WP 7
NEUROFIBROMATOSIS

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on behalf of all WP7 partners

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

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

Four disease trial-ready clinical networks

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

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.

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.

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.

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
Approximate timing of possible NF1 manifestations

**Birth**
- **Skin:** freckling in underarm, groin
- **Learning or behavioral issues**
- **Eye:** optic pathway glioma
- **Growth:** short stature, large head size
- **Bone:** scoliosis (early-onset type)
- **Hypertension**
- **Migraines**

**Infancy**
- **Skin:** café-au-lait spots
- **Bone:** orbital, long bone abnormality
- **Neurofibroma:** plexiform

**Early Childhood**
- **Eye:** Lisch nodules
- **Neurofibroma:** cutaneous, spinal
- **Bone:** scoliosis (later-onset type)
- **Puberty:** early or delayed

**Adolescence**
- **Neurofibromas:** increase in size and number
- **Malignancy:** increased risk of MPNST, breast cancer, high grade glioma
- **Hypertension**

**Adulthood**

NF1 multi sysytem disorder

Bone dysplasias, Scoliosis, vascular anomalies, and cardiovascular abnormalities

Risk for malignancy: 5 fold higher

CNS tumors 20%
Plexiform neurofibroma 50%
MPNST 8-13%
Tibial pseudoarthrosis 5%
PROGRESSION OF NF2 – THE SCIENCE

Approximate timing of possible NF2 manifestations

- Vestibular schwannoma – hearing loss, tinnitus, imbalance
- Visual Loss*
- Mononeuropathy*
- Meningioma progression, swallowing issues
- 0
- 10
- 20
- 30
- 40
- 50
- 60+
- Cranial Meningioma – Seizures, headache, visual loss (optic or pressure)
- Spinal tumor – Schwannoma, ependymoma, meningioma

*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%

Cutaneous schwannoma

Meningioma  
50%

Spinal ependymoma  
50%

Peripheral schwannoma
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
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Identifying challenges in neurofibromatosis: a modified Delphi procedure


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NF1
- Sarcomas/MPNST
- (High grade) gliomas
- Peripheral benign nerve sheath tumors
- Cutaneous neurofibromas

NF2
- Tumor

SWN
- Pain
Lessons learned from drug trials in neurofibromatosis: A systematic review


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.
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
WHO IS INVOLVED

EUROPEAN UNIVERSITY HOSPITAL ALLIANCE (EUHA) HOSPITALS

PATIENT ORGANISATION

EUROPEAN RESEARCH INFRASTRUCTURES

DATA, STATISTICS

BIOPHARMACEUTICAL COMPANIES / EFPIA / ASSOCIATED PARTNERS

OTHER HOSPITALS

REGULATORY

UNIVERSITIES

PROJECT MANAGEMENT