interventions. In the cmRCT design, patients consent to participate in a cohort for ongoing data collection. The aim is to recruit 2,500-3,000 patients from centers across the world within a period of 5 years (2013-2018). Eligible participants are at least 18 years of age with a diagnosis of scleroderma. In addition to baseline medical data, participants will complete patient-reported outcome measures every 3 months. Upon enrolment in the cohort, patients will consent to be contacted in the future to participate in intervention research and to allow their data to be used for comparison purposes for interventions tested with other cohort participants. Once interventions are developed, patients from the cohort will be randomly selected and offered interventions as part of pragmatic RCTs. Outcomes from patients offered interventions will be compared to outcomes from trial-eligible patients who are not offered the interventions.

DISCUSSION

SPIN is a unique endeavour that, through the use of the cmRCT design, the development of self-guided eHealth interventions, and partnerships with patient organization, is able to develop, rigorously test, and effectively disseminate supportive interventions in scleroderma, and may serve as a model to help facilitate research in this area for other rare diseases as well.

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PPi-01. Congenital Anomalies as Preventable Rare Diseases

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EUROCAT, in existence since 1979, is a European network of geographically defined population-based registries (representing the unselected experience of all who live in the population) for epidemiologic surveillance of congenital anomalies (CA). EUROCAT currently surveys over 1.7 million births per year in Europe (31% of the EU birth population), via 37 registries in 21 countries. EUROCAT activity has been funded through the DG Sanco Public Health Programme (2008-2013) as a Joint Action (JA) of the EU and Member States (MS) from January 2011 to December 2013 and as an Operating Grant for 2014.

CA are a major cause of perinatal mortality, childhood morbidity and disability, with a total prevalence of 2.5% of births. Most CA are Rare Diseases (<5 per 10,000 population). The live birth prevalence of rare CA in 2010 was 96.2 per 10,000 births, extrapolating to approx 4.7M affected persons in the EU, 12-15% of the total estimated persons affected by Rare Diseases.

EUROCAT' s mission is to support the primary prevention of CA and the provision of appropriate services to pregnant women, affected children and their families by the ongoing collection, analysis, interpretation and dissemination of population-based epidemiologic data. Epidemiologic surveillance should reduce teratogenic risks preconceptionally and in early pregnancy, inform policies and interventions in order to secure high quality diagnostics, treatment and counseling and to reduce the size of, and inequalities in, the public health burden of CA.

Many CA are potentially preventable, nevertheless the prevalence of CA has remained stable in recent decades, despite growing knowledge regarding prevention. As part of the EUROCAT JA (www.eurocat-network.eu) a working group was created in collaboration with EUROPLAN (European Project for Rare Diseases National Plans Development, www.europlanproject.eu) to establish policy recommendations on primary prevention of CA to be implemented in National Plans or Strategies for Rare Diseases. The recommendations were developed and shared through a multistep process. A preliminary phase covered collection and analysis of relevant literature to define the main evidence-supported risk factors for CA followed by identification of public health actions for the primary prevention of CA in themed working groups (i.e. medicinal drugs or folic acid). A consensus draft was elaborated jointly by the EUROCAT JA working groups and EUROPLAN, and presented to and subsequently endorsed by EUCERD (European Union Committee of Experts on Rare Diseases).

Areas for policy actions are specified in the field of medicinal drugs, food/nutrition and lifestyle, health service, and environmental pollution including the workplace. Levels of preventive action include advice to future parents by health professionals during individual preconceptional and early pregnancy consultations tailored for high and low risk couples; health education campaigns targeted to potential future parents; regulatory actions which affect risk factors at source such as medicines, foods, tobacco and alcohol and other recreational drugs; surveillance, research and evaluation generating evidence for the initiation or updating of primary preventive measures.

In conclusion, the recommendations represent a first step towards an integrative prevention strategy. Their implementation in National Plans will be further monitored by EUROCAT and EUROPLAN.

PPi-02. Rare diseases and disabilities: three orphanet projects to improve the information currently available

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Objective: There is currently very little information available about the disabilities encountered by rare disease (RD) patients. Orphanet [www.orpha.net] has developed new projects to improve the knowledge and visibility of disabilities associated with RDs, and to provide tools to help the stakeholders.

METHODS AND RESULTS

Three projects have been set up, funded by the *Caisse Nationale de Solidarité pour l'Autonomie*.

Orphanet Encyclopaedia for the General Public (OEGP): Content was added to the texts of the OEGP (135 in June 2014) about the daily difficulties associated with the disease and its management. This information, which is validated by medical experts, disability specialists and patient support groups, is provided through three topics: "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".

Orphanet Disability Encyclopaedia: A specialised collection of texts dedicated to professionals and social service providers was created. These disability factsheets (17 available in French in June 2014) focus on the disabilities associated with a specific RD. They provide a brief overview of the medical aspects of the disease, validated by medical experts, and describe the disabilities experienced by patients and their management.

Orphanet Disability Project: Orphanet is currently indexing 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]) and including additional terms to describe cognitive abilities, sleep, temperament and behaviour. Through a questionnaire sent to medical experts, disability specialists and patient organisations, the following data is collected for each RD: activity limitations and participation restrictions (113 terms), 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 environmental factors of importance for the disease. Data is then analysed and standardised to constitute the Orphanet Functioning Database. More than 900 RDs are already indexed and hundreds more are in progress, thanks to the contribution of hundreds of people and organisations from 46 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 in each RD.

CONCLUSIONS

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.

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PPi-03. Dissemination of good quality clinical practice guidelines for rare diseases through the orphanet website

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Introduction: Clinical practice guidelines (CPGs) for rare diseases (RDs) are scarce and sometimes difficult to identify from Internet search. While large collections of guidelines are gathered through national and international databases, RD guidelines are often lost among the numerous common disease guidelines, which makes them even more difficult to be found by health professionals and patients who do not have time or skills to search for relevant information. In addition, CPG quality may vary greatly depending on the source and methodology.

OBJECTIVE

In keeping with its goal to contribute to the improvement of the diagnosis, treatment and care of patients, Orphanet (http://www.orpha.net) is collecting clinical guidelines on RDs. The aim of this project is to provide easy (and free) access to relevant, accurate and specific recommendations for the management of RDs.

METHODS

Guidelines are identified from bibliographic databases, websites of research networks, expert centres or medical societies. As much as possible, their content must target rare medical conditions as a whole rather than a single aspect and must cover the full pathway of care. Then, each guideline is assessed according to quality criteria derived from the Appraisal of Guidelines, REsearch and Evaluation (AGREE II) instrument. In line with our open access policy, only freely accessible CPGs are linked on Orphanet. This implies that only documents for which permission from the copyright holders are given to Orphanet are eventually linked on our website.

RESULTS

In June 2014, 291 CPGs were linked on Orphanet. No language restriction is applied, and so far 9 languages are represented, with a predominance of guidelines in English, French and German (93% of all CPGs). A larger proportion of diseases (or groups of diseases) having linked guidelines belong to rare oncologic, neurologic, rheumatologic or hematologic diseases, inborn errors of metabolism, or rare developmental defects during embryogenesis. This distribution partly reflects the higher coverage of these areas in term of guideline production, but it may also be due to the selection of factors such as quality level, specificity for RDs and availability (free or under permission) for distribution in Orphanet. Besides the general CPGs, anesthesia guidelines produced by Orphananesthesia (http://www.orphananesthesia.eu/en/) are also linked on Orphanet. As of June 2014, anesthesia guidelines for 39 RDs were linked. All of them are available in English, with some also translated in German and Spanish. All guidelines can be found in the "detailed information" section on the specific disease pages of the Orphanet Encyclopaedia. They can also be accessed through the full disease list of the Encyclopaedia for professionals.

CONCLUSION

Initiated in 2012, this guideline collection project responds to a real need from both professionals and patients, as observed from our annual surveys and from direct users' feedback. It is continually growing, with about 150 new guidelines linked in 2013.

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PPi-04. A proposal for a novel funding mechanism to address the global crisis in gaucher disease

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Gaucher disease is a rare lysosomal disorder with a birth frequency of about 1 in 70000 in most populations. The most frequent subtype is type 1 Gaucher disease (GD1), which presents often in childhood with progressive hepatosplenomegaly, severe cytopenia with anaemia and bleeding, and devastating bone disease. Similar findings with central nervous system involvement are found in GD3.

Currently, enzyme replacement therapy is the first choice treatment of GD1 and visceral manifestations of GD3. Reductions in liver and spleen, improvement in cytopenia, bone symptoms and quality of life can be achieved. Three different enzymes are available: imiglucerase (Genzyme a Sanofi Company), velaglucerase alfa (Shire) and taliglucerase alfa (Protalix Biotherapeutics/Pfizer). The last enzyme is authorized in the USA and ten other countries, but not in Europe.

The cost of treatment in many countries is covered by the Government or health insurance funds; however, many countries cannot afford this costly treatment, although there is a very high need: many children with severe forms of GD1 or GD3 are known from countries in Asia and the Middle East particularly in Egypt, India, Pakistan, Jordan, Sudan and Tunisia.

Although Humanitarian aid is provided by the pharmaceutical industry for hundreds of patients, this does not provide care to all the patients in need. The current process of only relying on the pharmaceutical industry for donations is not optimal and whilst processes are being put in place to enhance industry support, without absolving the companies of responsibility in this area, this will never satisfy the total global need. In addition the logistical challenges of treating patients in these countries are huge. Finally it is vital that such an expensive treatment programme is underpinned by sustainable, high-quality training for clinicians and laboratory scientists.

A novel mechanism is required and examples of successful global programs such as Global Alliance for Vaccines and Immunization Alliance (GAVI), The Global Fund to Fight AIDS, Tuberculosis and Malaria are models that we can learn from, bringing together funding contributions from all stakeholders to provide the care, such as the pharmaceutical company facilitating access to treatment, government created programs, academic groups providing training, advocates raising funds and individual donors providing financial support.

Suitable models will need to take into account the rarity of both the disorder as well as the available expertise. One such model will be discussed.

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PPi-05. Europlan: produce optimal value with limited resources

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For nearly two decades, the European Union has promoted actions that aim at sharing information and knowledge regarding rare diseases (RDs) in order to reach out beyond the single countries border and optimize the limited resources for RDs scattered in each Member States. In many Countries, in fact, there aren't sufficient means and enough knowledge to appropriately diagnose and treat RDs, and therefore international collaboration is the most effective way to achieve a high level of access to treatment and medicines. In this contest, since 2008, the EUROPLAN project (www.europlanproject.eu) has supported tenaciously EU policies on RDs. In its first triennium (2008-12), the project has created and divulged tools for the development and implementation of National Plans and Strategies for RDs across Europe. Currently, its innovative efforts are focused in the facilitation of the dialogue and collaboration among the different stakeholders in field of RD, both nationally and internationally. Within each State, the EU supports the EUROPLAN EURORDIS National Conferences (www.eurordis.org), which gather around a table patients, politicians and society for the identification of areas of strength, weakness and of needs in RD management in each country. Furthermore, at international level, it creates opportunities for discussion and collaboration through workshops, events, activities and training courses for representatives of all the European states. In order to increase its impact, the project promotes the active collaboration with other European initiatives and projects, sharing the efforts for a common goal and a more cost-effective. EUROPLAN team is also carrying out a work on indicators, which begun in first period with the development of 59 indicators, tailored to monitor the phases of development and implementation of the National Plan or Strategy. In the current triennium, a stepwise elaboration on specific indicators was carried out to select a set of "Core Indicators" that were adopted by EUCERD in June 2013. Subsequently, a study has been conducted in order to explore the degree of usability of the core indicators in selected EU Member States and to identify problems in relation to the use of the indicators. The study highlighted indicators usefulness in giving a snapshot of the main areas of concern for national planning for rare diseases. The core indicators represent an excellent opportunity to share knowledge and comparability among MS. However, it is important to acknowledge the strengths and weaknesses of the single tools and be aware that quantitative indicators may not reflect qualitative substantial aspects of the issue they are measuring, that may be studied with appropriate and different tools, according to the objectives that have been set for the matter under study.

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PPi-06. The italian national helpline for rare diseases "telefono verde malattie rare": a contributory task aimed to enhance the empowerment of persons with rare diseases

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Information on rare diseases (**RDs**) is crucial in health and welfare systems to foster integration among patients, clinical and bench research and to drive patients, family and healthcare professionals choices. As it is increasingly clear that appropriate information in RDs can reduce diagnostic delays, improve coordination of care and access to experimental treatments, helplines are becoming a core feature within the national framework for RDs.

A national helpline (*Telefono Verde Malattie Rare* - **TVMR**) for RDs was established at the Italian National Centre for Rare Diseases - *Istituto Superiore di Sanità* since 2008, working as a free anonymous public service 5 days/week from 9am to 1pm, handled by paid psychologists and medical doctors. A caller profile analysis of TVMR has been recently published within the context of a larger analysis of the European Network of RDs helpline ([1]): TVMR results revealed the majority of enquires were made by telephone being most commonly related to exemption from health costs, diagnosis, treatment and management of RDs. Patients and their relatives called to obtain psychological and emotional support as well.

OBJECTIVES

To explore the experience of the psychological and medical operators at the TVMR in charge of handling the enquiries on RDs.

MATERIAL AND METHODS

Systematic review of (overt and hidden) psychological-related concerns driven from about 18.000 caller enquiries recorded over a 6-year-period. Enquiries were coded, categorized and qualitatively analyzed according a grounded theory approach.

RESULTS

Although only a small percentage of enquires was explicitly related to a need of a psychological support, this was often recognized as an implicit request of help among all the enquires.

Emotions regarding RDs were a central topic of the conversation. Often, informative questions were an introduction for bringing up emotional problems. Callers receiving support by an active listening and empathy were supplied with verbal information and referred to support services.

CONCLUSIONS

Our findings suggest that helplines for RDs can provide callers with room and sufficient time to discuss their issues anonymously. Helpline evaluations tend to be intricate due to the anonymous nature of these services, even though existing published studies commonly convey high levels of user satisfaction. Counselling methodology allows a helping relationship to decode enquires, providing personalized responses and orientating callers to appropriate services, centres of expertise and patient association. It is crucial to frame the helpline as a strong service organization and multi-specialised team as callers' help-seeking behaviour is multifaceted, with callers' psychosocial needs being intrinsically intertwined with their information or advice-seeking needs. More in general, people with RD, their families and health care professionals frequently face with a critical lack of information and support, experiencing a sense of isolation and/or powerlessness. It is useful to recognise and decode the implicit requests of psychological support in order to identify unmet needs and drive callers towards an appropriate and feasible personalised clinical, social and psychological pathway. The telephone helpline appears to be an easily accessible and empathic source, this study provide a basis for the design of an interactive eHealth approach to improve patients' empowerment.

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PPi-07. National registries of rare diseases in Europe: an overview by the epirare project

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Background: The European Union (EU) policy for healthcare requires the establishment of a system of European Reference Networks, Union wide information databases, and registries for rare diseases (RD) based on shared criteria. The EPIRARE project (www.epirare.eu) studied the feasibility of a EU Platform for Rare Disease (RD) Registries and, together with the definition of a platform model, reference indicators and a related common data set, concluded that, beside the major contribution which can be given by spontaneous registries, the national authorities have an important role to play: establishing national registries; promoting interoperability with identifying and agreeing on common references and standards; ruling and streamlining the information flow for the achievement of the completeness of case ascertainment; and supporting longitudinal data collection designs.

OBJECTIVES

Here we report on a comparative analysis of the current situation of National institutional RD registries in the European Union.

METHODS

the EPIRARE project convened a meeting (4-5 March 2014) with experts of the competent health authorities to discuss the role of national institutional rare disease patient registries in supporting EU patient registration and the room for international cooperation.

RESULTS

The presentations in the Workshop dealt with: the Belgian, French, Italian, Nordic Countries' (NC) and Spanish RD registries, which were already in operation; the Bulgarian plans for a national RD Registry; the German plan for a federal portal for RD Registries. The establishments of the registries reflect different approaches and needs of the country health systems (HS) for RD patient care. The established and planned registries are all integrated in the country HS and receive data from the HS healthcare centres. Most registries intend to collect data on all diagnosed rare diseases and declare to have aims spanning from health service and research planning, to epidemiological and clinical research, and to supporting translational research. All existing registries dedicate attention to data quality with at least formal controls of data accuracy and completeness. All existing registries have independently developed sets of common data elements (CDE) based on national needs and features; although addressing a number of similar information domains, the CDEs have different extensions and do not overlap completely.

CONCLUSIONS

The need for a systematic and cross-country registration of RD patients is now widely recognized for many different purposes. It is still likely that comparable information can be produced by different Countries for many different purposes. However, it seems difficult that a single set of CDE can be adopted in EU, as well as a common or shared patient registration system.

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PPi-08. World wide collaboration in practice: experience from working in a cmtc-ovm organization

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Lex van der Heijden is father of a child with the rare disease CMTC (Cutis marmorata telangiectatica congenita or van Lohuizen syndrome), and raised in 1997 a world-wide non-profit organization for this disease (www.cmtc.nl). In 2012 an American chapter was established and in 2014 a Canadian Chapter. Today we have members and volunteers all over the world which requires e-collaboration and access/data availability about any location. We will hereby present the organizations structure and achievements.

METHODS

We have for each organisation a board with a number of people located in different countries (and states in the USA). The action items of i.e. board meetings are stored by means of an application within the website Content Management System tool which enables users to raise action items and to assign them to i.e. other board members. We use for instance for international board meetings video conferencing by means of Skype group calls. The websites for our organisations (at this very moment 4 which will be soon 5) are looking at the front separated websites but are coupled 'under water' in order to have a single virtual organisation. We share knowledge/experience/ideas between all organisations such as the concept of the Family Day which is intended to break the ice between patients (and their families) before the actual member meeting in order to remove thresholds regarding sharing i.e. personal experiences. We collaborate with organisations such as Eurordis, ICORD, Genetic Alliance, NORD, DIA and VSOP. We collaborate with other country based rare disease organisations (i.e. Finland, Slovakia and the UK).The worldwide CMTC-OVM (includes CMTC and vascular anomalies) organisation has designed and built a series of templates (i.e. presentations, letters, volunteer contracts and procedures) which give new organisations a jump start. We apply social media fully by means of a Facebook group, Facebook page, Twitter, YouTube and a LinkedIn page. A person has been assigned to coordinate, collect and post material by means of specific software both automatically as well as manually. The worldwide CMTC-OVM organisation offers free medical examinations in the Netherlands as well as the USA. We have 4 professors, 2 doctors and 2 (medical) psychologists available who travel with us to the USA to perform medical diagnosis for free. Our information folder material is currently available in 6 languages and soon in 8 languages. These folders are downloadable for free from our websites. We have a CMTC-OVM cloud in order to share large amounts of data, to transfer i.e. videos of meetings in the USA and the Netherlands for further processing and publishing, and also for sharing brain scans between patients and medical specialists. A private cloud has been installed in order to prevent the American government having access to sensitive personal information (Patriot Act).

RESULTS AND CONCLUSIONS

CMTC-OVM world-wide organization has experienced a fast grow and find mutual empowering in international collaboration by means of current electronic facilities and interaction with larger and more experienced patient organizations.

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PPi-09. Prevention, diagnosis and treatment of rare disease. A prospect from Iran

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Comparing to western countries, the incidence of rare diseases are very high in Iran. Available evidence suggests that congenital and genetic disorders are responsible for a substantial proportion of infant mortality, morbidity, physical and mental handicap in this country with population over 70 million. Hemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency, autosomal recessive syndromes, several metabolic disorders and many other genetic disorders are among diseases with high prevalence. The population characteristic that give rise to this high prevalence of rare diseases include large family size, high maternal and paternal age, high level of inbreeding with consanguinity rates in the range of 50% with a very high rate of first cousin marriages.

Major steps have been taken in confronting rare diseases and their burden on patients and their families in Iran. Health care policy makers has long recognized and acknowledged the importance of national preventive programs in dressing challenges that county faces in regard to rare diseases. After a successful national program for premarital carrier screening for haemoglobinopathies, now national newborn screening program are being progressively instituted. Along this preventive measures selective termination of pregnancy of an affected fetus with certain disorders are approved and established practice in the country.

Several non-profit organizations in partnering with government or free standing are active in the area of rare diseases and provide services to patients and their families. In recent years, diagnosis and treatment of these disorders also has benefited from private diagnostic entities and pharmaceutical companies with product for rare disorders. Most importantly today, most disease specific treatments and even some molecular prenatal diagnostic testing cost for rare diseases are fully subsidized by government or health care insurance system.

In 2014, Annual Rare Disease Day was marked with various activities, including international scientific conferences and workshops that were held in Tehran. Rare Disease Day celebration event was attended by over 3000 patients, their families and their public supporters, in Milad Tower in Tehran.

Recent commitment and progresses has brought hope at highest point for the rare diseases community in Iran, for acceptance and recognition of their special needs. Nevertheless, global collaboration in education, medical genetic services, and research remains essential for future advancements.

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PPi-10. Background of an educative project for latin-american and caribbean (la&c) health advocates in rare diseases prevention

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Introduction: The LA&C health context is highly influenced by global economic conditions, social inequities, high disability indexes, new ethics paradigms in policies, etc. urging the application of changes in health care providers. Among the unmet needs, rare diseases (RD) impact on around 40 million people in the LA&C region, and because they are barely known, disperse, and mostly neglected in current health programs the impact in the affected, caregivers and social environment is undesirable severe and growing. Therefore we present a project devoted to train health advocates in RDs at the local University (reg. OCS 1747, UNMDP, Dec 2011; and further national laws) which will be hereby described aiming to describe its present status, and debate the proposed model, mainly in relationship with similar projects functioning in other countries.

MAIN OBJECTIVES

The project aims 1- the inclusions of RDs issues within the regular academic programs, modifying the current poor information status in the topic; 2- To identify and strength the already working forces, 3- to generate consciousness trough workshops open to the community, 4- to cooperate with official health institutions, and 5- install the RDs needs within the public interest and policies.

RESOURCES AND METHODS

Consists, as part of a comprehensive working plan, in the design of programs, proposals for the building of links and nets within experts and interested parties, including the support from international expertise, the creation of specific and educated working groups and a formal service of information and good practices. The activities will be guided by a selected teaching staff, comprising mandatory communitarian practices, and will be devoted to students of the University (Fac. of Health Sciences, Psychology, Law and Economic Sciences), interested in RDs issues, and the affected and its families as well, living in the area of influence of the University. The accepted attendants will discuss selected bibliography, share experiences and activities together with government personnel and members of patient NGO´s at different health sites. Complementary workshops are planned in order to globalize the information, including invited experts from abroad. Finances and the teaching staff will be provided by each participant faculty, and coordinated by one member of them. The process of health advocates education will be monitored and evaluated following different stages, from starting to final presentation of results. The whole schedule of the project will be displayed to enable its open discussion and visualization of the interactive parts.

Status and pespectives: The project is already in its starting phases, being formally approved to be developed in the University. **Beyond the expected academic results, the project aims to be influential in the local and regional sanitary agenda, contributing** and backing specific norms and regulations, registries, etc.

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PPi-11. New e-health services for the european reference network on rare anaemias (E-ENERCA)

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Rare Anaemias (RA) are Rare Diseases (RD) with prevalence in Europe less than 5 per 10.000 individuals. Major forms require red blood cell transfusions and iron chelating therapy as main therapeutic options. Beta-thalassaemia major is predominant in Italy and Cyprus, and sickle cell disease (SCD) in African population. During the last 20 years, SCD is increasing in Europe due to African immigration, leading to an important impact on health care burden in several countries. Preventive programs aiming to epidemiological control and a better diagnosis and clinical management of major RA are therefore crucial for decreasing the affected birth rate and achieving an efficient balance between disease morbidity and patient's life capacity.

Since 2003, ENERCA has taken an active role for improving this situation by : a) the creation of a European Reference Network (ERN) of Centres of expertise in RA b) the promotion of best clinical and laboratory practices c) the publication of ENERCA recommendations d) by improving of continuous medical education by the organization of topic specific training courses e) the empowerment of patients by cooperation with Patient's Associations and co-organizing a annual European Symposium on RAs with interactive patients-health professionals sessions. In September 2013 a new phase of the project has been started, "e-ENERCA", aiming to provide professionals and patients with e-Health tools to assure the same level of RA services across Europe, independently from the country of practise and the origin of the patient. e-Health services will be developed through the implementation of three e-platforms endorsed on the ENERCA website (www.enerca.org) with the following goals: 1) To set up a e-registry for gathering patient's data to achieve the required sample size for epidemiological surveillance and clinical research 2) To set up a e-learning platform for the dissemination of knowledge and best practices improving continuous medical education independently the country of practice and 3) To develop a telemedicine platform to provide expertise at distance avoiding the need of physical travelling. e-ENERCA. It will also be promoted the recognition of Centres of expertise by the national health authorities necessary for its promotion and its recognition as a European Reference Network (ERN) on RA.

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On behalf ENERCA consortium

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PPi-12. Let's join us! We are always beside you. The activity of Werner syndrome patient/family group in Japan

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Chief secretariat of Werner syndrome patient/family group in Japan

The author introduce the recent situation of Werner syndrome and he activity of Werner syndrome patient/family group in Japan.

What is Werner Syndrome? Werner syndrome is characterized by the dramatic, rapid appearance of features associated with normal aging and this disease is the premature aging disease that develops on Adulthood. In many cases, it is aging progresses with twice as fast as the normal aging after the 20 years old. Many Werner syndrome patients die between mid-40 to mid-50 years old. It has been nominated as one of the top ranking progeroid syndrome. Based on the statistical survey, there are about 1200 cases in the world reportedly ever and 80% of them are Japanese. Japanese Researcher groups have established the diagnosis criteria and the clinical practice guideline about Werner syndrome. However, there is no cure or specific treatment and patients must be periodically screened for an increased risk of cardiovascular and cerebrovascular disease and malignancies. Among the many findings, leg ulcers significantly affect the patient's quality of life.

The Activity of Werner syndrome patient/family group in Japan: Werner syndrome patient/family group in Japan (WSPG) was launched in 2011. It is the first established organization for Werner syndrome patients in the world. The main activities are; 1) offering a platform to exchange information among the patients and families, 2) providing the peer-to-peer counseling on Werner syndrome, 3) enhancing the social cognition about Werner syndrome. Since the majority of the numbers of patients are Japanese, WSPG has a plan to expand its activity to the world for demonstrating WSPG's initiative and supporting all patients in the world. One of the future challenges of WSPG is finding patients in the world.

The Challenge of global collaboration in this field: Based on the above challenge, WSPG has started the several projects. One of them is establishment the patient's autography. The author is the founder of WSPG, named as Hiroyuki Endo. He had struggled the symptoms of Werner syndrome for many years. During his live carrying against it, he lost his both legs and one eye and voice. However, he had enjoyed for his entire life and he has passed away at the age of 64 in April 2012. WSPG has spread his story through the website and all people are able to read on it. The author would introduce our experience; the case of Dutch. One of patient at Netherland found it on the web and he has decided to translate it to Dutch. Then he visited to Japan for meeting WSPG staff and discussed how to corporate each other. There is no patient group related to Werner syndrome, but WSPG is able to support for setting up a new patient group in EU area.

Our slogan is "We are always beside you." We will introduce our activities more in detail at ICORD2014 and hope this opportunity for all Werner syndrome patients to make a bridge between both regions.

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PPi-13. A first glance on the costs for patients without diagnosis and the InterPoD (interdisciplinary competence unit for patients without a diagnosis) a subunit of the centre for rare diseases Bonn

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The purpose of this study is to provide a first cost analysis for patients without diagnosis. For these patients, the center for rare diseases Bonn (ZSEB) offers a specialised contact point in the form of the interdisciplinary expertise unit for patients without diagnosis (InterPoD). Here, on the basis of the medical documents presented by the patient, the stations of the "Medical Odyssey" can be evaluated. In our study, previous medical consultations were categorized in consultations with resident doctors, outpatient and inpatient hospital treatment, and were associated with specific costs according to the medical specialty involved. A maximum of the last five years prior to contacting InterPod were considered. Under conservative assumptions, the patients (n = 13) had mean average Odyssey costs of over 11,000 EUR. This compares with per case maximum costs by InterPod of 640 EUR. InterPod costs are neither covered by health insurers nor by patients. A shortening of the Odyssey phase is humanly, medically and economically desirable and could justify cost compensation for InterPod and comparable units.

PPi-14. Facing the rareness: introducing the interdisciplinary competence unit for patients without diagnosis.

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According to the latest European definition, a "rare" disease is a disease that affects less than 1 in 2,000 people in Europe or < 200 000 people in the United States [1]. In Germany, around 4 million individuals have a rare disease. Rare diseases therefore represent a major public health issue, and the demand for rare disease experts and points of contact for affected patients is correspondingly large. In 2011, the University Hospital of Bonn established a Center for Rare Disease (ZSEB) in order to address this unmet need. From an early time-point, it became apparent that in a very large number of referred patients, no diagnosis can be assigned using standard classification systems. Such patients are typically characterized by a long history of suffering, and of multiple clinical assessments and investigations. In 2012, the ZSEB founded a new sub-unit, the „interdisciplinary competence unit for patients without diagnosis" (InterPod), in order to improve the management of these patients. In this pilot approach, specialists from diverse medical fields and students meet to discuss cases and assign a diagnosis. Some case are assessed in an interdisciplinary manner, with a full review of all diagnoses assigned to date.

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PPi-15. Determining the social value of interventions for rare and ultra-rare disorders (URDs)

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Orphan drug legislation provided for a broad range of incentives for research and development (R&D) into interventions for the prevention and treatment of rare and ultra-rare disorders. These measures have contributed to a steady stream of new medications, some of which rank among "the most expensive drugs in the world." In times of economic austerity, health care policy makers increasingly wonder whether these interventions offer "value for money" – but struggle with the absence of accepted validated tools to determine – and to ideally quantify in monetary terms – the social value of such interventions.

OBJECTIVES

To identify the most promising ways forward to address this issue, against the background of the key challenges that arise when interventions for URDs are subjected to formal Health Technology Assessments (HTAs).

METHODS

An international group of clinical and health economic scholars was formed to analyze the limitations of the current evaluation paradigm and propose feasible alternatives. To date, the group has met twice in conjunction with the Annual European ISPOR Congresses in November 2012 and 2013.

RESULTS

The group reached consensus that the complexities of R&D of new treatments for URDs may require conditional approval and reimbursement policies, but this should not be used as a justification for settling for surrogate endpoint improvement only. Strong evidence of clinical effectiveness should be expected within reasonable timeframes. Hence, well-established principles of evidence-based medicine (EBM) should be applied.

In striking contrast, the logic of cost effectiveness – as advocated by many health economists and used by some HTA agencies (including benchmarks for incremental cost per quality-adjusted year, QALY, applied by some agencies as a measure of "value for money") – does not adequately capture prevailing social norms and preferences regarding health care resource allocation. Beyond efficient use of resources, such preferences include, but are not limited to, a priority for care for the worst off (related to initial health state), for those with more urgent conditions (the so called "rule of rescue"), and a relatively lower priority based upon capacity to benefit, as well as a dislike against "all or nothing" resource allocation decisions that might deprive certain groups of patients from any chance to access effective care.

A strong need was identified for an improved or alternative paradigm to determine value for money. Three groups of criteria were defined to systematically appraise the evaluation alternatives, namely, covering the following dimensions: theoretical basis (normative premises, i.e., links to moral and economic theories), empirical aspects (attributes related to the health condition or the person afflicted with it), and pragmatic aspects (feasibility of implementation and potential for bias). Most promising candidates for further appraisal are believed to include multi-criteria decision analysis (MCDA) approaches, direct social value measurement using the relative social willingness-to-pay or person trade-off instruments, and a greater role for budget impact analysis.

CONCLUSIONS

Evaluation of clinical effectiveness should adhere to the principles of EBM and be used more consistently, whereas valid economic evaluation will require the further development and adoption of alternatives to the conventional logic of cost effectiveness.

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PPi-16. The Norwegian National Advisory Unit on Rare Disorders - an appropriate way of organizing services for rare disorders

Stein Are Aksnes, leader NKSD, Norway; Lena Lande Wekre, special advisor NKSD, Norway

The Norwegian National Advisory Unit on Rare Disorders (NKSD) main task is to ensure that people with rare disorders receive holistic and individually based care. NKSD offers services which are not expected to be provided within the main social- and healthcare systems in Norway. Our vision is to make rare disorders more known through knowledge and collaboration.

NKSD consist of national Centres of Expertise on Rare Disorders where patients, their families and professionals can seek help and advice. The centres, each responsible for specific disorders, accept inquiries without a physicians referral.

The purpose of NKSD is to establish better quality of services through

- empowering patients and strengthening advocacy
- making rare disorders more visible in today's society
- ensuring easier access to services
- strengthening networks and collaborations of professionals,
- working towards a more effective use of resources in total

People with a rare disorder outside the groups provided for by the Centers of Expertise can contact NKSD for help and advice, e.g. through our National Helpline for Rare Disorders (800 41 710).

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