

# FRENCH NATIONAL PLAN FOR RARE DISEASES 2018-2022

Sharing innovation,  
a diagnosis and a treatment  
for all



**maladies rares**



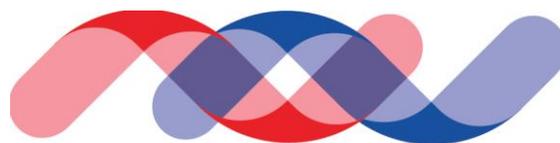
MINISTRY OF  
SOLIDARITY AND  
HEALTH

MINISTRY  
FOR HIGHER  
EDUCATION,  
RESEARCH AND  
INNOVATION



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# FOREWORD

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The Ministry for Solidarity and Health and the Ministry for Higher Education, Research and Innovation present the 3rd rare diseases plan (PNMR3).

Rare diseases concern a large number of people, representing more than 7,000 specific diseases and affecting over 3 million of our fellow citizens here in France.

This 3rd plan is the result of the concerted efforts of health professionals, researchers, pharmaceutical companies and patient associations, all committed to promoting an ambitious health and research policy designed to help patients with rare diseases and their families. The drafting of this plan was coordinated by two qualified persons: Professor Yves Levy, President of Aviesan (French national alliance for life sciences and health), and Professor Sylvie Odent, a professor of medical genetics and manager of a rare disease reference centre.

## **Why a 3rd rare diseases plan?**

The first two plans contributed to some major advances. They boosted our national excellence - in both treatments and research - and helped France become a European leader. However, this position needs to be further reinforced. Competence centres, reference centres and clinical networks now form the basis of an organisational structure ensuring access to care and expertise for all. This structure has also enabled the concentration of the clinical and biological data essential for treatment, prevention and research. The field of rare diseases is a remarkable one, in which the links between the organisation of care, the production of knowledge and the benefits to patients form a virtuous circle. The creation of cohorts and biocollections, and the identification of molecular defects help us to gain a greater understanding of molecular mechanisms, providing a platform for therapeutic innovations and new care strategies that can be assessed and made available to all thanks to the structuring of healthcare provision. Finally, the first plan encouraged patient associations and healthcare players to liaise more closely.

Nonetheless, the organisation of healthcare for these patients continues to pose some specific problems, related to access to a diagnosis, with a diagnostic delay that remains excessively long, requiring continued efforts in terms of structuring and coordination. These diseases also pose a number of specific research challenges. Given their rarity, they require the creation of national databases, which must be able to interact with European databases. These tools will make it possible to speed up the development of knowledge and the assessment of new care strategies and new treatments. Lastly, research into rare diseases falls within the general scope of the growing role of genomics in the elucidation of the molecular mechanisms

of diseases and, consequently, the challenges go beyond the actual diseases themselves. To meet these challenges, the 3rd plan is divided into 55 measures, grouped together into 11 focuses. In particular, it aims to:

- **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.**

We are acutely aware that, ultimately, the fight for life is a lonely one, with this sense of solitude ever present in people suffering from rare diseases. Yet this sense of solitude yearns for just one thing: the kindness of family, doctors and fellow citizens, giving each life the dignity it deserves.

With its third national plan, which lays down concrete, coherent measures, France is more determined than ever to continue its efforts and implement a proactive, inclusive policy, supported by the strong commitment of all partners.

**Agnès Buzyn**

Minister for Solidarity and Health

**Frédérique Vidal**

Minister for Higher Education, Research  
and Innovation



# EDITORIAL BY QUALIFIED PERSONS

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**A disease is described as “rare” in relation to its prevalence in the general population. However, on an individual level, for each person affected, it is “his or her own disease” and, hence, his or her unique need for care, treatments and support.**

**Since the implementation of the first national plan for rare diseases, significant progress has been made in terms of improving patient care and this long-term structuring has proved useful and beneficial. Today, the new plan has been designed to accentuate and accelerate the benefits that each patient, and their families, can derive from easier access to scientific advances and more efficient organisation of their medical and social care.**

## ***Why was it decided to launch a new rare diseases plan and how was it designed?***

The new national plan for rare diseases addresses a strong demand on the part of patients and, consequently, a request formulated by the Ministry for Solidarity and Health and the Ministry for Higher Education, Research and Innovation to two qualified persons. The aim is to drive a national momentum, underpinned by key measures that should lead to important improvements in terms of diagnosis, care provision, our understanding of these diseases and the development of effective treatments. As with the previous two plans, the method chosen brought together all the relevant stakeholders from the community, patient associations, Ministries, state agencies, health and research professionals and industry players, and care was taken to ensure the plan is in line with European Commission initiatives. This huge collective task

involved more than 160 people, working together to construct the plan, the name of which encapsulates its considerable ambitions: “Sharing innovation: a diagnosis and treatment for all”.

## ***What are the objectives of this new Plan?***

The Plan maintains the continuity of the previous plans’ ambitions, with the same determination to promote access to diagnosis, the emergence of new expertise, the prevention of disabilities and the physical, psychological and social suffering endured by patients with rare diseases, the improvement of care pathways, research and therapeutic innovation.

The new plan incorporates major changes and improvements and is hinged around three ambitions: to enable a rapid diagnosis for all, to innovate in order to treat, and to improve the quality of life and care pathway of patients.

In order to turn these ambitions into reality, two key levers have been identified: communication and training, on the one hand, and modernisation of organisations and national funding mechanisms on the other. All these objectives will be pursued with a constant focus on ensuring an overlap between care and research activities and with a determination to make sure rare disease clinical networks play a strong role in the implementation of all these actions.

## ***What are the main lines of the actions selected to achieve the desired advances set out in the Plan?***

To reduce diagnostic delays and undiagnosed diseases, the rare disease reference centre (CRMRs) system was restructured in 2017. The 2017-2022 labelling process was conducted for the 23 rare disease clinical networks: 109 CRMRs have been created, identifying 387 reference centres, 1,757 competence centres

and 83 resource and competence centres (CRCs). This system should form the foundation for renewed momentum in terms of the coordination of care pathways. In addition, the call for proposals underpinning this new labelling process made it possible to officially list competence centres for the first time.

The creation of a dynamic observatory for the monitoring of patients “without a diagnosis”, under the control of the clinical networks and reference centres, the management of patients in whom no diagnosis has been found, expert professional synergies hinged around complex diagnoses, with the more widespread implementation of multidisciplinary consultation meetings (RCPs) and earlier diagnoses are major actions included in this plan.

To boost innovation: more efficient access to treatments, with disease-based approaches instead of drug-based ones and amplification of the drug repositioning process; support adapted to rare diseases, to the emergence of innovation and better synergies between professionals, patients and industry, specific research projects designed to form a bridge between clinical practice and research; the sharing of national rare disease data with a constant view to interoperability with European and international databases in order to improve their collection, use and promotion.

To reinforce education and training: better sharing of teaching tools and the development of patient education in the field of rare diseases.

To encourage patient support: the promotion of quality for key moments in the care pathway, personalised medical-social, education and professional mechanism.

The plan also reflects an ambition to significantly improve the care of patients with rare diseases in French overseas regions.

On a national level, this plan is obviously conceived in line with the objectives of current national health strategy and ongoing public health policies, such as the France Genomic Medicine 2025 plan, the national e-Health 2020 strategy, the rare disabilities scheme and the 3rd cancer plan, as well as the revision of the law on bioethics. On an international level, it incorporates international challenges in the area of rare diseases, such as the new objectives of the International Rare Diseases Research Consortium (IRDiRC), the European Reference Network (ERN) structure and the future European research programme for rare diseases (European Joint Programme/EJP).

**In sum, this new plan stems from a determination and a duty to be ambitious, insofar as it should enable France to consolidate its position as an international leader in the fight to minimise the sense of isolation felt by patients with rare diseases and offer them the best chances. It has therefore been designed with three central aims: to provide a diagnosis, treatment and innovations to every patient concerned.**

**Sylvie Odent (PhD)**

Head of the Clinical Genetics Department,  
Rennes University Hospital Centre

**Yves Lévy**

President of Aviesan

## Definitions:

**Rare disease:** a disease that affects fewer than one in 2,000 people in the general population (definition from the European Regulation (EC) n°141/2000 on orphan medicinal products).

**Diagnostic delay:** the diagnostic delay is the period between the onset of the first symptoms and the date on which an accurate diagnosis is made.

**Undiagnosed disease:** an undiagnosed disease results from the failure to define the precise cause of the disease after having implemented all the investigations currently available. It concerns patients suffering from an atypical form of a known disease or from a disease for which the genetic or other cause has not yet been identified.



## Rare diseases: a few figures<sup>1</sup>

<b>7,000</b> rare diseases	<b>3,200</b> genes identified as responsible for rare diseases	<b>20%</b> of rare diseases are non-genetic	<b>350 million</b> patients with a rare disease worldwide and 3 million in France
<b>75%</b> of patients are children	<b>50%</b> of patients have no accurate diagnosis	<b>95%</b> of rare diseases have no curative treatment	<b>1/4</b> of people affected wait 4 years before a diagnosis is considered
<b>1.5 years:</b> average delay before a diagnosis is made and more than 5 years for 1/4 of people affected	<b>5</b> diseases for which there is neonatal screening	<b>12%</b> of new medicines are "orphan" medicinal products	<b>50%</b> of new gene therapies apply to rare diseases

1. Source: IRDiRC conference, Paris February 2017



## Resources:

- **23 national rare disease clinical networks (FSMRs) mirroring the 24 European reference networks (20 of which concern rare diseases);**
- **109 multi-site rare disease reference centres (CRMRS) formed from 387 reference centres and more than 1,800 competence centres or resource and competence centres;**
- **Over 220 patient associations.**

France created and hosts Orphanetz; it also hosts the secretariat of the IRDiRC and Eurordis.



## Main quantitative objective of PNMR3:

In line with the vision of the IRDiRC<sup>3</sup> consortium, this plan aims to ensure all people living with a rare disease receive an accurate diagnosis, care, and available therapy within one year of their first specialised medical consultation.

The only patients without an accurate diagnosis one year after their first consultation with a specialist are limited to those for whom current scientific and technical knowledge does not enable an accurate diagnosis to be made.

This plan also aims to ensure that all currently undiagnosable patients enter a globally coordinated diagnostic and research pipeline.

2. Information programme on rare diseases and orphan medicinal products

3. If a rare disease is suspected, an accurate diagnosis made within a year following the first consultation with a specialist when the molecular basis of the disease is known, and 1,000 new treatments developed by 2027.

**A NATIONAL PLAN  
CONVEYING  
5 AMBITIONS HINGED  
AROUND 11 FOCUSES**





Following two successive national plans leading to genuine advances in terms of the organisation of care of rare disease patients in France, the issue of diagnostic delay remains central, with more than half of all patients without an accurate diagnosis. In addition, the number of available therapies remains extremely limited.

The current context of development of molecular diagnostic methods and the adoption of the France Genomic Medicine 2025 plan (PFMG) is particularly favourable in terms of reducing diagnostic delays and undiagnosed diseases and positioning France as a leader in the organisation of rare disease care and research in Europe.

This third rare diseases plan (PNMR3), drafted in consultation with the principal professionals and patient associations, aims to address the recommendations resulting from evaluation of the second plan (PNMR2) conducted by the French High Council for Public Health (HCSP) and the French High Council for the Evaluation of Research and Higher Education (HCERES).

Its link with European initiatives relative to rare diseases is crucially important. The PNMR3 is, thus, in line with the vision of the international IRDiRCs consortium, aiming to ensure all people living with a rare disease receive an accurate diagnosis, care, and available therapy within one year of their first specialised medical consultation.

In this respect, the national rare disease clinical networks (FSMRs) set up in 2014 play a particularly important role, in relation to the European reference networks (ERNs) recognised by the European Commission in March 2017. The FSMRs will, thus, form the organisational bedrock of the PNMR3 and will be identified as driving forces behind the development of research and innovation.

The third national plan for rare diseases (PNMR3) carries with it 5 ambitions:

- To enable a rapid diagnosis for all in order to reduce diagnostic delays and undiagnosed diseases;**
- To innovate in order to treat, so that research increases therapeutic resources;**
- To improve the quality of life and autonomy of patients;**
- To communicate and train, promoting the sharing of knowledge and expertise in the field of rare diseases;**
- To modernise organisations and optimise national funding mechanisms.**

4. The first plan defined the national landscape, creating a network of reference centres for rare diseases. This territorial network has significantly improved access to care and patient management. It is also a powerful instrument for medical research and healthcare professional training. The first plan also promoted Orphanet (created in France in 1997 on the initiative of France's National Institute for Health and Medical Research (Inserm) and the General Directorate for Health (DGS) and supported by the European Commission since 2001), as the reference portal for all information concerning rare diseases, developing the provision of information for the general public and emergency services on the site.

- The second plan further enhanced the reference centre system, with the creation of 23 rare disease clinical networks, grouping together all the players involved in patient care, research development and international visibility in each of the specific fields of rare diseases. By creating these clinical networks, the plan enabled France to very quickly establish the organisational structure required to aid its integration within the European Reference Networks (ERN) and to help improve the cross-border care of patients.

5. If a rare disease is suspected, an accurate diagnosis made within a year following the first consultation with a specialist when the molecular basis of the disease is known, and 1,000 new treatments developed by 2027.

It is organised around 11 focuses:

- **Focus 1: REDUCING DIAGNOSTIC DELAYS AND UNDIAGNOSED DISEASES**
- **Focus 2: IMPROVING NEONATAL SCREENING AND PRENATAL AND PREIMPLANTATION DIAGNOSTICS TO ENABLE EARLIER DIAGNOSIS**
- **Focus 3: SHARING DATA TO AID DIAGNOSIS AND THE DEVELOPMENT OF NEW TREATMENTS**
- **Focus 4: PROMOTING ACCESS TO TREATMENTS IN RARE DISEASES**
- **Focus 5: GIVING NEW MOMENTUM TO RESEARCH IN THE FIELD OF RARE DISEASES**
- **Focus 6: PROMOTING THE EMERGENCE OF AND ACCESS TO INNOVATION**
- **Focus 7: IMPROVING CARE PATHWAYS**
- **Focus 8: FACILITATING THE INTEGRATION OF PEOPLE WITH RARE DISEASES AND THEIR CARERS**
- **Focus 9: TRAINING HEALTH AND WELFARE PROFESSIONALS TO BETTER IDENTIFY AND MANAGE RARE DISEASES**
- **Focus 10: REINFORCING THE ROLE OF RARE DISEASE CLINICAL NETWORKS IN CARE AND RESEARCH ISSUES**
- **Focus 11: SPECIFYING THE POSITIONING AND MISSIONS OF OTHER NATIONAL PLAYERS IN THE FIELD OF RARE DISEASES**

Each focus will be steered by a national project leader, who will work with the relevant players to develop detailed action sheets defining the schedule for roll-out of actions and follow-up and results indicators. The actions will be delegated to a national operator where appropriate. Patient associations and healthcare professionals will be closely involved in the roll-out of actions. All the actions will be conducted in accordance with the necessary ethical principles and with a view to reducing social inequalities.

PNMR3 will supplement other national initiatives in the field of rare diseases, aimed at structuring care and research activities. These initiatives include:

- **The France Genomic Medicine 2025 national plan and the cancer plan, which serves as a reference for personalised medicine strategies;**
- **National health strategy;**
- **National e-health strategy;**
- **The national roadmap of the Interministerial committee for disability;**
- **The rare disabilities scheme and the circular of 2 May 2017 concerning the transformation of medical and social service provision;**
- **National occupational health strategy;**
- **The national health data system;**
- **Regional health agencies (ARS) via their regional health projects (PRS).**



# FOCUS 1: REDUCING DIAGNOSTIC DELAYS AND UNDIAGNOSED DISEASES



## Context

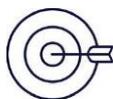
Today, only one in two people with a rare disease has an accurate diagnosis and more than a quarter of patients wait longer than 5 years for a diagnosis. **Diagnostic delay** results in a potential worsening of the patient's condition, delayed access to genetic counselling options and the wasting of medical resources (multiplicity of diagnostic consultations).

**Undiagnosed diseases** result from the failure to define the precise cause of the disease after having implemented all the investigations currently available. This situation makes management more difficult and the undefined nature of the disease is a source of additional suffering. Undiagnosed diseases concern atypical forms of known diseases or diseases for which the genetic cause has not yet been identified.

Following two public health plans for rare diseases and the launch of the France Genomic Medicine 2025 plan, PNMR3 aims to **reduce diagnostic delays and undiagnosed diseases**. After PNMR3, the only patients without an accurate diagnosis within one year following their first consultation with a specialist will be those for whom current scientific and technical knowledge does not enable an accurate diagnosis to be made.

### Links with other national plans and programmes:

- **France Genomic Medicine 2025 plan which, under controlled ethical and organisational platform access conditions, will help reduce undiagnosed diseases.**



## Objectives

- **To structure and harmonise diagnostic strategy in order to reduce diagnostic delays;**
- **To regularly reassess the cases of currently undiagnosed patients in order to obtain a diagnosis in light of scientific advances.**



## Action

**Action 1.1: Encourage the management of any person with or suspected of having a rare disease within a rare disease reference centre (CRMR)**

6. ERRADIAG declarative survey (February 2016, Rare Diseases Alliance)

7. Currently, 3,200 genes have been identified, enabling the cause of 4,500 rare diseases to be defined.

- Awareness-raising campaigns (in particular via the Rare Diseases Info Service (MRIS), associations, learned societies, the College of General Medicine (CMG), the bulletins of professional associations) and training initiatives for physicians will be organised so that all potential sufferers of a rare disease can be systematically referred to a rare disease competence centre (CCMR) or a rare disease reference centre (CRMR) with a view to a more rapid diagnosis.

### **Action 1.2: Structure genetic and non-genetic diagnostic provision**

With the support of FSMRs, the French Biomedicine Agency (ABM) and Orphanet, in particular, it is necessary to:

- Make the organisation of and links between diagnostic technical facilities (biochemistry, haematology, pathology, foetal pathology, electrophysiology and imaging, molecular genetics laboratories, the NGS platforms of PFMG 2025) more transparent and disseminate this information to professionals and the general public;
- Monitor and annually analyse the activities of genetics laboratories in the field of rare diseases;
- More routinely involve molecular genetics laboratories in the work of FSMRs;
- Assess the needs of these laboratories on the basis of scientific and technological advances in genetic diagnostic tools;
- Specify the contribution of ERNs and their interface with FSMRs in diagnostic service provision.

### **Action 1.3: Define and organise access to the ultra-high-throughput sequencing platforms of the France Genomic Medicine 2025 plan**

It is necessary to:

- **Define and set up a mechanism for controlled access to the national platforms of PFMG 2025 for the diagnosis of rare diseases, supported by measure 6 of this plan and the implementation of multidisciplinary consultation meetings (RCPs) before and after ultra-high-throughput sequencing, directly involving the CRMRs and the molecular genetics laboratories.**

### **Action 1.4: Establish a diagnosis observatory, supported by the clinical networks steering committee**

- The FSMRs will help set up this observatory, which will act on two operational levels: within the multidisciplinary committees of each FSMR and via a cross-disciplinary group dependent on the steering committee (COFIL) of the FSMRs (see Actions 10.1 and 10.2);
- The objective of this observatory will be to ensure the consistency of practices and the incorporation of diagnostic innovations in the management of patients, supported by scientific, technological, clinical, regulatory and ethical surveillance activities.
- It will enable the production of annual indicators, in particular relative to diagnostic delay and undiagnosed disease evolutions in France, drawing on the national rare disease data bank (BNDMR);
- It will be required to interact with and be represented in PFMG 2025 bodies;

### **Action 1.5: Organise and promote the systematic implementation of multidisciplinary consultation meetings**

The implementation of multidisciplinary consultation meetings (RCPs) helps improve the security of the diagnosis:

- Their composition, content and operating methods are defined by the FSMRs in consultation with the genetics laboratories;
- Upstream and downstream RCPs will be systematically implemented in all CCMRs and CRMRs;
- An RCP tool will be made available to CRMRs, CCMRs and FSMRs for the conduct of RCPs;
- The arrangements for recourse to the expertise of the ERNs during multidisciplinary consultation meetings will be defined by the FSMRs.

### **Action 1.6: Structure foetal pathology and neonatal autopsy activities in liaison with the CRMRs and the multidisciplinary prenatal diagnosis centres (CPDPNs)**

It is necessary to:

- Prepare an inventory of the requirements for these activities in consultation with the FSMRs and the multidisciplinary prenatal diagnosis centres (CPDPNs);
- Perform a review of the current organisation of these activities and assess whether the requirements are consistent with this organisation.

**Action 1.7: Task the CRMRs, with the support of the FSMR, with compiling a dynamic national registry<sup>8</sup> of currently undiagnosable patients on the basis of the national rare disease data bank (BNDMR)**

Patient cases need to be re-assessed as knowledge and technologies advance. This will reduce the risks of loss of opportunity in terms of treatment. It is particularly important on a diagnostic level.

It is necessary to:

- Construct an interoperable national registry drawing on data from the national rare diseases data bank (BNDMR) for people identified as “without a diagnosis” in the minimum data set;
- Promote the implementation of research projects (see focus 5): this registry will facilitate the implementation of research projects concerning undiagnosed diseases. Wherever possible, it will be combined with biobanks that have already been compiled (identified by the FSMR) or, if applicable, with new biobanks depending on the requirements identified;
- Task the diagnostic observatory (see action 1.4) with the production of an annual review of the data collected and the studies conducted using this registry.



### Cost

- Undiagnosed diseases registry: MIG (work in the public interest) funding of €3 million/year, i.e. €15M over 5 years
- RCP tool: MIG funding of €500 K once in 2018



### Time-frame

2018:

- Setting up of the diagnostic observatory;
- Organisation of systematic upstream and downstream RCPs;
- Start of construction of the national registry of currently undiagnosable patients.

Continuation of work to structure the provision of genetic - in liaison with the BNDMR - and non-genetic diagnostic service provision.

2019:

- Roll-out of the national registry of currently undiagnosable patients;
- Structuring of foetal pathology and neonatal autopsy activities.



### Leader

- Leader: General Directorate for Care Provision (DGOS);
- In collaboration with General Directorate for Research and Innovation (DGRI).

8. Registry in the Anglo-Saxon sense of the term, i.e. a structured data warehouse.

# FOCUS 2: IMPROVING NEONATAL SCREENING AND PRENATAL AND PREIMPLANTATION DIAGNOSTICS TO ENABLE EARLIER DIAGNOSIS



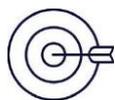
## Context

The 2018-2022 National Health Strategy in France and the Priority Prevention Plan aim to:

- Reinforce neonatal screening and assess the possibilities of increasing the number of diseases screened for - particularly rare diseases -, ensuring a high quality, coordinated downstream care pathway in each region;
- Guarantee access to prenatal diagnosis.

The aim of the French national neonatal screening (NNS) programme is to ensure the secondary prevention of diseases with a high level of morbidity and mortality for which the manifestations can be prevented or minimised by appropriate treatment when initiated very soon after birth. The programme currently concerns 5 rare diseases (phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis and sickle cell disease in at-risk infants), along with permanent congenital hearing loss that may be a sign of rare disease. To extend the scope of the diseases screened for, prior evaluation by the French National Authority for Health (HAS) and the opinion of the French Biomedicine Agency (ABM) are also required.

The possible impact of NGS sequencing on the performance of prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) must be anticipated, both in terms of resources and in terms of organisation of a reflection process concerning the ethical issues raised and the existing regulatory framework. Preparations for the revision of the bioethics law are an ideal opportunity to implement this reflection process.



## Objectives

- **To increase the number of diseases screened for as part of the national neonatal screening programme;**
- **To accelerate the implementation of new neonatal screening tests;**
- **To reinforce resources for PND and PGD depending on requirements;**
- **To tackle the ethical and regulatory issues raised by PND and PGD and the performance of postnatal screening in the general population, in the context of revision of the bioethics law.**



## Action

### **Action 2.1: Complete the regional and national reorganisation of neonatal screening in 2018, a necessary prerequisite to the implementation of new screening tests involving biomedical investigations.**

- The existing national and regional organisational structure, hinged around associations, was modified on 1 March 2018 by the establishment of a regional neonatal screening centre (CRDN) in each region, designated by the regional health agency and located in university hospital centre (CHU), and by the designation of a national coordinating centre in the second half of 2018. In their region, CRDNs will all liaise with the CRMRS responsible for the diseases screened for, within which reference doctors for the various diseases screened for will be responsible for confirmation of the diagnosis and follow-up of diagnosed infants. The aim of this revised organisation is notably to facilitate the implementation of new neonatal screening tests;
- As regards the national neonatal screening programme for infants in French overseas regions, the majority of biomedical investigations are currently performed in mainland France, and this will remain the case. The time-frame for the implementation of the screening programme within the new organisation will be a focus of attention.

### **Action 2.2: Accelerate the implementation of new neonatal screening tests**

- **Monitoring the scope of the neonatal screening (NNS) programme:** in the context of the reorganisation of neonatal screening, the HAS will now be responsible for permanently monitoring NNS being trialled or considered in France or elsewhere in the world, or already implemented in another country, enabling optimal anticipation of the evaluation of new screening tests. This monitoring is currently in the process of being organised within the HAS;
- **Updating by the HAS of criteria enabling recommendation of new NNS tests:** in 2018, the HAS has begun a methodological reflection process relative to the criteria and conduct of the assessment procedure it uses to issue opinions with respect to the implementation of a new NNS test. A comparison with the methods and criteria used on an international level will be conducted;
- **Use of genetic tests (target gene panels) in place of conventional biological tests in the context of NNS:** the assessment of biological tests is part of the prior assessment of an NNS test conducted by the HAS, in collaboration with the ABM where appropriate. The use of genetic tests will be assessed by the HAS as part of its regulatory mission and within the updated methodological framework as defined.

### **Action 2.3: Adapt access to prenatal diagnosis (PND) to evolving technologies**

- **Reinforce the links between PND players:**
  - o Ensure a closer link between CPDPN consultations and CRMRS consultations in the field of prenatal diagnosis (PND);
  - o Better identify, preserve and reinforce the expertise of the players currently involved in PND (consultation of CRMRS and specialised genetics laboratories for rare diseases groups).
- **Assess needs and adapt the resources of genetic laboratories participating in PND (in accordance with the legal framework governing PND):** the growing identification - due, in particular, to NGS techniques - of genes responsible for rare diseases expands PND possibilities. "Molecular" PND is only possible if one or more pathogenic variants have first been identified, irrespective of whether an NGS or conventional method is used. In order for PND provision to develop in parallel with these discoveries, it is necessary to identify the needs (and adapt the resources) of specialised genetics laboratories for rare disease groups involved in PND so that PND implementation time-frame requirements are met for waiting couples;
- **Rules for access to France Genomic Medicine Plan platforms:** Make access to PFMG 2025 platforms a priority for family sequencing requests within the context of a PND process when the use of these platforms is necessary;
- **Ethical issues related to NGS in the context of PND:** identify all the ethical questions raised by the use of NGS in the context of PND in order to consider these issues as part of the preparations for revision of the bioethics law. This action is under way.

#### **Action 2.4: Meet preimplantation genetic diagnosis (PGD) needs**

- **Ethical issues related to NGS in the context of PGD:** PGD activities are very closely regulated in terms of procedures and objectives. The issue of recourse to NGS for PGD has been raised. As part of the preparations for revision of the bioethics law, it is necessary to identify all the ethical questions raised by NGS in the context of PGD. This action is under way. In particular, concomitant testing for chromosomal defects, alongside the PGD process, which the regulations stipulate must be focused on a gene, is currently prohibited and could be discussed within the framework of this revision;
- **Evaluate the possible contribution of NGS techniques:** an NGS approach could reduce the time it takes to develop a diagnostic test and hence the waiting time for each couple. Once the ethical and regulatory obstacles have been identified, pilot studies assessing the contribution of NGS in the context of PGD (reduction in development time and waiting time for couples, relative efficacy, etc.) could be envisaged .

#### **Action 2.5: Put in place interactive electronic consent for the genetic diagnosis process**

- Given the development of genetic diagnosis by whole exome or whole genome sequencing for rare diseases, in conjunction with PFMG 2025, it is necessary to:
  - o Provide patients with all the information they need to give their informed consent for the genetic diagnosis process and the use of the resulting data for research purposes;
  - o Better guarantee the conditions for information and informed consent, within a time interval adapted to each case, in a complex context. This implies a prior assessment of the technical, regulatory and ethical obstacles. This reflection process will be conducted in the context of the revision of bioethics laws. If the implementation conditions are feasible, consent could be linked to the patient's shared medical record (DMP), which will include a rare diseases section. These arrangements would make it possible for patients to modify their consent in the course of their care pathway, with the option of withdrawal of consent using the "blue button"<sup>9</sup>.

#### **Action 2.6: Modify the legislation to allow post mortem access to genetic traits**

- Today, the post mortem access to an individual's genetic traits is legally authorised only if the person has previously given his/her express consent. This prevents post mortem diagnoses that could be useful in preventive terms for the family of the deceased individual. A legislative change is essential and could be envisaged within the context of the revision of the bioethics law in 2018.

#### **Action 2.7: Conduct a reflection process concerning screening for rare diseases in the general population, with priority given to performance of an international analysis**

Screening of the general population, free from any known genetic diseases or mutations in target or non-target genes (actionable genes, i.e. those liable to mobilise preventive and/or curative measures, or even non-actionable genes) raises numerous important ethical questions, despite being technically possible today. The question is particularly relevant in the pre-conception period, primarily for the genes targeted, particularly since this type of screening is authorised in some countries for rare diseases with a significant prevalence.

It is essential to begin by conducting an ethical reflection process, supported by the French national ethics committee (CCNE). Preparations for revision of the bioethics law is an ideal opportunity to launch debate concerning the issues raised.

9. Registry in the Anglo-Saxon sense of the term, i.e. a structured data warehouse.



## **Cost**

Project to extend neonatal screening from 2019 worth €1.8 million, i.e. €7.4 million over 5 years - pending, dependent on revision of the Bioethics law and the Social Security Financing Bill (PLFSS)



## **Time-frame**

- Finalisation of reorganisation of NNS in 2018.
- Structuring by the HAS of NNS monitoring activities and launch of a reflection process concerning NNS assessment criteria in 2018.
- Launch of a reflection process in 2018 concerning extension of the scope of NNS.



## **Leader**

- Leader: DGS
- In collaboration with DGOS, DGRI, DSS, HAS, ABM, CCNE

# FOCUS 3: SHARING DATA TO AID DIAGNOSIS AND THE DEVELOPMENT OF NEW TREATMENTS



## Context

A major obstacle to identifying new diseases, understanding their mechanisms and hence diagnosing them, managing and treating them, is related to the inability to collect pertinent, good-quality data and to match, analyse and exchange this data. Due to the rarity of the diseases concerned, complex data for each patient needs to be compared with a large number of national and international, multiple and heterogeneous, genetic and clinical data from patients presenting similar diseases. However, the rare disease data warehouses constructed by the CRMRs and the FSMRs are numerous, dispersed and heterogeneous. The creation of new, high quality, accessible, interoperable and reusable data warehouses for rare diseases ("FAIR<sup>10</sup>" data) is, therefore, crucially important in order to accelerate research in the field of rare diseases and improve care. This work focus will need to be studied in conjunction with work to pre-develop the "Health Data Hub", the health data analysis laboratory launched by the French Ministry of Solidarity and Health.



## Objectives

The objective is to develop the collection and exchange of good-quality data on rare diseases to promote their analysis and use for the benefit of patients. This will be achieved via:

- **the deployment of the national rare diseases data bank (BNDMR), which will collect a minimum data set for all CRMR patients;**
- **the development of FAIR data warehouses, interoperable with European or international data warehouses;**
- **the implementation of conditions for the reuse of data collected using e-health tools for research in the field of rare diseases.**

10. Findable, Accessible, Interoperable and Reusable.



## Action

### Action 3.1: Deployment of the BNDMR in CRMRS in conjunction with hospital information systems

- The BAMARA application based on a minimum data set for rare diseases (SDM-MR) and interoperable with hospital information systems (computerised patient record - DPI) enables the collection of named care data within CRMRS. It will be used in all rare disease centres;
- The integration and anonymisation of data collected in BAMARA within a national rare disease warehouse that could be matched with other databases (French national health data system (SNDS), cohorts, registries etc.).

This mechanism, with objectives specific to each of these two pillars, will enable strategic and medical steering of the CRMRS, provide the indicators required to monitor the plan and enable the implementation of studies that can generate new knowledge in the field of rare diseases, professional practices or the feasibility of clinical trials.

### Action 3.2: Support the collection of clinical and biological data, from cohorts and registries, for their compilation, use and valuation.

- France will participate via INSERM in the rare disease "implementation network" of the Go-FAIR<sup>11</sup> initiative, which will help define interoperability standards for data warehouses on rare diseases;
- The development of the ORPHA nomenclature and links with other medical and disability-related terminologies will be continued by Orphanet in order to make it the reference nomenclature;
- Warehouses of secure data that can be used for research and complying with FAIR principles will be developed within FSMRS hinged around innovative research projects. They will, therefore, be interoperable with the BNDMR, with the rare disease data warehouses of the ERNs, and with the future data platform of the EJP for Rare Diseases (EJP-RD). These projects will be selected in two phases via a call for proposals aimed at FSMRS. "FAIR Data" certification will then rapidly be sought;
- A unit to support the assembly of data warehouses will be created, linked to the RaDiCo (Rare Disease Cohorts) programme, the platform of which meets the necessary security, quality and interoperability criteria. It will offer data warehouse coordinators methodological support for the collection of FAIR data, in liaison with the "implementation network" of the GoFair initiative mentioned above.

### Action 3.3: Implementation of conditions for the reuse of data collected using e-health tools for research in the field of rare diseases

All the e-health tools used in the context of national e-health policy must be mobilised for the benefit of rare diseases, both in terms of research in this field and fair access to care (see focus 7).

As regards research, this action will aim to facilitate the implementation of a dynamic electronic consent process, the secure sharing of healthcare data for research and feedback of research results to patients. Preparations for revision of the bioethics law. This action is under way.



## Time-frame

Deployment of BAMARA in all CRMRS in 2018 Implementation of the BNDMR in 2019

In 2019, selection of 5 FSMRS to lead a project for a period of 4 years.

In 2021, selection of a further 5 FSMRS to lead a project for a period of 4 years.

11. Principles defined by the IRDIRC for data harmonisation and interoperability: Findable, Accountable, Interoperable, Reusable



## Cost

National rare disease data bank (BNDMR):

- o €600k/year, i.e. €3 million for the period of the plan to fund the operational unit;
- o €3 million to support the deployment of the rare disease module in the computerised data records (DPIs) as a single instalment in 2018.

New FAIR data warehouses: €1.6 million per project.



## Leader

- DGRI and DGOS;
- In collaboration with the DGS and the DSS.

# FOCUS 4: PROMOTING ACCESS TO TREATMENTS IN RARE DISEASES



## Context

The incentives put in place on both a European Union level (Regulation (EC) No 141/2000 of the European Parliament and the Council) and a national level have promoted research/development in the field of rare diseases for almost 18 years and have led the European Medicines Agency to grant more than a hundred marketing authorisations for “designated orphan medicinal products”. However, numerous therapeutic needs remain unmet by medicinal treatments authorised for the treatment of rare diseases.

In this context, off-label practices have developed on the ground for the treatment of rare diseases. These have not been exhaustively identified at present and the patients benefiting from them have not been the subject of precise, systematic follow-up that would make it possible to elucidate these practices, demonstrate their relevance and, if applicable, regulate them via the establishment of a temporary recommendation for use (RTU) by the French National Agency for the Safety of Medicines and Health Products (ANSM). Off-label prescription also raises the question of the covering of costs, which is an area that needs to be looked at closely.



## Objectives

- **To promote rapid access by patients to therapeutic innovations that are already authorised or in the process of being so;**
- **To reinforce real-life knowledge of medicinal products authorised in the treatment of rare diseases;**
- **To have access to a regularly updated inventory of therapies (medicinal products, medical devices, non-medicinal treatments) offered to patients in the treatment of rare diseases, be they products in the development pipeline, medicines or products prescribed outside the authorised framework, medical techniques, in order to be able to detect new substances of interest, substances to be repositioned, to identify interesting proofs of concept, off-label uses, non-medicinal approaches or development or investment needs;**
- **To attempt to regulate off-label prescribing practices by establishing a temporary authorisation for use (RTU) when the available data are deemed to be insufficient by the ANSM or, failing this, improve knowledge of these practices.**



## Action

### **Action 4.1: Use existing upstream assessment mechanisms more systematically in order to accelerate the registration of medicinal products and medical devices**

- Patient associations and rare disease experts could consult pharmaceutical companies to encourage the more systematic use of the HAS upstream assessment process (Early meetings, procedure for “medicinal products assumed to be innovative”, fast-tracking / accelerated procedures, etc.).

### **Action 4.2: Create an observatory of treatments within multidisciplinary consultative assessment committees in each rare disease clinical network**

- To detect new substances of interest, substances to be repositioned, interesting proofs of concept, relevant off-label uses, and interesting non-medicinal approaches;
- To identify innovative medical devices helping to improve patient care and/or follow-up;
- To identify development or investment needs;
- To support the development of opinions designed to advise patients and health professionals in the choice of reliable and medically relevant connected objects (a number of which can be qualified as medical devices).

This action will be rolled out in close liaison with national operators (ANSM, HAS, CNAMTS, OMEDIT, ARS) but also with European operators.

### **Action 4.3: Manage real-life knowledge in order to reinforce knowledge of medicinal products with an MA for one or more indications in the treatment of rare diseases and set up a national organisation for the real-life follow-up of medicinal products.**

- Promote the implementation of medico-economic studies or real-life studies to generate and collate data for all medicinal products with a marketing authorisation for the treatment of a rare disease and certain relevant medical devices. Calls for proposals such as PREPS (Performance for health systems) or PRME (Medico-economic research programme) could support studies of this type;
- Organise data collection by CRMRS and CCMRs using a methodology enabling the follow-up of these data in real-life conditions using a disease-based method rather than drug by drug, drawing on existing databases, registries and cohorts;
- Schedule the collection of a minimum data set by CRMRS for all off-label uses in order to elucidate practices. To this end, the minimum data set of the national data bank must be determined as soon as possible;
- Guarantee the effectiveness of data collection implemented in the context of temporary recommendations for use (RTUs) and temporary authorisations for use (ATUs) established or issued in the treatment of rare diseases;
- Make use of data collected by patients and families (e.g. via rare disease communicating record, via expert patients, via mechanisms such as COMPILIO, etc.);
- For medical devices, the French national committee for the assessment of medical devices and health technologies (CNEDIMTS) may request additional studies or real-life studies in the context of its assessment of a device or a device category.

### **Action 4.4 Better regulate off-label prescribing practices**

Proposals, to be examined in conjunction with the ANSM, the FSMRs, the CRMRS and the stakeholders within a working group, will be worked upon within the framework of PNMR3 in order to develop proposals for adaptation of the RTU system to the specificities of rare diseases.

These will be based, in particular on:

- the organisation of a survey to be conducted by the rare diseases clinical networks (FSMRs) and the rare diseases reference centres (CRMRS) enabling the preliminary identification and prioritising of indications and medicinal products that are candidates for an RTU;
- the establishment of dynamic off-label prescription follow-up using the rare disease module of computerised patient records (DPI);
- National care and diagnosis protocols (PNDS), the development of which schedules identification of medicinal products prescribed off-label, will indicate the off-label prescriptions considered relevant by the FSMRs and the CRMRS following the abovementioned survey. PNDS must, nonetheless, indicate that the medicinal products concerned are not covered by the national health insurance system in these uses;
- The performance of clinical trials, asking the FSMRs to mobilise available funding sources: "University Hospital Networks calls for projects (RHU of the French "Investissement Avenir" ("Investments for the future") programme), Clinical research hospital programme (PHRC<sup>12</sup>), calls for proposals for the funding of non-commercial research<sup>13</sup>. These trials will make it possible to increase the available data concerning the off-label prescribing practices given priority within each clinical network with a view to making them eligible for an RTU.



## Time-frame

- 2018:
- Organisation of the survey to be conducted by FSMRs and the CRMRS enabling the preliminary identification and prioritising of indications and medicinal products that are candidates for an RTU.
- 2019:
- Establishment by each clinical network of applications, supported on the basis of current scientific and technical knowledge, concerning medicinal products that are candidates for an RTU, aimed at the ANSM. There will be upstream consultation between the ANSM and the clinical networks in order to best meet the requirements of the ANSM;
  - Selection by the clinical networks of the off-label prescribing practices identified by the survey for which clinical trials would appear to be necessary in addition to the available medical and scientific data (the clinical networks will be responsible for seeking a sponsor and funding).
- 2020:
- Ramp-up of RTU examinations by the ANSM and, if applicable, of the number of clinical trials funded.



## Cost

- The pharmaceutical company covers the cost of follow-up of patients treated within the context of an RTU. However, since the follow-up of medicinal products prescribed off-label without an RTU is not funded, it will be necessary to find or unblock funding sources in order to guarantee - over the period of the plan - the establishment of registries by disease by the CRMRS, which forms one of the central ambitions of this working focus;
- The funding sources identified will be mobilised to enable the performance of the clinical trials required to improve our knowledge of a significant number of off-label prescribing practices identified in the context of the survey conducted by the FSMRs.

12. The Clinical research hospital programme (PHRC) enables funding of the entire cost of a clinical trial by the national health insurance system.

13. This involves funding by the national health insurance system of investigational medicinal products or auxiliary products prescribed off-label in the context of non-commercial research on the basis of the provisions stipulated in 2°, III of article L. 1121-16-1 and article R. 1121-3 of the French Public Health Code. This option would make it possible to promote the repositioning of certain substances.



- DGS and DSS;
- In collaboration with the DGOS, ANSM, HAS.

# FOCUS 5: GIVING NEW MOMENTUM TO RESEARCH IN THE FIELD OF RARE DISEASES

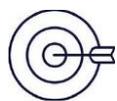


## Context

A very broad range of research concerns rare diseases. This research supplies fundamental information enabling the diagnosis of rare diseases, an understanding of their pathophysiological mechanisms, the design and development of therapeutic strategies and the evaluation of their effects. Clinical research into rare diseases more specifically enables assessment of the safety and efficacy of medicinal products, medical devices, diagnostic products and treatment regimens. Finally, research in the fields of public health, epidemiology and human and social sciences - in particular, studies focusing on medico-economics, care, organisational aspects and educational processes - are essential in order to facilitate access to treatment by patients with rare diseases.

Research into rare diseases conducted by French teams is funded by a set of mechanisms of varying degrees of specialisation. A bottleneck exists when it comes to transfer studies and clinical trials, which are more expensive and for which relatively few private partners can be found in the field of rare diseases.

The strong support given to research into rare diseases and the adoption of a rare diseases plan in 2005 have enabled France to become established as a European leader in this field. For example, for more than ten years, France has been the coordinator of EraNet<sup>14</sup> E-Rare, which proposes transnational calls for research projects. In addition, in 1997, it created the Orphanet information platform, deployed in Europe and beyond and it is currently responsible for the joint RD-Action<sup>15</sup>. The country also hosts the secretariat of the IRDiRC international research consortium and Eurordis, the European alliance of rare disease patients' organisations. It plays a prominent role within the new European reference networks (ERNs) introduced in March 2017. It is currently leader of the European Joint Programme Cofund on Rare Diseases (EJP RD), which aims to maximise the impact of research into rare diseases for the benefit of patients. European research in the field of rare diseases is, thus, entering a phase of consolidation and structuring, with a number of important challenges to be overcome, particularly with respect to data matching and sharing on a European and world scale (see focus 3). France must actively contribute to the creation of this structure if it is to maintain its prominent position.



## Objectives

The objective is to give fresh impetus to research in the field of rare diseases in France and to reinforce the country's role as a European leader in order to reduce the number of patients without a diagnosis and accelerate the development of new treatments:

- **By coordinating the participation of national players in European fundamental, translational and clinical research programmes in the area of rare diseases;**
- **By launching a French research programme focusing on undiagnosed diseases;**
- **By developing human and social sciences-based research into rare diseases.**

14. Funding programme for rare diseases research developed by the European Commission's DG Research  
15. Action 2015-2018 of the DG Health (European Commission) for Rare Diseases composed of 6 themed working groups



## Action

### Action 5.1: Create a research coordination group

In particular, this group will include AVIESAN, the ANR (French National Research Agency), the FSMRs (Europe and research group), the IHU IMAGINE (university hospital network) Orphanet, RaDiCo, the FMR (French Rare Diseases Foundation) and the Ministry for Higher Education, Research and innovation (MESRI). Its mission will be to coordinate the participation of French players in the field of rare diseases in the activities of the EJP RD, to support the creation of consortia, via the clinical networks, for the submission of collaborative projects for European or international calls (for example IMI<sup>16</sup> or the health programme of Horizon 2020 then Horizon Europe<sup>17</sup> from 2021), to proactively propose ideas designed to ensure fluidity between fundamental research and clinical research in order to benefit patients, with a particular focus on the intermediate link in the chain: translational research. This group will produce an annual report analysing research activity in the field of rare diseases.

### Action 5.2: Steer the construction of the EJP and coordinate the participation of French teams

- The EJP RD will group together research funding activities, a data sharing and services platform, training initiatives and assistance for the transfer of research in the field of rare diseases, working closely with the ERNs. The coordinator will be INSERM. The ANR will contribute to its research funding activities.

### Action 5.3: Develop human and social science-based research

- The evaluation of the PNMR2 conducted by the HCERES highlighted the need to encourage cross-disciplinary collaboration in the field of human and social sciences (epidemiology, sociology, psychology, health economics, etc.). Patient associations, the FMR, the ATHENA and AVIESAN alliances and the CNSA (National Solidarity Fund for Independent Living) all have a key and complementary role to play in this action of the PNMR3, liaising closely with the CRMRs, the clinical networks, the ANSM and the HAS. A partnership needs to be developed with economists and health organisation specialists, particularly in the academic sector.

### Action 5.4: Launch of a French research programme into undiagnosed rare diseases, in conjunction with the European UDNI and Solve-RD initiatives

Undiagnosed patients are those for whom it has not been possible to reach a diagnosis based on current knowledge, including after genomic analysis. A collaborative post-genomic research programme for diagnostic and therapeutic purposes will be developed within a research network bringing together the FSMRs and fundamental research laboratories. This programme will seek to understand the mechanisms of complex or non-genetic rare diseases. This programme is similar to that of the international UDNI (Undiagnosed Disease Network International) network and the European "Solve-RD" programme, with which it will be linked.

### Action 5.5: Develop mechanisms to support existing clinical research

It is necessary to:

- Reinforce the specialisation of certain clinical investigation centres (CICs) for rare diseases<sup>18</sup> and explain the contribution of CICs to rare disease research with the parties involved (practitioners, patients, researchers);
- Publicise and reinforce the OrphanDev system, an F-CRIN-labelled platform dedicated to rare diseases hosted by Aix-Marseille University (Orphan Drug Designation, assistance with protocols, etc.) in order to expand its scope;
- Task the F-CRIN with a support role for clinical research into rare diseases, making it easier to consult CICs, Clinical Research Units (URCs) and Clinical Research Departments (DRCs).

16. European Innovative Medicines Initiative

17. Horizon Europe: European Commission's 9th framework programme for research and innovation

18. The foundations already exist (80% of the 30 multi-themed CICs are allied to a CRMR, 5 CICs specialise in biotherapies, 50% of paediatric clinical trials are conducted in the field of rare diseases and 90% of rare disease trials concern paediatrics).

## Action 5.6.: Give priority to translational research into rare diseases

The scientific approach, which consists in starting with patients to identify genes, study their function and understand the mechanisms involved, is particularly appropriate for rare diseases. This approach requires close cooperation between clinical, genetic and pathophysiology and research teams, which share the same medical and scientific interests. Given the medical and scientific challenges, as well as the expertise found within CRMRS and FSMRS, it is necessary to support this translational research. To this end, translational research projects in the field of rare diseases will be given priority by the ANR and cofunded by the Ministry of Solidarity and Health (MSS) and the Ministry for Higher Education, Research and innovation (MESRI).



### **Time-frame**

- Launch of the rare diseases research coordination group in 2018
- Construction of the EJP RD in 2018 and launch in 2019
- Training a group to set up an undiagnosed diseases programme in 2018 and launch of the programme in 2019.



### **Cost**

- Undiagnosed diseases programme: €4 million;
- EJP Rare Diseases: €3 million per year i.e. €15 million over 5 years.



### **Leader**

- AVIESAN;
- In collaboration with the DGRI and the DGOS.

# FOCUS 6: PROMOTING THE EMERGENCE OF AND ACCESS TO INNOVATION

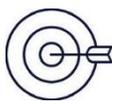


## Context

The PNMR3 aims to increase the number of treatments available on the market for rare diseases. To achieve this acceleration of innovation, it is first of all necessary to identify potential difficulties throughout the innovation chain, from research to marketing and monitoring of medicinal products in real-life conditions.

The innovation support landscape in France already presents a wealth of financial and technology transfer mechanisms and instruments, but the field of rare diseases demonstrates certain very specific characteristics, in particular: i) a very large number of diseases, but a low number of patients per disease; ii) the development of new treatments that may be based on gene or cell therapies involving complex and expensive technologies, and require; iii) specific regulations for innovative-therapy medicines.

In this context, the provision of treatments for rare diseases is crucially important and a public health priority for patients. It is to address some of these specific characteristics that medicines meeting the definition of orphan medicinal products benefit from European incentive measures designed to facilitate their access to the market. The provisions include scientific aid for the development of the drug, tax exemptions and a commercial exclusivity period. This mechanism can present certain limits that need to be analysed.



## Objectives

The objectives are to promote the more rapid development of innovative diagnostic products or treatments, as well as the repositioning of drugs and their market access:

- **By establishing an innovation coordinating body tasked with defining new innovation strategies for rare diseases;**
- **By facilitating access to market of innovations for rare diseases;**
- **By proposing specific research and development mechanisms in the field of rare diseases.**



### **Action 6.1: Creation of a rare disease innovation coordination group**

Led by the AVIESAN research alliance and ARIIS (Alliance for Health Industry Research and Innovation), this coordination group will bring together all rare disease innovation players (ministries of solidarity and health, higher education, research and innovation, economy and finance and ecological and inclusive transition, Athéna human and social sciences alliance, rare disease research operators and funders - including IHU Imagine and FSMRs -, patient associations, medical or paramedical professional associations, health industry unions (LEEM, FEFIS, France- biotech, SNITEM, SIDIV) and BPI France. Its mission will be to propose new innovation strategies for rare diseases and organise information sharing. It will also participate in the implementation of specific rare disease research and development mechanisms.

### **Action 6.2: Facilitate access to market of innovations for rare diseases**

The rare disease innovation coordination group:

- Will identify the innovation actions already under way on a national, European and international level in the field of rare diseases, in order to optimise the work;
- Will help update the inventory of ongoing or finalised clinical trials in conjunction with the Orphanet platform and IRDIRC;
- Will draw up a map of innovation support mechanisms linked with the corresponding measures of the Health industries strategic council (CSIS) and the Health industries and technologies sector committee (CSF);
- Will formulate proposals to promote:
  - the development of new medico-economic studies for health technologies or medicinal products destined for a limited number of patients;
  - the repositioning of medicinal products;
  - the development and financial sustainability of pharmaceutical-grade biotherapy bioproduction centres in accordance with competition regulations and the regulations governing the single European market;
  - the performance of medico-economic studies or the development of real-life knowledge required by the authorities and national assessment bodies, particularly as regards academic sponsors;
  - the development of therapies with proof of concept but neglected by manufacturers.

### **Action 6.3: Implementation of specific research and development mechanisms in the field of rare diseases**

The rare disease innovation coordination group:

- accompany the development of rare disease projects, from proof of concept to market, supported, in particular, by SATTs (French technology transfer acceleration companies);
- develop a "proof of concept" club to encourage companies to take an interest in proofs of concept obtained in FSMRs or academic laboratories;
- encourage companies, the FSMRs and French research laboratories to participate in French and European innovation programmes (FUI, PSPC, IMI etc.);
- raise awareness within the European Commission of the need to develop dedicated calls for proposals on the theme of rare diseases within the context of European projects;
- create with BPI France an event dedicated to SMEs and clinical network and laboratory players, to coincide with the launch of the plan.



## **Time-frame**

- The rare disease innovation coordination group will be created in 2018;
- The process of identifying possible issues with respect to the emergence of innovation will take place from 2018 to 2019.

Proposals for innovation transfer support and specific rare disease research and development mechanisms will be put in place in 2019.



## **Cost**

No additional costs.



## **Leader**

- DGRI;
- In collaboration with the DGS, DSS, DGE and DGOS.

# FOCUS 7: IMPROVING CARE PATHWAYS



## Context

The number and diversity of rare diseases generate complex care situations for patients, their families and healthcare professionals.

There are a number of particularly important moments in the course of the disease throughout a patient's care pathway. Good management of these phases is a quality factor in good patient care.

The absence of regular patient follow-up generates a sense of isolation and has an impact on their care pathway, both for patients in whom the diagnosis process is under way, those who already have a diagnosis and those whose disease remains undiagnosed.

Multiple players are involved, requiring good coordination and practical support. Patients can be major players in their own care.

Progress was made during the previous plans; however, the quality of the care pathway needs to be consolidated and is part of a continuous improvement process.



## Objectives

This action will make it possible to:

- **Create accompaniment phases to enable medical, care and psychosocial support teams to more effectively manage and adapt certain key moments in the patient care pathway and provide tailored, progressive and respectful information. There will be a particular focus on diagnosis delivery, follow-up in the event of an undiagnosed disease and the transition from adolescence to adulthood;**
- **Organise emergency situations without disruption to the care pathway;**
- **Incorporate patient education programmes in the care pathway, enabling patients to be more active and autonomous in their own care;**
- **Facilitate communication between players to improve coordination of the care path, identifying designated contact persons for patients and developing facilitator technical tools.**



## Action

### Action 7.1: Develop information to make existing structures visible and accessible

The development of information should be based on regular, coordinated and efficient communication, not restricted to the world of rare diseases alone. Too many patients, families, care-givers and social players are unaware that resources exist to help them cope with the disease and its consequences: CRM, FSMR, ERN, associations. Everyone should have easy access to good quality, clear information, be given relevant medical guidance or appropriate social support and know where to get help, in exactly the same way as in other areas of health. The public health information service (SPIS), Orphanet, the MRIS, associations and the FSMRs already fulfil this mission. A genuine long-term communication strategy therefore needs to be implemented, based on:

- Dedicated information sites, linked to general sites;
- A rare disease section on general information and guidance sites (SPIS, ministry websites, etc.);
- Regular interventions at professional conferences.

### Action 7.2: Guarantee appropriate diagnosis delivery conditions

Since this is the first key moment in the care pathway, the quality of delivery of the confirmed diagnosis - or suspected diagnosis if it has not been possible to confirm it - is crucial in the management of the patient's care pathway.

It is necessary to:

- **Raise awareness and train health professionals in diagnosis delivery**, offering aids to professionals developing tailored information supports for patients, their care-givers and their families;
- **Better promote the care activity of rare disease centres** in line with the necessary resources;
- Promote consultations requiring the mobilisation of several professionals (doctors, psychologists, social workers, genetic counsellors, physiotherapists, etc.) and time dedicated, and sometimes repeated, to delivery or modification of the diagnosis, follow-up in the event of an undiagnosed disease, and at pivotal moments, such as the transition from adolescence to adulthood;
- Incorporate comorbidities in the assessment of hospital stays.

### Action 7.3: Facilitate access to patient education

It is necessary to:

- Facilitate the dissemination of patient education programmes already authorised in a region and set up sharing tools;
- Open up patient education sessions to multiprofessional themes;
- Allow carers and siblings to have access to these sessions;
- Trial online modules within patient education programmes and encourage access to these;
- Create an information forum of existing patient education programmes (ETP), overseen by the FSMRs.

### Action 7.4: Mobilise care coordination mechanisms

It is necessary to:

- Get general practitioners involved in their own right, via the greater use of hospital-community liaison letters;
- Step up the production of national care and diagnosis protocols (PNDS), specific recommendations (adolescence-adulthood transition, emergency, etc.) and European guidelines applied to the French context to accompany and support good practices. This will be the subject of a specific network-based action plan;
- Create 4 coordination platforms in French overseas territories, operating in close liaison

with the CRMRS in mainland France via telemedicine;

- Develop rare disease expertise platforms (action 10.6) in healthcare establishments housing several CRMRS;
- Recognise and develop the care pathway coordination function in centres with territorial players;
- Develop the broader use of emergency care support solutions (emergency medical assistance service (SAMU) information system, operational resources directory (ROR), etc.);
- Reinforce the regional healthcare programmes (PRS) of regional health agencies (ARS) in the field of rare diseases.

### **Action 7.5: Develop telemedicine and innovation in the field of e-health**

It is necessary to:

- Make telemedicine services accessible in all Overseas reference and competence centres to enable access to mainland France reference centres and in all centres to enable access to the European expert centres of ERNs;
- Create an expanded patient's shared medical record (DMP) for all rare disease patients in order to ensure the portability of data and facilitate the e-pathway, which is particularly important for rare diseases.



### **Time-frame**

2018:

- Creation of 4 Overseas coordination platforms.

2019:

- Definition of a service flat-rate to complete the valuation of complex, multi-professional consultations;
- Creation of an expanded DMP for all rare disease patients.

2020-2022:

- Updating of all national care and diagnosis protocols (PNDS) over a 5-year period;
- Setting-up of expertise platforms in establishments housing several CRMRS.



### **Cost**

- €400K per year for the creation of Overseas coordination platforms (€100k/year for each sector: Réunion, Guadeloupe, Martinique and French Guiana), i.e. €2 million over 5 years;
- €50K for a PNDS produced or updated after its 5th year, with a target of 100 PNDS each year, on a call for proposals basis. €20 million will be dedicated to this action over 5 years;
- €2 million per year for patient information on a call for proposals basis, i.e. €10 million over 5 years;
- €300K per year for the funding of Orphanet, €260K per year for the funding of MRIS, €70K per year for the funding of the Rare Diseases Alliance, i.e. a total for these 3 mechanisms of: €3.15M million over 5 years.



### **Leader**

- General Directorate for Care Provision (DGOS);
- In collaboration with the DGS and the DSS.

# FOCUS 8: FACILITATING THE INTEGRATION OF PEOPLE WITH RARE DISEASES AND THEIR CARERS



## Context

Rare diseases can have consequences on various aspects of the lives of the people concerned and can result in disability. These disabilities can be of various types and severities. Some diseases can lead to very specific disabilities due to the rarity of the combined deficiencies involved. In these instances, the term "rare disabilities" is used. 30% of rare disabilities are related to a diagnosed rare disease or a non-labelled rare syndrome.

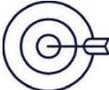
To address their needs related to the disability (human assistance, technical aids, support, schooling, professional activity, etc.), people suffering from rare diseases have access to solutions specific to the disability sector, in particular those related to a decision or opinion issued by *Departmental* level centres for disabled people (MDPH).

The measures undertaken in the context of the previous rare diseases plans, as well as the various ongoing projects aimed at improving specific mechanisms for disabled people are designed to make it possible to address the difficulties encountered by people suffering from a disability related to a rare disease. Actions still need to be taken in order to:

- improve knowledge of rare diseases for local players;
- improve knowledge of mechanisms that may be deployed, particularly in the area of disability, by users and professionals;
- adapt medico-social care;
- simplify administrative processes.

### **Conjunction, link with other Plans, Strategies, Schemes and Projects**

- The 2014 -2018 rare disabilities scheme;
- The 2016-2020 occupational health plan
- The "a guided solution for everyone" approach and the transformation of medical and social services for disabled people;
- the IMPACT project that aims to simplify administrative processes with MDPHs;
- the objectives and actions of the interministerial disability committee of 20 September 2017.



## Objectives

Improve the quality and continuity of life paths and access to medico-social mechanisms, reinforcing the link between the public health and medico-social approach in order to:

- **Facilitate access to mechanisms, rights and services aimed at disabled people and their carers;**
- **Organise partnerships with the “rare disabilities” mechanism;**
- **Encourage the development of health autonomy support projects specific to rare diseases;**
- **Take into account the specific situations of people with rare diseases in their educational and professional pathways.**



## Action

### **Action 8.1: Facilitate access to mechanisms, rights and services dedicated to disabled people and their carers**

The aim is to strengthen relationships between FSMR and MDPH players, particularly during pivotal phases in the care pathway or when the situation of rare disease patients and their carers changes. To this end, it is necessary to:

- Develop specific tools, on an individual FSMR or inter-network basis, for the transmission of information specific to the disability;
- Supplement the information given to MDPH multidisciplinary teams as concerns disabilities resulting from rare diseases;
- Improve the information supplied to FSMR concerning changes to mechanisms and the medico-social services available.

### **Action 8.2: Organise partnerships with the rare disabilities scheme on a national and regional level**

The first and second national rare disabilities schemes resulted in the establishment of a “rare disabilities” scheme, which comprises, on a national level, a national rare disabilities coordination group and four national rare disabilities centres. On a regional level, the scheme takes the form of 12 rare disabilities relay teams (ERHR) that may be consulted by people with rare disabilities, families, associations, medico-social establishments, MDPHs, and care and/or welfare players. It is now necessary to: Reinforce the partnerships between players from the FSMRs and the rare disabilities scheme.

### **Action 8.3: Improve support processes in order to better address the needs of people with disabilities due to rare disease**

It is necessary to take into account the specific needs, expectations and pathway of people with disabilities due to rare disease in conjunction with the “a guided solution for everyone” approach and the strategy for the transformation of medical and social services.

### **Action 8.4: Encourage the development of health autonomy support projects specific to rare diseases**

The aim is to ensure the follow-up of pilot projects specific to rare diseases, undertaken in the context of the experimentation scheduled in article 92 of French law No. 2016-41 of 26 January 2016, intended to produce co-constructed assessment elements in the context of this experimentation and enable the collection of reproducible elements with a view to potential long-term application.

### **Action 8.5: Enable all children to have access to schooling**

This action will make it possible to:

- Put in place the necessary schooling adaptations taking into account the health status of children with rare diseases, including for children who do not have a disability or whose disability is not recognised by the MDPH. This involves ensuring that schooling is continued in the event of repeated hospital admissions, home care or repeated treatments;
- Improve the exchange of information between the various players in children's schooling pathways.

### **Action 8.6: Help people with rare diseases remain in or return to employment**

The aim is to ensure that rare disease patients are properly taken into account in National occupational health plan actions and manage any specificities.



#### **Time-frame**

2018-2022.



#### **Cost**

No additional cost identified.



#### **Leader**

- DGCS;
- In collaboration with DEGESCO, DGT, DGEFP, DGS and the CNSA.

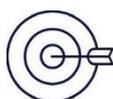
# FOCUS 9: TRAINING HEALTH AND WELFARE PROFESSIONALS TO BETTER IDENTIFY AND MANAGE RARE DISEASES



## Context

Training professionals in the health, welfare and non-hospital sectors to identify, diagnose and care for rare disease patients helps improve the coordination of their care pathway and quality of life. In parallel, if the general population and associations have greater knowledge of research and clinical trial problems, this improves their understanding of the care and treatments proposed and helps them gain a better grasp of the ethical issues related to the arrival of new technologies such as ultra-high-throughput sequencing.

As regards technological advances in the area of diagnosis, the significant increase in the number of individuals with - or suspected of having - rare diseases tested and in the number of genes identified requires the development of molecular genetic laboratory capacities and a clarification of their organisation. Reinforcing the human resources of these laboratories and enhancing their level of skills to include genomic medicine expertise is a priority. This aspect is particularly relevant for genetic counsellors and bioinformatics specialists. This focus is consistent with the France Genomic Medicine 2025 plan.



## Objectives

- **Specify the role of new professions liable to improve the diagnostic care of patients (genetic counsellors, bioinformatics specialists, etc.) and increase the training and number of these professionals;**
- **Adapt the initial and continuing training of health and social professionals in order to promote a “culture of questioning” and knowledge of the healthcare organisation system in France for the management of rare diseases.**



## Action

### **Action 9-1: Clarify the status of genetic counsellors and bioinformatics specialists and increase their training and recruitment**

#### **For genetic counsellors**

The "Directory of Hospital Public Service professions" recognises the profession of genetic counsellor since French law No. 2004-806 of 9 August 2004 relative to public health policy<sup>19</sup>. However, given, in particular, the low numbers of personnel trained via the degree-masters-doctorate programme in "Genetic Counselling and preventive medicine" at Aix-Marseille University (183 graduates in March 2017), there is no community of genetic counsellors, which raises issues with respect to their recruitment, remuneration and recognition.

With a view to expanding the use of genetics and genomics in the management of rare disease patients, the ministries concerned, along with the French Association of Genetic Counsellors (AFCG), will conduct several studies in order to:

- Identify and quantify needs;
- Undertake studies to ensure greater recognition for genetic counsellors in the clinical care network;
- Ultimately authorise delegation to genetic counsellors of prescription of medical genetic tests;
- Increase the training capacities of genetic counsellors and expand them to include genomic themes, with recognition within the context of continuing professional development (DPC).

#### **For bioinformatics specialists**

The "Directory of Hospital Public Service professions" already recognises the profession of bioinformatics specialist. Although there is no established community, these professionals are recruited as senior hospital technicians and therefore have a statutory and index-related status enabling healthcare establishments to recruit them in technical and scientific fields (such as genetics and genomics, with the qualifications concerned making specific reference to bioinformatics).

In view of the expansion of applied genomics applications to care and research in the field of rare diseases, it is necessary to:

- Identify and quantify needs.

### **Action 9-2: Reinforce initial training policy in medicine, pharmacy and biology programmes**

The objective is to:

- Develop training modules on rare diseases via health simulation tools aimed at medical personnel, specialised or otherwise in rare diseases;
- Introduce theoretical teaching modules in the field of genomics into medicine, pharmacy and biology **programmes**;
- Put in place dedicated professional career paths in "Rare diseases research (Masters in biology / Health, contracts within biology / health doctoral schools and, **in particular EURs** (graduate research schools).

19. Articles L. 1132-1 to L. 1132-7 of the French Public Health Code (CSP) and articles R.1132-1 to R1132-20 of CSP

### **Action 9-3: Develop continuing training in the field of rare diseases**

It is necessary to:

- Consult continuing training organisations and learned societies in order to create modules dedicated to rare diseases (classroom-based, digital, etc.) with continuing professional development (DPC) labels as incentives aimed at medical personnel;
- Develop national DIUs (inter-university diplomas) in liaison with European DIUs including, among others, health simulation training;
- Pool initiatives and resources on an inter-FSMR level, or even with ERNs.

### **Action 9-4: Encourage mixed professional/patient/family training**

- This involves including patients and associations in training courses for non-hospital and hospital doctors and paramedical personnel in order to raise awareness of real-life data (quality of life, etc.) among health professionals, and enable them to learn from the experience of patients, in particular via health simulation tools.



#### **Time-frame**

2018-2022.



#### **Cost**

€2 million/year, i.e. €10 million over 5 years, will be dedicated to training.



#### **Leader**

- DGOS
- In collaboration with DGEIP.

# FOCUS 10: REINFORCING THE ROLE OF RARE DISEASE CLINICAL NETWORKS

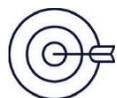


## Context

The 23 rare disease clinical networks (FSMRs) were set up within the context of PNMR2. They each cover a broad and coherent field of rare diseases that are similar in either their manifestations, consequences or treatment, or affect the same organ or system. Each of the 109 rare disease reference centres (CRMRS) labelled for the 2017-2022 period is attached to one of these networks. Each FSMR brings together all the players involved in a defined theme within the field of rare diseases, including medical personnel, researchers, patient representatives and industry. Therefore, in addition to providing care, they are identified as drivers of research and innovation, as well as training. The FSMRs are linked to the 20 European Reference Networks for rare diseases (ERNs) created in 2017, in terms of themes and missions.

The current missions of each clinical network with respect to a group of diseases enable:

- coordination of centres within their clinical networks, pooling coordination and steering resources;
- for all patients and their general practitioners, identification within the health system of the most appropriate care arrangements for their particular case;
- better coordination of diagnostic, therapeutic and medico-social management;
- coordination of research actions;
- organisation of the collection of clinical and biological data for epidemiological research purposes and monitoring of its quality;
- pooling of resources and expertise on a national level in order to raise visibility on an international level, in particular via European reference networks.



## Objectives

The FSMRs care and research coordination missions on care and research of the FSMR will be reinforced, in particular, by the collection and sharing of data, in relation with national mechanisms to support research and set up collaborative spaces for targeted actions promoting exchange between entrepreneurs, healthcare professionals, patients and regulatory players.

In order to coordinate their approaches, the steering committee (COFIL) of the clinical networks will be responsible for setting their organisational, strategic and operational priorities. While maintaining their specific characteristics, they will therefore ensure complementarity and cross-functionality in order to pool actions and resources to address the multi-system symptoms and consequences of numerous diseases.

FSMR representatives will be members of the strategic committee and the operational committee of the PNMR3.



## Action

### **Action 10.1: Attribute additional missions to the FSMRs over and above their current missions**

- The initial missions of the FSMRs will be extended in line with the actions of the plan and will be adapted to enable individual and collective assessment;
- In order to make sure that their missions have an effective and productive link with the CRMRs, a multidisciplinary consultative committee will be set up for each clinical network.

### **Action 10.2: Structure the FSMR steering committee**

The existing clinical network steering committee will evolve:

- Its meetings will be jointly organised by the Ministry of Solidarity and Health (MSS) and the Ministry for Higher Education, Research and innovation (MESRI);
- Patient associations, along with national rare disease players such as Orphanet, MRIS, RadiCo, the FMR and IHU Imagine will be regularly invited;
- Inter-network exchange will be fed by the work of themed groups (Diagnostics, Therapies, Databases and Biobanks, Research, Europe, Care pathways, Training) in close liaison with clinical network multidisciplinary consultative committees.

### **Action 10.3: Ensure assessment of FSMRs and their CRMRs**

A monitoring committee for labelled CRMRs and FSMRs will be appointed and will

- Ensure the durability and structuring of labelled centres and clinical networks;
- Analyse specific situations arising during the mandate;
- Assess the performance of these structures in line with their activities and missions;
- Make proposals for the revision of activity indicators and the distribution of available funds;
- Propose medium or long-term changes regarding their scopes.

### **Action 10.4: Renewal of FSMRs**

Since the mandate of the FSMRs ends in 2018, following an assessment of the scope of the FSMRs and their coherence with the ERNs, a new FSMR designation process will be carried out in 2018, via projects incorporating healthcare, medico-social, research and innovation and training aspects, submitted by candidate network leaders.

### **Action 10.5: Consolidate the operational resources of FSMRs**

In order to ensure that their operational resources evolve in line with the implementation of their missions:

- A Ministry of Solidarity and Health/FSMR/Establishment housing the FSMR/competent Regional Health Agency agreement will clarify the conditions for the allocation of basic funding for their operation (excluding specific calls for proposals);
- Basic rules of procedure specifying full members (research team representative, association representative, etc.) and the missions will be adapted for each FSMR, containing paragraphs specific to their field;
- Consortium agreements could be put in place in order to clarify the distribution of funds, intellectual ownership rules, a single authorised representative, etc.

## **Action 10.6: Encourage healthcare establishments to set up rare disease expertise platforms to strengthen inter-network links within the host establishments of several labelled centres**

Rare disease expert platforms group together- within the same university hospital group, group of healthcare establishments or regional hospital grouping - reference centres that organise the care network for different rare diseases, diagnostic laboratories and research units, as well as the patient associations concerned.

The aim of these platforms is to share expertise and pool knowledge and skills on a local level in order to:

- Raise the profile of labelled rare disease centres;
- Support diagnostic and therapeutic innovation and research;
- Reinforce links between centres and patient associations;
- Promote the implementation of rare disease databases;
- Facilitate medico-social actions in centres.

Rare diseases expertise platforms are not intended to replace existing structures, such as competence centres or national clinical networks. On the contrary, their purpose is to help health establishments work more effectively together.



### **Time-frame**

2018:

- Appointment of the CRMR and FSMR labelling monitoring committee
- Ratification of multipartite agreements on FSMR resources.
- Call for proposals concerning the renewal of FSMRs

2019:

- Establishment or revision of rules of procedure
- Implementation of the clinical network multidisciplinary committee.



### **Cost**

- €119 million/year, i.e. €597 million over 5 years for the CRMRs
- €12.7 million/year, i.e. €63.5 million over 5 years for the FSMRs
- €200K/year for the initiation, on a call for proposals basis, of expertise platforms within healthcare establishments or hospital groupings hosting several CRMRs, i.e. €8 million over 5 years, for 40 platforms (call for proposals for 10 establishments in 2018, 2019, 2020, 2021).



### **Leader**

- General Directorate for Care Provision (DGOS);
- In collaboration with General Directorate for Research and Innovation (DGRI).

# FOCUS 11: SPECIFYING THE POSITIONING AND MISSIONS OF OTHER NATIONAL PLAYERS IN THE FIELD OF RARE DISEASES



## Context

Rare disease patients benefit from the action of several national players, such as the ORPHANET information platform, recognised as the world's biggest source of knowledge and information on rare diseases; the Rare Diseases Foundation (FMR), particularly recognised for its contribution to the development of animal models of rare diseases, genomics projects, treatment screening, and in the field of human and social sciences or innovation support; the RaDiCo programme, which developed a platform of interoperable data and launched the assembly of 16 cohorts in the field of rare diseases.



## Objectives

The objective is to specify the positioning and missions of these national players to better incorporate them with the rare diseases ecosystem and optimise their impact.



## Action

### **Action 11.1: Maintain and amplify the contribution of patient associations and relatives' associations in the definition and implementation of rare disease policy**

- Increase their participation in steering bodies and at all levels in the operational implementation of this policy, particularly in the steering committee of FSMRs;
- Identify innovative experiences and practices in terms of the participation of patients and their increased autonomy in order to further improve the roll-out of health democracy;
- Train patient associations in adapted clinical trial methodologies (questionnaires, surveys, database use, etc.) and ethical issues, via training courses leading to qualifications.

### **Action 11.2: Reinforce the role of ORPHANET and ensure its long-term funding**

- Information concerning the resources and organisation of the care pathway in France will be supplemented to better address the information needs (emergency situations, related disabilities, information

documents for patients) of all the field's players.

- Orphanet will continue its actions in the area of the production, updating and dissemination of ORPHA nomenclature, necessary for the interoperability and reuse of rare disease data in France and Europe.
- A reflection process on the financial sustainability and status of Orphanet, launched within the framework of the joint RD-Action, will be completed.

### **Action 11.3: Encourage the Rare Diseases Foundation (FMR) with research alliances**

The role of the FMR is particularly well known in the field of human and social sciences, animal models, treatment screening and genomics projects. Whilst it must maintain its status and funding sources, it must nonetheless be better integrated into the dynamics of the actions proposed for rare diseases. The following is proposed:

- A more integrated relationship with the AVIESAN Alliance, with the scientific collaboration of the FMR in the Genetics Genomics Bioinformatics (GGB) Multi-organisation themed institute (ITMO) without compromising the operation of the Foundation and its missions;
- To include representatives from the AVIESAN and ATHENA alliances in the FMR's Scientific Board.

### **Action 11.4: Reinforce the role of RaDiCo in the integration of research data for rare diseases**

The support unit for structuring of data used by RaDiCo will be enhanced:

- establishing operational links with the National rare disease data bank (BNDMR);
- proposing technical and ethico-regulatory support for the creation by the FSMRs of new interoperable data warehouses, and studying the possibility of hosting these new warehouses on the RaDiCo platform;
- establishing operational links with the data platform of the EJP RD and the databases of the European Reference Networks that are in the process of being assembled.



## **Time-frame**

2018:

- Closer collaboration between the FMR and the Aviesan alliance, 2018-2019;
- Reinforcement of the role of RaDiCo in the integration of research data for rare diseases.

2019:

- Proposal of methods to ensure the sustainability of Orphanet



## **Cost**

See action 7.1



## **Leader**

- DGS, DGOS and DGRI;
- In collaboration with AVIESAN.

# APPENDICES

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# APPENDIX 1:

# GOVERNANCE

**The Strategic Committee** ensures application of the plan by mobilising partners and resources. It guides its implementation and proposes adjustments to the plan on the basis of the evolving context. It validates the annual report proposed by the operational committee that it submits to the Prime Minister.

It is chaired by the cabinets of the Ministry of Solidarity and Health and the Ministry of Higher Education, Research and Innovation.

## **It is composed of:**

- the central departments of these two ministries: DGOS, DGS, DGCS, SGMAS, DGRI, DGEISIP;
- representatives of the Ministries for the Economy and Overseas and of the secretariat of State for Disabled People;
- two representatives from the rare disease clinical networks;
- a representative of the National Association of Molecular Genetics Practitioners (ANPGM);
- the project leader of the France Genomic Medicine 2025 plan;
- the President of Aviesan;
- representatives of patient associations: French Myopathy Association (AFM), Rare Diseases Alliance, Eurordis, Vaincre la mucoviscidose (VLM - cystic fibrosis association), French Haemophiliacs Association (AFH);
- the presidency of the HAS;
- a representative from general directors of the regional health agencies;
- a qualified person having coordinated the drafting of the report on PNMR3: S. Odent;
- the chair and vice-chair of the operational committee (see below);
- a representative of the LEEM and a representative of SNITEM.

It meets at least once a year.

**The Operational Committee** is responsible for implementing the actions of the Plan and reporting back to the Strategic Committee. It ensures actions are implemented in accordance with the scheduled calendar, assesses the results of the Plan using indicators and monitors spending compared to the scheduled budget. It prepares the annual report for the Plan. The operational committee is chaired by two personalities appointed by the Ministry of Solidarity and Health (MSS) and the Ministry for Higher Education, Research and innovation (MESRI) (chair and vice-chair), who are assisted by the rare diseases mission, composed of MSS and MESRI members and the secretariat of which is handled by the General Directorate for Care Provision (DGOS).

## **It is composed of:**

- representatives from the DGOS, DGS, DGCS, DGRI and DSS and AVIESAN, piloting the 11 focuses;
- representatives of the agencies and operators involved in the plan's actions: ABM, HAS, ANSM, ANSP, CNSA, AVIESAN, Orphanet, FMR;
- representatives of three patient associations;
- representatives of two rare disease clinical networks;
- the president of the CRMR and FSMR labelling monitoring committee (see Focus 10).

It meets at least once a year.

# APPENDIX 2:

# FUNDING OF PNMR3

Focus	Funder	Time-frame	Actions	Comments concerning funding
Focus 1: REDUCING DIAGNOSTIC DELAYS AND UNDIAGNOSED DISEASES	MSS	Ongoing	<b>Action 1.1:</b> Encourage the management of any person with or suspected of having a rare disease within a rare disease reference centre (CRM)	€119 million per year, i.e. €597 million over 5 years dedicated to rare disease reference centres
		2018	<b>Action 1.5:</b> Organise and promote the systematic implementation of multidisciplinary consultation meetings	Implementation of a multidisciplinary consultation meetings mechanism for all centres and FSMRs (€500K)
		2018-2019	<b>Action 1.7:</b> Task the CRM, with the support of the FSMR, with compiling a dynamic national registry <sup>8</sup> of currently undiagnosable patients on the basis of the national rare disease data bank (BNDMR)	Creation of an undiagnosed disease registry from the BNDMR: €3 million/year, i.e. €15 million over 5 years
Focus 2: IMPROVING NEONATAL SCREENING AND PRENATAL AND PREIMPLANTATION DIAGNOSTICS TO ENABLE EARLIER DIAGNOSIS	MSS	2018	<b>Action 2.1:</b> Advance the regional and national reorganisation of neonatal screening in 2018, a necessary prerequisite to the implementation of new screening tests involving biomedical investigations - pending, subject to conditions	Project to extend neonatal screening from 2019 worth €1.8 million, i.e. €7.4 million over 5 years - pending, dependent on revision of the Bioethics law and the Social Security Financing Bill (PLFSS)
Focus 3: SHARING DATA TO AID DIAGNOSIS AND THE DEVELOPMENT OF NEW TREATMENTS	MSS	2018-2019	<b>Action 3.1:</b> Deployment of the BNDMR in CRM in conjunction with hospital information systems	Project management of the BNDMR (€3 million over 5 years) and support for the deployment of the "rare disease" module in the computerised data records (€3 million over 5 years)
	MESRI - PIA	2019 and 2021.	<b>Action 3.2:</b> Support the collection of clinical and biological data, from cohorts and registries, for their compilation, use and valuation. <b>Action 3.3:</b> Implementation of conditions for the reuse of data collected using e-health tools for research in the field of rare diseases	New FAIR data warehouses: €1.6 million for 10 projects, i.e. 16 million euros over 5 years
Focus 5: GIVING NEW MOMENTUM TO RESEARCH IN THE FIELD OF RARE DISEASES	MESRI - MSS - PIA	2019	<b>Action 5.2:</b> Steer the construction of the EJP and coordinate the participation of French teams	€3 million/year, i.e. €15 million over 5 years
		2018-2019	<b>Action 5.4:</b> Launch of a French research programme into undiagnosed rare diseases, in conjunction with the European UDNI and Solve-RD initiatives	€4 M over 5 for research into undiagnosed diseases ("investments for the future" plan - PIA)
Focus 7: IMPROVING CARE PATHWAYS	MSS	Ongoing	<b>Action 7.1:</b> Develop information to make existing structures visible and accessible	Funding of Orphanet (€300K/year), from MRIS (€260K/year), the Rare Diseases Alliance (€70K/year) i.e. €3.1 million over 5 years
		2018	<b>Action 7.3:</b> Facilitate access to patient education	€2 million will be dedicated annually to patient education in rare diseases, i.e. €10 million over 5 years
		2018	<b>Action 7.4:</b> Mobilise care coordination mechanisms	Launch of calls for proposals for the production of national care and diagnosis protocols (PNDS) with a target of 100 PNDS/year developed or updated, i.e. €20 million over 5 years  Coordination structures in Overseas territories (€100K/year for each sector: Réunion, Guadeloupe, Martinique French Guiana), i.e. €2 million over 5 years
Focus 9: TRAINING HEALTH AND WELFARE PROFESSIONALS TO BETTER IDENTIFY AND MANAGE RARE DISEASES	MSS	2018-2022	<b>Action 9.1:</b> Work on the roles of genetic counsellors and bioinformatics specialists and increase their training and recruitment	€10 million is dedicated over 5 years to the training of healthcare professionals in rare diseases
			<b>Action 9.2:</b> Reinforce initial training policy in medicine, pharmacy and biology programmes	
			<b>Action 9.3:</b> Develop continuing training in the field of rare diseases	
			<b>Action 9.4:</b> Encourage mixed professional/patient/family training	
Focus 10: REINFORCING THE ROLE OF RARE DISEASE CLINICAL NETWORKS IN CARE AND RESEARCH ISSUES	MSS	2018-2019	<b>Action 10.1:</b> Attribute additional missions to the FSMRs over and above their current missions	€63.5 million for FSMRs to fund their missions stipulated in the PNMR3 over the 5-year period
			<b>Action 10.6:</b> Encourage healthcare establishments to set up rare disease expertise platforms to strengthen inter-network links within the host establishments of several labelled centres	Aid to start up expertise platforms within 40 establishments (calls for proposals for 10 establishments in 2018, 2019, 2020, 2021) for a total of €8 million over 5 years (€200K/project)

TOTAL PNMR3	777,659,100 euros
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# INDEX

<b>ABM</b>	Agence de la biomédecine - Biomedicine Agency
<b>AFCG</b>	Association française des conseillers en génétique - Association of Genetic Counsellors
<b>AFM</b>	Association française contre les myopathies - Myopathies Association
<b>MA</b>	Marketing Authorisation
<b>AMR</b>	Alliance maladies rares - Rare Diseases Alliance
<b>ANR</b>	Agence nationale pour la recherche - National Research Agency
<b>ARIIS</b>	Alliance pour la recherche et l'innovation des industries de santé - Alliance for Health Industry Research and Innovation
<b>ARS</b>	Agence régionale de santé - Regional Health Agency
<b>ATHENA</b>	Alliance thématique nationale des sciences humaines et sociales - National themed alliance for human and social sciences
<b>ATU</b>	Autorisation temporaire d'utilisation - Temporary authorisation for use
<b>AVIESAN</b>	Alliance pour les sciences de la vie et de la santé - Alliance for Life and Health Sciences
<b>DB</b>	Database
<b>BNDMR</b>	Banque nationale de données maladies rares - National rare disease data bank
<b>BPI France</b>	Banque publique d'investissement - French Public investment bank
<b>CCMR</b>	Centre de compétence maladies rares - Rare disease competence centre
<b>CCNE</b>	Comité consultatif national d'éthique - Ethics committee
<b>CIC</b>	Clinical Investigation Centre
<b>CNAMTS</b>	Caisse nationale d'assurance maladie des travailleurs salariés - National health insurance fund for employed workers
<b>COFIL</b>	Steering committee
<b>CRDN</b>	Centre régional de dépistage néonatal - Regional neonatal screening centre
<b>CNEDIMTS</b>	Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé - National medical device and health technologies assessment committee
<b>CNSA</b>	Caisse nationale de solidarité pour l'autonomie - National Solidarity Fund for Independent Living
<b>CPDPN</b>	Centre pluridisciplinaire de diagnostic prénatal - Multidisciplinary prenatal diagnosis centre
<b>CRMIR</b>	Centre de référence maladies rares - Rare disease reference centre
<b>CSF</b>	Comité stratégique de filière - Health industries and technologies sector committee
<b>CSIS</b>	Conseil stratégique des industries de santé - Health industries strategic council
<b>DGCIS</b>	Direction générale de la compétitivité de l'industrie et des services - Directorate General for Competitiveness in Industry and Services
<b>DGCS</b>	Direction générale de la cohésion sociale – General Directorate for Social Cohesion
<b>DGEFP</b>	Délégation générale à l'emploi et à la formation professionnelle - General delegation for employment and professional training
<b>DEGESCO</b>	Direction générale de l'enseignement scolaire - General Directorate for School Education
<b>DGOS</b>	Direction générale de l'offre de soins - General Directorate for Healthcare Services
<b>DGRI</b>	Direction générale pour la recherche et l'innovation Directorate General for Research and Innovation
<b>DGS</b>	Direction générale de la santé - General Directorate of Health
<b>DGESIP</b>	Direction générale de l'enseignement supérieur et de l'insertion professionnelle - General Directorate for Higher Education and Professional Integration
<b>DMP</b>	Dossier médical partagé - shared medical record
<b>DNN</b>	Dépistage néonatal - Neonatal screening (NNS)
<b>DPC</b>	Développement professionnel continu - Continuing professional development
<b>DPI</b>	Diagnostic préimplantatoire - Preimplantation genetic diagnosis (PGD)
<b>DPI</b>	Dossier patient informatisé - Computerised patient record
<b>DPN</b>	Dépistage post-natal - Postnatal screening
<b>DRC</b>	Direction de la recherche clinique - Clinical research department
<b>DSS</b>	Direction de la sécurité sociale - Directorate for Social Security
<b>ECRIN</b>	European clinical research infrastructures network
<b>ERHR</b>	Equipe relais « handicap rare » - "Rare disability" relay team
<b>EJP</b>	European joint program
<b>ETP</b>	Education thérapeutique - Patient education
<b>EUCERD</b>	European Union committee of experts on rare diseases
<b>EURORDIS</b>	European organization for rare diseases
<b>ERN</b>	European Reference Network
<b>FCRIN</b>	French clinical research Infrastructures Network
<b>FEFIS</b>	Fédération française des industries de santé - French Federation of health industries
<b>FMR</b>	Fondation maladies rares - Rare Diseases Foundation

<b>FSMR</b>	Filière de santé maladies rares - Rare disease clinical network
<b>FUI</b>	Fonds unique interministériel - Single Interministerial Fund
<b>HAS</b>	Haute autorité de santé - French National Authority for Health
<b>HCERES</b>	Haut conseil de l'évaluation de la recherche et de l'enseignement supérieur - High Council for assessment or research and higher education
<b>HCSP</b>	Haut conseil de santé publique - High Council for public health
<b>IHU</b>	Institut hospitalo-universitaire - University Hospital Institute
<b>IMI</b>	Innovative medicines initiative
<b>INSERM</b>	Institut national de la santé et de la recherche médicale - National Institute for health and medical research
<b>IRDIRC</b>	International rare diseases research consortium
<b>ITMO</b>	Institut thématique multi-organismes - Multi-organisation themed institute
<b>ITMO GBB</b>	Institut thématique multi-organismes génétique, génomique et bio-informatique - Multi-organisation genetics, genomics and bioinformatics institute
<b>Leem</b>	Les entreprises du médicament - Pharmaceutical companies' representative body
<b>LMD</b>	Licence - master - doctorat - Degree-Masters-Doctorate (DMD)
<b>MDPH</b>	Maison départementale des personnes handicapées - <i>Département</i> -level centres for disabled people
<b>MESRI</b>	Ministère de l'enseignement supérieur et de la recherche et de l'innovation - Ministry of Higher Education, Research and Innovation
<b>MIG</b>	Missions d'intérêt général - funding for work "in the general interest"
<b>MRIS</b>	Maladies rares Info services - Rare Diseases Info Service
<b>NGS</b>	New-generation sequencing
<b>OMEDIT</b>	Observatoire du médicament, des dispositifs médicaux et de l'innovation thérapeutique - Observatory for medicinal products, medical devices and therapeutic innovation
<b>PFGM</b>	Plan France Médecine Génomique 2025 - France Genomic Medicine 2025 plan
<b>PHRC</b>	Programme hospitalier de recherche clinique - Clinical research hospital programme
<b>PIA</b>	Programmes d'investissements avenir - Investments for the Future Programme
<b>SME</b>	Small and medium-sized enterprises
<b>PNDS</b>	Protocole national de diagnostic et de soins - National care and diagnosis protocols
<b>PREPS</b>	Programme de recherche sur la performance du système de soins - Research programme on healthcare system performance
<b>PRME</b>	Programme de recherche médico-économique - Medico-economic research programme
<b>PRS</b>	Projet régional de santé - Regional health project
<b>PSPC</b>	Projets de recherche et développement structurants pour la compétitivité - Key research and development projects for competitiveness
<b>Radico</b>	Rare disease cohorts
<b>RCP</b>	Réunion de concertation pluridisciplinaire - multidisciplinary consultation meetings
<b>RHU</b>	Réseaux hospitaliers universitaires - University hospital networks
<b>RGPD</b>	Règlement général sur la protection des données - General data protection regulation
<b>ROR</b>	Répertoire opérationnel des ressources - Operational resources directory
<b>RTU</b>	Recommandation temporaire d'utilisation - Temporary recommendation for use
<b>SATT</b>	Société d'accélération du transfert de technologies - Technology transfer acceleration company
<b>SDM MR</b>	Set de données minimum maladies rares - Minimum data set for rare diseases
<b>SHS</b>	Sciences humaines et sociales - Human and social sciences
<b>SIDIV</b>	Syndicat de l'industrie du diagnostic in vitro - Union for the in vitro diagnostics industry
<b>SIGAPS</b>	Système d'interrogation, de gestion et d'analyse des publications scientifiques - System to search, manage and analyse scientific publications
<b>SI SAMU</b>	Système d'information pour les services d'aide médicale urgente (SAMU) - Information system for the emergency medical assistance service (SAMU)
<b>SPIS</b>	Service public d'information en santé - Public health information service
<b>SNITEM</b>	Syndicat national de l'industrie des technologies médicales - National medical technologies industry trade association
<b>EU</b>	European Union
<b>UNDI</b>	Undiagnosed diseases network international
<b>URC</b>	Unité de recherche clinique - Clinical research unit







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