EU-PEARL
EU PATIENT-CENTRIC
CLINICAL TRIAL PLATFORMS

WP 7
NEUROFIBROMATOSIS

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on behalf of all WP7 partners

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WHAT IS EU-PEARL?

Strategic alliance between the public and private sectors to:

Transform the way clinical trials are conducted

Improve and accelerate drug development processes

Place the patient at the center (co-designed by patients)

by developing a common framework
for platform clinical trials/Integrated Research Platforms (IRPs)

EU-PEARL WILL DELIVER

1 A trusted sustainable entity ready to setup and coordinate the operation of Integrated Research Platforms in any disease.

2 A Clinical Trial Platform Framework that can be used for any disease, plus four disease clinical trial platforms ready to operate at the end of the project

3 Four disease trial-ready clinical networks

- Major Depressive Disorder
- Tuberculosis
- Non-Alcoholic Steatohepatitis (NASH)
- Neurofibromatosis

EU-PEARLAIMS TO:

1. **Collaborative mindset and multi-stakeholder effort (public & private).**
   A trusted environment for knowledge sharing and science-driven debate amongst patients, clinicians, industry, researchers, regulators and health authorities. Advance science together.

2. **A new paradigm set to facilitate the development of new treatments, faster.**
   IRPS will bring more efficiency to the design and implementation of clinical trial protocols.

3. **Patients are right at the center.**
   Their voice is incorporated in the design of clinical trials.
   They will potentially gain faster access to more effective and personalised techniques and treatments.

4. **Trusted framework to conduct platform trials.**
   It will allow running multi-company platform trials in a safe and effective environment.
   High-quality results based on strong data networks and statistical methods.

6. **Set to develop four disease IRPs and clinical networks ready to operate.**
   Major Depressive Disorder (MDD), Tuberculosis (TB),
   Non-Alcoholic Steatohepatitis (NASH) and Neurofibromatosis (NF).

WHAT CHARACTERISES NEUROFIBROMATOSES?

Rare condition

Neurofibromatosis type 1	**1:3.000**
Neurofibromatosis type 2	**1:40.000**
Schwannomatosis	**1:100.000**

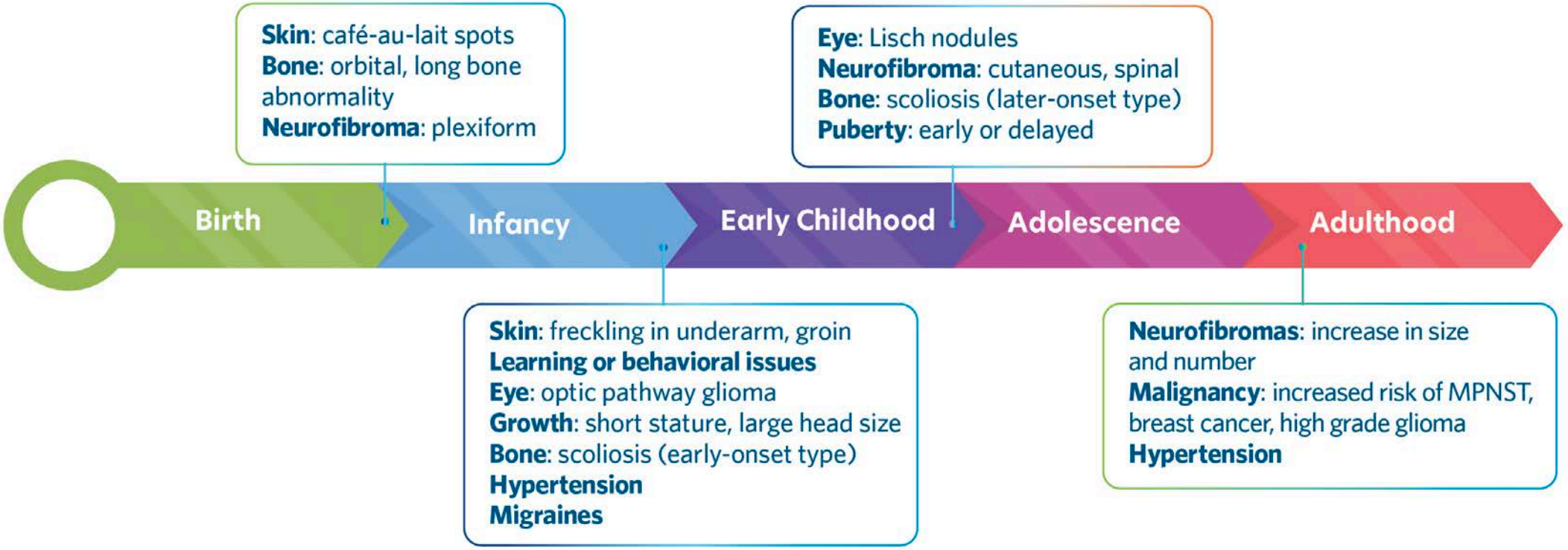
Pediatric presentation

NF1

symptoms variable in presenting age and severity

PROGRESSION OF NF1 – THE SCIENCE

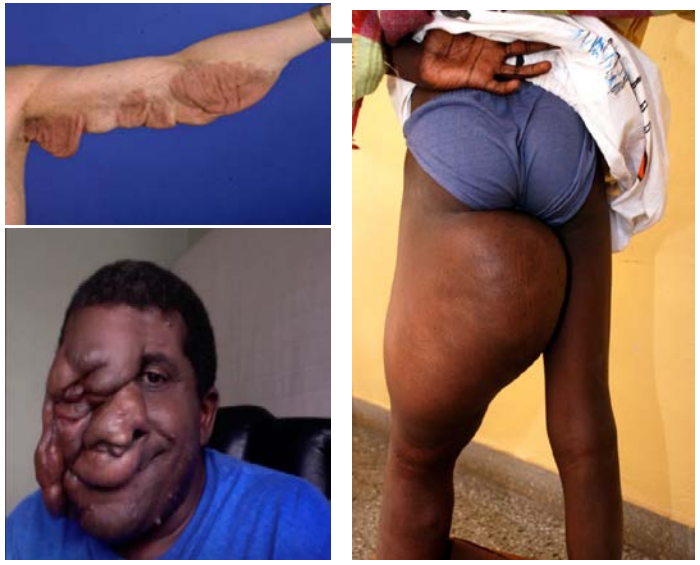
Approximate timing of possible NF1 manifestations



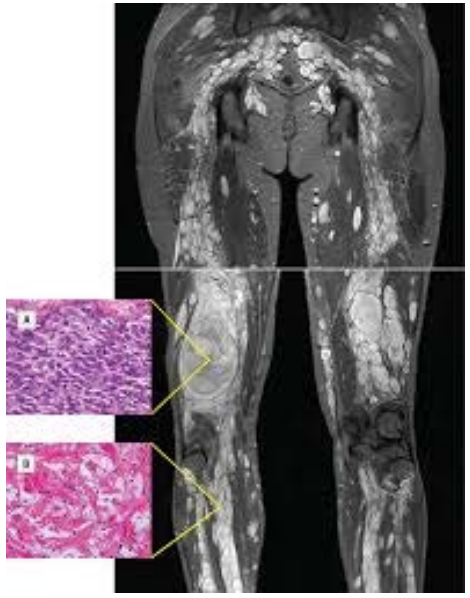
Gutmann DH, et al. "Neurofibromatosis type 1." *Nat Rev Dis Primers* 3.17004 (2017).

SYMPTOMS OF NF1 – THE CLINIC

CNS tumors 20%



Plexiform neurofibroma 50%



MPNST 8-13%

NF1 multi sysytem disorder

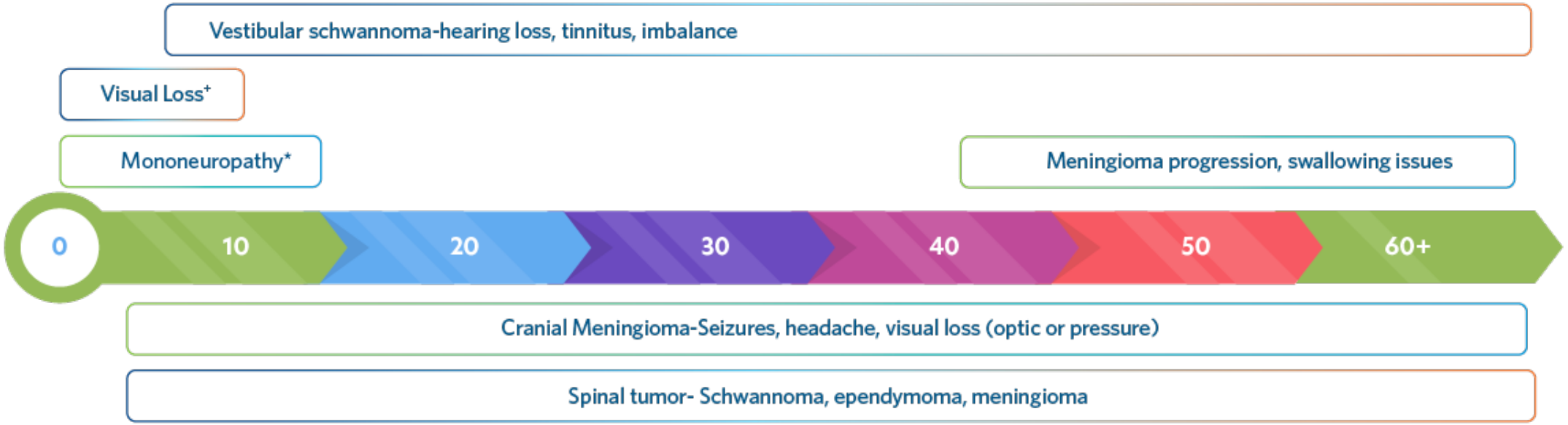
Bone dysplasias, Scoliosis, vascular anomalies, and cardiovascular abnormalities

Risk for malignancy: 5 fold higher

Tibial pseudoarthrosis 5%

PROGRESSION OF NF2 – THE SCIENCE

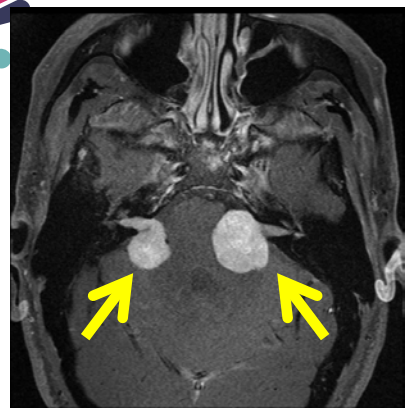
Approximate timing of possible NF2 manifestations



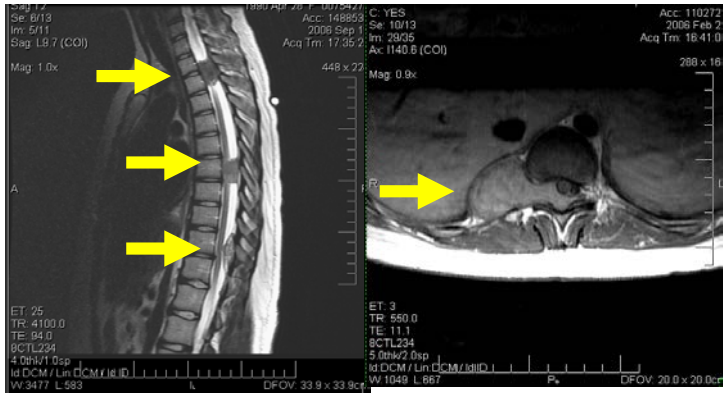
*Facial, 3rd nerve, foot drop, wrist drop
+ amblyopia, congenital cataract, hamartoma

Unpublished, Kindly provided by Dr. G. Evans

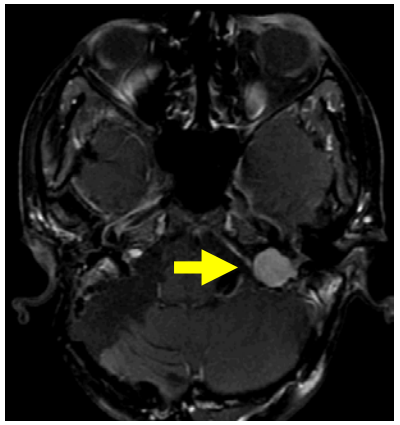
SYMPTOMS OF NF2 – THE CLINIC



Vestib schw.
>95%



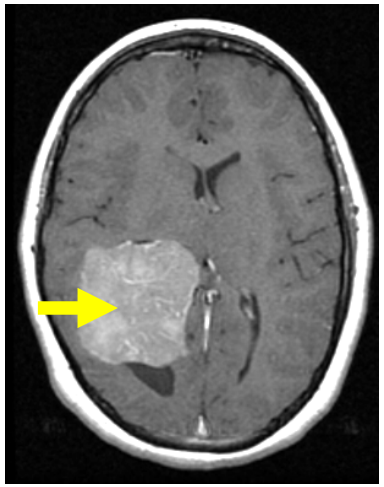
Spinal schwannoma
25-50%



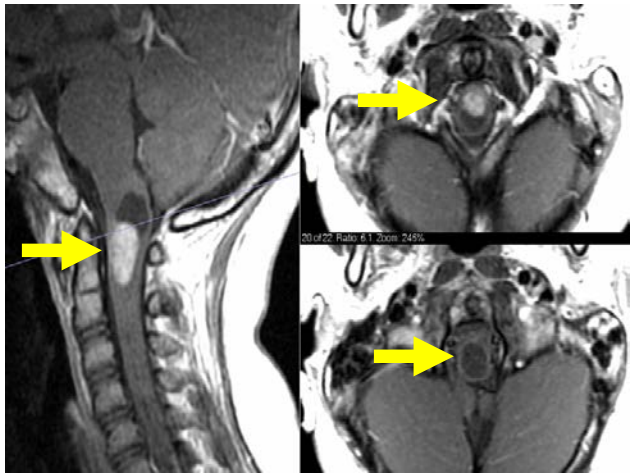
Cranial nerves
25-50%

Peripheral
schwannoma

Cutaneous
schwannoma

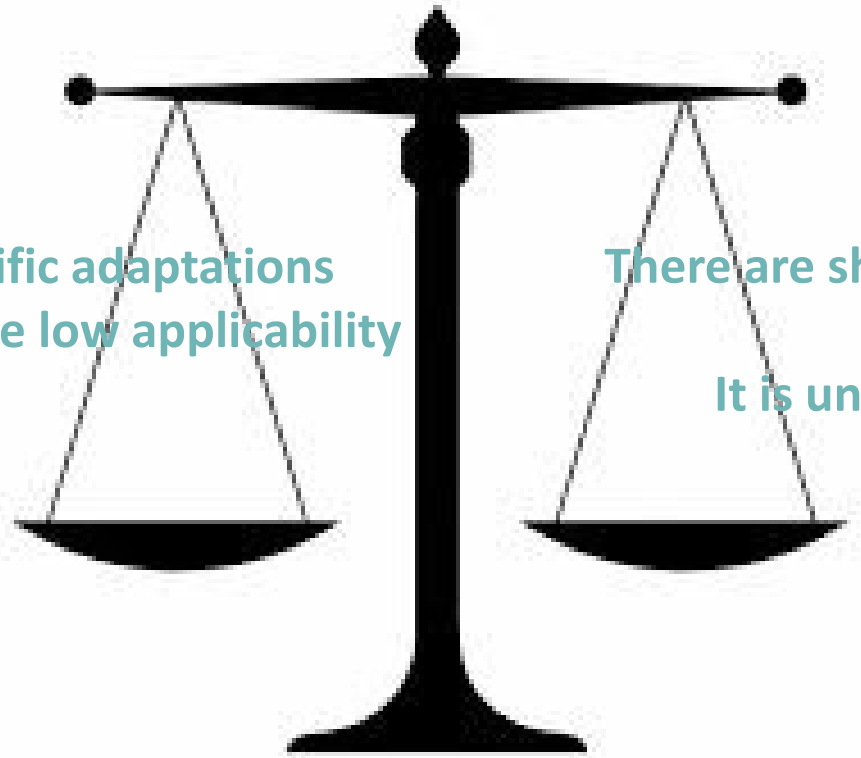


Meningioma
50%



Spinal ependymoma
50%

CHALLENGES IN PEDIATRIC TRIALS FOR RARE CONDITIONS



Trials in children need specific adaptations
Drugs for orphan drugs have low applicability

There are shelf drugs that may be applicable to rare conditions
It is unethical not to benefit the patient

CHALLENGES IN PEDIATRIC TRIALS FOR RARE CONDITIONS

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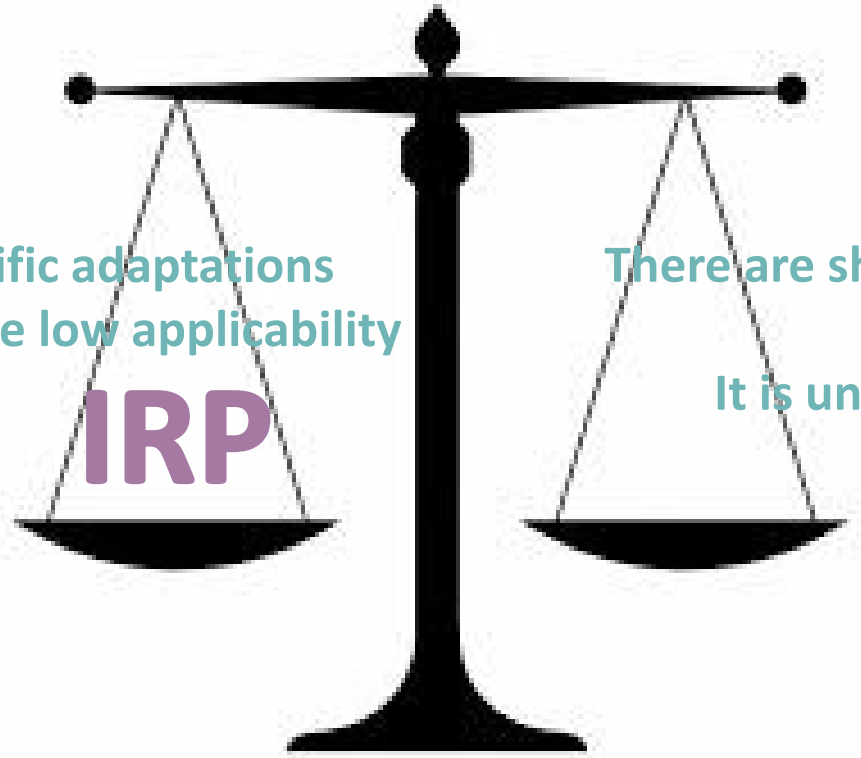
Drugs for orphan drugs have low applicability



There are shelf drugs that may be applicable to rare conditions
It is unethical not to benefit the patient

Output

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ESHG

ARTICLE

Identifying challenges in neurofibromatosis: a modified Delphi procedure

Britt A. E. Dhaenens[1,2] · Rosalie E. Ferner[3] · Annette Bakker[4] · Marco Nievo[4] · D. Gareth Evans[5] · Pierre Wolkenstein[6] · Cornelia Potratz[7] · Scott R. Plotkin[8] · Guenter Heimann[9] · Eric Legius[10] · Rianne Oostenbrink[1,2]

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NF1

- *Sarcomas/MPNST*
- *(High grade)* gliomas
- Peripheral benign nerve sheath tumors
- Cutaneous neurofibromas

NF2

- Tumor

SWN

- Pain

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imi innovative medicines initiative efpia

SpringWorks THERAPEUTICS TB Alliance CHILDREN'S TUMOR FOUNDATION

Output

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Lessons learned from drug trials in neurofibromatosis: A systematic review

Britt A.E. Dhaenens [a,b], Rosalie E. Ferner [c], D. Gareth Evans [d], Guenter Heimann [e], Cornelia Potratz [f], Edwin van de Ketterij [g], Angela M. Kaindl [f,h,i], Geesje Hissink [a], Charlotte Carton [j], Annette Bakker [k], Marco Nievo [k], Eric Legius [l,m], Rianne Oostenbrink [a,b,m,*]

Single arm, single country trials
Plexiform neurofibromas (NF1) or vestibular schwannomas (NF2)

Gap for cutaneous manifestations and high-grade gliomas in NF1, non-vestibular schwannoma in NF2 and trials for SWN.

Drug development in NF may profit from innovative trials on multiple interventions and increased international collaboration.

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INTEGRATED RESEARCH PLATFORM FOR PEDIATRIC TRIALS IN NF1

IRP for

Optic pathway glioma

Plexiform neurofibroma

Cutaneous neurofibromas

Low grade glioma

Pediatric applicable and relevant outcomes
Design adapted to children
Regulatory adapted to children
Network of clinical sites/access to pediatric NF1 patients

BENEFIT AND CHALLENGES OF EU-PEARL PLATFORM TRIALS

- More efficient testing of drugs
- Faster procedures of trials
- Network with high number of patients
- Higher number of trials

- Multiple drug compounds needed
- Use of the IRPs
- Collaboration of clinical sites
- Participation of patients

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WHO IS INVOLVED

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Vall d'Hebron Institut de Recerca
Vall d'Hebron
Erasmus MC
Assistance Publique Hôpitaux de Paris
UniSR Università Vita-Salute San Raffaele
Medizinische Universität Wien
King's College London
KU Leuven
Charité

OTHER HOSPITALS

LMU Klinikum der Universität München

UNIVERSITIES

University of Oxford
Manchester 1824 The University of Manchester
Tartu Ülikool 1632 Universitas Tartuensis
Università degli Studi di Milano
Newcastle University

PATIENT ORGANISATION

EPF European Patients Forum

DATA, STATISTICS

The European Institute For Innovation Through Health Data
Berry Consultants
Custodix

REGULATORY

Paul-Ehrlich-Institut
euroscan

PROJECT MANAGEMENT

teamit Research

EUROPEAN RESEARCH INFRASTRUCTURES

eatris
ECRIN European Clinical Research Infrastructure Network

BIOPHARMACEUTICAL COMPANIES / EFPIA / ASSOCIATED PARTNERS

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