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7th European Rett Syndrome Conference
7&8 OCTOBER 2023
WORLD TRADE CENTER MARSEILLE
Organized by the French Association of Rett Syndrome
AFSR Association Française du Syndrome de Rett www.afsr.fr

POLITICAL INVOLVEMENT

Maladies rares et
plans de santé publique :
National plan for rare diseases.

Context: Rare diseases - Obstacles

- Diagnostic error
- Limited information
- Geographic dispersion
- Access to treatment

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PNMR 1

2004 **2008**

RDs became a public health issue
131 labelled CRMR
in 120 French Hospitals

PNMR 2

2011 **2014(16)**

Structuring of FSMR
9 Hospitals
Work on the establishment of the BNDMR
AP-HP Hospital
Rare Disease Foundation

PNMR 3

2018 **2023**

4th, July 2018
Third Rare Disease Plan (PNMR3)

PNMR3 2018-2023

Sharing innovation, diagnosis and treatment for everyone

5 ambitions

- Enable rapid diagnosis for everyone;
- Innovate to treat;
- Improving the quality of life and autonomy of patients;
- Communicating and training;
- Modernising organisations and optimising funding.

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- Make sure each patient receives a faster diagnosis and reduce diagnostic delay, with a quantified objective reduced to 1 year;
- Reinforce the structuring of databases in order to increase research potential;
- Boost the role of clinical networks to coordinate the actions of the multiple players concerned and support certain key phases, such as delivery of the diagnosis;
- Ensure greater clarity of the care pathway for both patients and their families;
- Encourage innovation and make it accessible;
- Put in place new neonatal screening programmes;
- Reinforce France's role as a driving force in Europe.

Background: the objectives of the 3rd Plan

PNMR 3 – 2018-2023

Guide (CRMR) + Coordinate (FSMR) + Share (data, BNDMR): MR house

Efforts to structure and coordinate are still needed.

Specific research challenges.

The need to set up national databases, and their interaction with European databases.

A Europe of rare diseases with the 24 ERNs to be built.

The role of stakeholders and associations in care and research to improve the efficiency of care pathways;

Linking the organization of care, the production of knowledge and feedback to patients creates a virtuous circle:

AAP PNDS (over 300), AAP ETP (over 200), information days, etc.

Structuring into center of expertise and networks organize access to care and expertise for all: governance of the FSMRs with the associations, rare disease expertise platforms in the regions, initial and continuing training for professionals with all the stakeholders involved, etc.

Therapeutic innovations and new treatment strategies in research and care, participatory research: upstream of registries, construction of endpoints for clinical trials, feedback of research results, taking qualitative aspects into account by integrating the voice of patients, etc.

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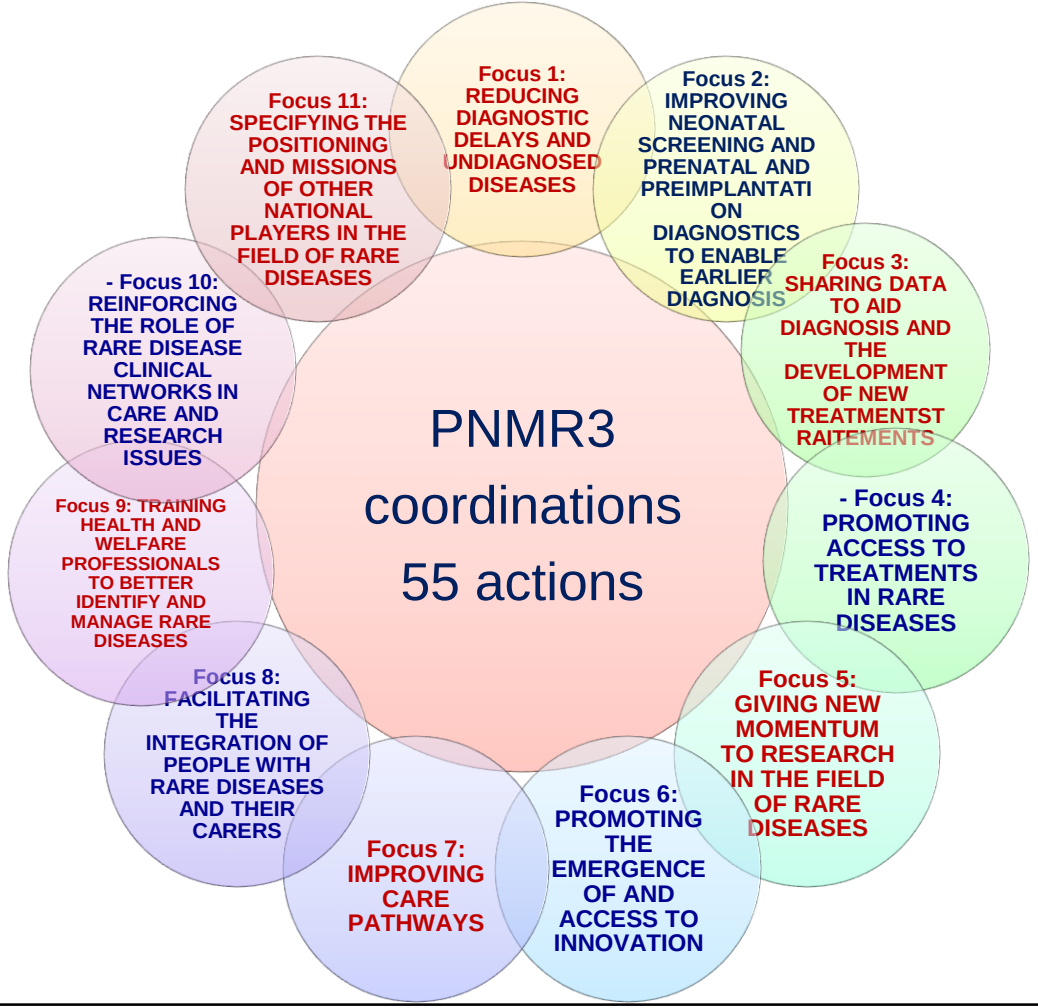

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maladies rares

The hospitals :
the ecosystem for rare diseases and for the 3rd national plan

Research

Universities

social health-care institutions

Pharmaceutical industries

FSMR

Coordination bettween the stakeholders

Patients' Organizations

Biological laboratories

others

CRMR

CRMR

CRMR MISSIONS : **1/ expertise 2/medical referral 3/ training 4/ research**

SITE COORDONNATEUR

+ 5/Coordination

SITE(S) CONSTITUTIF(S)

Compétences | Compétences | Compétences | Compétences | Compétences

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National Plans : A CLEAR PATIENT PATHWAY

FSMR

GP → Specialist → CCMR → CRMR

If needed

CCMR

If endorsed as a HCP

ERN, HcP : Hospital authorizations

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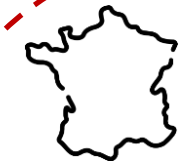
France: Rare diseases network in 2023

3ème plan
maladies rares

Plateforme d'expertise
Maladies Rares

National Plan for rare diseases (3 plans since 2004)
+ Regional rare disease expertise platforms (23)



Depuis 2023

24 ERN
European Reference Networks

23
filières de santé
maladies rares

603
centre de référence
maladies rares

1723
centre de compétence
maladies rares

Alliance
maladies rares
UNIS POUR VAINCRE

Plus de 240 associations de personnes malades

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The actions of the 3rd national plan and the prospects of the future 4th national plan around health data

- **WP Life-course and care / from territories to Europe:**
  - The town-hospital link
  - Neonatal screening, new born screening
  - Information and training
  - The dissemination of a rare diseases policy within the countries of the EU:
    - the sharing of health data with Europe as part of the joint action JARDIN to integrate European reference networks into health systems

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FOCUS 10.6	Encourage health establishments to set up platforms of expertise in rare diseases fileld in order to reinforce inter-center of expertise coordination	2019 2023

RARE DISEASES IN REGIONAL AREAS
an action to be continued in the 4th national plan for rare diseases

19 plateformes d'expertise maladies rares en métropole

4 plateformes de coordination en Outre-mer

PEMR en Ile-de-France

Plateforme d'Expertise Maladies Rares et Handicap AP-HP Centre Université de Paris

ESMARA (Plateforme d'Expertise Maladies Rares Grand Paris Est)

Plateforme d'Expertise Maladies Rares Paris Nord

Plateforme d'Expertise Maladies Rares AP-HP Paris Saclay - Université de Paris

Plateforme d'Expertise Maladies Rares AP-HP Paris Sorbonne - Université de Paris

Specific objectives JA ERN Coordination

Infrastructure for data sharing across the EU

with the development of European-wide patient registries

ERNs

- An extension of national healthcare systems;
- To provide an additional dimension of EU-wide networked care in addition to that provided at national level,
- A paradigm shift in their respective fields of clinical excellence but also made important steps towards a sharing of know-how around rare diseases between a large number of medical specialities across the EU in a short time;
- Concerted actions from the very first days of the COVID pandemic are probably the best proof of how this has worked.

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24 european reference network (ERN)

ERN BOND	Réseau européen de référence sur les troubles osseux
ERN CRANIO	Réseau européen de référence sur les anomalies craniofaciales et les troubles ORL
Endo-ERN	Réseau européen de référence sur les maladies endocriniennes
ERN EpiCARE	Réseau européen de référence sur les épilepsies rares
ERKNet	Réseau européen de référence sur les maladies rénales
ERN-RND	Réseau européen de référence sur les maladies neurologiques
ERNICA	Réseau européen de référence sur les anomalies héréditaires et congénitales
ERN LUNG	Réseau européen de référence sur les maladies respiratoires
ERN Skin	Réseau européen de référence sur les troubles de la peau
ERN EURACAN	Réseau européen de référence sur les cancers chez l'adulte (tumeurs solides)
ERN EuroBloodNet	Réseau européen de référence sur les maladies hématologiques
ERN eUROGEN	Réseau européen de référence sur les maladies et affections urogénitales

7 ERN France

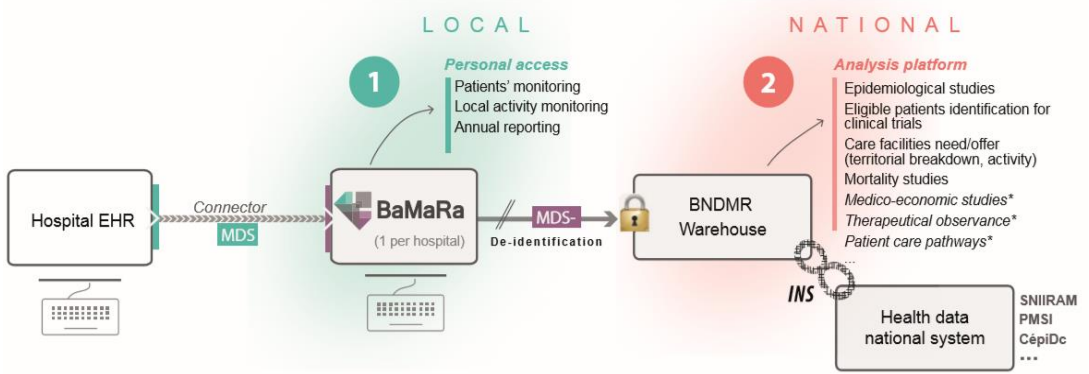
ERN EURO-NMD	Réseau européen de référence sur les maladies neuromusculaires
ERN EYE	Réseau européen de référence sur les maladies des yeux
ERN GENTURIS	Réseau européen de référence sur les syndromes génétiques du risque de tumeur
ERN GUARD-HEART	Réseau européen de référence sur les maladies du cœur
ERN ITHACA	Réseau européen de référence sur les malformations congénitales et une déficience intellectuelle rare
MetabERN	Réseau européen de référence sur les troubles métaboliques héréditaires
ERN PaedCan	Réseau européen de référence sur le cancer pédiatrique
ERN RARE-LIVER	Réseau européen de référence sur les maladies hépatologiques
ERN ReCONNET	Réseau européen de référence sur les maladies du tissu conjonctif et de l'appareil locomoteur
ERN RITA	Réseau européen de référence sur l'immunodéficience, les maladies auto-inflammatoires et auto-immunes
ERN TRANSPLANT-CHILD	Réseau européen de référence sur la transplantation pédiatrique
VASCERN	Réseau européen de référence sur les maladies vasculaires multi systémiques rares

Gathering in a single database one of the largest rare disease cohort in the world: **the French national rare disease registry data**

Thibaut Pichon, Claude Messiaen, Louis Soussand, Céline Angin, Nabila Elarouci, Anne-Sophie Jannot
Banque Nationale de Données Maladies Rares – BNDMR (AP-HP), Paris (France) contact.bndmr@aphp.fr

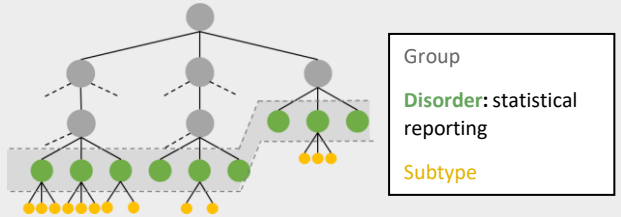
The French national rare disease registry data
Banque Nationale de Données Maladies Rares (BNDMR)

The BNDMR was created as part of the second National Plan for Rare Diseases. Its aim is to collect from all expert centers on rare diseases in France a Minimal Data Set (MDS), either from a web app (BaMaRa) or from the electronic health record (EHR). In the end, these data are sent to the BNDMR data warehouse to allow national analyses.



Rare diseases coding in the BNDMR

To identify the patients' rare disease(s), the BNDMR uses the Orphanet nomenclature (July 2021 version).
Each clinical entity is assigned a unique identifier that is stable over time: the ORPHA code. ORPHA codes are organised into three classification levels: disease groups, diseases and disease subtypes.



Orphanet nomenclature classification levels representation

Specific objectives JA JARDIN ERN Coordination

WP8

- To develop solutions allowing for semantic and technical interoperability amongst HCPs for national and European it-tools;
- To manage the diversity within and between national health systems and ERNs by design;
- To develop a solution for describing the rare disease health care system and ERN/NRN structures;
- To develop solutions to overcome organisational and legal barriers for accessing data;
- To demonstrate these solutions through a set of use cases.

JA JARDIN

To develop recommendations ensuring the interoperability of data structures on MS level (local, regional, national) and ERN level

Deliverables: Recommendations (document):

1. “Practical solutions” for implementation of an extensive interoperability of Member State data structures (local, regional, national) and ERN data structures

2. A roadmap for the FAIR management of MS (national, regional and local) and ERN data structures

From the French national rare disease registry (BNDMR) towards ITHACA ERN registry (ILIAD):

Data reusability to ease the burden of data entry

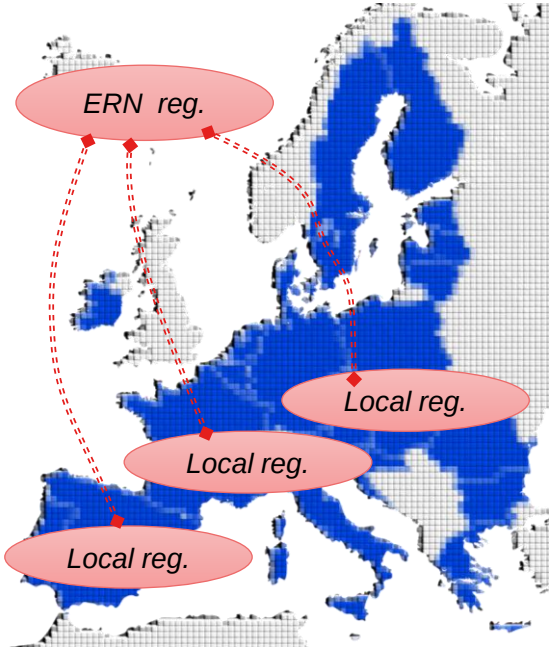
Arnaud Sandrin[1], Céline Angin[1], Morris Swertz[2], Fernanda De Andrade[2], Klea Vyshka[3,4], Alain Verloes[3,5]

contact.bndmr@aphp.fr

[1] French National Rare Disease Registry (BNDMR) - Assistance Publique-Hôpitaux de Paris, Paris, France | [2] University Medical Center Groningen, Dept. of Genetics, Genomics Coordination Center, Groningen, Netherlands | [3] Assistance Publique-Hôpitaux de Paris - Université de Paris, Department of Genetics, Paris, France | [4] CERCRID, UMR 5137, "Centre de Recherches Critiques en Droit", Université de Lyon, Lyon, France | [5] INSERM UMR 1141 "NeuroDiderot", Hôpital R DEBRE, Paris, France

BNDMR
Banque Nationale de Données Maladies Rares
bndmr.fr

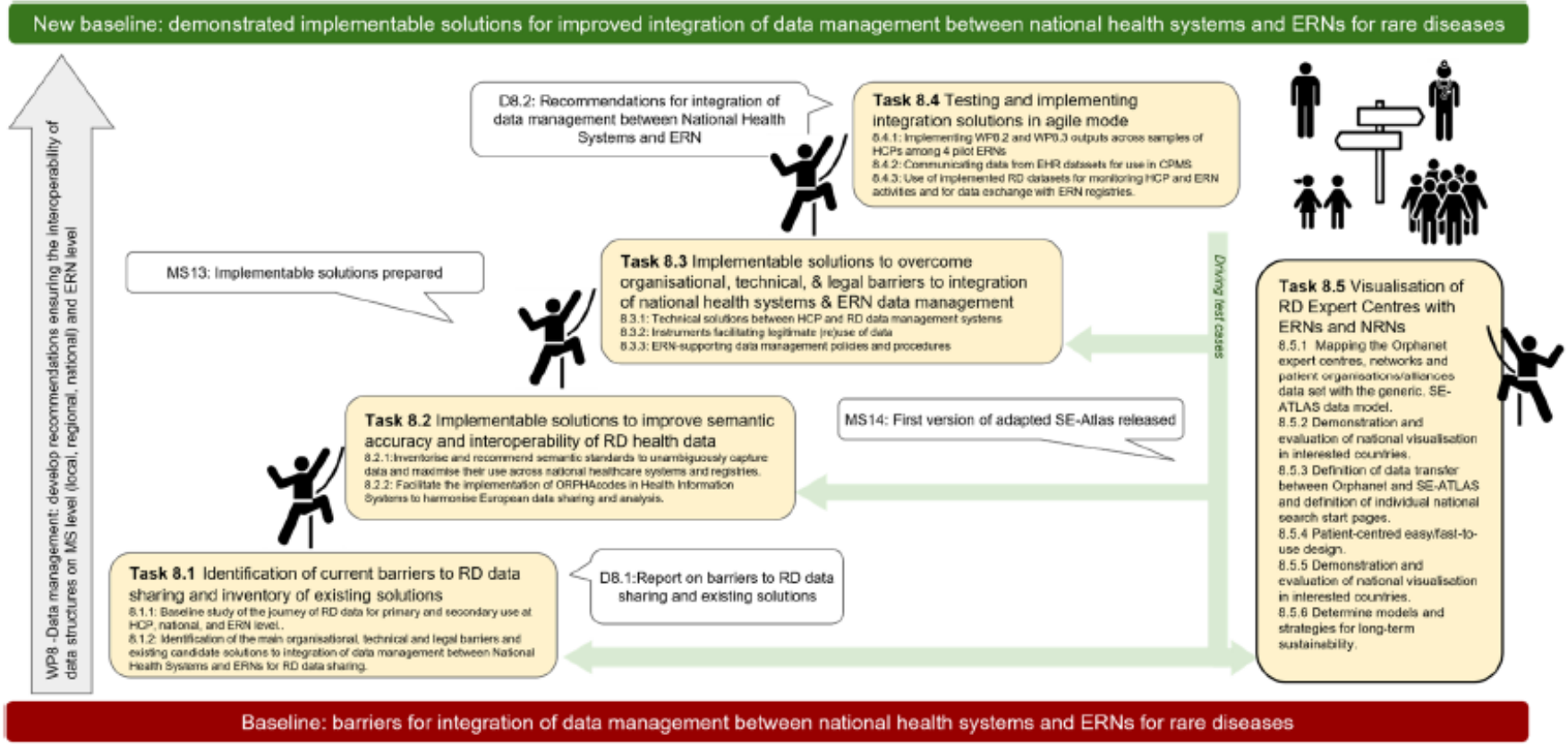
All European Reference Networks (ERN) are currently developing registries in order to collect or make Findable, Accessible, Reusable and Interoperable (FAIR) the **common data elements (CDE)** required by the European Joint Research Consortium (JRC) are



Connecting such a large number of local registries altogether is an unprecedented interoperability effort. It faces significant challenges of various sorts :

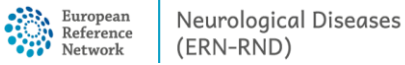
- **Regulatory** : patient re-information *and* inter-HCPs contracts requiring law and data protection regulation expertise
- **IT** : compliancy with interoperability international standards requires highly technical IT development and infrastructure expertise
- **Data** : managing inconsistencies, data duplication, data source tracing is mandatory in a fully automated system

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS



Supplementary Figure 2: Work Package 8. The objective of WP8 is to develop recommendations ensuring the interoperability of data structures on MS level (local, regional, national) and ERN level. WP8 follows a process that acknowledges the diversity between member states. Current barriers for integration per MS are analysed and existing solutions to address them are inventoried (Task 8.1, D8.1); existing solutions are tested and where needed reprocessed and documented to become implementable solutions for health systems in MS (Tasks 8.2, 8.3; MS13); improvement upon the baseline is tested and demonstrated in MS and HCPs selected using the baseline study in close collaboration with ERNs (Task 8.4). In parallel, a tool that helps patients and non-specialised medical professionals to find RD experts and expert centres is deployed to work in all MS (Task 8.5; MS14). Integration stewards will play an important role in developing guidance making WP8 recommended solutions implementable in national health systems of MS (Tasks 8.1-8.5; D8.2). The driving test cases (Task 8.4) are used throughout WP8, from helping define scope and requirements (Task 8.1) to testing and refining solutions (Tasks 8.2-8.5).

Involved partners : the 3 Neuro ERNs and ITHACA (for the genetic and neurodevelopmmental issues), supported by French registry on RD



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The actions of the 3rd national plan and the prospects of the 4th national plan around health data

o **WP Diagnosis :**

- The observatory for the diagnosis of rare diseases
- Genomic medicine and links with the France Genomic Medicine Plan (PFMG)
- Foetopathology
- Medical biology laboratories in liaison with clinicians for functional validations.

Focus 1:
REDUCING DIAGNOSTIC DELAYS AND UNDIAGNOSED DISEASES

Ensuring that practices are consistent and that diagnostic innovations are taken into account in the care provided to patients, based on a scientific, technological, clinical, regulatory and ethical watch.

To enable the production of annual dashboards giving an account of the evolution of diagnostic errancy and impasse in France, using the national database on rare diseases (BNDMR).

Interact with and be represented on the PFMG 2025 bodies

Strengthening the diagnostic axis with better knowledge of life and care pathways: strategic data for assessing public policies

Perspective PNMR4: Focus on actions for neonatal screening

- Medico-economic evaluation of neonatal screening candidates: medico-economic opportunity of these new screens (not implemented in France, but implemented in other countries) via a BNDMR-SNDS chain study

- Specific data collection added to BaMaRa for new neonatal screening: biannual retrospective study of these screenings to characterise the health status of patients who have undergone these screenings.

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o **WP Innovations and treatments:**

The BNDMR, matched with Assurance Maladie data (Social Security), will make it possible to carry out major public health studies for 6,000 rare diseases on the consumption of care and drugs, both in towns and hospitals, with 10 years' hindsight.

- The rare disease treatment observatory
- The collection of real-life data for early access and compassionate use
- Supporting market access for innovation in rare diseases

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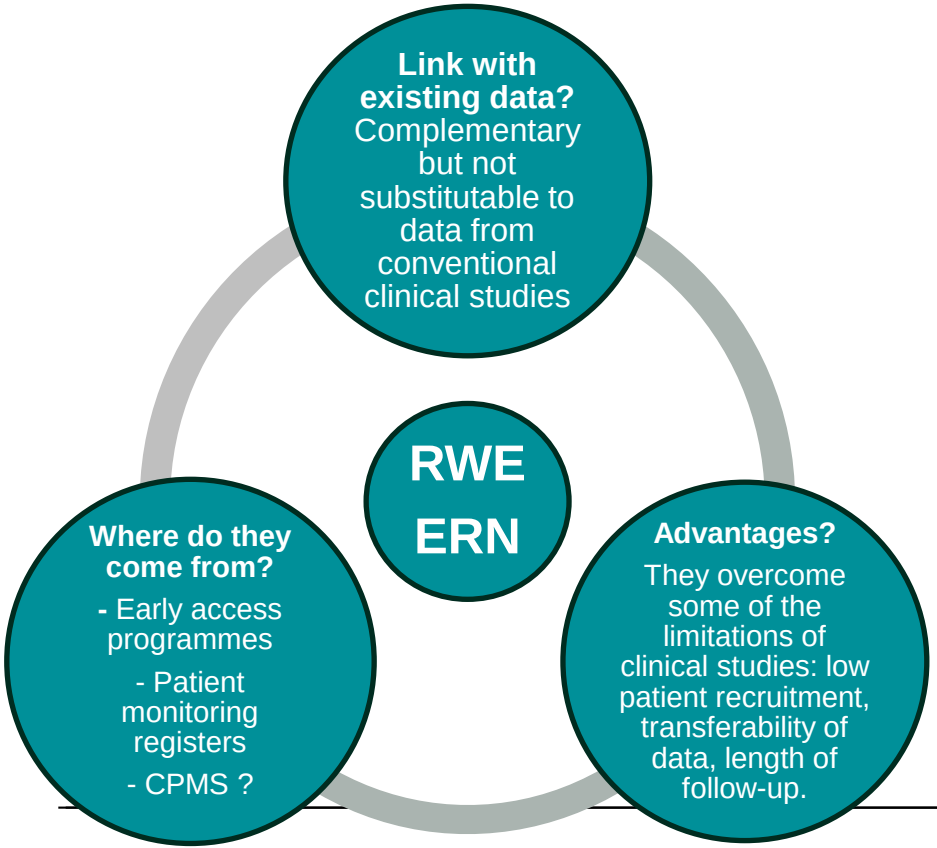
Real World Evidence - RWE

maladies rares



RWE allows health authorities and payers to

- Obtain **additional information** after bringing to market;
- **Re-evaluate the benefit** of a product, clarify its place in the therapeutic strategy;
- Enable the implementation **of innovative financing models** or the **product price revision** ;
- Obtain a marketing authorisation in a niche indication in the case of a **use outside the scope of the marketing authorisation** ;
- Have a **more global understanding** of the care pathway of rare disease patients.

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Background since 1999 Transforming research practices for rare diseases with patient and association involvement

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Association Française du Syndrome de Rett
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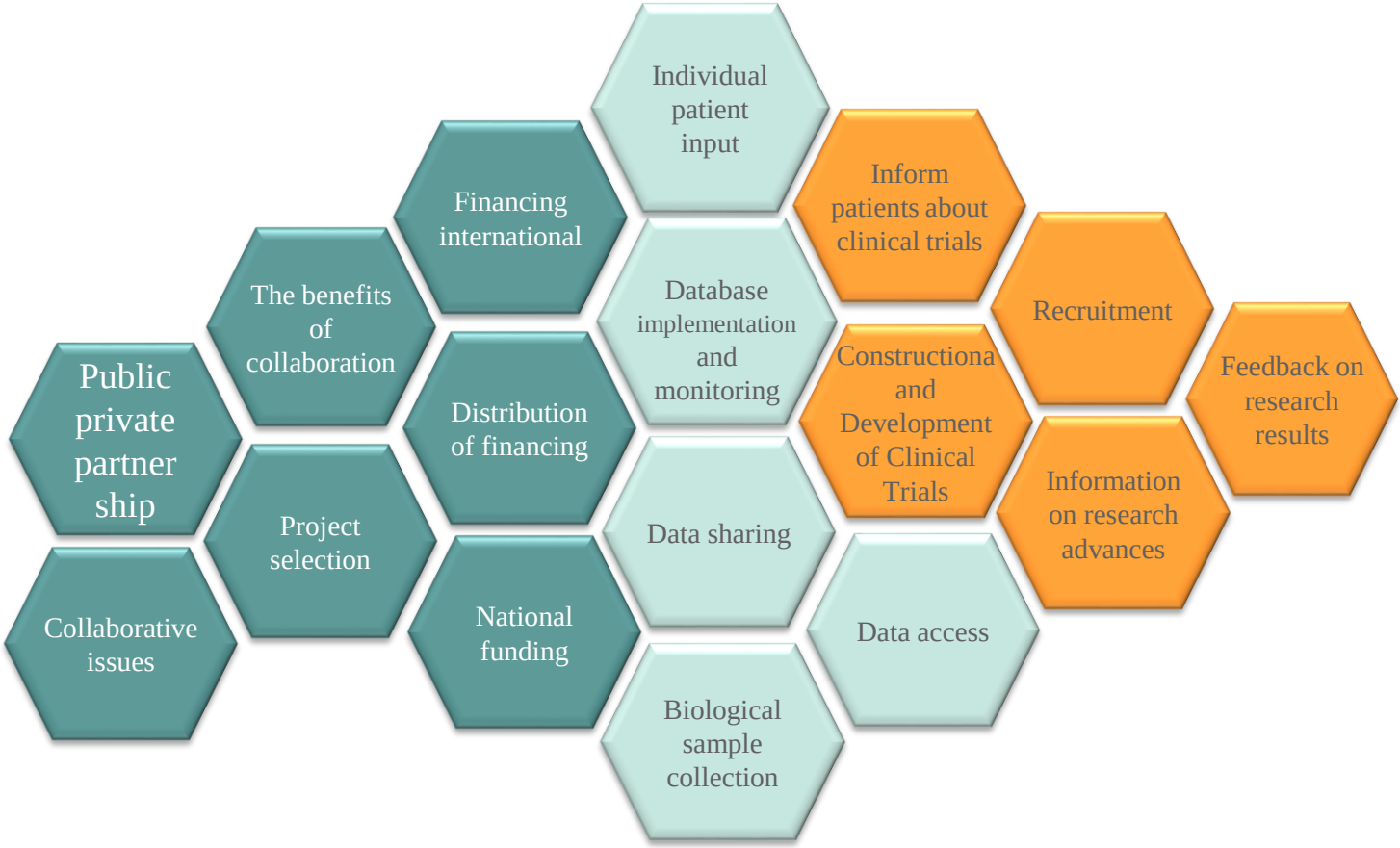

How to promote RD Research ?

- Identify ongoing research projects and existing research resources so as to share the results and make the best use of these efforts
- Continue to identify needs and priorities for basic, clinical, translational and social research making a link with centres of expertise
- Create new additional financial resources for research
- Cover biomedical, public health and social research,
- Foster participation of new researchers in EU-funded projects on RD
- Promote public-private partnership (help the bench-to-bed transfer)
- Find appropriate funding mechanisms for the long-term sustainability of research infrastructures such as biobanks, databases, registries, clinical research infrastructure… because of the nature of rarity
- **Involve patients, a prerequisite to develop the knowledge, to raise awareness and to ensure the dialogue between all actors**

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