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Proceedings from the VIII international conference on rare diseases and orphan drugs (ICORD). St. Petersburg (Russia), October 31-November 2, 2013

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Proceedings from the VIII international conference on rare diseases and orphan drugs (ICORD)

St. Petersburg (Russia), October 31-November 2, 2013

Introduction: from the Presidency.

It has been a great joy for us to welcome all the attendees of the new **ICORD** conference developed at the magnificent city of Saint Petersburg (Russia Federation). **ICORD** has previously developed similar events in Western Europe, North and Latin America, Asian-Pacific, and now focused in Russia and East European countries. Along these encounters we gain in understanding the great diversities in the regional rare disease world, and the urgent need of global cooperation to develop more, better and accessible orphan drugs. **ICORD** pursue integration of excellence in research, the high tech combined with social responsibility in industry, open minded projects and facilitating laws by governments, and the free participation of leading patient groups, which gives transparence and expedite priorities for the hundreds of diagnosis and therapeutics tools still need to be developed, to satisfy most of the 7 thousands rare diseases affecting people world-wide.

ICORD is the first international organization enabling join discussions to facilitate the development of models and ideas in the field. The institution has balanced conflict of interest at its membership and board composition, and follows the ethical criteria sustaining the needs of the affected patients as it main objective. This VIII Conference offered a comprehensive program including the participation of most of the international leaders of opinion, as well as recognized representatives of the Russian and regional countries. A number of free poster works enhanced the information, and satellite symposiums and conferences allowing the exposition of a wide spectrum of topics inherent to orphan products and the rare diseases. Of great value were the opportunities of joining Working Groups and achieving contacts with experts.

ICORD wills to empower the local organizations by assimilating their knowledge, needs and projects. This year, **ICORD** focused its efforts on “Building Global Bridges for Rare Diseases and Orphan Drugs”. As all the historic bridges of the Neva River in St. Petersburg, that connect and favours the fluid exchange between different areas, **ICORD** behaves as a human bridge, helping to learn about the successful experiences and initiatives from the more developed regions, and reflecting the priorities and needs from the less advanced ones. **ICORD** links all between each other from and at different parts of the world.

In this sense, we have now started a new bridge between Russia organizations and its peers from the rest of the world, and it is our motivation to continue empowering and constructing the mutual cooperation in the region. We highly acknowledge the effort of Genetic Russia and the local organizers, which assumed the task of making this event possible within a very short period of time, raising funds, and making positive contacts with government, academia and industry key players, and by inviting representatives from the neighbouring countries as well. **ICORD** also encourage to the attendants and readers to become permanent members of our institution and to participate in the coming annual events as well.

I remain yours,

Virginia A. Llera, MD

ICORD President
GEISER President
www.ICORD.se

From National Association of Patients with Rare Diseases “Genetica”, Russia

The National Association of Patients with Rare Diseases “Genetica” with great joy received the 8th International Conference on Rare Diseases and Orphan Drugs, which was held in our wonderful city of St. Petersburg, October 31 – November 2, 2013.

We realize that the conference served as a convenient platform for global dialogue between international and Russian experts, it has behave as a vector of further exchange and experiences, and has developed common approaches for the sustainable global development assistance to patients with rare diseases.

It’s a great honour for us to represent initiatives and priorities of **ICORD** in Russia. It has been important for us to insert Russia as a member of the developing global work that **ICORD** has been making for many years. We expect that the Russian Federation and the international community will consider and implement in practice the proposals that emerged during the work of the conference.

The conference was functional to the scientific community, researchers, and the representatives of governments, business and civil society organizations, which found a suitable place to organize a constructive dialogue between them and to establish a joint solution of actual problems.

I congratulate all the participants for such productive deliberations and specially recognize the political and personal support given by Mr. Aleksandr P. Torshin representative of the Federation Council and First Deputy Chairman of the Federation Council, Mr. Sergey V. Kalashnikov from the Committee of the State Duma of the Russian Federation on Health, Mrs. Olga A. Kazanskaya Governor of The Government of Saint-Petersburg, Mr. Nikolai N. Starikov Deputy of Staff of the inter-faction Deputy Association “Eurasia” in the State Duma of the Federal Assembly of Russian Federation and Mr. Vladimir Y. Dmitriev Deputy of the Legislative Assembly of St. Petersburg.

Sincerely,

Svetlana Karimova

President of National Association of Patients with Rare Diseases “Genetica”

www.nacgenetic.ru

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These abstracts are published as received from the authors, plus some editorial adaptations on its structure. The opinions and views expressed are those from the authors who accept the responsibility for the statements made or the accuracy of the data presented.

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Working Groups

Working groups (WG) are activities open to all ICORD members. Attendants to the annual meetings can also participate. Contributors can suggest topics of interest, debate and organize specific actions, including events and/or join publications. Each year a group coordinator and facilitator is nominated by the WG coordinator, which summarizes previous outcomes, suggest initial topics, and maintain further communications within the group. Reports from Working Group discussions were done on November 1st 2013, at St Petersburg, and the WG coordinator before publishing reviewed final reports.

WG Coordinator, **Desiree Gahved** (Stockholm, Sweden)
2013 WG-A (Regulatory) coordinator, **Timothy Coté** (Washington DC, USA); facilitator, **Megan Hill** (Washington DC, USA).
2013 WG-B (Research) coordinator, **Emilio J. A. Roldán** (Buenos Aires, Argentina); facilitator, **Maja Stojiljkovic Petrovic** (Belgrade, Serbia).
2013 WG-C (Patient Organizations) coordinator, **Yukiko Nishimura** (Tokyo, Japan); facilitator, **Rumen Stefanov** (Plovdiv, Bulgaria).

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Future ICORD meetings

- **Ist Accord with Industry**, at Karolinska Institute, Stockholm (Sweden), May 2014.
- **IX ICORD**, in association with ZonMw and the Dutch Congress of Medicines, The Netherlands. October 2014.
- **X ICORD**, in associations with the Mexican Federation of Rare Diseases FEMEXER, and the World Congress of Rare Diseases and Orphan Drugs. México FD (México) September 2015.

Any members of ICORD can suggest the inclusion of topics and/or speakers at 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). Free-presentations will be scored and the highest will be offered for oral presentations within the official program, remaining the others as posters presentations.

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

Abstracts of the VIII ICORD: OP= Oral presentation; PPa=Poster presentations (Academia); PPI=Poster Presentations (institutional); WG= Working Groups Report; SS= Satellite Symposia and Free Oral Presentations.

OP-01 Perspectives for worldwide rare disease research networking through IRDiRC

Lasko P.

Chair, IRDiRC Executive Committee.

The International Rare Diseases Research Consortium (IRDiRC) has established two ambitious goals for the end of the decade: to deliver 200 new therapies for rare diseases and also the means to diagnose most of the 6000-8000 diseases that have a prevalence of less than 1 in 2000 individuals. At present, 34 public and private research funding organizations from over a dozen nations have joined IRDiRC, and each has dedicated a minimum of USD 10 million to research into rare diseases. Their collective commitment exceeds one billion dollars. IRDiRC remains open to new members who wish to join, and the procedure for doing so was presented. IRDiRC strives to foster closer coordination and greater international scientific collaboration in this critical research area. It has identified several challenges that it believes can be best addressed through collaborative actions: establishing and providing access to harmonised data and samples, performing the molecular and clinical characterisation of rare diseases, boosting translational, preclinical and clinical research, and streamlining ethical and regulatory procedures. To guide its activities, IRDiRC has established three Scientific Committees that include internationally prominent researchers from the public and private sectors, representatives of regulatory bodies, representatives of patient organizations, as well as ethical and legal experts. The Diagnostics Committee, co-chaired by Kym Boycott (Ottawa, Canada), Han Brunner (Nijmegen, Netherlands), and Michael Bamshad (Seattle, USA) advises on research related to the diagnoses of rare disease, including sequencing and characterization of these diseases. The Interdisciplinary Committee, chaired by Hanns Lochmüller (Newcastle, UK) advises on issues related to ontologies, natural history, biobanking, and registries. The Therapies Committee (chaired by Yann LeCam, EURORDIS), focuses on how to best facilitate pre-clinical and clinical research aimed at delivering on the goal of delivering 200 new therapies. IRDiRC's plan for action and an update on its achievements so far will be presented.

OP-02 European platforms for rare diseases: EPIRARE and RD-Connect

Taruscio D.¹, Vittozzi L.¹, Heslop E.², Lochmüller H.².

¹ Italian National Centre for Rare Diseases, Italian National Institute of Health, Rome (Italy), ² University of Newcastle, Institute of Genetic Medicine – Newcastle upon Tyne (United Kingdom). E-mail: domenica.taruscio@iss.it

Introduction: Collaborative research is of utmost importance in the field of rare diseases, since it provides the opportunity to collect a wider patient population, which can allow building a better evidence base for sound advancement in scientific knowledge and care of these diseases. Many international networks have been established for research and care focused on a number of rare diseases; the EU has funded in excess of 70 projects in biomedical and public health research on a single or groups of related rare diseases in the last years. However, the need to maximise the exploitation of the information collected, as well as extending research to the many other rare diseases traditionally less attractive to researchers, requires that a more transversal approach be adopted. Therefore, several initiatives have been promoted around the world to develop platforms for rare disease research. In particular, we present two on-going projects funded by the EU: EPIRARE and RD-Connect.

EPIRARE aims at building consensus and synergies for the registration of RD patients via a platform that promotes standardization of patient registration, procedures for interoperability and data comparability. The platform supports the establishment and rolling out of quality RD registries, thus representing a tool supporting research on RD. In addition the platform ensures the production of information, with a specific - although not exclusive - focus on public health (RD epidemiology and health services), and patient recruitment.

RD-Connect aims to build an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. Therefore, RD Connect is more specifically focused on the needs of cutting-edge RD research, establishing operative and interactive scientific research networks among registries, biobanks and genomic research platforms, thereby supporting the objectives of the IRDiRC global initiative to deliver 200 new therapies by 2020.

In this way the two projects are activating a stimulating interaction in two different environments with different focuses, which will facilitate the merging of two diverse visions and solutions into one common result.

OP-03 Innovative collaborations models to fund discovery stage rare disease research

Lemoine A.

GlaxoSmithKline Rare Diseases, e-mail: Adrien.a.lemoine@gsk.com, (presented by P. Ledger).

S **ituation:** TRANSFORMING innovations from academic centres into clinical project candidates usually requires external financing, at a development stage where most venture capital firms do not operate. Creative financing and collaboration within such projects will combat inadequate resources to avoid delaying innovations of significant therapeutic value to rare disease patients.

Objectives: Secure alternate funding & collaboration models for early stage projects that are flexible enough to respect the innovation ecosystem, share respective expertise and ensure a balanced risk profile for the investor and/or partner.

Methods: GSK has been applying creative approaches to find and fund innovative early stage rare disease science in academic laboratories through:

* Indirect project financing: participation in a venture capital fund.

* Direct financing: creative partnerships with academic institutions through dedicated alliance management unit.

Results: GSK has invested €17.5M in the first financing round of Kurma BioFund II, the first VC fund dedicated to rare diseases. The fund is notably positioned to create companies in the field of rare disease from innovation and IP, originating from leading European academic centres. Through its investment in the fund, GSK will actively provide scientific and commercial advice to help foster technology transfers in the creation of companies within the funds' portfolio.

Since 2010, GSK has financed seven partnerships with academic centres on rare disease projects through its dedicated "Discovery Partnerships with Academia" (DPAC) research unit. Academic teams maintain complete control of development programs but can tap into GSK's expertise.

Conclusion: Alternative and industry-driven financing models accelerating translation of early stage innovation in rare diseases into patient therapies are already a reality. These models should be picked up and expanded to meet the demands of other numerous promising projects not progressing due to lack of seed funding and/or support from experienced structures such as VCs or pharmaceutical companies.

OP-04 Primary prevention of congenital anomalies from science to policy: an European document

§ Mantovani A., ^Taruscio D., *Dolk H. and the EUROCAT-EUROPLAN Primary Prevention Working Group.

§ Department of Food Safety and Veterinary Public Health and National Centre for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy, *Ulster University, Belfast, UK

C ongenital anomalies (CAs) are a main factor for stillbirths and neonatal mortality as well as being a paramount "early exposure-lifelong consequences" case: most CAs are multifactorial conditions, involving genetic (often polygenic) pre-disposition and exposure to non-genetic triggers, which appear prominent in some instances (e.g., teratogenic infections and drugs, methyl mercury). Therefore, the chances of events leading to teratogenesis would be reduced by targeted actions to improve maternal health, diet, lifestyles and environment; accordingly, CAs primary prevention prompts to the translation of science into evidence-based policies. The EU-funded projects EUROCAT (www.eurocat-network.eu) and EUROPLAN (www.europlanproject.eu) jointly elaborated Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases, recently approved by the European Union Committee of Experts on Rare Diseases (EUCERD, http://www.eucerd.eu/wp-content/uploads/2013/03/Eurocat_Reco_PrimaryPrevention.pdf) The recommendations pivot on the added value of reducing risk factors and promoting protective factors. Thus, topics include medicinal drugs (e.g., guidelines on risk-benefit balance for use in pregnancy), food (e.g., minimizing the risks of deficiency and/or excess of nutrients and the exposure to teratogens), lifestyles (e.g., reducing active and passive smoke, promoting alcohol avoidance), health services (e.g., evidence-based vaccination policies for relevant infectious agents; preconceptional care to women with diabetes or epilepsy) and environment (e.g., implementing policies on high-concern chemicals, minimizing workplace exposures). Most recommendations are evidence-based (e.g., improving periconceptional folate status, preventing obesity), whereas some are precautionary (e.g., managing endocrine disrupters to reduce male reproductive malformations). The recommendations call for an integrated strategy involving women's empowerment, education of the public, guidelines for health professionals, regulatory policies as well as research (e.g., on drug teratogenicity in humans): indeed many actions target the general population, but with a major impact on next generation's health. Policy makers are called to take such challenge, while exploiting the support provided by science.

OP-05 Challenges and opportunities of screening initiatives in rare diseases

Pulles T.

Global Medical Affairs, Shire Rare Diseases, Nyon, Switzerland.

Diagnosis of a rare disease is difficult and delays may occur. Early detection of disease can result in considerable health benefits. However, inevitably it also always implies negative effects. In the terms of Wilson and Jungner (1968): “The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease, and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy.”¹ Screening can be defined as the application of a test or procedure to asymptomatic, apparently well individuals, in order to separate those with a relatively high probability of having a given disease from those with a relatively low probability of having the disease (performing tests on individuals at high risk would be called diagnosis rather than screening).² Screening is also different from diagnostics. Screening is offered to people who either do not have or have not recognized the symptoms of the disease(s) that the screening relates to. A screening test is not intended to be diagnostic. Screening aims to identify people at sufficient risk to benefit from referral for diagnostics. A recent evaluation of the prevalence of surgical interventions in Mucopolysaccharidosis type II (MPS II) or Hunter syndrome patients may allow narrowing of the time gap between onset of symptoms and diagnosis of the disease. Screening for MPS II among boys undergoing a specific cluster of surgeries that occur early in the disease progression, and often prior to the diagnosis, may yield the greatest number of children found to have this disease. Recent research by Mendelsohn et al suggests that nearly half of the children with MPS II require tympanostomy, tonsillectomy, adenoidectomy and/or hernia repair by approximately 3 years of age.³ The validation of this high risk population could provide us with an understanding of the role paediatric ENT surgeons can play in screening and identifying young children with MPS II early.

¹ Wilson JM, Jungner YG: *Principles and practice of screening for disease. In Public Health Papers No 34. Geneva: WHO; 1968::1-163.*

² Dekel R. *Screening, the Everlasting Quest for the Needle in the Haystack. IMAJ 2005;7:650 652.*

³ N. Mendelsohn et al., *Importance of Surgical History in diagnosing MPS II: Data from the HOS Outcome Survey, Genet Med 2010;12(12): 816 – 822.*

OP-06 The collaboration in the field of rare diseases in Eastern European countries: today experience and tomorrow prospects

Kvividze O.

Georgian Foundation for Genetic and Rare Diseases (GeRaD), Tbilisi, Georgia.

The history of activities in the field of rare diseases at the NGO level in our country is relatively short, counting, with a few exceptions, a bit more than 4 years. Our organization, Georgian Foundation for Genetic and Rare Diseases (GeRaD), was formed at about that time. GeRaD represents a group of people personally affected by the problem of rare diseases in Georgia (patients, their parents, doctors, nurses etc.).

International collaboration is one of the basic mechanisms of effectively addressing rare diseases problems in the countries that are lacking relevant experience and knowledge and we can discuss it endlessly. We'd like to talk about how Georgia got engaged in the process and how this process is developing in this country. We'll emphasize collaboration with post-Soviet countries, although contribution of other Eastern Union countries to the formation of our organization as well as the whole rare diseases movement is very significant. For a few exceptions, the situation in all post-Soviet countries is the same. Because we have so much in common and because problems are better solved when they are addressed in a concerted manner, we have always felt support of the people working in rare diseases in those countries. We'll bring a few examples of such collaboration.

* Jointly organized conferences:

Eastern European Conferences for Rare Diseases and Orphan Drugs (St Petersburg and Istanbul); South Caucasus Conferences on Rare Diseases (Yerevan 2010 and Tbilisi 2011); First Eurasian Conference on Rare Diseases & Orphan Products (St Petersburg 2012); Russian, Ukrainian, Georgian National Conferences on Rare Diseases held in the frame of the EUROPLAN 2 project. Those conferences aimed to create preconditions for the development of National Plans/Strategies in Rare Diseases.

*** Participation in joint programs and projects:**

Collaboration in the frame of some projects financed by European Commission within the EU Program of Community Action in the field of Public Health, particularly, EUROPLAN, EPIRARE and Rare-BestPractice; Programs at the region level, particularly, in the advocacy field in Georgia and Azerbaijan; The program in the field of the RD management with participation of Georgia, Ukraine and Russia.

*** Helping rare diseases patients receive adequate medical services:**

Treatment of patients from Azerbaijan in Georgia; Diagnostics for Georgian patients in DNA-labs in Russia and Ukraine; Help in acquiring contacts in clinics and labs in Europe and the U.S.; Creation of regional and international professional networks.

*** Collaboration in research and education:**

Development of contacts among scientific-research and academic institutions of Georgia, Azerbaijan, Armenia, Ukraine, Russia, and Belarus; Sharing experiences in creation of educational programs in rare diseases among medical doctors, residents, students, and patients; Sharing information in the field of scientific research; Exchange programs for young researchers.

*** Collaboration among patient organizations:**

Participation in joint advocacy programs in Georgia and Azerbaijan; Georgian organization initiated formation of the first patient organization in Azerbaijan; Regular sharing of information on solving problems of access to treatment among patient communities of Russia, Ukraine, Georgia, and Armenia; Providing recommendations for each other in the process of integration into European patient structures.

In the nearest future we have to enhance collaboration among countries, and this is bound to bring about the real results.

OP-07 Filling the gap between common and rare diseases - policy needs and practical examples from the industry

Pirard V.

Director Public Affairs Europe, Middle East and Africa at Genzyme - a Sanofi company.

Several jurisdictions have adopted orphan drug legislations and rare disease policies using an arbitrary incidence or prevalence cut off to define rare diseases. These legislations aim at correcting market failures that affect diseases with small patient population and to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry.

The needs of rare disease patients within a healthcare system are however much larger than approved medications. Many aspects of health care that are taken for granted in more common diseases can be lacking for infrequent diseases. For example, accurate information on the disease cause and course might be lacking, healthcare professionals unaware, validated easy to perform diagnostic tests not available, diagnostic and treatment infrastructures not existing and guidelines absent. Patients might feel isolated, not understood and with few advocates. When new therapies are available the need for dedicated process of care becomes even more critical. Modern, well-equipped hospitals and clinics are crucial to ensuring that patients have access to treatments.

For companies with a patient focus much more needs to be done than developing and delivering products. They also need to take responsibility for helping patients obtain access to unique therapies, regardless of their location, financial circumstances or other obstacles.

To provide the right services the key to success is for industry to partner with multiple stakeholders like patient organizations, authorities and academics to develop solutions adapted to the local health care systems and geographic situations (travel distances, ease of access to primary care facilities, logistics – cold chain,...).

When designing new policies different scenarios will emerge to cater for all kind of needs but authorities should always consider the long term and the process of care to optimize patient's outcome. Rare diseases are often chronic severe conditions affecting children in half of the cases. Policies targeted at children for example need to take in account they will grow in adulthood.

OP-08 Statistical planning to collect good evidence

Day S.

Clinical Trials Consulting & Training Limited, e-mail: simon.day@CTCT-Ltd.co.uk

Ovious statistical considerations for designing clinical trials include such elements as blinding, randomisation and – the inevitable – consideration of the necessary size of a study. Sample size considerations in the usual way we think of them quickly meet barriers when planning studies of rare diseases.

There are other aspects of statistical thinking that should also be considered and that will help to strengthen the evidence-base, without necessarily increasing study size. General comments about how a series of studies may link together will be given – both from the perspective of competitive companies, but also from that of collaborative organisations. Some anonymised examples (mostly of bad linking of studies) will be given to illustrate these points.

Case study 1 is of a single study with two potentially different subgroups. Whilst it is hoped that the treatment works in all patients, it may not work in one or other sub-group, and recruitment may be difficult in one of the subgroups in particular. How should an interim analysis and possible adaptive design trial be planned to avoid the trial struggling to recruit patients from a subgroup that will never be able to demonstrate benefit, and what changes might be made at an interim analysis?

Case study 2 is of a set of 3 studies: one in children with the “right” endpoint (survival), one in adults with a “wrong” endpoint (symptoms) and lesser quality data from an adult registry with survival (and only survival) as the endpoint. The extent that the overlap does or does not allow a conclusion of survival in adults is discussed.

Case study 3 is of a quite traditional looking development programme (albeit one with very few patients). It consists of 2 randomised controlled trials (RCT 1 and RCT 2), one of which has a long-term open-label extension; 1 uncontrolled study (UCT 3); and a survey (SVY 4) documenting the (untreated) natural course of the disease. Further details of the set of studies and opportunities for a more cohesive development plan – even within the constraints of the very small patient numbers – will be given.

Conclusion: To best serve patients when testing potential new treatments, we need to look beyond designing individual studies (whether they be randomised controlled trials or something else), and look to prospectively plan to collective a cohesive totality of evidence.

OP-09 The conduct of clinical trials in rare diseases in Russia

Chernov V.M., Tarasova I.S.

Federal Research Center of Pediatric Haematology, Oncology and Immunology named after Dmitry Rogachev, Moscow, Russian Federation.

An orphan drug is a pharmaceutical agent that has been developed to treat a rare disease. More than 7000 rare diseases are described in the world. However, the orphan drugs could treat only about 200 of them. The assignment of orphan status to any drug developed to treat it is a matter of public policy in many countries, and has resulted in medical breakthroughs that may not have otherwise been achieved due to the economics of drug research and development.

Many hematologic and oncologic diseases are rare diseases. For example, the incidence of aplastic anaemia is 1 case per million in a population per year, the incidence of acute leukaemia is 3–4 cases per 100,000 children per year, and the incidence of haemophilia is 1 to 2 cases per 10,000 boys born alive. The main problems with organizing clinical trials in rare diseases in Russia are: (1) the imperfection of the legislative base, (2) problems with recruiting sufficient number of patients to evaluate the treatment effectiveness.

Multicenter studies may allow recruiting the number of patients that is sufficient to obtain correct results, conducting randomized controlled trials, and using of new treatment methods in clinics that are part of a multicenter trial.

Russia has some experience in organizing multicenter studies. Using world experience and research results of our scientists, since 1991 we have developed the programmed therapy – Moscow–Berlin series protocols (principal investigators: Prof. G.Henze, Berlin, Germany, Prof. A.Karachunsky, Moscow, Russia) and organized a large multicenter trial to treat paediatric acute lymphoblastic leukaemia (ALL). Since then the results in treatment of paediatric ALL have dramatically improved. Prior to using programmed therapy the 20 years event-free survival (EFS) in children with ALL (n = 39) in Russia was only $51 \pm 9\%$. Using ALL-BFM-90 protocol (n = 601) has improved the survival rate up to $64 \pm 2\%$, using ALL-MB-2002 protocol (n = 1548) – up to $72 \pm 1\%$, and using ALL-MB-2008 protocol (n = 1612) – up to $87 \pm 1\%$. Organizing multicenter studies and the use of modern protocols helped obtain good results in the treatment of other malignancies. The overall survival (OS) in children with acute promyelocytic leukaemia (APL) that were treated with all-trans retinoic acid in combination with chemotherapy – APL-93/98 (n = 62) and APL-2003 (n = 61) protocols – was $84 \pm 5\%$ and $93 \pm 3\%$ respectively. The EFS in children with Hodgkin’s lymphoma receiving therapy by GPOH-HD-2002 protocol (n = 75) was $93 \pm 0,29\%$.

Diagnostics of haemophilia have also significantly improved in Russia in the past. The National treatment protocol has been created. The treatment of haemophilia patients is covered by the state. Preparations of blood clotting factors obtained by recombinant DNA have been developed and manufactured in Russia (Coagil-VII, oktofactor, “GENERIUM”, Russia). The treatment outcomes and the quality of life in haemophilia patients have been significantly improved.

Conclusions. Joint efforts are required to resolve problems with diagnostics and treatment of rare diseases. Russia has all the opportunities to develop, manufacture and to use the orphan drugs. Conducting cooperative multicenter trials could prove the effectiveness in treatment of rare diseases.

OP-10 E-RARE - a transnational platform for rare diseases research funding

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E E-Rare, ERA-Net for Research Programs on Rare Diseases, which was launched in its first phase in 2006 and in its second, phase in 2010 (E-Rare-2; 2010-2014), is currently funded under the ERA-Net Scheme in FP7 by the European Commission. The major goal of E-Rare is to build the foundation for a transnational research program on rare diseases. The E-Rare Consortium gathers a group of seventeen research funding organizations from Austria, Belgium, France, Greece, Germany, Hungary, Italy, Israel, Portugal, Romania, Spain, The Netherlands and Turkey (as well as Poland, as an observer), which are cooperating under this single umbrella to maximize the added value of coordinated transnational research funding in the field of rare diseases. Since 2007 the E-Rare Consortium has launched 4 joint transnational calls for collaborative multidisciplinary research projects open to any rare disease and a wide range of topics and approaches. A total of 475 multinational applications involving more than 1900 research groups from European and associated countries were submitted. The participating national funding agencies from 6 (2007) and 10 (2009, 2011, 2012) countries provided funding for 53 consortia for a total of 37.5 Mio Euros. Importantly, the 4th Joint Transnational Call (2012) was dedicated specifically to “European Research Projects on Rare Diseases driven by Young Investigators”. The aim was to provide to promising independent investigators the opportunity to build transnational collaborations in the field of rare diseases research. To continue and expand its activities in accelerating the development of new diagnostics and therapeutics for patients suffering from rare diseases, the « E-Rare Group of Funders » recently joined the International Rare Diseases Research Consortium (IRDiRC) that teams up researchers and organizations investing in rare diseases research in order to achieve two main objectives by the year 2020: to deliver 200 new therapies and the means to diagnose most rare diseases.

OP-11 EU policy development on hta-regulatory interface and implications for global harmonization

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Efforts to harmonise EMA and FDA regulatory processes have been moving ahead with some success. At the same time, Europe has been experimenting with public policy initiatives that aim to reduce the gap between data available for new medicines at the time of marketing authorisation and the data requirements of HTA bodies in Europe. Orphan drugs have been at the forefront of these EU policy developments. Attempts to harmonise data requirements or bridge the evidence gap between regulatory and HTA decisions in Europe may be effective in improving market access for new orphan medicines in the EU, but may cause EU processes to diverge from the US, limiting the scope for regulatory harmonisation. A brief survey of pilot projects involving regulatory and HTA bodies (not limited to orphan drugs) that aim to shape the regulatory/HTA interface in Europe is outlined, and areas where these may impact EMA/FDA harmonisation of orphan medicines regulation are presented.

OP-12 New treatment of rare diseases by the example of CTEPH

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Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to result primarily from incomplete lysis of acute pulmonary embolism with subsequent organization of the obstructing material to vessel walls and obstruction of pulmonary vascular blood flow. The estimated cumulative incidence of CTEPH is 2-4% among patients presenting with acute pulmonary thromboembolism. CTEPH is a rare and life-threatening complication of pulmonary thromboembolism. It is associated with significant rates of mortality and morbidity. The three-year mortality was reported as 90% in the patients with PAP > 50mmHg. CTEPH is included in group IV according to the 2008 DANA point classification.

The pathogenesis of the disease has not been fully elucidated, and factors contributing to its development remain poorly defined. Although current data suggest that CTEPH does not result from traditional, known thrombophilia or defective plasma fibrinolysis. It has been suggested that elevated levels of factor VIII and antiphospholipids antibodies thrombophilic factors, differences in the expression of type-1 plasminogen activator-inhibitor associated with current thrombosis, thrombosis in situ, are contributing to the disease progression.

Update guidance on the management of pulmonary hypertension (PH) has recently been provided by the Fourth World Symposium on Pulmonary Hypertension and the European Society of Cardiology, and the European Respiratory Society Task Force for the diagnosis and treatment of pulmonary hypertension. In agreement to these recommendations, CTEPH can be cured surgically through the pulmonary thromboendarterectomy. The most difficult aspect of patient selection to surgical procedure is the differentiation between proximal obstruction due to macroscopic pulmonary emboli and PH with thrombosis in the distal part of the segmental arteries. Advanced medical therapy is considered in patients with inoperable disease, as a bridge to pulmonary thromboendarterectomy or in those with persistent or recurrent pulmonary hypertension. PAH-specific medical therapies include prostacyclin analogues, endothelin receptor antagonist and phosphodiesterase inhibitors. More recently, a randomized controlled trial with guanylate cyclase stimulators, riociguat, achieved its target and showed hemodynamic, as well as functional, improvements within 4 months of CTEPH therapy. This is an essential step for the understanding of the risk factors, effective and targeted management, and potential limitation progression of a rare disease as CTEPH.

OP-13 An overview of the RARE-Bestpractices project

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Objectives: RARE-Bestpractices is a 4-year project (2013-2016, www.rarebestpractices.eu) funded by the Seventh Framework Programme of the European Union (FP7/2007-2013). The project aims to improve clinical management of patients with rare diseases (RD) and narrow the existing gap in quality of healthcare among countries by creating a sustainable networking platform to collect, evaluate and disseminate high quality and up to date information on RD.

Methods: A synergistic collaboration among experts in RD research as well as in clinical practice guidelines (CPG) and systematic reviews is promoted to reach the project goals. The project involves 15 partners from academic institutions, governmental bodies, patient organizations and networks across Europe.

Results: RARE-Bestpractices is intended to yield the following results: creation of standards and transparent procedures for the development and evaluation of CPG for RD; development of a collection of CPG in a publicly searchable database to provide professionals, patients and policy makers with high quality and up to date information about diagnosis and management of RD; identification of available notations for graphic representation of processes within CPG to improve user understandability and implementation; identification of strategies to identify and prioritize RD clinical research needs to optimize the research agenda on RD; definition of the extent to which conclusions from cost-effectiveness analyses for pharmaceuticals are accounted for and implemented in best practice guidelines across a range of countries; training events organized to support stakeholders in developing and evaluating CPG for RD.

Conclusions: The availability of reliable and comparable knowledge on the management of RD is needed to improve patient outcomes. RARE-Bestpractices is conceived to respond to this need. The project will also contribute to the application of the Directive 2011/24/EU which includes the "capacity to produce good practice guidelines" among the criteria to be fulfilled by European Reference Networks for designation.

OP-14 Clinical guidelines and practices: examples from international collaboration in clinical practice

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Introduction: We all here share a common aim, to improve diagnostics and treatments for individuals with rare diseases. However, defining diagnostic guidelines and identifying the most appropriate treatment can be difficult, particularly in rare diseases. During recent years, there is an increasing tendency to monitor and to report various outcome measurements. This will likely increase the implementation of diagnostic and therapeutic guidelines in routine clinical care and, as a result, improve the quality of care. Although this is much more difficult in rare disorders, it can still be done in international collaboration.

Our team was interested in a then invariably fatal disease when untreated, with a median survival of only 1-2 months after diagnosis, called familial hemophagocytic lymphohistiocytosis (FHL), clinically characterized by fever, large liver and spleen, and low blood counts (cytopenia), and in some patients also neurological impairment as a result of inflammatory activity in the brain. Because of the dismal survival there was an urgent need for improved diagnosis and improved therapy in this disease.

Method: The rareness of the disease, with only two new patients per year in our country (Sweden), prompted us to seek an internationally collaborative approach in gaining a large enough patient material on which reliable conclusions could be drawn. Notably, this was made through a partly parent-supported society, the Histiocyte Society, which includes physicians and scientists. Through this international collaboration we initiated a prospective therapeutic study and we were able to recruit altogether 249 patients from 25 countries that fulfilled the study inclusion criteria, started the therapy, and had data reported upon - with a 91% follow-up after 5-years.

Result: This study shows in itself that it is possible to run a, fully academic, clinical study in a large number of countries. Moreover, not only were the survival data rewarding, with an estimated 5-year probability-of-survival of $54\pm 6\%$, but in addition a great number of clinical conclusions on the disease itself could be drawn based on the large clinical material.

Conclusions: It is possible to develop evidence-based clinical guidelines and practices through international collaboration, also in rare diseases. Moreover, patient organizations can have a central role in providing an environment, such as medical meetings, for such collaborations to thrive. Hopefully ICORD may develop further, into a large Rare Disease Forum, where many rare diseases have their annual meetings. Part of the program could then be common for these societies, with anything from excellent statistical experts to discussions on how to support clinical studies in rare diseases, where industry, regulators, patient organizations and clinical scientists can meet and learn from each other.

OP-15 The urea cycle disorders consortium: lessons from a multi-institutional research network in rare diseases

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The Urea Cycle Disorders (UCD) Consortium was established in 2003 as one of the initial Rare Diseases Clinical Research Centers, funded through a grant from the Office of Rare Diseases Research and the National Institute of Child Health and Human Development of the NIH. Initially consisting of 5 US sites, it has now evolved into an international consortium of 14 sites, with additional sites having been funded primarily through philanthropy. As of July 2013, there were over 700 subjects enrolled in the UCDC's various studies, with the greatest number of these subjects enrolled in a natural history study. The goals of the UCDC are to: develop a better understanding and improve outcomes of UCDs through clinical research; train the next generation of investigators in UCD; develop resources with information on UCDs for clinicians, researchers and patients; and develop and test novel medications and treatments that improve survival and outcome through collaboration with pharmaceutical and biotech industry. Since its establishment, the UCDC has facilitated this type of collaborative clinical research, and its partnerships with industry have enabled the development and approval of 3 new orphan drugs. This talk illustrates lessons learned from this multi-institutional network.

OP-16 Rare treatment technology: therapeutic apheresis in rare diseases treatment

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Therapeutic Apheresis (TA) is a process of cells or molecules' removal from the blood, those that have an important role in pathogenesis for numerous diseases. This removal is performed by means of extracorporeal blood (plasma) perfusion via specific devices. Modern TA operations such as immune-adsorption, double filtration plasmapheresis, HELP and etc. has nano- and bio-technologies in their base and allows to remove pathological substances from the blood with high selectivity and efficacy. Unfortunately they are rarely used due to their high cost (usually in routine use they take 30-100 thousand Euros annually), but they could have a crucial important role in rare diseases control, if there are no effective alternatives.

One of the nice examples for application of TA in effective Rare Diseases control is Familiar homozygote hypercholesterolemia. Therapeutic Apheresis is a part of treatment protocols in GB, Germany, Italy, Japan and some other countries. Last few years some investigators clearly demonstrated effectiveness of TA in Refsum's disease (Zolotov, Wagner et al, 2012), cerebrotendinous xanthomatosis and phytosterolemia (Matysik, Orso et al, 2011), Schmitz G. et. al., 2012), pulmonary hypertension (Dandel, Wallukat et al. 2013), autoimmune bullous disorders (Schmidt, della Torre et al 2012; Schmidt and Zillikens 2013 and others).

We also have some practical advances for TA usage and blood purification in catastrophic anti-phospholipid syndrome, autoimmune hepatitis, autoimmune myasthenia gravis, severe Wilson's disease and lipoprotein glomerulopathy.

Besides practical importance TA technologies has incredible basic science significance. Biochemical analysis of effluent substances allows to expand the pathogenic mechanisms' understanding and to clarify targets for pharmaceutical treatment and drug research and alternative treatment strategies.

Our research for copper concentration in cerebrospinal fluid during TA and blood purification treatment let us to clarify underlying pathogenic mechanisms for some neurologic variants of Wilson's disease.

Summary:

1. TA technologies are effective in some rare diseases (RD) treatment when no other treatment has been discovered.
2. The new created infrastructure for RD (legislation, information resources, registers, expert centers and etc.) is desirable to have separate branch for Orphan Medical Technologies, such as TA.
3. Manufacturers who develop Hi-tech medical technology are not able to compete with pharmaceutical industry because of market size, so the innovation for these technologies in clinical practice needs an additional support.
4. Practical usage for TA in RD treatment needs a specific way of process organization similar to renal replacement therapy.

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OP-17 Current situation regarding NANBYO policy in Japan

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In 1972 the outline of measures against Intractable Diseases (NANBYO policy) was formulated by Japanese government, which was the first established national policy in the world related to this field. The word of NANBYO comes from Japanese, and its meaning is included with RARE and INTRACTABLE diseases. Since this period Japanese government has set up the various types of laws and policies and has established the subsidy system for new drug (OD) development (1979, support system centering on financial aid has remained), formulated livelihood supporting project (1996, enhancement of healthcare for RD patients), established special promotion project for RD (1998, securement of inpatient facility for intractable RD patients), established RD counselling and support center (2003), and revised the parts of Child Welfare Act (2004, enshrine project of paediatric/chronic diseases in law) etc. However, the ideal situation of NANBYO has changed in circumstances surrounding its field, compared with the period of enactment of NANBO policy (1972): the number of patients is about 710,000 (56 diseases) but was less than 5,000 (8 diseases), the number of intended diseases is several thousand but was less than 100, the items to be studied are various types as understanding the pathogenesis of NANBYO diseases, establishing methods of treatments, confirmation of the patients' condition, promotion of researches, development of medicines and enhancement of QOL. Under the present NANBYO situation, we have been discussing NANBYO policy and related measures to make a fundamental reform. The NANBYO national committee issued the proposal for enshrining into law in January 2012, as a part of a plan to reform, "Total Supports for Persons with Disabilities Act" executed in April 2013. The target of this act included with NANBYO patients. Regarding to the enforcement of the act, there were major changes as follows: 1) Regional government has assumed a responsibility to set up the support projects for NANBYO patients, 2) Welfare policy is altered by a change in the definition of disability (the target of welfare for the disabled is not only patients who have fixed disabilities but have changed (e.g. NANBYO)), 3) NANBYO patients is regarded as targets for job assistance under the act. NANBYO national committee restarted to discuss in September 2013. In this presentation, the presenter will report the progress of discussions and consider the consequences before making decision from patients' perspective.

OP-18 Rare diseases national plans in Eastern European countries

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While on European level policy makers widely agree on the fact that rare diseases (RD) should be considered a top public health priority, on national level there are significant differences in how these political guidelines are being transposed and implemented. From an Eastern European perspective there are three key factors, showing how and why the adoption of RD national plans could be substantially beneficial for this region – increasing EU integration and cohesion, improved public awareness of RD and upcoming EU cross-border healthcare directive.

Bulgaria, Czech Republic and Slovakia are the only of all Eastern European countries to officially adopt such a political public health document. The Bulgarian national plan was officially approved at the end of 2008 and officially launched in 2009 for a 5-year term. It was a significant event for RD community from all over Eastern Europe, because a relatively small and resources-limited Eastern European country has become the second after France to start implementing a specific RD strategy. These three countries have demonstrated that the national plan for RD is not an option only for high-income Member States. The adoption and implementation depends much more on the presence of a core advocacy group rather than the country's economic situation.

OP-19 Rare Diseases national plan in Russian Federation

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Theoretical bases of strategic planning were laid in Russia in 20th years of XX century. The base for this was formed by Marxism about necessity of the planned leadership of economic systems which achieved of the high level of socialization in order to ensure balanced development of the economy, as well as the conviction of Russian scientists (Vernadsky, Krzhizhanovsky, Kondratieff, B. A. Bazarov and others) in the need for an active government policy to transfer a dilapidated economy for the newest scientific and technical base in that time. Nowadays politics of Russian Federation directed on the budget oriented on the results with using of the long-term strategies. Current legislation in the field of rare diseases cannot fully satisfy the need individual category of citizens – patients with rare diseases, in the early screening, adequate medical treatment and proper social rehabilitation patients as well as an adaptation their families. It's time to change the order passed by at the moment, to develop new mechanisms taking into account the years of experience that will improve the situation of such patients. It's time to change the order accepted by at the moment, to develop new mechanisms taking into account the years of experience that will improve the situation of such patients. Despite on significant advances in diagnosis and treatment of patients with rare diseases in our country and the adoption of a number of important legislative acts, many of the issues of providing social, medical and psychological care to patients with rare diseases remain open. The most urgent is the situation in the Russian Federation, the majority of which are not institutionalized, not financially prepared to introduce a package of measures aimed at improving the health and social care for patients with rare diseases. Since the existing rule of law is very fragmented, dot amendments do not regulate complex solutions mentioned problems do not cover all aspects in an adequate and timely medical therapy, a presence of diagnostic, conduct epidemiological registry and bio-bank, an adaptation and socialization, there is no uniform approach to the implementation of the state policy in the field of rare diseases - this is the reason for the creation and adoption of an uniform for all documents for the regulation of relations in the field of rare diseases determining the processing relations and the distribution of funding sources of the aggregate of the Russian Federation - is the strategy of such a document.

OP-20 Social-economic burden and health-related quality of life in patients with rare diseases in Europe (BURQOL-RD)

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Objectives: The BURQOL-RD project is 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. Preliminary results from Spain are presented here.

Methods: On-line survey of patients and carers affected by Cystic Fibrosis, Prader-Willi Syndrome, Haemophilia, Duchenne Muscular Dystrophy, Epidermolysis Bullosa, Fragile X Syndrome, Scleroderma, Mucopolysaccharidosis, Juvenile Idiopathic Arthritis or Histiocytosis was launched through national patients' organizations in eight countries: Spain, UK, France, Germany, Sweden, Italy, Hungary and Bulgaria.

Socioeconomic costs per patient were calculated. Costs were divided in 4 categories: direct healthcare costs (drugs, medical visits, exams, material), direct non-healthcare formal costs (professional careers, social services), direct non-healthcare informal costs (unpaid carers) and indirect costs (patient's and carer's productivity loss).

Both patients and their carers completed a generic scale EQ-5D to measure HRQOL.

Results: A total of 3,185 responses from patients and their careers were obtained, most of them affected by Cystic Fibrosis (910), Scleroderma (590) and Haemophilia (399), as these diseases are relatively more prevalent.

Total annual costs differ from country to country, depending mostly on prices of healthcare resources and time of unpaid carers. The costs of informal care (unpaid carers) formed an important part of total costs through all countries.

Regarding the HRQOL measured by EQ-5D, the most affected patients were those with Mucopolysaccharidosis, Duchenne Muscular Dystrophy and Histiocytosis, which correlated with the HRQOL of their careers and total costs.

Conclusions: Besides results on costs and HRQOL presented, the main outcome of BURQOL-RD is an integrated and harmonized set of instruments to assess and monitor socio-economic burden and HRQOL of patients affected by rare diseases and their carers. The tools developed by BURQOL-RD will also improve RD awareness and literacy among European citizens.

OP-21 Patient priorities in primary prevention, diagnosis and clinical care of rare diseases

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We hereby examine priorities for primary prevention and diagnosis of rare diseases in Russia. It has been noticed that treatment of patients with rare diseases is one of the biggest problems of the health system, and not only in Russia. Diagnostics of such diseases is often difficult or unavailable; treatment is ineffective because of the lack of appropriate medicines, treatments. The results of these factors are unfavourable forecasts for patients. The most important priorities are: Epidemiological Registry, monitoring the situation throughout Russia; educational programs for physicians and paediatricians who are the first to identify the symptoms of rare diseases patients, implementation of national programs for genetic testing to determine the risk of disease before symptoms appear, the introduction of territorial program for each region - promoting a healthy lifestyle and attachment "roadmap" patient. In the implementation of these programs will be achieved the goal of reducing morbidity and mortality population based on a complex problem solving prevention and diagnosis of treatment and rehabilitation, as well as prolongation of the quality of life of patients with rare diseases.

It was also drew the particular attention to the work of the Resource Information Centre for Rare Diseases, which is established by the National Association of organizations of patients with rare diseases "Genetics". We stressed that today it is the only existing Russian information centre that fully supports patients with rare diseases. In the Resource Information Centre for Rare Diseases received calls from all regions of the Russian Federation, where patients get the information about possible methods of rehabilitation, treatment, prevention, assistance in increasing the efficiency between patients, health professionals, public authorities, representatives of science and business, the distribution of legislative and legal acts, providing regional public authorities information about the state of the situation on rare diseases in their regions.

OP-22 Rare diseases in Latin America: identifying the needs and finding appropriate solutions

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Background: Rare diseases affect millions of individuals round the world. There are between 5,000 - 8,000 rare diseases identified with some affecting very few individuals while others affecting millions. The diseases are usually genetic in nature or at least have a genetic component. Most of these diseases have currently no or a less than optimal treatment.

Need: Identifying individuals with rare diseases remains a challenge especially in developing countries where access to care, including basic diagnostic testing can be limited. Latin America and the Caribbean have a population of approximately 590 million people with about 61% concentrated in South America. The prevalence of rare diseases in Latin America is not well known, but there are currently millions of individuals affected. Strategies aimed at finding the prevalence of rare conditions in Latin America, as well as identifying the main areas of need from a patient population, health care provider, academia and government perspectives is paramount.

Finding solutions: Creating awareness about rare diseases at the local, national and regional level is a key aspect in order to achieve the recognition of rare diseases as a real health problem in Latin America. Synergistic work between key stakeholders such as academia, health care organizations, patient groups, foundations, government and the overall community are necessary to identify areas of need for rare diseases in the region. These key stakeholders can work along with regional organizations to provide alternatives for patients in terms of care, research and education. The collection of relevant national and regional data to identify the main areas of need is one of the first steps of these networks. To start, allowing individuals and families with rare diseases to have access to basic diagnostic testing and care should become one of the main goals of any rare disease program in the region. A possibility also is to create specialized local research centers in Latin America as Centers of Excellence in Rare Diseases that can compile local data while providing diagnostics capabilities and access to basic care for patients. These Centers of Excellence could also work alongside with other stakeholders and local authorities in establishing priorities for care, research and education that fosters the development of new therapies for the most needed conditions. References: <http://www.tradingeconomics.com/latin-america-and-caribbean/population-total-wb-data.html>

OP-23 Challenges and opportunities across the life course

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Conferences on Rare Diseases and Orphan Drugs invariably have a strong emphasis on the process of drug discovery, clinical trials, drug registration, and reimbursement. And so they should, as these topics are a very important part of delivering improved health and quality of life to rare disease patients.

However there are many other important ways in which health systems can improve outcomes for rare disease patients and their families, through programs such as primary prevention, antenatal and newborn screening, improved diagnostic techniques, and earlier interventions. These topics seem to generate less discussion at such conferences, and also less focus in many health systems, yet they actually have the potential to deliver more benefits to more rare disease patients and families, in a shorter timeframe.

This presentation argues that we need a wider view in our discussions, not as an either/or approach, but as a both/and approach. Priority actions for rare diseases need to address all the areas of gain that are possible and all stakeholders in the rare disease field need to address these wider needs. It is pleasing to note that IRDiRC, the international rare disease research consortium, has adopted this dual mission.

ICORD's Yukiwariso Declaration on the need for worldwide policy and action plans for rare diseases is discussed as a tool for patient advocates, academia, clinicians, industry and health officials, to refer to in their work and actions to reduce the burden of rare diseases on individuals, families and all of society.

PPa-01 The Italian External Quality Assessment in conventional cytogenetics of the national centre for rare diseases: state of the art and results of the 8th round (2012)

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The External Quality Assessment (EQA) in conventional cytogenetic, coordinated by the National Centre for Rare Diseases-Istituto Superiore di Sanità, started in 2001 and covers prenatal, postnatal and oncological diagnosis. The scheme is retrospective and each part of the scheme stands alone; a web-utility dedicated to the EQA has been developed.

Since 2009 the EQA is an institutional activity and laboratories pay a fee for each scheme (GU n.199-28th August 2009). Participation is open either to public and private laboratories. Assessment takes into account: banding quality, karyotype reconstructions, completeness/accuracy of the analysis, ISCN nomenclature, written description of the result, interpretation, completeness/accuracy of the report and reporting times. 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. Until now eight rounds have been completed; the 9th round (2013) is in progress. The total number of laboratories participating in 2012-8th round was 75; 55, 67 and 26 laboratories participated in the prenatal, postnatal and oncological scheme respectively. The quality of the analysis was sufficient/satisfactory in the majority of cases sent by participants. However critical errors were identified either in constitutional and oncological diagnosis. In particular, critical errors in prenatal and postnatal cytogenetics schemes concerned: a) a banding quality inadequate for a correct reconstruction of karyotypes, b) errors in chromosome pairing, c) an incorrect use of the ISCN nomenclature, d) an incorrect/absent description of the result. In the oncological cytogenetics scheme an analytical/interpretative error was identified in one case; moreover an incorrect/inaccurate use of the ISCN nomenclature and incompleteness/inaccuracy in the description/interpretation of the result were detected. Objective of this work is to show the state of the art of the EQA in conventional cytogenetics and detailed results relative to the eighth round.

PPa-02 Anakinra treatment in drug-resistant Behcet's disease: a case series

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Objective: To report treatment with the interleukin (IL)-1 receptor antagonist anakinra in patients with multiorgan Behcet's disease (BD).

Methods: Comparison of clinical manifestations, previous treatments, markers of inflammation, concomitant medications, treatment regimen modifications, relapses and adverse events before and during anakinra administration among patients with BD.

Results: Nine BD patients (mean age 34.55±16.30 years) refractory to tumour necrosis factor-blockers and standardized therapies are reported in our survey. Their mean age at disease onset was 25±13.88 years and their overall disease duration was 9.55±5.33 years. All patients were positive for the HLA-B51 allele. Within 1 or 2 weeks following the initiation of anakinra, eight out of nine patients promptly responded, and most of them were maintained on 100 mg of daily anakinra with low doses of prednisone. However, most patients experienced a relapse in one or more clinical manifestations over time (mean time to relapse: 29±21.65 weeks), and only one patient remained completely under control on anakinra monotherapy. Despite a relapse in one or more disease manifestations, treatment was continued in most patients for a mean period of 13.75±6.49 months. No serious adverse events occurred.

Conclusions: Eight out of nine refractory BD patients showed a prompt improvement after starting anakinra, supporting the concept that IL 1 plays a pathological role in this disease. Nevertheless, after several months, most patients experienced a relapse. It remains unclear whether increasing the dose of anakinra would have prevented the reoccurrence of disease activity.

PPa-03 First report of circulating microRNAs in tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

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Objectives: Tumour necrosis factor-receptor associated periodic syndrome (TRAPS) is a rare autosomal dominant auto-inflammatory disorder characterized by recurrent episodes of long-lasting fever and inflammation in different regions of the body, such as the muscle-skeletal system, skin, gastrointestinal tract, serosal membranes and eye. Our aims were to evaluate circulating microRNAs (miRNAs) levels in patients with TRAPS, in comparison to controls without inflammatory diseases, and to correlate their levels with parameters of disease activity and/or disease severity.

Methods: Expression levels of circulating miRNAs were measured by Agilent microarrays in 29 serum samples from 15 TRAPS patients carrying mutations known to be associated with high disease penetrance and from 8 controls without inflammatory diseases. Differentially expressed and clinically relevant miRNAs were detected using GeneSpring GX software.

Results: We identified a 6 miRNAs signature able to discriminate TRAPS from controls. Moreover, 4 miRNAs were differentially expressed between patients treated with the interleukin (IL)-1 receptor antagonist, anakinra, and untreated patients. Of these, miR-92a-3p and miR-150-3p expression was found to be significantly reduced in untreated patients, while their expression levels were similar to controls in samples obtained during anakinra treatment. MiR-92b levels were inversely correlated with the number of fever attacks/year during the 1st year from the index attack of TRAPS, while miR-377-5p levels were positively correlated with serum amyloid A (SAA) circulating levels.

Conclusions: Our data suggest that serum miRNA levels show a baseline pattern in TRAPS, and may serve as potential markers of response to therapeutic intervention.

PPa-04 The expanding spectrum of low-penetrance *tnfrsf1a* gene variants in adults presenting with recurrent inflammatory attacks: clinical manifestations and long-term follow-up

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Objective: To analyze the clinical manifestations and response to treatment in a cohort of adult patients with tumour necrosis factor receptor-associated periodic syndrome (TRAPS) presenting with recurrent inflammatory attacks and carrying low-penetrance *TNFRSF1A* mutations, as well as to provide data on their long-term follow-up.

Methods: We performed a retrospective chart review of 36 patients carrying low-penetrance *TNFRSF1A* mutations. Sixty genetically negative patients treated for recurrent inflammatory attacks were also analysed. Detailed demographic and clinical data were collected at the time of molecular screening and at each follow-up visit. Treatments and markers of inflammation were also assessed.

Results: Patients with low-penetrance *TNFRSF1A* variants present a low frequency of the most typical clinical manifestations of TRAPS, including abdominal pain, skin rash and myalgia. A lower occurrence of eye involvement and a higher rate of pericarditis are significantly associated with low-penetrance mutations. With regard to medications, no significant differences were found between the two groups as for usage of non-steroidal anti-inflammatory drugs, colchicine, or corticosteroids, whereas a significant difference was found for the administration of biologics, which was however required in the most difficult-to-treat patients of both groups.

Conclusions: Our study confirms that low-penetrance *TNFRSF1A* variants can be associated with an auto-inflammatory phenotype whose distinguishing features are a relatively low frequency of typical ocular, cutaneous, abdominal, and muscular TRAPS manifestations and a higher rate of pericarditis.

PPa-05 Italian external quality assessment in molecular genetic: results of VIII round

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Since 2001 the Istituto Superiore di Sanità established an External Quality Assessment (EQA) for molecular genetic testing that covers 4 pathologies: Cystic Fibrosis (CF), Beta Thalassaemia (BT), Fragile X-Syndrome (FX) and Familial Adenomatous Polyposis Coli (APC). Since 2009 the activity has been regulated by governmental document (GU.199 28/8/2009).

Eight rounds have been performed until now and the ninth (2013) is in progress.

Laboratories receive 4 DNA samples with mock clinical indications. They analyse the samples using their routine procedures. A panel of assessors reviews the raw data and the reports taking into account the correctness and completeness of genotyping, interpretation and reporting; all data are managed anonymously through a web-utility. Evaluation of the results was performed on the basis of criteria developed in according to European EQA. In the VIII round 68 laboratories participated for 1 or more schemes: 55, 22, 21, 5 laboratories for FC, BT, XF and APC scheme respectively. Results have shown that about 75% of laboratories have obtained a satisfactory result, while 25% has made critical errors in the analysis of the genotype (incorrect or inconclusive result) or in the interpretation of the result (misinterpretation or absence of interpretation). In particular, critical errors in genotyping results concerned: 1) failure to correctly genotype samples; 2) failure to detect mutations on two samples in BT scheme; 3) mutation correctly detected but not correctly reported. Critical errors in interpretation results concerned: 1) absence of a clear reference to the state of affection or healthy carrier; 2) error in calculating genetic reproductive risk.

Results also show that the majority of laboratories has made critical errors participated for the first time to the EQA. All data collected within the framework of the EQA highlighted the need and the importance to carry on this activity in order to ensure adequate quality standards for the genetic tests performed in all laboratories.

Objective of this work is to show the state of the art of the EQA in molecular genetics and detailed results relative to the eighth round.

PPa-06 The Spanish Rare Diseases Registries Research Network - SPAIN-RDR

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Background: The Spanish Rare Diseases Registries Research Network-SpainRDR is a project financed by the Institute of Health Carlos III (ISCIII) for the years 2012 to 2014. ISCIII is a full member of IRDiRC.

Objective: SpainRDR aims to build the National Rare Diseases Registry in Spain based on the input of two different strategies: patient registries addressed to patient outcome research and population-based registries addressed to epidemiologic research and social and health systems planning.

Methods: This project involves all Health Departments of the Autonomous Communities (regions) of Spain, the Spanish Ministry of Health, the Spanish Centre of Reference for People and Families affected by Rare Diseases (CREER), Spanish Medical Societies, four research networks, pharmaceutical and biotechnological organizations (ASEBIO, AELMHU and FARMAIN-DUSTRIA), the Spanish Federation of Rare Diseases (FEDER) and its foundation (FEDER TELETHON). The Institute of Rare Diseases Research (IIER) acts as coordinator and leader of this network. SpainRDR (<https://spainrdr.isciii.es/en/>) is organised in six work packages: WP1 Coordination and Management, WP2 Registering activity related methods, WP3 Data analysis and outcomes research, WP4 Quality Assessment and ethical and legal issues, WP5 Dissemination and impact, and WP6 Patient registries.

Results and Conclusions: The National Rare Disease Registry will provide an organized and efficient source of information for the members of the medical community that require this knowledge. With the unprecedented collaboration and support of the Autonomous Communities of Spain and various biomedical entities, the National Rare Disease Registry will provide an effective and absolutely necessary way to improve prevention, diagnosis, prognosis, treatment and life quality for patients who suffer from RDs. In conjunction with the IRDiRC, the Spanish National Rare Disease Registry will ensure that RD patients are able to receive the high level of care that all patients expect and deserve from the medical community today.

PPa-07 Molecular genetic markers as a base for administration of orphan drugs in acute promyelocytic leukemia

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The first molecular targeted therapy was introduced in rare haematological malignancies. The development of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) for the treatment of acute pro-myelocytic leukaemia (APL) has shifted the strategy of treatment from conventional chemotherapy to cell differentiation. ATRA and ATO are orphan drugs, both meeting the requirements for an ideal therapeutics, which eliminate early molecular pathogenic events responsible for the disease. ATRA annuls the existence of differentiation block caused by the presence of t (15; 17) chromosomal translocation and fusion of the PML and RARalpha genes. ATO degrades the PML-RARalpha fusion protein, and it causes differentiation and apoptosis of the APL cells. In this study, reverse transcription polymerase chain reaction (RT-PCR) was used for detection of PML-RARalpha fusion transcripts in order to follow-up the course of the disease and the effectiveness of the treatment in adult APL patients. The patients were followed for at least 3 years. They underwent standard treatment for APL patients, the combination of ATRA and chemotherapy, during both induction and consolidation phase of treatment. Among 22 APL patients (8M/14F, mean age 39.5 years), 18 were PML-RARalpha negative after consolidation therapy and 17 of them stayed in a long-lasting remission, while 1 patient developed molecular relapse within 3 years. 4 patients were PML-RARalpha positive after completion of the consolidation therapy. Two of them were treated by ATO. The first one is in a long-lasting remission, while the other expressed persistent molecular positivity, underwent allogenic bone marrow transplantation and is in a remission for 4 years. The results of this study showed that the absence of the PML-RARalpha fusion transcripts after completion of consolidation therapy and beyond, predicts stable long-lasting remission. Introduction of molecular diagnosis and follow-up enabled the application of different orphan drugs and personalized therapeutic approach for APL patients in Serbia.

PPa-08 Newborn screening system for congenital disorders in Italy: a nation-wide analysis

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Background: Newborn screening debuted as a public health program in Italy in 1992 for three congenital diseases: hypothyroidism (CH), phenylketonuria (PKU) and cystic fibrosis (CF). Since then, only a limited number of regions have extended their neonatal screening programs to additional congenital disorders including Galactosemia, Leucinosis, Biotinidase deficiency, Homocystinuria, Congenital Adrenal Hyperplasia and Glucose-6-phosphate Dehydrogenase deficiency. The introduction of tandem mass spectrometry (MS/MS) in clinical laboratories and a further expansion of the new-born screening panel to a number of detectable inborn errors of metabolism (expanded new-born screening – ENS), has contributed to deepen the differences in regional new-born screening program across Italy.

Objective: To assess the state of the Italian Newborn Screening Programs and to define a unique national model of policy/procedures for newborn screening programs.

Methods: Detailed questionnaires were sent to the national newborn screening centres through the 21 Regional Coordinating Centres for rare diseases.

Results: Fourteen regions fill out the questionnaire. Eight regions adopted variable facultative screening programs by means of non-MS/MS technologies. Eight regions (including 3 of those, which adopted variable facultative screening programs) performed the ENS (of whom 4/8 regulated by regional decrees and the remaining by local pilot studies). In 1/14 region newborn screening was conducted only for the three congenital diseases defined from official public health program in Italy. Detailed data analysis revealed strong regional differences in term of panel of screened disorders in ENS and of organization of laboratory diagnostic and clinical management pathways.

Conclusions: The aim of newborn screening is to detect new-borns with severe, treatable disorders in order to facilitate appropriate interventions to avoid or ameliorate adverse outcomes. The present findings highlight the need of appropriate public health policies aimed to expand and uniform nation-wide screening programs for early diagnosis and management of rare disorders so as to provide equal opportunities to new-borns regardless their region of origin.

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PPa-09 General practitioners in the rare diseases field: identity and context. a pilot study

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B **background** - General practitioners (GPs) are a point of reference for the daily management of patients affected by rare diseases (RD). The GP deals with daily health problems and, moreover, helps connecting the National Health Service and the patient, whose symptoms can be without a diagnosis.

Objectives - To analyse practitioners' knowledge, personal experiences, and needs with regard to RD in a Local Health Unit.

Methods - The sample consisted of 19 GPs working in the area of Naples (Italy), in relation with RD. Practitioners were interviewed by psychologists on their professional experiences with RD patients. A qualitative study has been done on the resulting interviews, using the TLab software (textual data have been examined by a semiautomatic procedure). A thematic analysis of images (cluster analysis) and of latent size (correspondences analysis) has been carried out.

Results - The thematic analysis of images showed four different representations of GP: (1) ideological (3/19), who consider RD as an ideological challenge; (2) operative (4/19), trying to solve problems; (3) technical (7/19), who see RD as a threat for the discipline; (4) aiding (5/19), considering RD as a social problem. The thematic analysis of latent size underlined two dimensions: (1) identity (the physician's role goes from being a mission to representing a technology in aid of the patient); and (2) the representation of the context (it does not aim to transform but to care for).

RD seems to bring out a new kind of relationship between GP and patient.

Conclusions - On the basis of these preliminary results, we are planning to extend this research all over the country, in order to obtain additional data on this topic, to be used in specific training courses for the GPs. The aim will be to raise the awareness on RDs and facilitate the doctor/patient relationship.

PPa-10 EUROPLAN: a project to support the development of national plans and strategies on rare diseases in Europe

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I **ntroduction** - National Plans (NP) or Strategies (NS) for Rare Diseases (RD) are the common denominator of current public health policy concerns on RD across European Countries. They conjugate the European objective that aims at ensuring that patients with RD have access to high-quality care - including diagnostics, treatment and rehabilitation - with the national priorities of selecting specific measures for adoption and implementation.

Objectives - EUROPLAN (www.europplanproject.eu) is co-funded by the EU Commission and is coordinated by the Italian National Centre for Rare Diseases (Istituto Superiore di Sanità). The main goal is to promote the implementation of NP/NS to tackle RD and share relevant experiences within Countries, linking national efforts, through a common strategy at European level. In order to fulfil this objective, EUROPLAN involved many Countries and many stakeholders (health authorities, clinicians, scientists and EURORDIS).

Results - EUROPLAN was launched in 2008 and envisaged two implementation phases: Phase 1 (2008-2011) to build the consensus definition of operational tools (recommendations and indicators); Phase 2 (2012-2015), contained in the EUCERD Joint Action 'Working for Rare Diseases', mainly aimed at increasing capacity building with the proactive involvement of multi-level stakeholders. EUROPLAN is facilitating and accelerating the implementation of NP/NS in almost all EU and several non EU Countries.

Conclusions - EUROPLAN is an International process more than a project, and it could be defined as a "litmus test" demonstrating how the collaboration between health authorities, clinicians, scientists and Patients' associations can accelerate the process of awareness and development of policies and actions.

PPa-11 Rare allergic pathology in professionally exposed to materials from the military industry. Case report

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Allergic reactions experienced by individuals involved in the military industry are not so rare. However, they are seldom made available to the medical community because of the classified nature of many military industries. The mechanisms that arise in the allergic disorders of patients exposed to materials in the military industry are also interesting. The chemical compositions of these substances are often unknown. It is even more interesting to note the presence of several allergic diseases in the same person working in military production.

Another problem in which there are few publications and single view in medical literature is weather allergic reactions and diseases of workers in the military industry are manifestations of sensitization potential of a particular material, or if they are caused by other mechanisms such as toxins, irritants and others. That is why we have presented a clinical case which should arouse the interest of physicians of different specialties to include allergists, dermatologists, and toxicologists, both in the fields of military medicine and working in institutions of general health care professionals.

PPa-12 Story of a life with a congenital vascular malformation: a qualitative study of high school student's tales about

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Background - Alessandra Bisceglia, a journalist suffering from birth from a rare disease, a congenital vascular malformation, that has taken away the autonomy in adolescence, but she always looked at life with joy and enthusiasm fighting and overcoming all obstacles.

Objectives – 1) To raise awareness within young people and their teachers about congenital vascular malformations. To promote a careful reflection about-facing the difficulties that a young person encounters in its life path. 2) To stimulate students to the achievement of the awareness of their own responsibilities they will become discouraged in front of the first obstacle that they meet.

Methods - Thirteen high-school classrooms (student's average age: 17) were involved in one year. In each classroom, a) the project was explained, b) the audio-visual documentary tracing the life story of Alessandra from the birth until reaching imported steps was projected, c) after the vision, the students were left free to write what the story sparked. Student's narrations were collected and codified using the NVivo software. A qualitative data analysis was conducted.

Results. 292 student's narrations were collected. Words frequently recurrent are "life" (264 times) and "strength" (158 times). Students feel weak (65%), sad (19%), superficial (13%), and alone (3%) with respect to the difficulties of life. The Alessandra's life story sent them strength and courage (53%), love of life (28%): she was considered an example also (19%). To overcome the obstacles, the most used strategy is to reflect and enhance their resources (41%).

Conclusions. The several narratives demonstrate that the project was able to raise awareness on congenital vascular malformations, through Alessandra's life story. Her story is helpful to bring out feelings and experiences, providing an inspiring example. The project will continue next year.

PPa-13 An Italian toll-free helpline for congenital vascular malformations and disability

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B **ackground.** The congenital vascular malformations (CVM) are birth defects that can cause severe forms of disability and also lead to death. The CVM represent a public health problem of great importance, because of the relevant serious implications on the medical and social level as well as on a psychological level.

Objectives. To promote the dissemination of validated and correct information in the field of congenital vascular malformations and disabilities, through a dedicated toll-free helpline. The goal of this helpline is to promote the construction of a network of people involved in vascular abnormalities and consequent disabilities in developmental age in voluntary work, specialist centres, hospitals and associations. The project aims at creating a helpline to inform on the congenital vascular malformations and disability, addressed to patients and their families, health professionals and social workers.

Methods and results. 1) The toll-free helpline was designated on the experience of the Italian National Helpline “Telefono Verde Malattie Rare” (TVMR) carried out by the Italian National Institute of Health. 2) A training program has been designed and implemented with an interactive teaching methodology, including cooperative learning techniques and role-play. It has involved 18 volunteers of the Foundation, in two Italian regions (Basilicata and Lazio).

Conclusions. The course will bring the distribution of a national toll-free helpline for users, starting before the end of this year, in collaboration with the TVMR. It will permit to advise patients, their families, health care professionals and social workers on the different paths and on the congenital vascular malformations specialists and disability rights. It will also promote the knowledge of the “Ale’s rooms” service, a free specialized medical centre carried out by the Foundation, already active in the Italian Regions Basilicata and Lazio.

PPa-14 Congenital vascular malformations: promoting the network to general practitioners (GPs) and paediatricians

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B **ackground.** Diagnostic classification problems and the lack of knowledge of rare diseases (RD) are causing a delay in diagnosis and proper treatment. Specifically, congenital vascular malformations have proven to be an issue that deserves special attention. These pathologies develop and worsen over years and can eventually lead to death.

Objectives. 1) To increase the awareness of General Practitioners (GPs) and Paediatricians on the congenital vascular malformations and generally RD; 2) to improve the diagnostic suspicion and the effective communication in the different stages of the congenital vascular malformations.

Methods. The project includes 1) Needs analysis through a self-report questionnaire on the professional experience of GPs and Paediatricians treating patients with congenital vascular malformations; 2) Training course aimed at GPs and Paediatricians, with Problem-Based-Learning method (two editions in Basilicata and Lazio - Italian regions).

Results. The project is still in progress. To date, the needs analysis showed that GPs perceive that 33% of rare disease patients and their families are greatly confused on their disease. For Paediatricians, this percentage drops to 9%. Almost 100% of GPs and Paediatricians believe in the importance and necessity of continuous professional training on rare diseases. W Ale Foundation and Italian National Institute of Health are preparing specific training on diagnostic suspect of congenital vascular malformations for GPs and Paediatricians.

Conclusions. GPs and Paediatricians deal with daily health problems and, moreover, help to connect the National Health Service and the patient, whose symptoms may not have been properly diagnosed. The aim will be to raise the awareness of RDs and specifically on the congenital vascular malformation and facilitate the doctor/patient relationship. The main purpose is to improve the quality of life of patients and their families, through the consolidation of the network between the National Health Service, GPs and Paediatricians and the spread of the model at the national level.

PPa-15 The feasibility of common data elements in the European Union

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B **background:** The EPIRARE project, funded by the European Union, aims at preparing a proposal for a European Platform for Rare Disease (RD) Registries. This platform is intended to improve the use of RD patient data promoting standardization of data collections, supporting the registration of patients and the use of data both for research and public health purposes. The EPIRARE project is informing the EU initiatives in the field of RD registries.

Methods/Research Design: Survey, with a web-based questionnaire, on the current practice of registration of more than 50 selected data elements pertaining to patient, healthcare centres, disease, treatment and outcomes. It was carried out between February and April 2013 among RD registries involving European centres. The definitions and reference tools proposed by the US GRDR were taken into consideration as far as possible, not to hinder future developments of global cooperation in RD. Therefore, the results presented refer to the collection of data according to data element definitions and formats specified in the survey questionnaire.

Results (based on the analysis of the first 141 out of about 170 total respondents): A first domain of interest referred to the collection of data elements of election for the definition of a unique identifier (Johnson et al, *J Am Med Inform Assoc* 2010;17:689). It appears that the set of full given name(s), full family name, full date of birth and sex is collected by 74 registries; further 22 registries could be adapted to collect it as specified. Out of these registries, 66 collect or could collect also the city of birth. 95 and 89 registries collect the patient city of residence and the date of death, respectively, following adaptations; these numbers become 112 and 110. The names identifying the diagnosis or treatment centres are collected, respectively, by 91 or 90 registries, and could be up to 125 or 119 registries. 92 and 76 registries collect date of diagnosis and of first appearance of symptoms; with adaptation, further 31 and 22 registries could collect this data as specified. Ninety-six registries collect genetic data regarding the disease; 18 more registries could be adapted to do it. Registries collecting data on OD treatment (name of active ingredient) are 49. Collection of data on treatments with drugs other than OD (name of active ingredient) is carried out by 60 registries. Information on other types of treatments is collected by 82 registries, of which the majority (66) refers to surgeries. Data of patient willingness to donate biological samples or to participate in clinical trials could be collected up to 92 or 99 registries, respectively. Further survey data elaborations will be presented to show how the data commonly collected by registries could support the production of information pieces of use of public health planning and the added value of a common platform for RD patient registration.

Conclusions: The results indicate that the definitions and formats, which were proposed for a selection of data elements, are already used or can be complied with by a large fraction of the responding registries; and that a EU platform for RD registries can be very useful to promote the standardization of data collections for selected data elements.

PPa-16 Newborn screening practice for rare disorders in the European Union

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Introuction: Neonatal screening has been extended in many European countries to a variety of neonatal screening programs after the introduction of tandem mass spectrometry technique. With the aim of informing national and EU policy-makers on the status of neonatal screening, this work provides the first comprehensive overview of the NBS process in Europe, spanning from the supporting legislation to confirmation diagnostics and start of treatment. For each step it addressed existing guidelines, actual practices, quality assurance and training schemes. Ethical aspects and the systematic evaluation of the screening programs have also been investigated.

Results: In spite of the wide variety of screening panels adopted in the EU Countries, there is a remarkable uniformity in the approaches used to make decisions. About half the jurisdictions surveyed reported to have laws or regulations mandating participation in newborn screening. Most jurisdictions allow for opting-out or dissent. Written policies are limited where ethical aspects are more important. The patterns of communications on neonatal screening are rather different among countries. The practice of informed consent and opting-out is not uniformly applied. The initial steps of NBS have a very similar timing across countries, whereas confirmatory investigations and treatments in some countries start rather late compared with other countries. Quality control and quality assurance schemes are applied satisfactorily at the laboratory test stage, whereas subsequent steps of the process draw lesser attention and therefore their performance relies essentially on the general quality control systems operated locally. Based on estimates of the responders, the fraction of symptomatic cases at the start of treatment is rather significant for some diseases. Training of professionals in communication with parents varies across diseases. Training for psychologists and social workers are rare. Training is most often offered for cystic fibrosis (25%), followed by metabolic (20%) and endocrine (17%) disorders. For haemo-globinopathies, training is offered only for the clinical nurse specialist and the geneticist. But for the feedback of confirmed diagnoses to the screening laboratory, other activities of use to assess the effectiveness of NBS programs are loosely regulated. It is remarkable that epidemiological evaluations and the monitoring of long term outcomes of many screened diseases are carried out as spontaneous initiatives.

Conclusions: This work highlighted that: 1) Proximal steps of the programs (information of parents and laboratory procedures) are better regulated than distal steps (epidemiological evaluation by registries and evaluation of the outcome of treatment); 2) Training of professional groups involved in NBS programs is poorly developed and offers opportunity for substantial improvement especially regarding the communication with parents; 3) The systematic assessment of the procedural and clinical aspects as well as the cost-effectiveness of neonatal screening programs would benefit from the development of systems coordinating the collection and exchange of data (e.g. registries).

PPa-17 Clinical and social adaptation in osteogenesis imperfecta: the role of interdisciplinary team

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Background: There are at least 10000 patients with Osteogenesis Imperfecta (OI) in Russia. However, very few of them receive adequate medical help and their mobility level does not correspond to the severity of the disease.

Objectives: To evaluate reasons of ambulation problems in OI patients, develop the comprehensive approach for management of OI in children by organizing interdisciplinary team (Center of Inborn Pathology) and to evaluate the efficacy of multidirectional therapy.

Patients and Methods: 224 patients with OI were referred to Center of Inborn Pathology in 2006-2013. The study group consisted of 110 children. During the first course of treatment multidisciplinary team assessed all patients. Pamidronate was administered according to established International treatment protocol. During the first admission and later every 6 months densitometry (DXA) was performed. Every hospitalization assessment of family interactions, level of activity, pain intensity, and fracture rate were performed.

Results: In 84 of 110 hospitalized patients the grade of ambulance difficulties did not correspond to severity of the disease. Only 12 patients (all with type I) could walk with support on first admission. In 52 patients the tactics of excessive immobilization prior to admission have caused additional hypokinetic osteoporosis, problems in sensory integration and social adaptation. After the 3rd course of treatment average increase of bone mineral density (BMD) by densitometry data was 42%. Ambulation level of all children with OI improves during combination therapy.

Conclusion: The grade of disability of OI patients depends not only on severity of the disease but additional factors - immobilization level, psychological interactions and access to comprehensive treatment. Significant increases in social activity, mobility, DXA parameters, reduce of pain syndrome were observed in children with OI after 2 years of treatment. Multidisciplinary approach leads to increase of life quality and mobility in OI children.

PPa -18 Rare NLRP12 variants associated with the NLRP12-autoinflammatory disorder phenotype: an italian case series

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Objectives: The NLRP12-autoinflammatory disorder (NLRP12-AD) is caused by monarch-1 dysfunction leading to de-regulated inflammatory responses with recurring fevers, skin rashes, joint and muscle pains, triggered by exposure to cold. Conflicting data on the putative role of interleukin-1 signalling in patients with NLRP12-AD have been reported. Methods: We describe the features of 6 Italian patients with histories of fever, arthralgia, myalgia and fatigue, which were negative for mutations of MEFV, TNFRSF1A and NLRP3, who were analysed for the NLRP12 genotype, resulting positive for the F402L and G448A mutations.

Results: Two out of these 6 patients underwent anakinra administration, but a sustained clinical remission was observed only in one case.

Conclusions: We suggest that F402L and G448A variants represent low-penetrance mutations and hypothesize that the cytokine secretion pattern in patients with NLRP12-AD might be variable with a potential influence of additional and still unknown genetic or environmental modifiers.

PPi-01 The italian national centre for rare diseases' experience of a telephone helpline

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Background - A nation-wide Telephone Helpline (TH) for rare diseases works at the National Centre for Rare Diseases in Rome since February 2008. It is a public service reached on 800 896949. The line is free and anonymous working 5 days per week from 9 am to 1 pm. A team of psychologists and medical doctors trained and experienced on telephone counselling, public health policies and clinical management of rare diseases are involved. Main aim of the service is to inform, orient and support individuals with rare diseases, their families, health care professionals and citizen responding to their needs and issue of concern.

Objectives - To evaluate the role and activities of a nation-wide TH for people dealing with the complex needs of rare diseases.

Methods - Observational and descriptive quantitative study on the activity of TH over a period of five years.

Results - We electronically recorded a total of 16277 queries. Main purposes of contact included exemptions from health care expenses; network of specialised medical centres; information on rare diseases; legal procedures on health care; lay groups; how to reach other patients, search for specific items in the scientific literature and/or in other reference sources for rare diseases, national and international clinical trials and orphan drugs. Psychological counselling regarded a limited number of enquires. Among the most common queries were those about undiagnosed conditions and childhood diseases.

Conclusions - Health care is changing in terms of service provision and delivery, with an increased focus on person-centred care, prevention and community-based services.

The expanding number of helplines on rare diseases across Europe meets the increasing demand from people with special and different needs in this field.

Our findings evidence that the service is of benefit and support for patients, their families, caregivers and health professionals seeking advice and information about rare diseases. A multidisciplinary group with specialized knowledge and skills is fundamental to offer best use of this service and to increase customization of service.

PPi-02 Health policy of rare diseases in Serbia

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A ccording to the National Organization for Rare Diseases, Serbia (NORDS), there are half a million people in Serbia suffering from rare diseases (RDs). However, the National Plan for RDs still does not exist in Serbia, nor does the RDs Registries. Health policy creators do not recognize RDs as a public health problem. Health resources are limited and directed towards the most common diseases. Modern diagnostics for some RDs is available, but most of the patients are sent abroad for confirmation of the diagnosis. Aimed at improving the quality of life of persons with RDs, seven existing organizations joined in 2010 and formed the NORDS - the umbrella organization that gathers patients' associations and individuals with various RDs. NORDS has developed good cooperation with authorities, medical professionals and the media and RDs have been introduced into the legislation for the first time in Serbia in 2011 (the Laws on Health Care and Health Insurance (HI) and The Lottery Law). This initiated the creation of the fund within the Ministry of Health of the Republic of Serbia (MH) to cover RDs. The best treatment is provided for patients suffering from rare cancers. But, in 2013, the Republic Expert Commission for RDs within the MH (consisting of medical experts, with the task to set priorities in treating various RDs) approved treatment for only 8 children with RDs (besides cancer patients). Moreover, most RD patients are not recognized in the system of HI. As for the orphan drugs, among 1969 registered drugs with proprietary name from 2012-drug list of the HI Fund; only 28 drugs specific for RDs were listed. Under the auspices of EURORDIS and the MH, this December NORDS (www.norbs.rs) is organizing the First National Conference on RDs. This event will initiate joint action towards improvement of health policy for RDs in Serbia.

PPi-03 Medical insurance, government assistance, charity aid, corporate sponsorship – a co-payment for rare diseases insurance system

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N ot having an independent law dedicated to rare diseases (RD) insurance, with huge medical expenses for RD patients, and a limited medical insurance fund, all these facts makes very difficult to set up a medical insurance policy to cover every RD patient in China, and especially for those RD patients challenged by high medical costs. Comparing with the common disease patients, more resources will be needed to introduce an appropriate medical insurance system in order to support RD patients. We hereby show the experience of an initiative working in Shandong. The main idea of RD medical Insurance system is as follows: The initiative should be led by the government, including co-operation and co-payment, equitable and accessible; being the reimbursement of RD medicine cost composed of a supplier discount, plus 70-90% coverage by medical insurance funding, given by the charities organizations under corporate sponsorship. This model has been applied in Qindao since 2011, such as the 2011 Haemophilia Patient Aid system, and since 2012 for the pulmonary hypertension program (covering Tracleer®) and MS Betaseron®), and for patients with acromegaly (covering Somatuline®). The patients involved in these programs are receiving good treatments without financial burden for them. Now we are working with new RD diseases programs extending this type of co-payment medical insurance system.

PPi-04 Global collaboration with/among rare disease patient associations –theory and practice

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There are several types of patient groups (PGs) and patient advocacy groups in the world and these are clustered together to form associations at the regional/national level. Collaboration between/among patient organizations are rapidly gaining significance in all related people in the world. People living with rare diseases are facing many challenges in common that could be better addressed on an international basis. In this study, we provide an overview of growing collaboration among rare disease national alliances. We also discussed the importance of global collaboration with/among rare disease patient associations and advanced a theory. Based on this theory, we introduced several challenges in the world and also practiced ours with future subjects.

We found there are some differences between connection with/among patient groups and collaboration with/among national associations. Regarding the case of individual PGs, they focus on specific diseases and their interaction is for the purpose of addressing issues for disease-specific patient communities. These activities help them discuss individual/specific disease with a deep understanding. On the other hand, in the case of associations (national level), the association has a role to perform to raise the entire society. Associations can make an appeal of agendas related to whole target area to the society, and also aggregate the challenges that are scattered throughout the world. It means the association discusses not only for individual issues but also for all diseases in the target area. Since individual PGs are clustered together to form associations, there are various discussion topics; policy making/recommendation, QOL improvement, promote/support research (for the target area), easier/global access to care, connect with/among other patient associations, and integrate/provide valuable information from local/global, and so on. Counter persons/organizations are also slightly different and the targets are governments, associations, companies, and researchers related to whole RD area within the region.

Recently, many associations have come to understand the importance of the collaboration and there are several cases in the world; e.g. NORD-EURORDIS (strategic partnership, 2009), JPA-NORD (MoU, 2013), EURORDIS-JPA (MoU, 2013). Based on these agreements, EURORDIS-NORD-CORD release a Joint Declaration of 10 Key Principles for Rare Disease Patient Registries in 2012. Rare Disease Day is one example of the ways in which these associations are working together now.

The goal of our challenge is divided into 3 categories on the basis of the term. As the goal of short-term, the national associations seek to connect their disease-specific PG members. As that of mid-term, those collaborations will help advance research and better understanding of rare diseases globally. The long-term goal is for, rare diseases to be addressed as a global public health issue with international collaboration to address challenges that are the same from country to country. All associations need to cooperate to realize a common goal and work toward the achievement of the targets respectively.

PPi-05 National survey of NANBYO patient groups in Japan

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In this study, we conducted the nation's first large-scale survey of the current situation and awareness of collaboration between NANBYO patient groups (PGs) and study groups funded by Ministry of Health (MHLW) in Japan. The purpose of this study is effecting recommendation and reform of the active collaboration and accelerating communication between the PGs and the study groups for promoting research. Based on this survey, we also discussed how PGs accelerate efforts in the field of research collaboration and promotion from the association's perspective.

Method: we conducted 3 types of survey; 1) Survey of individual PGs, 2) Secondary survey of PGs, and 3) Survey of study groups funded by MHLW. Survey 1 (N=162, recovery rate is 58.6%) is included with several basic questionnaires (the mission, kinds of activity, financial situation, personnel organization, etc.). We also asked whether PGs had experiences of the relationship with study groups on Survey 1, and then conducted the Survey 2 (N=70, RR is 51.4%) to PGs that answered the former question as "yes". We had questionnaires about research collaboration (when, with/among whom, kinds of collaboration, satisfaction, note of caution, etc.) on Survey 2. The contents of Survey 3 are included with the same questionnaires of Survey 2 from researchers' perspective and the RR of Survey 3 (N=162) is 58.6%. All surveys corrected data by mail and website (each PG could choose the method of response) in 2012 and time of response was 1 month, 3 weeks, and 1 month, respectively. We did several additional researches on Survey 2 and 3 as a follow-up survey and personal interviews in 2013. The details are given in our poster.

Result and Discussion: From the results, both the groups were building expectation of collaboration in the field of research promotion and the relationship between them will be continued growth. Both answers of the necessary matters of research collaboration are almost the same (the report after conducting researches, the explanation before starting researches, the communication between researchers and patients or PGs, the explanation of research incentive and disadvantage, and financial supports). Regarding the satisfaction of collaboration, patients are satisfied with research groups. However, researchers are not relatively satisfied. We discussed the reason people at PGs feel happy only to join the research and some of them don't understand the research in detail. On the other hand, researchers think it is not easy to explain their researches because of the high degree of professionalism and worry about their communication way. We also think that the meaning of "collaboration" has different meaning for both groups and need to formulate the guideline especially to PGs people for understanding "collaboration" more in detail. As to the question about the importance of the conflict of interest and accountability, many respondents answered as "not carry out their responsibility" or "not need to do". We think it seems like people don't understand the significance of both words. On the basis of these results, we decide to prepare to formula the guideline regarding research collaboration with PGs and research groups from PGs perspective with actual international cases.

*NANBYO is Japanese and the meaning is "rare and intractable diseases". *This research is funded by MHLW.

PPi-06 Dermacamp as a tool for patient empowerment and improving education

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Objectives - Face the prejudice against children with severe and or rare skin problems. Give children the conditions for their social insertion. Make the children real citizens. In DERMACAMP project, children from 08 to 12 years of age, suffering from chronic and severe skin problems, have the opportunity to participate in a series of actions that seek to help them recover and raise their self-esteem. For some days, they live together with other children also suffering from skin diseases.

Methods - We use, as special strategies, social and recreational activities in an environment of joy, understanding, respect, cooperation, where children can simply be children, doing activities that they usually are out, such as: camping, swimming, rowing, fishing, playing soccer and volleyball, dancing, playing theatre, sculpture, arts and crafts, spending some days out home, without their parents, in the company of other children with skin problems. Children go to a Camp, with a trained staff consisting of companions, monitors, nurses, doctors, activities specialists, for some days. They go alone, without parents. All the staff persons are voluntary and children do not pay for participating. They go for free. DERMACAMP is a large project that uses as strategy, group activities, between children and volunteer monitors, and also between parents and caregivers and volunteers teams. Among these strategies, CAMP activity is the most visible but not the only nor the most important activity. Although it is for the kids, the most desired one. During Camp, every activity is planned to have a special objective. Every Camp has a special theme. Could be - The Environment, Living with the differences, The Image, The Nature, The Music, Saving Energy, The Food, and so on. Since 2001, we had a Camp every year, for children between 08 and 12 y.o. More than 250 children have participated. Some diagnosis; EB, Ichthyosis, EHK, XP, Haemangiomas, Ehlers-Danlos, PPK, Olmsted, Neurofibromatosis, Vitiligo, Cutis Laxa, Atopic Dermatitis.

Results - Better socialization of children in school and family- Increased interest in treatment and care, - Better understanding of their illness and the desire to organize themselves to seek support and access to treatment- Greater adherence to treatment and / or medical service which is linked - Feel more vain, more careful with their appearance-Greater security to cope with everyday situations, specially situations of prejudice and discrimination- Sense of belonging and group membership that welcomes and respects them as they are- Reduced use of medications or dosage such as: antidepressants, anti-allergies- Broader perspectives and formulation of personal life projects: a greater interest in daily activities, the school and have a better future, a profession- Increased security for exposing himself in a group, to wear modern clothes that expose more areas affected by injuries- Exchange experiences between parents and children about skin care and the rights to access resources for their treatment- Increasing parental involvement, improving family and group relationships.

Conclusions. We believe that the medical treatment alone is not enough for children with severe skin diseases. More than medications, children need understanding, teaching, knowing how to cope the disease, fun, joy, love. It costs very few money.

PPi-07 The role of patient groups in the rare diseases field as transmitters and coordinators of state-of-the-art information and education for medical professionals: the example of the osteogenesis imperfecta community

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Objective: We aim to demonstrate that the active interaction between patient groups for rare diseases and medical professionals can be decisive for a successful therapeutical approach. While patient groups (associations, foundations) have been traditionally considered within the medical community as well meant, self-help initiatives, useful only for practical non-medical related activities such as personal support and recaudatory purposes, our 15-year experience in the field of Osteogenesis Imperfecta (OI) patient organisations proves that well managed patient groups and initiatives in the rare diseases sector are an excellent instrument for both concentration and transmission of high quality medical information on an international level, and also, through the organisation of well managed public-private initiatives, even for building major treatment and medical infrastructures for patients that live in countries lacking a solid public health management system.

Methods and results: We will present examples of first-rate infrastructures for the treatment of patients with Osteogenesis Imperfecta that have been created from the germ of very small patient groups. Such groups have grown to support an international well-coordinated network of educated and well prepared medical care professionals who are now able to apply their so acquired knowledge and skills in the care of patients suffering from the condition. In little less than ten years, the OI Network has helped to educate medical professionals from three different fields of expertise (Orthopaedics, Metabolism and Physical Therapy) and is actually providing with medical state-of-the-art treatments for OI-patients in Europe, Asia, Africa and Central and South America.

The Osteogenesis Imperfecta Network interacts with expert medical professionals and manages to transfer modern knowledge on this rare condition to isolated doctors and health professionals treating patients in remote areas of the Globe. Patient groups are also built and coordinated within the OI Community, and organizational and financial help is also in some cases provided for in order to facilitate an optimal medical care of the OI-patients. Methods and examples of our work will be presented.

Conclusions: The actual example of the Osteogenesis Imperfecta Network shows that, if well organized, patient organisations in the rare diseases field can be the most useful tool both for medical professionals and patients to 1. Increase the quality of state-of-the-art knowledge of health care professionals' community, 2. Educate society on special needs of rare diseases patients, and 3. Dramatically improve the quality of life of people living with rare diseases.

PPi-08 Access to orphan medicines: a systems failure, or: what about me? It isn't fair

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Access to medicines in NZ is managed through Pharmac, the pharmaceutical management agency, controlling access through a schedule of subsidised medicines, and an exceptional circumstances (EC) scheme for those not listed. Till recently, funding for specialised medicines for rare "orphan" diseases has generally been sought through the exceptional circumstances scheme, but with very limited success. Concern about restricted access led to a review of the EC scheme in 2011 but the new scheme (NPPA) made rarity largely an exclusion criteria rather than an entry consideration. The decision criteria under NPPA remain the same for all medicines, rare or common, resulting in an inherent disadvantage for orphan diseases where small populations mean poorer disease knowledge, poorer quality evidence, and often-modest benefit from novel "first-in-class" therapies. Patient advocacy groups have identified the need for fairness, equity and community values to be included in medicine decision criteria, to balance health economics and budget management factors. Pharmac is the only part of our health system where such moral considerations are excluded from decision criteria. Patient groups consider this a breach of their right to health and an unacceptable form of discrimination. This view is supported by academic analysis and legal advice and complaints have been made to the Ombudsman to seek redress. The solution sought is to remove responsibility for specialised orphan medicines from Pharmac's responsibility to the Ministry of Health under a scheme similar to that for high cost treatments or surgeries often performed overseas.

PPi-09 New Zealand's "Old Macdonald" has unique treasures down on the farm

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The New Zealand Institute for Rare Disease Research Ltd (NZIRDR) is a charitable company wholly owned by the New Zealand Organization for Rare Disorders (NZORD). NZORD's mission is to improve information for patients, their family and professionals, to build partnerships to improve diagnosis and clinical care, and to accelerate research towards control and cure of rare disorders. NZIRDR performs the role of promoting and supporting the research initiatives. One such initiative is a catalogue of naturally occurring rare disease animal models, which has been established to improve interest in rare disease research and provide opportunities for such research to occur. Currently there are 29 rare disease animal models listed in NZIRDR's catalogue. In New Zealand, there has been significant work on many of these models, leading to clinical findings that assist diagnosis and therapies for humans. Large animal models are especially good for studies involving the brain and central nervous system. NZIRDR has plans for the discovery of more rare disease models through an active search amongst the NZ farm animal population, much of which is becoming well characterised genetically and is thus a good source for further research. NZ has one of highest companion animal ownership rates in the world and this will be investigated also. We are interested in collaborations that might assist the rapid discovery of more large animal models for rare diseases.

PPi-10 Development of the new zealand rare disease biobank

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The New Zealand Rare Disease Biobank was initiated after discussion of the concept at the NZ Organization for Rare Disorders conference in 2004. The biobank initially developed a virtual collection of naturally occurring animal models of rare disease, then applied for ethical approval to collect human samples, receiving this in 2010. A sample management database was developed, and facilities and consumables acquired. It can collect samples, as well as providing an option for samples that would be prone to being 'lost' i.e. at retirement of a researcher. It has obtained a few samples, but has operated at a very low capacity, due to limited resources to actively promote or facilitate major collection. NZIRDR Ltd, the charitable research arm of NZORD, is working in partnership with the University of Otago Pathology Department to develop the biobank, to encourage, promote and facilitate rare disease research. It aims to approach donation at support group level, ideally with the assistance of a clinical or research affiliate, to assist coordination of donation and increase numbers of donations of similar disease types. Subject to resource limitations and collaboration opportunities, NZIRDR is preparing to increase collection and thus opportunities for rare disease research. Developing the biobank was quite a learning process, and challenges continue. These include resource constraints, practical aspects of consent processes across various ages, and managing consent where different people and locations are involved. Opportunities exist for clinicians and researchers interested in biobanking and research to work with us to develop this resource.

PPi-11 Preimplantation genetic diagnosis – seven year's experience in New Zealand

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Guidelines, which authorised the use of Pre-implantation Genetic Diagnosis (PGD) in New Zealand, were issued in May 2005 and six months later the Minister of Health announced public funding to ensure equitable access to this procedure, by those at risk of inherited genetic diseases in future pregnancies. The first procedures commenced around the middle of 2006 once clinics had set up their equipment and procedures and organised the required testing facilities. This poster provides figures on the number of procedures, the range of conditions, which triggered the procedure, and outcomes in pregnancies achieved, over the past seven years. Discussion includes aspects of administration of PGD funding through District Health Boards, regional access issues, and the monitoring of outcomes by ACART – the Advisory Committee on Assisted Reproductive Technologies.

WG-01 Working group A: harmonizing international regulatory components

Coté T.R., Hill M., Bemus P., Andrusov A., Andrusov E., Heathfield A., Pavlovic S., Cure P.

Summary of the Working Group Goal - Discuss Building and International Network; Rare Disease Patient Care and Summary Regulatory Action.

* Regulatory harmonization; the easiest or most achievable goal is the establishment of universal criteria for orphan designation.

* International harmonization in other related areas (such as patient registries, data collection standardization, healthcare system and infrastructure development plans, etc.) would benefit developing countries while understanding the regulatory dynamics of each region and reduce the duplication of effort.

* Successful examples from which these infrastructures could be modelled include Children's Oncology Group, the European reference networks (groups of leading hospitals and organizations), and the European clinical trials directive (collective IRB approval)

* The mechanism by which these systems could be implemented includes driving organizations such as ICORD, WHO, Pan American Health Organization

Guidelines are needed for:

* Data standardization/patient registries (what needs to be collected about the disease, outcomes, etc.)

* Healthcare system development plan (Patient access to care and treatment. Do not reinvent the wheel! Quality of life data)

The group was diverse: UK, Russia, Serbia, US, Latin America: and patient advocacy, industry, physicians, regulatory

Questions discussed: How can we use the force and energy of an entire nation (for example Serbia) that has the Ministry of Health behind it to initiate change for orphan drugs? How can regulators in different countries recognize their mutual ambition and intention? **Answers from Tim Coté:**

* Mutual recognition for orphan designation between US, EU, Japan, and others.

* This is perhaps the lowest level of regulatory action that can be achieved (the simple process of recognition)

* The issue is within the different authorities

* This change would require a grassroots movement (as opposed to from within the government)

* Would require act of US government, EU

* This is a global effort, science, and patient groups are global but the regulatory actions are secular and considerations are taken within a vacuum

Clinical Trials,

* There is a perception that US trials are favoured (or even required) over international trials

* Recent guidance that was published in 2012 regarding the acceptability of overseas clinical trials was not done under IND (Investigational New Drug).

- The specific components adhere to the ICH (International Conference on Harmonization) guidelines.

- A large focus on the IRB (ethics committee) process, clinical sites need to be available to be inspected

- "The FDA doesn't care where things are done, but they do care how things are done"

- This draft guidance moved away from the declaration of Helsinki (which was initially done after Nazi war experiments) because of the disagreement of the ethics of doing placebo-controlled trials (More accepted in the US than the EU. EU has diverged much farther from the placebo controlled trials by using different comparator, may be pricing and reimbursement).

Harmonization of Patient Data (registries): How do countries share patient registry data? Could they ever be good enough to use as a comparator?

* Lots of the data are not consistent

* Issue in Russia – cannot link quality of life data to patients in other countries because comparisons have to be so similar (criteria, type of data collected, etc.) – statistically it is not valid and cannot be presented to the government

* If there were guidelines created by an expert body that countries could collectively follow then there could be an exchange of data between countries

* There are no specific guidelines, and this kind of harmonization would help a lot of smaller countries developing systems, not only build their capabilities but also leverage those guidelines to government institutions

* Developing countries (Russia and Serbia feel as though they are reinventing the wheel)

* Is it possible to have one systematic approach?

* **Guidelines for:** Etiologies, general data, healthcare system development plan (Access to care, collection of patient data), treatment and diagnosis (In Russia, i.e. the guidelines are not accepted in Russia so rights of patients cannot be protected in the case of, say, misdiagnosis. An international board or experts who agreed upon and supported these could be leveraged in these developing countries to adopt/approve. Countries are more likely to adapt to a collective effort as opposed to those proposed by just one country - conversely, an international panel with representatives from each part of the world would be more likely to be adopted-) Barriers: each country has its own health system, regulatory policies, and political environment

* The French have the best national plan (especially in terms of rare disease patients)

* Has EURORDIS attempted this?

Starting Point:

* Universally define what an orphan/rare disease is (with the ultimate goal of defining those diseases for which treatments would not be developed without an incentive)

Example of Good Practice:

In paediatrics (Children's Oncology Group) there has been some movement (part of haematology and oncology group) – they have created a system in which you only submit one IRB on contract template, and that information is interchangeable. There is something to be learned by this, maybe possible to learn best practices? Could be an excellent model but success in harmonizing IRB groups is no small feat.

Are there any examples of successful efforts to date? There is hope provided by the fact that rare diseases are specific and it would be easier to reach harmonization. In some cases countries are ready and willing to make it easier but companies do not have a good model to propose.

Barriers: Some countries (Russia) are resistant to outside expertise and tend towards corruption.

Who does this? What is the mechanism?

ICH? People have looked to the WHO – how do we engage them as an influence/perhaps publish something?

Is there a comparable group to the panel that implemented this at Children's Oncology Group?

European reference networks (groups of leading hospitals and organizations) are new.

In the European Clinical Trials Directive there was a discussion on collective IRB approval.

Who is the authority to lead the effort? Does ICORD have the power?

WG-02 Working group B: research collaborations in rare diseases; epidemiology, basic research and clinical trials

Roldán E., Stojiljkovic M.,

on behalf of the Research Working Group.

Needed that were discussed, in summary:

- * International collaboration for success in research on rare diseases.
- * Written guidelines for clinical studies with small sample size
- * More epidemiological studies of rare diseases, registries conducted under clear protocols can provide data.
- * Improved diagnostic facilities
- * Education of physicians and researchers interested in rare disorders.

The critical factor for successful research in rare diseases is collaboration. Collaborations are needed to join knowledge and experience, and to synchronize and complement efforts at an international level. Epidemiological and bio-statistical studies of rare diseases, along with comprehensive national registries are the ground point for the establishment of any national strategy for rare diseases. Basic research is needed to understand pathophysiology, molecular and clinical characteristics of a particular rare disease, to identify and validate important biomarkers, to enable new diagnostic procedures and most importantly to identify new therapeutic options. Clinical trials are irreplaceable in the process of translating basic research findings into an orphan drug for the treatment of patients.

Among the ideas discussed during the session was a proposal for guidelines for conducting clinical studies with small sample-sizes that would allow for further prospective meta-analysis to increase the validity of data. International collaboration in rare diseases needs to be organized, including studies (such as long-term phase IV trials), which are often not for registration of therapies, but essential for the daily work of practitioners. Epidemiological studies of rare diseases are desperately needed because very few data is available; notwithstanding, they are difficult and expensive. As an option, registries can help for estimation or to back plans, provided they are conducted under clear protocols. Guidelines for patients' consent in order to exchange data from multiple centers, across national borders were also discussed. Also important is the relevance of improving diagnostic facilities, and education of physicians and researchers interested in rare disorders were two other capital issues to be managed through suitable cooperation. Finally, can ICORD become a bridging tool for worldwide researches? Yes, guidelines, meetings, publications, interactions with other institutions, can be duly promoted by the organization, specially having the opportunity of introducing the ideas within the regions less developed in the field. Big organizations, as well as small initiatives can be supported from ICORD and linked to other driving means.

WG-03 Working group C: relationship between/among patient group(s)

Nishimiura Y., Stefanov R.,

on behalf of the Patient Organizations Working Group.

Working Group C was adopted to talk as a free discussion style. All participants are non-English native, so the direct communication was valuable. At first, we introduced ourselves each other and also our activities and historical background. Since our conversation style was very frankly, all participants joined the discussion. There are several types of patient groups (PGs) and patient advocacy groups in the world and these are clustered together to form associations at the regional/national level. Collaboration between/among patient organizations are rapidly gaining significance in all related people in the world. We also discussed the importance of global collaboration with/among rare disease patient associations and advanced a theory. After the discussion, we decided to exchange our situations at associations' level between countries until the next ICORD. We didn't adopt to use phone conference, but Skype video meeting. We would like to know what the topics for collaboration are suitable for such kind of communication style. We will report the result at the next ICORD. Finally, we discussed the value of ICORD in this topic. Face to face communication is the most important, especially for non-English native speakers with different background. We think ICORD is the best chance for us as a regular opportunity. We would like to continue to discuss this theme after the next ICORD.

SS-01 The need for collaboration in clinical research in rare diseases

Henter J-I.

Childhood Cancer Research Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm Sweden.

Introduction: We all here share a common aim, to improve diagnostics and treatments for individuals with rare diseases. However, development of novel treatments has become increasingly expensive. We all share this problem; doctors, clinical researchers, basic researchers, industry (Big Pharma and smaller Biotech companies), patients and patient advocacy groups, governments, and, as a result, the society as a whole. The gap between promising ideas, often developed in academic settings, and the final products, often developed by industry, has become too wide.

Method: It is likely that we can be more successful if all stakeholders collaborate, preferably globally. ICORD can serve as such a collaborative forum, since ICORD is a global and transparent global organization, with all stakeholders included, working with both rare diseases and orphan drugs.

Result: ICORD is already an available and transparent global platform for solving common issues, and we welcome all stakeholders to take advantage of these opportunities. As a result, ICORD may develop further as platform for international linkage, collaboration, and debate of ideas for academia, patients groups, governmental institutions, and industry. I have a vision that ICORD Annual Meetings develop further into a large Rare Disease Forum, where many Rare Diseases have their Annual Meetings. Part of the program could be common for all these Societies, with anything from excellent statistical experts to discussions on how to support clinical studies in Rare Diseases, maybe with FDA/COMP. Moreover, Industry would get many meetings in one, Regulators get close to researchers and industry, and Patient Organizations can meet and learn from each other.

Conclusions: ICORD is already a global meeting point for issues on Rare Diseases and Orphan Drugs. Together we, all stakeholders, can develop this forum further, into a larger collaborative international platform, beneficial for all stakeholders in order to stimulate collaboration further.

SS-02 There is a tendency to treat patient interests in token ways. So what needs to change?

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Orphan drugs access is not a straightforward thing once regulators have approved them for marketing. Access can be problematic in many countries, even in some of the wealthier countries, because of various health system policies and political issues in different jurisdictions. There is often considerable frustration on the part of patients and their advocacy groups, as they are usually excluded from any meaningful part in the dialogue between drug supplier and health system purchaser. Co-opting of patients and patient groups is a criticism often levelled at industry at such times. Sometimes this criticism may seem warranted because the engagement with patient interests seems to occur primarily when the drug is available on the market and before reimbursement is approved. Counter-criticism of co-opting by payers is less frequent but is a real phenomenon too.

The pattern in most countries, with limited exceptions, is one of patients and their advocacy groups being largely kept in the dark about important aspects of drug development and access. This problem includes being largely excluded from effective engagement with regulators about clinical trials and efficacy evaluation, and from payers' consideration of reimbursement decisions.

It is time for all stakeholders to model different behaviours in the relationships with patients and their advocacy groups. Industry has a significant role to play in that too.

Real engagement should be closer, longer term, and more transparent dealings with patient groups by all stakeholders, and they must be more respectful.

SS-03 U.S. orphan drug development 30 years

Yuwen H.

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This year marks the 30th anniversary of the U.S. Orphan Drug Act, a landmark legislation designed to incentivize the development of drugs to treat rare diseases. Tremendous success is seen in the U.S. for the last 30 years that include, as of August 2013, 2,870 orphan drug designations granted and 444 drugs approved for orphan indications thanks to a growing orphan drug industry with creative business model in pharmaceutical R&D and commercialization. Most importantly, tens of thousands of patients with rare diseases benefited, and their lives saved or changed forever. However, there are on average about 10 new orphan drug approvals per year for the last 30 years. At the current pace, we would need another 650 years to develop treatments for all known 6,800 rare diseases, let alone new rare diseases are being identified every week. As a community, we should realize the challenges and identify ways to expedite orphan drug development by reviewing key factors such as existing orphan drug policies and incentives, current regulatory review/approval processes, international harmonization in regulatory review and recognition, community resources, and improving communications and collaborations among stakeholders.

SS-04 New genomic technologies applied to personalized medicine: the challenge of XXI century

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Stratifed Medicine, Personalized Clinical Trials and Pharmacogenomics hold huge potential in the development and commercial innovation of new treatments and orphan drugs. FDA is strongly addressing the identification of new biomarkers related to patient genotype and their response to treatments, for instance patient exome sequencing is beginning to be analysed in clinical trials with this purpose. This point is emerging as the crucial concept in clinical science to improve efficacy, safety and cost effectiveness of new treatments. Within this frame, Sistemas Genómicos (SSGG) has consolidated its experience in genomic research and genetic diagnostic, specifically in rare diseases. During the last five years SSGG has translated all its experience in research into clinical diagnostic and treatment by using Next Generation Sequencing (NGS) approaches: RNA and Exome Sequencing, Bioinformatics and Systems Biology analysis. The company has been a worldwide pioneer in the application of NGS to clinical genetic diagnostic.

Objectives: By using these tools the company aim is to integrate this cutting-edge technology into all the steps of new drugs development and evaluation such as therapeutic targets identification, patient stratification in clinical trials, efficacy and safety validation, pharmaco-genetic biomarkers identification and pharmaco-surveillance.

Methods: SSGG is equipped with the most advanced high throughput technology for genetic testing: NGS sequencers in house, genotyping platforms or CGH arrays and also has developed a proprietary web Bioinformatics platform (Genesys) in cloud which allows the analysis and exploitation of massive genomic data.

Results: Our Company is involved in most of the processes of discovery, development and validation of new drugs:

- Leadership in transcriptomics, bioinformatics integration in an FP7 project focused on an innovative change of paradigm in drug discovery using venomous organisms to discover potential leads at preclinical phase. <http://www.venomics.eu/>
- Involvement in targeted projects in pharmacologic research field for the identification of new miRNA biomarkers for prognostic or treatment response for breast cancer <https://www.proyectolife.com/user/login?destination>
- Launch of services for personalized diagnostic and treatment in oncologic patients: Tumouromics for somatic variants or CNVs identification for the clinical selection of the best drug.

Conclusions: The application of NGS to the development of new drugs has potential advantages: a) Benefits for pharma industries: Saving money and time in the stages to achieve new more effective drugs, b) Benefits for society and rare diseases patients: Reducing the process to have personalized treatments at their disposal and increase of new orphan drugs. It's becoming a real business for innovative pharmas: developing the "biomarker and drug" pack.

SS-05 The legislative basis for state regulations in the Russian Federation in the field of rare disease. A workshop report

Karimova S.

National Association of Patients with Rare Diseases "Genetica" www.nacgenetic.ru

The First Deputy Chairman of the Federation Council of the Russian Federation A.P.Torshin has welcomed the participants of ICORD 2013 on behalf of the Federal Assembly of the Russian Federation. In his speech he has admitted this is an authoritative discussion platform, which held a substantive, thoughtful discussion on key issues in the field of medical affairs rare diseases and orphan drugs. A.P.Torshin also emphasized that debatable discussion of the topical and sensitive issues will contribute for developing common solutions, and expressed confidence, that this meeting will give a new impulse for developing national health care and will help to solve actual points in the theory and practice of medical treatment of rare diseases. He has full comprehension about real existence of this problem in Russia where are 83 subjects of the federation. He told to the participants of the conference about work of the Senator from Penza region, founder of Bioteck B.I.Shpigel. And also gave words of encouragement from the Minister of Health V.I.Skvortsova. Alexander Porfirievich expressed his gratitude to the National Association of Organizations of Patients with Rare Diseases "Genetics" for the fact that it gives hope for the people with rare diseases, "fights to the last" for the each life.

Vice Governor of the Government of St.-Petersburg O.A.Kazanskaya has welcomed the participants of ICORD 2013 on behalf of the Government St-Petersburg and on behalf the Governor of St.-Petersburg. In her presentation Kazanskaya has noted that the main goal of the Conference is developing of the constructive international partnership which leads to the global improvement of the life of patients with rare diseases and developing of the Trans boundary cooperation in the treatment of rare diseases, development of the orphan drugs and rarely used medical technologies. The Conference ICORD 2013 gathered world-class experts, physicians, researchers, representatives from Pharm industry, public authorities, Patients movement from many countries, and people, connected by desire to improve quality of life of patients with rare disease and their families conducting new researches, developing new technologies and increasing their knowledge. The forum is striking confirmation, that problem of rare diseases and laws about people suffering from it, unites all stakeholders and knows no national boundaries. She also emphasized this is an honour for Saint Petersburg to be a place for holding the Conference because this city has advanced achievements of the science, technology and medicine. In Saint Petersburg there are more than 470 people including 166 children suffering from rare diseases. This is important to build the common system which provide favourable conditions for treatment and life of patients and which will connect all stakeholders: health and social services, community organizations, representatives of executive and legislative power of the city, charitable foundations.

Deputy Chief of headquarters of interfractional deputy association "Eurasia" in the State Duma of the Federal Assembly of the Russian Federation N.N.Starikov expressed his sincere gratitude to all the participants who came to the conference from different countries who devote their attention and energy to help people with rare diseases and their families. In his speech he said that today it is important that the international community is paying special attention to rare diseases. And Russia in this work is one of the main participants.

Following, Klaus Mittmann presented the report behalf on of Malcolm Allison. In his speech he highlighted the problem of CTEPH treatment and reimbursement in Europe. He emphasized the importance that patients it is essential that patients, who are suspected of having PH, are sent to Specialist Centres for assessment. CTEPH is curable by surgery in more than half the cases, so surgery should always be considered as the first option. For patients, for whom surgery is not an option, or for whom surgery has not resulted in complete restoration, Riociguat is the first agent to show successful outcomes. Riociguat was generally well tolerated with a good safety profile in patients with CTEPH.

Rosa Yagudina, Head of the organization of drug supply and pharmacoeconomics First Moscow State Medical University named Sechenov, spoke about the contradictory method "analysis of the impact on the budget" for a decision on funding of orphan drugs and selecting criteria for inclusion in the public drug program. On an example of the treatment of multiple myeloma drug bortezomib and lenalidomide.

SS-06 Clinical and social aspects of the rare diseases therapy in hematology: the role and influence of decision-making on access to innovative treatments

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The concept of rare disease must have a serious impact on the therapy efficiency or cost evaluation process. The traditional evaluation of economic expediency of orphan drug administration is impeded by the small number of patients with rare disorders, as well as the typical lack of effective alternative treatment modes, which results in inferiority and insufficient objectivity of comparison methods in decision-making. At present, the market offers practically no drugs to treat rare diseases, which would be “cost-effective” in terms of standard health technology assessment initially, designed for evaluating the relative cost of expensive treatment modes, which have alternative methods. Thus, it is necessary to consider different criteria and approaches enabling assessment and decision-making in relation to access to orphan drugs’ market, including clinical & social ones, which are more appropriate in terms of medical estimation of their necessity and usefulness. Otherwise, the application of only traditional methods of economic health modelling may have a discriminating impact on patients with rare diseases in their access to healthcare innovations and limit doctors’ capabilities in delivering care to such patient population.

By the example of rare diseases in haematology, the report suggests that instead of the treatment price, analysing should be based on the clinical & social aspects of orphan products’ administration and their influence on the increase of longevity and stable life quality improvement, which is a fair value indicator both for the patient and society. It also suggests the discussion of the following significant assessment criteria:

- Progressive, disabling and life-threatening nature of rare diseases;
- Epidemiology/prevalence (very small number of patients);
- Trustworthy (proved) clinical advantages of orphan drug in particular clinical situations, their impact on survival capability and lifetime;
- Shortage/lack of alternative accessible and effective treatment modes;
- Social effects of orphan drugs’ application.

Besides, we need to remember that each specialist and public health official must offer hope to the affected individuals in their nation, making sure that such hope does not discriminate the patients with rare disorders among those having more common diseases. That may be attained by reasonable differentiation subject to the requirements of fairness and informal equality, aimed at meeting the medicament needs of individuals whose health is threatened by the nature of disease and its rarity.

SS-07 SITUATION OF RARE DISEASES IN RUSSIA. Asanov A.Y.1, Sokolov A.A.2 1. I.M. Sechenov First MSMU, Moscow, Russia; NPP NC «RareDisExpert», aliy@rambler.ru; asanov@mma.ru, 2. North-Western State University named after I.I. Mechnikov, Saint-Petersburg, Russia, NPP NC «RareDisExpert», dr.sokolov@list.ru.

The contents of the main provisions of the legislation of the Russian Federation in the field of health are presented. Some of the fundamental problems in delivery of care to patients with rare (orphan) diseases that are engendered by geographic, demographic, ethno-territorial and population-genetic characteristics of the Russian Federation are identified. The mechanisms, ways and sources of financing of implementing the provisions of Federal law «about foundations of health protection of citizens in the Russian Federation», concerning the provision of medical care to patients with rare (orphan) diseases are discussed. The some priority problems calling for action by today are: 1. Difficulties diagnosis of RD. 2. The limited treatment options, even if the diagnosis is confirmed. 3. Treatment exists, but Orphan Drugs are not yet registered in Russia. 4. Orphan Drugs has been registered, but the cost is so high that they cannot be used. 5. Even if an orphan drug is available: no experience usage (especially in province). 6. There are only separate standards and patient treatment protocols. 7. Very few hospitals agreed to use Orphan Drugs. 8. No therapy monitoring system

SS-8 Advancing knowledge in rare diseases

Parker S., Paberze E.

www.orphan-europe-academy.com

The rarity of patients and the high phenotypic heterogeneity of rare diseases combined with the lack of knowledge, information and training result in frequent delays in correct diagnosis, appropriate care, treatment and quality of life. Orphan Europe launched the Orphan Europe Academy advanced education for rare diseases in 2000.

The mission of the Academy is to promote the accurate diagnosis and management of patients affected by a rare disease. The specific objectives are:

- * Developing tailored solutions in live training and educational activities for healthcare professionals involved in the diagnosis and management of patients affected by rare diseases.

- * Developing an e-learning platform to provide individuals, worldwide, with clinically useful and most up-to-date information concerning the current knowledge and management strategies.

- * Collaborating with rare disease centres of expertise and European Reference Networks on the provision of training, patient information and support

The academy is unique. It proposes training and education on RDs for which there is currently no continued education; and where most centres are unable to gain expertise, as patient numbers are very small.

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De Santis Marta	PPa-10, PPa-13, PPa-14, PPI-01	Kvlividze Oleg	OP-06
Dickie Laura J.	PPa-03	Kodra Yllka	OP-20
Di Cosmo Raffaella	PPa-12	Lal Jonathan A.	OP-13
Di Filippo Francesco	PPa-16	Langellotti Maria	PPa-13, PPa-14
Dinarello Charles A.	PPa-02	Laricchiuta Paola	OP-13
Dionisi Vici C.	PPa-08	Larizza L.	PPa-08
Dolk Helen	OP-04	Lasko Paul	OP-01
Donati Carlo	PPa-09, PPa-10	Latrofa Manuela	PPI-01
Dunkle Mary	PPI-04	Le Cam Yann	OP-13, PPa-10
Emmi Giacomo	PPa-18	Ledger Paul	OP-03
Emmi Lorenzo	PPa-18	Lemoine Adrien	OP-03
Ensini Monica	OP-13	Lenzini Elisabetta	PPa-01
Errezola Manu	PPa-06	Leo Carlo G.	OP-13
Facchin P.	PPa-08		

Linertová Renata	OP-20	Radice Paolo	PPa-05
Lisukov Igor A.	SS-06	Ramalle-Gomarra Enrique	PPa-06
Llera Virginia A.	OP-22	Ramet José	OP-13
Lochmüller Hanns	OP-02	Ramos Julián M.	PPa-06
Loeber Gerard J.	PPa-16	Ravani Anna	PPa-05
López-Bastida Julio	OP-20	Resta Nicoletta	PPa-05
Lucherini Orso Maria	PPa-02, PPa-03, PPa-04, PPa-18	Restaino Raffaella	PPa-12, PPa-13
Maggio M.C.	PPa-18	Rigante Donato	PPa-02, PPa-04, PPa-18
Magnotti Flora	PPa-03	Ritchie Karen	OP-13
Makaeva Albina V.	OP-19	Rivero-Santana Amado	OP-13
Mancini Marco	PPa-01	Rizzo G.	PPa-08
Mandelbaum Maria H.S.	PPi-06	Roldán Emilio J. A.	OP-22, WG-02
Mandelbaum Samuel H.	PPi-06	Romano M.	PPa-18
Manson Jan	OP-13	Rosatelli Cristina	PPa-05
Mantovani Alberto	OP-04	Russo Silvia	PPa-05
Manzo Stefano	PPa-09	Sabina Saverio	OP-13
Margolles Mario J.	PPa-06	Salvatore Marco	PPa-01, PPa-05
Marin Francesca	PPa-13, PPa-14	Sanseverino Antonella	PPa-08, PPi-01
Marra Manuela	PPa-01, PPa-05	Santana Milagrosa	PPa-06
Matamala N.	SS-04	Santillán S.	SS-04
Mazzucato M.	PPa-08	Scalini Perla	PPa-02
McDermott Michael F.	PPa-03	Scapinelli Francesca	PPa-09
Meerpohl Joerg J.	OP-13	Schieppati Arrigo	OP-20
Melis Maria-Antonieta	PPa-05	Schünemann Holger	OP-13
Merlini Giampaolo	PPa-03, PPa-04	Seia Manuela	PP-05
Meshcheryakova Elena	PPa-17	Sejersen K.	OP-13
Milosevic Jelena	PPi-02	Sejersen Thomas	OP-13
Mincarone Pierepaolo	OP-13, PPa-10	Senecat Juliette	OP-13
Minozzi Silvia	OP-13	Serrano-Aguilar Pedro	OP-13, OP-20
Miñambres-Herraiz Rebeca	SS-04	Shostak Nadezna A.	OP-12
Miteva-Katrandzhieva Tsonka	OP-13	Siderius Elisabeth	OP-13
Mittman Klauss	SS-05	Silvestri Elena	PPa-18
Mollo Emanuela	PPa-13, PPa-14, PPa-15	Simonini Gabriele	PPa-02
Morales Antonio	PPa-06	Sokolov Alexey A.	OP-16, SS-07
Morciano Cristina	OP-13	Solovyev Andrei G.	OP-16
Mori Yukiko	PPi-05	Starikov Nicolai N.	SS-05
Nagamori Shiori	PPi-05	Stefanov Rumen	OP-13, OP-18, OP-20, PPa-10, PPa-11, WG-03
Navarro Carmen	PPa-06	Stioui Sabina	PPa-01
Nicod Elena	OP-13	Stojiljkovic Petrovic Maja	PPa-07, PPa-02, WG-02
Nishimura Yukiko	OP-17, PPa-04, PPa-05, WG-03	Tarasova Irina S.	OP-09
Novelli Antonio	PPa-01	Taruscio Domenica	OP-02, OP-04, OP-13, OP-20, PPa-01, PPa-05, PPa-08, PPa-09, PPa-10, PPa-13, PPa-14, PPa-15, PPa-16, PPa-01
Obici Laura	PPa-03, PPa-04	Terlizzi Mónica	PPa-09
Oguro Hiroshi	PPi-05	Torshin Aleksandr P.	SS-05
Orlando Gaetano	PPa-09	Tosic Natasa	PPa-07
Paberze Evelina	SS-08	Tosto Fabrizio	PPa-01, PPa-05
Palazzo Fabio	OP-13	Trottestam Helena	OP-14
Palomar Joaquín A.	PPa-06	Trujillo-Martín Maria M.	OP-13
Papa Antonio	PPa-09	Turdrop David	OP-13
Parker Samantha	SS-08	van Kranen Henk S.	OP-13
Pavlovic Sonja	PPa-07, PPa-02, WG-01	Varesco Liliana	PPa-05
Pelo Elisabetta	PPa-05	Villani Flavia	PPi-01
Perestelo-Perez Lilisbeth	OP-13	Villaverde-Hueso Ana	PPa-06
Pérez-Ramos Jeanette	OP-13	Vitale Antonio	PPa-02, PPa-04, PPa-18
Persson Ulf	OP-20	Vittozzi Luciano	OP-02, PPa-08, PPa-10, PPa-15, PPa-16
Piccirillo Carmen	PPa-09	Weinman Ariane	PPa-10
Piccirillo María	PPa-09	Yagudina Rosa I.	SS-05
Piombo Giuseppe	PPa-01	Yamazaki Yoichi	PPi-05
Pirard Vinciane	OP-07	Yuwen Howard	SS-03
Pirozzi Carmen	PPa-09	Zuñiga S.	SS-04
Pizza Antonietta	PPa-12	Zurriaga-Llorens Oscar	PPa-06
Polizzi Agata	PPa-08, PPa-01		
Posada de la Paz Manuel	OP-13, OP-20, PPa-06, PPa-10		
Privitera M.G.	PPa-08		
Pulles Tom	OP-05		
Punzi Leonardo	PPa-02, PPa-04		
Quaglietta Maria Carmela	PPa-12		