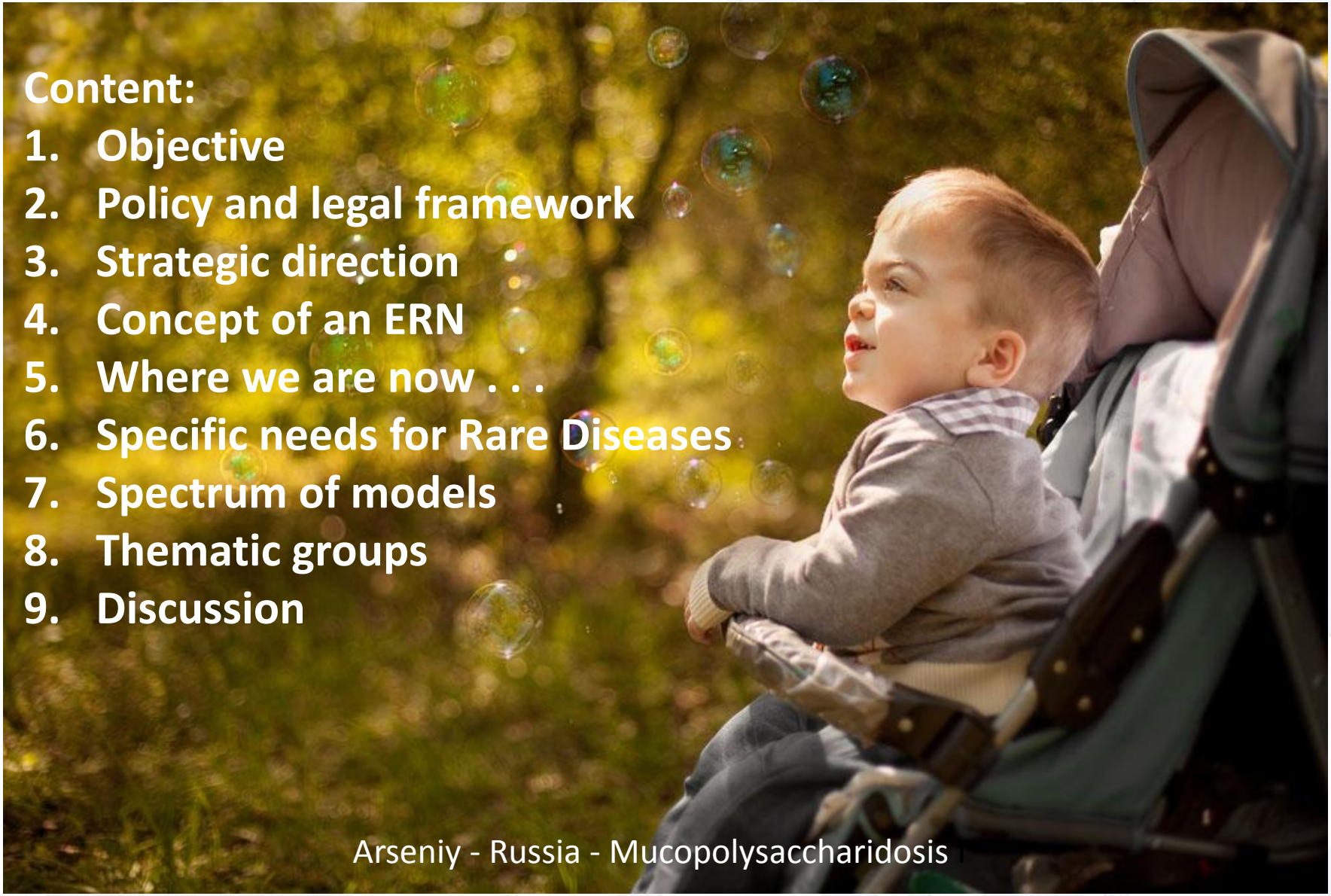
EURORDIS
Rare Diseases Europe

Organisation of Centres of Expertise and European Reference Networks for RDs

Council of European Federations 14 October 2014


Content:
1. Objective
2. Policy and legal framework
3. Strategic direction
4. Concept of an ERN
5. Where we are now . . .
6. Specific needs for Rare Diseases
7. Spectrum of models
8. Thematic groups
9. Discussion
Arseniy - Russia - Mucopolysaccharidosis

Objective

1. To stimulate discussion on models for the organisation of European Reference Networks (ERNs) with the capacity to meet the needs of all rare diseases (RD).

2. To capture discussion and opinions to inform the development of RD ERNs.

3. Develop and capture a shared advocacy messages to strengthen our unified voice on the development of RD ERNs

Common policy and common legal framework

- Commission Communication, call to address Europe's challenge for Rare Diseases
- Council Recommendation
- National Plans require the development of Centres of Expertise and registries
- CBHC Directive: concept and legal instrument of ERNs was adopted
- **Delegated decision and Implementation decision**
  - The legislative 'What' and the 'How'
  - **Patient Organisations not specifically** included in governance, assessment and evaluation, **of networks in legislation**. Legislation does not excluded networks to do this.
  - **Networks are required by law to be, and demonstrate patient centric care and patient empowerment**

http://www.rare-diseases.eu/wp-content/uploads/2014/05/0102_Enrique_TEROL2.pdf

Our Ambition

Individual ambition:

- No decision about me, without me!

National ambition (Committee Experts for Rare Diseases):

- All Rare Diseases covered by at least one ERN which focus on groups of diseases

European ambition (International Rare Diseases Research Consortium):

- 200 new therapies for rare diseases
- Means to diagnose most rare disease by 2020

Integration and interoperability

New emerging landscape for Rare Diseases:

- European Patients' Academy on Therapeutic Innovation
- Connecting Big Data revolution for RD
- Integration of Research Infrastructure and transitional research pathway focused on RD
- **Centres of Expertise accreditation to 'connect up'**
- **European Reference Networks to 'level up' of expertise and knowledge**

Healthcare dynamic

Healthcare responsibly:

- Common policy and legislation, but healthcare is a 'shared competency'
- ERNs are a European benefit, based on cooperation not investment
- Handing the 'baton' from Commission to Member State

European Commission:

- Coordinators of assessment process
- Time is pressured with an ambitious roadmap for delivery
- Lack of articulated common shared vision or coordinated strategic approach

Member States:

- Experience and expectation variable
- Responses in some MS is slow to stimulate debate and appetite
- RD National Plans key lever at a national level

Scope of an ERN

Rationale:

- Centralization of expertise or resources for
- Rarity of expertise, low prevalence, complexity, or high cost treatment

Complexity defined as:

- Large number of possible diagnoses or management options and comorbidity
- Difficult interpretation of clinical and diagnostic tests data
- High risk of complications, morbidity, or mortality related to either the problem, the diagnosis procedure or the management

Note: European Reference Networks are not solely Rare Diseases

Challenge our concept of a Network

Rationale for European Reference Networks:

- Centralization of expertise or resources for
- Rarity of expertise, low prevalence, complexity, or high cost treatment

Concept of European Reference Network of Centres of Expertise:

- Demonstrate 'Added Value' at an EU level
- Healthcare, not research
- Effective networking, enhance communication
- Flexible in model, inclusive not exclusive,
- Centralised care vs. referral networks: shared care arrangements
- Leveling up of knowledge and expertise through dissemination
- Collaboration and cooperation

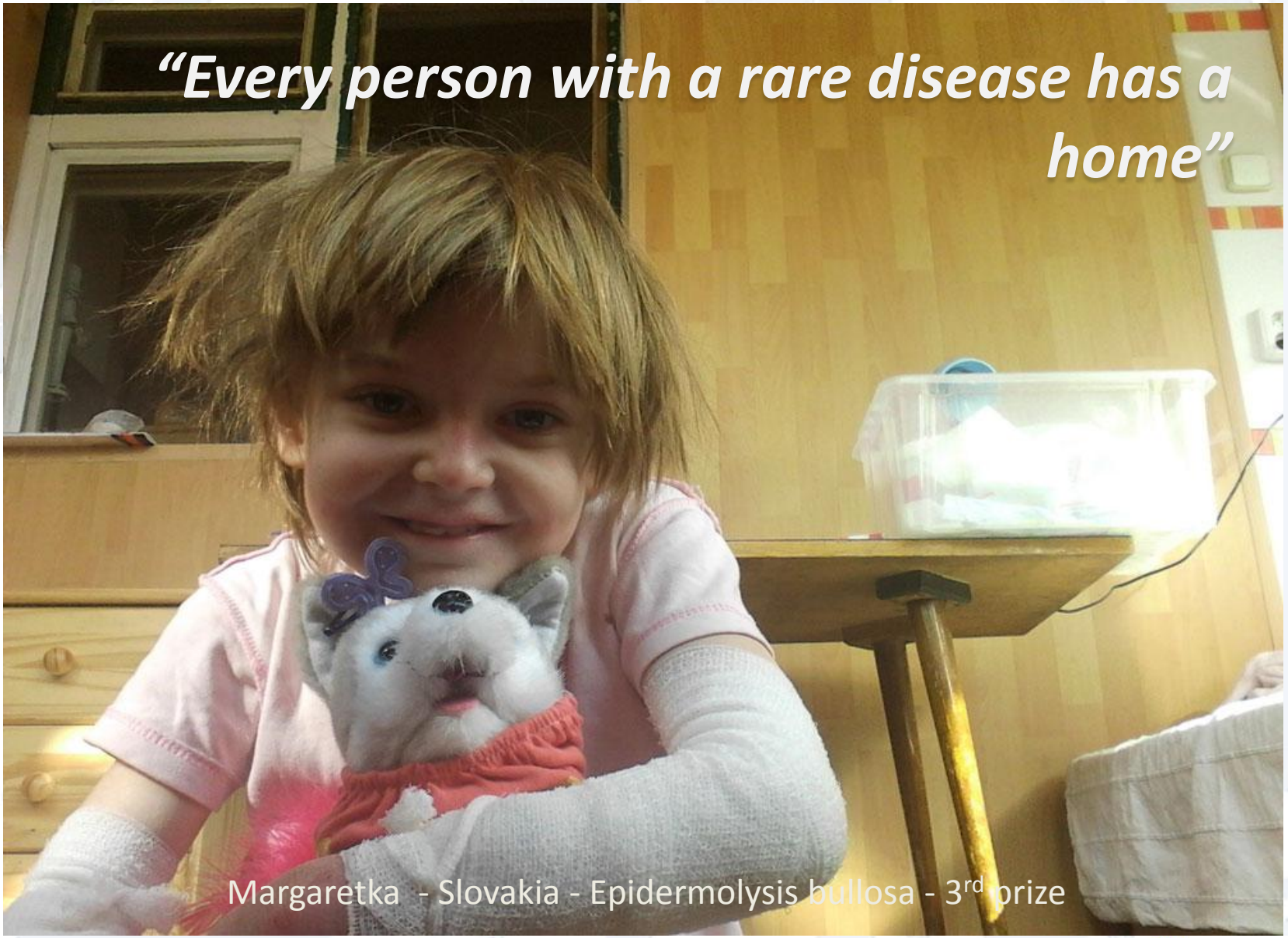
Application & Assessment Process

Networks are required to have:

- Minimum of 10 healthcare providers from 8 MS
- Member State must endorse Centres of Expertise
- Centres can be Associate or Collaborative National Centres
- Technical assessment completed based on a common assessment manual
- Assessment completed by an Independent Body
- Member State Board will approve applications
- No funding invested by MS
- Accreditation with EU Logo
- Positive assessments will be made public

Our journey ahead

• EUCERD (CERD) Recommendations	• Oct 2011
• Adoption legal acts	• March 2014
• Awareness campaign launched	• 23 June 2014
• Call for Assessment Manual and toolkit	• July 2014
• Identifying clusters of diseases workshop feedback to CERD	• November 2014
• **Selection of Independent Assessment body**(ies), and networks guidelines and technical documents	• Q4 2014
• **Call for Networks** – Complete individual's proposal and self-assessment	• Q4 2015
• Technical Assessment (criteria and conditions)	
• Positive assessment equates to approval of network with established membership with ERN logo awarded	
• Establish of Networks	



EURORDIS
Rare Diseases Europe

Advocacy messages …

Specific needs for Rare Diseases:

- Individually RDs is rare but with 6-8000 diseases is significant
- Multisystem conditions that require multidisciplinary and multiprofessional approach
- Critical mass - scares and isolated expertise, cases and data
- Time to diagnosis, level of mis-diagnosis (and treatment) and significant number of undiagnosed cases
- Inequities and difficulties in access to treatment, rehabilitation and care
- Loss of confidence and dissatisfaction with and in medical and social services
- Rejection by health professional for undiagnosed conditions or a long diagnostic odyssey
- People with rare diseases become the expert in their condition due to scares experience, knowledge and expertise in majority of healthcare systems

EURORDIS Rare Diseases Europe

Scope of ERNs and Centres of Expertise

Governance	Objective	Function	Area	Organisation
• Formal network • Informal network	• Improved access to high quality healthcare • Sharing of data, expertise • Critical mass of cases • Transfer of knowledge • Peer review activity	Referral network Vs Treatment network	AND / OR : • Rarity of expertise • Low prevalence • Complexity • High cost treatment	• Established cooperation • Maturity of network • Registry and data collection • Active patient organisation • Available therapeutic intervention (diagnosis or treatment)

Critical networks are developed to cover all Rare Diseases and more mature networks share knowledge with other conditions

Note: **based on** Plam W, Glinos I A, (Eds). Building European Reference Networks. Exploring concepts and national practices in the EU. Observatory Studies Series n. 28 (forthcoming 2013)

Modelling

- Undiagnosed and diagnosed areas (e.g. Network of networks which specialise in diagnostic methodology, tools, functional testing, genomics …)
- Clinical area (e.g. Neurology, Neuromuscular, Psychiatry, Skin, Kidney, etc)
- Clinical grouping (e.g. Genetic Disorders, Metabolic Disorders, Epilepsy, Oncology)
- Clinical intervention (e.g. Transplantation, Gene Therapy, Radiotherapy)
- Mixed models

Overview

Position:

- EURORDIS has advocated strongly that ERNs should not be created for every single RD, on the grounds that this would leave many patients without an ‘umbrella’ ERN, particularly the undiagnosed patients.

Rational:

- Impossible to create 6-8000 individual ERNs with no clinical benefit.

Proposal:

- Grouping diseases into ‘families’ which can then be addressed by a comprehensive ERN is more feasible and beneficial approach which would ensure every RD patient has a ‘home’ in a RD ERN.

EURORDIS Rare Diseases Europe

1. EURORDIS Proposal in development ...

1. Undiagnosed Conditions
2. Immunologically-mediated and Systemic
3. Cardio-Vascular Diseases
4. Malformations / Medical Genetics / Neuropaediatrics
5. Dermatological Diseases
6. Endocrinal Diseases
7. Hepatogastroenterological Diseases (including Severe Intestinal Disorders)
8. Non-Malignant Haemotological Diseases
9. Hereditary Metabolic Diseases
10. Neurological Diseases
11. Neuromuscular Diseases
12. Pulmonary Diseases
13. Kidney Diseases
14. Connective Tissue Framework (including Specialist Rheumatology Diseases)
15. Head & Neck Malformations (including sensory diseases, e.g.: rare opthalmological, congenital and genetic disease)
16. Cancers
17. Multi-system Disorders & Other Rare Diseases
18. Orthopaedic (including complex spinal disorders)
19. Women, neonatal and children

2. The ORPHANET classification

1. Rare cardiac diseases
2. Developmental anomalies during embryogenesis
3. Inborn errors of metabolism
4. Rare gastroenterological diseases
5. Rare neurological diseases
6. Rare abdominal surgical diseases
7. Rare hepatic diseases
8. Rare respiratory diseases
9. Rare urogenital diseases
10. Rare surgical thoracic diseases
11. Rare skin diseases
12. Rare renal diseases
13. Rare eye diseases
14. Rare endocrine diseases
15. Rare haematological diseases
16. Rare immunological diseases
17. Rare systemic and rhumatological diseases
18. Rare odontological diseases
19. Rare circulatory system diseases
20. Rare bone diseases
21. Rare otorhinolaryngological diseases
22. Rare infertility disorders
23. Rare tumours
24. Rare infectious diseases
25. Rare intoxications
26. Rare gynaecological and obstetric diseases
27. Rare surgical maxillo-facial diseases
28. Rare allergic disease
29. Teratologic disorders
30. Rare cardiac malformations
31. Rare genetic diseases

EURORDIS Rare Diseases Europe

3. The French filières

1. AnDDI-Rare developmental anomalies and malformations
2. CARDIOGEN transmitted heart diseases
3. DEFI SCIENCE (Challenge for Science) brain development diseases and intellectual disabilities
4. FAI2R rare auto-immunes and auto-inflammatory diseases
5. FILNEMUS neuromuscular diseases
6. FIMARAD rare dermatological diseases
7. FIRENDO rare endocrine diseases
8. G2M rare hereditary diseases of metabolic origin
9. MARIH immuno-hématologic rare diseases
10. MCGRE rare diseases of red cells and of erythropoïesis
11. MUCO cystic fibrosis and CFTR anomalies
12. ORKID rare kidney diseases
13. RESPIFIL rare respiratory diseases
14. SENSGENE rare sensory diseases
15. SLA amyotrophic lateral sclerosis

4. A UK Research Model

1. Cancer
2. Cardiovascular
3. Dementia and Neurodegenerative
4. Eye Disease
5. Gastrointestinal
6. Immunological Disorders
7. Metabolism
8. Musculoskeletal Disorders
9. Neuromuscular Disorders
10. Non-Malignant haematology
11. Paediatric (cross-cutting)
12. Renal Disease
13. Respiratory Disease
14. Skin

5. Classical Medical Ontology

Oncology and Hematology
- Neoplastic Disorders
- Hematopoietic Disorders
- Disorders of Hemostasis

Infectious Diseases

Disorders of the Cardiovascular System
- Disorders of Rhythm
- Disorders of the Heart
- Vascular Disease

Disorders of the Respiratory System
- Diseases of the Respiratory System
- Disorders of the Kidney and Urinary Tract
- Disorders of the Gastrointestinal System
- Disorders of the Alimentary Tract
- Liver and Biliary Tract Disease
- Disorders of the Pancreas

Disorders of the Joints and Adjacent Tissues
- Disorders of Immune-Mediated Injury
- Disorders of the Joints and Adjacent Tissues

Endocrinology and Metabolism
- Endocrinology
- Disorders of Bone and Mineral Metabolism
- Disorders of Intermediary Metabolism

Neurologic Disorders
- Diseases of the Central Nervous System
- Nerve and Muscle Disorders
- Psychiatric Disorders

Harrison's Principles of Internal Medicine 18th edition (Modified INDEX)

Specific needs of individual rare diseases

Neurofibromatosis Type 1:

- NF1 is a tumour disorder that is caused by the mutation of a gene or chromosome 17 that is responsible for control of cell division. NF-1 causes tumours along the peripheral nervous system.
- Symptoms include scoliosis (curvature of the spine), vision disorders, learning disabilities, epilepsy, skin discolouration and single or multiple non-malignant skin tumours, plexiforms on the body or face.
- Risk of developing MPNST, brain gliomas or optic nerve gliomas.
- Multisystem condition
- Common genetic condition with significant variation of symptoms due to where the deletion is on the phenotype
- Commonly mis-diagnosed
- Multidisciplinary approach essential as requires wide range of specialist input

- Neurological or oncological ERN?

Vein of Galen aneurysmal malformations:

- Arteriovenous malformations in infants and fetuses, consisted of a tangled mass of dilated vessels supplied by an enlarged artery. High blood flow into the great cerebral vein of Galen causes its dilation
- Endovascular treatments involve delivering drugs, insertion of balloons, coils or injecting a 'glue-like' substances to the site of the malformation through blood vessels via catheters. Dye-injections enhance imaging to provide anatomical and pathophysiological information.
- Multisystem condition
- Very small incidence rate in any one country
- Ultra specialist skill, only developed through hands-on approach by interventional radiologist

- Head and Neck Malformation ERN?

EURORDIS Rare Diseases Europe

Management of undiagnosed cases

The management of undiagnosed (or misdiagnosed) cases, which benefit from multidisciplinary input and approaches from different perspectives:

- Dedicated ERN for undiagnosed patients be feasible/desirable

Or

- Each ERN should maintain a ‘forum’ for undiagnosed patients suspected to fall within their clinical area/grouping/ intervention

Highly specialised treatments

- Genomic testing
- Gene therapy (cell therapy, tissue engineering)
- Radiotherapy (proton beam therapy, photon therapy, stereotactic radiosurgery)
- Extra corporeal membrane oxygenation service
- Stem Cell Transplant
- Bone marrow transplantation
- Transplantation (heart and lung including bridge to transplant, liver, pancreas small bowel, islets)

RD Networks

- ERNs would need to have the plasticity needed for an articulated approach to shared patients
- Each network will vary in its model and membership depending on the needs of the disease, phenotyping or treatment modality
- There will need to be signification collaboration across ERNs, as well as within.
- Separate reference networks will need to share patients, particularly undiagnosed patients, to optimise their chance for a timely diagnosis.
- Many RD are complex, multisystemic disorders, the question of how to 'assign' RD – and thus patients- to one ERN or another will need to be addressed.
- Common vision and language – fluidity and inter-communication between ERNs

Questions?

- How are MS progressing in developing formal accreditation process and selection of Centres of Expertise?
- Does National accreditation process have Patient Organisations involved in the selection of Centre of Expertise?
- Should there be a strategic approach by MS / Commission on thematic groupings for RD ERNs
- Are you influencing existing RD Networks to be single disease focused or encourage overarching disease groups

Thank you

Daniel - Spain - Sanfilippo syndrome

EURORDIS Rare Diseases Europe