EUROPLAN
European Project for Rare Diseases National Plans Development
Coordinated by the Italian National Centre for Rare Diseases
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2012-2015

Alliance maladies rares

EURORDIS
Rare Diseases Europe

FRANCE

EUROPLAN NATIONAL CONFERENCE

FINAL REPORT

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EUCERD
Joint Action

FOREWORD

The EUROPLAN National conferences are aimed at fostering the development of a comprehensive National Plan or Strategy for Rare Diseases addressing the unmet needs of patients living with a rare disease in Europe.

These national plans and strategies are intended to implement concrete national measures in key areas from research to codification of rare diseases, diagnosis, care and treatments as well as adapted social services for rare disease patients while integrating EU policies.

The EUROPLAN National conferences are jointly organised in each country by a National Alliance of rare disease patients' organisations and EURORDIS – the European Organisation for Rare Diseases. For this purpose, EURORDIS nominated 10 EURORDIS-EUROPLAN Advisors - all being from a National Alliance - specifically in charge of advising two to three National Alliances.

EUROPLAN National conferences share the same philosophy, objectives, format and content guidelines. They involve all stakeholders relevant for developing a plan/strategy for rare diseases. According to the national situation of each country and its most pressing needs, the content can be adjusted.

During the period 2008-2011, a first set of 15 EUROPLAN National Conferences were organised within the European project EUROPLAN. Following the success of these conferences, a second round of up to 24 EUROPLAN National Conferences is taking place in the broader context of the Joint Action of the European Committee of Experts on Rare Diseases (EUCERD) over the period March 2012 until August 2015.

The EUROPLAN National Conferences present the European rare disease policies as well as the EUCERD Recommendations adopted between 2010 and 2013. They are organised around common themes based on the Recommendation of the Council of the European Union on an action in the field of rare diseases:

1. Methodology and Governance of a National Plan;

2. Definition, codification and inventorying of RD; Information and Training;

3. Research on RD;

4. Care - Centres of Expertise / European Reference Networks/Cross Border Health Care;

5. Orphan Drugs;

6. Social Services for RD.

The themes "Patient Empowerment", "Gathering expertise at the European level" and "Sustainability" are transversal along the conference.

The EUROPLAN conference was organised under the auspices of the French Health Ministry

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GENERAL INFORMATION

Country	France
Date & place of the National Conference	13 January 2014
Website	http://www.alliance-maladies-rares.org/
Organiser	Alliance Maladies Rares
Members of the Organising Committee	Chair: Nathalie Triclin, Vice-President of the French Alliance Deputy to the Chair: Paul Gimenes EURORDIS-EUROPLAN Advisor: Christel Nourissier Aymeric Audiau Hélène Berrue-Gaillard Jean Boissonnas Catherine Dervieux Odile Guitaut Céline Hubert Bernadette Roussille Jean Saide Gérard Viens Viviane Viollet, Vice-President of the French Alliance
Names and list of Workshops	WS 1 Information, training of patients & professionals WS 2 Definition, codification, inventory of RDs, databases WS 3 Research on Rare Diseases WS 4 Centres of Expertise /European Reference Networks WS 5 Orphan Drugs WS 6 Social support
Workshop Chairs (and Rapporteurs, where applicable)	WS 1 Chair: Pr. Odile Kremp Rapporteur: Dr. Patrice Dosquet Official rep. French Alliance: Gérard Viens WS 2 Chair: Pr. Paul Landais Rapporteur: Dr. Charles Persoz Official rep. French Alliance: Claudie Baleydier WS 3 Chair: Pr. Nicolas Levy Rapporteur: Pr. Hélène Dollfus Official rep. French Alliance : A-S Lapointe WS 4 Chair: Pr. Sabine Sarnacki Rapporteur: Emmanuel Luigi Official rep. of French Alliance: Viviane Viollet WS 5 Chair: Christophe Duguet Rapporteur: Dr. Chrystel Jouan-Flahaut Official rep. of French Alliance: Hélène Gaillard

	WS 6 Chair: Marie-Sophie Desaulle Rapporteur: Dr. Juliette Bloch Official rep. of French Alliance: Meryl Asselino
ANNEXES	**1. Programme (in French)** **2. List of participants**

GLOSSARY

RC	**Reference Centres or Centres of Expertise for Rare Diseases (131 accredited in France)**
CC	**Competence Centres, regional relays of Reference Centres (502 accredited in France)**
AFM	French Neuromuscular Dystrophy Association, organises the telethon every year.
ANR	National Agency for Research
ANSM	French agency for the safety of medicine and health products
ARS	Health Regional Agency
ATU	French system for compassionate use of drugs before MA (“authorisation temporaire d’utilisation”).
CNRS	National research centre
CNSA	National solidarity fund for autonomy
EUCERD	European Union Committee of Experts on Rare Diseases
INSERM	National institute for health and medical research
MAIA	Houses for the Autonomy and Information of patients affected with Alzheimer or related diseases
MDPH	Local house for the disabled
MRIS	national French Helpline for Rare Diseases
Orphanet	Web portal for rare diseases and or phan drugs
PHRC	Hospital programmes for clinical research
PNDS	National protocols for diagnoses and care
PRTS	translational research programmes in the field of health
RTU	Recommendation for temporary use of a drug that has a MA but which is prescribed off-label

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THEME 1 – METHODOLOGY, GOVERNANCE AND MONITORING OF THE NATIONAL PLAN

1.1 EXISTING SITUATION AND RESOURCES

The preparation of the National Plan for Rare Diseases NPRD 2 (2011-2014) was largely based on a detailed evaluation of NPRD1 (2005-2008).

NPRD2 was preceded by many specific studies: self-evaluations of reference centres (RC) accredited during the first Plan, inventories of research projects funded during that period, financial results of actions launched under the Plan. Furthermore, a qualitative survey of 48 patients suffering from various rare diseases was undertaken between December 2008 and February 2009.

This material, complemented by hearings of the main stakeholders, was used by the evaluation Committee of NPRD1. The Committee was steered by the High Council for Public Health[1], an independent body of expertise attached to the minister of Health. Furthermore, the Committee organised in January 2009 an evaluation conference to investigate in depth all relevant issues (200 participants: professionals, experts, patient organisations, administrations).

As a result, an evaluation report (« Evaluation of the national plan for rare diseases 2005/2008 ») was delivered by the High Council for Public Health to the minister of Health in April 2009. It dealt essentially with epidemiology, screening, care, financial and social coverage, training of professionals, information of patients, drugs, research, national and European partnerships. The report was then circulated on the internet site of the ministry and on the site of the European Committee of Experts on rare Diseases (www.EUCERD.eu/ section : other website documents/country documents). It provided a precise description of the French system, including the *ad hoc* qualitative survey mentioned above.

1.2 ELABORATION OF THE NATIONAL PLAN/STRATEGY

1.2.1 The 2005/2008 plan

The first plan was drafted and budgeted very rapidly – in 6 months – by a group of experts, professionals and patient organisations, based on general epidemiological knowledge and on their experience.

1.2.2 The second plan 2011/2014

In 2008, under the French presidency of the European Union, the President of the Republic announced a second Plan. In September 2009, 4 ministers (health, research, industry, social affairs) commissioned Professor Gil Tchernia, a recognised specialist of sickle cell anaemia, to draft a NPRD2. In order to elaborate the Plan, 7 working groups were set up, comprising experts and professionals (31%), patient organisations (21%), administrations (41%) and representatives of the pharmaceutical industry (7%). The group rapporteurs were high level civil servants from the 4 ministries mentioned above. 34 meetings were held between October 2009 and January 2010, involving no less than 184 participants who based their work on 3 documents:

- proposals formulated in the evaluation report mentioned above;

- proposals from 2 departments of the Health ministry;

- proposals from patient organisations, in particular those from the Rare Diseases Alliance and EURORDIS.

[1] The High Council for Public Health has been set up to provide public authorities with the expertise needed to formulate and evaluate the public health policy, to prevent and manage sanitary risks, in collaboration with the health agencies.

As a result, a draft plan was submitted in January 2010 to all the working groups for a check of its coherence and completeness. The proposals were then submitted for final decisions to the directors of the ministries concerned and to their cabinets (4 meetings) and to the mandatory opinions of the High Council for Public Health and of the national Conference on health. After formatting of the document by the administration in charge (the health ministry), the research and health ministers both presented the final version of the Plan at a press conference on 28 February 2011.

Thus a gap of 3 years separated the two plans. During that period, NPRD1 was in fact continued.

1.3 STRUCTURE OF A NATIONAL PLAN

1.3.1 NPRD 1 (2005-2008)

The objective of NPRD1 was « *to ensure equal access to diagnosis, treatment and care ».* It comprised 10 areas:

Area 1: Improve knowledge on rare diseases epidemiology

Area 2: Acknowledge the specificity of rare diseases.

Area 3: Develop information on rare diseases for patients, healthcare professionals and the general public

Area 4: Train healthcare professionals for better identification of rare diseases

Area 5: Organise screening and access to diagnostic tests

Area 6: Improve access to care and the quality of treatment

Area 7: Continue efforts in favour of orphan drugs

Area 8: Meet the specific requirements for social services adapted to patients suffering from rare diseases

Area 9: Promote research on rare diseases

Area 10: Develop national and European partnerships

The budget was presented globally for each area, and no indicators of monitoring were planned.

1.3.2 NPRD 2 (2011-2014)

NPRD 2 follows the model and terminology recommended in the « book of public health plans » of the health ministry. It is 56 pages long, comprises 3 areas, 15 measures, 46 actions, and it has 4 main focuses, consisting in a precise description of institutions or key actions.

Following is a summary:

Area A: Improve the quality of patient care:

4 measures – 29 actions – 3 main focuses: the national bank of data on rare diseases – the specific needs of overseas patients – the action of patient organisations for rare diseases.

The aims of the actions are:

- improving the access to diagnosis and care of patients by structuring together the reference centres (RC) in networks, and ensuring a proper status for biology in parallel with clinical care;

- favouring the development of telemedicine, and improve data collection to meet the requirements of epidemiology, in particular by creating a national bank of rare diseases;

- optimising the procedures of evaluation and financing of RC by adapting especially the system of evaluation and of accreditation;

- intensifying efforts for the drafting of national protocols of diagnosis and care in order to increase their availability;

- guaranteeing the pertinence of drug prescription adapted to each patient, particularly by anticipating gaps in commercialisation and by improving knowledge on the use of specific drugs;

- developing links between persons in charge of medical care and social care, especially in the medico-social sector. This objective will be met by improving knowledge on the consequences of rare diseases in terms of disability, of impact on school attendance and quality of life, and also by answering the need for respite of rare diseases patients and their helpers;

- improving the practice of health professionals, by increasing their knowledge of rare diseases;

- improving the accessibility of information on rare diseases;

- positioning Orphanet as a reference tool for information and research.

Area B: Develop research on the Rare Diseases

4 measures, - 9 actions – 1 annex Current news – 1 main focus: The Rare Diseases Foundation

Objectives of the actions:

- creating a national body to impulse research, in association with the public and private sectors, in order to structure and harmonise the various actions undertaken in rare diseases research, especially on biotherapies, innovative therapies and pharmacological approaches ;

- promoting tools to increase knowledge on rare diseases, and set aside in the programmes of the National Agency for Research (NAR) a minimum amount of funds for rare diseases research ;

- promoting the development of therapeutic trials;

- favouring translational clinical and therapeutic research.

Area C: Amplify European and international cooperation

3 measures – 8 actions

Objectives of the actions:

- promoting the sharing of international expertise through the European reference network;

- improving the capacity to carry out multinational clinical trials, the access to diagnostic tests available at European scale, and the quality control of tests ;

- improving the access to diagnosis, care, research and information on rare diseases, by organising European and international co-operations.

The plan includes financial estimates for the 3 areas:

Area A: quality of financial coverage: 30.4 million euros.

Area B: research: 51 million euros

Area C: European and international co-operations: 5 million euros.

Total: 86.4 million euros.

1.4 GOVERNANCE OF NPRD 2

The Plan is placed under the direct responsibility of the minister of health and social cohesion and of the minister of research.

- Management of the Plan is entrusted to the General Director for the offer of care (health ministry) who chairs a "Committee for monitoring and orientation" (COSPRO) composed of: patient organisations, scientists active in patients care and in research, health agencies, scientific authorities and research organisations, directorates of central administrations.

- Two scientific vice-presidents (research and health) are responsible for the progress and coherence of actions carried out in their respective fields,

- A secretary general is commissioned by the health ministry to implement the Plan

- The regional Health Agencies (ARS)

The Committee for monitoring and orientation (COSPRO) is:

- the body overseeing the follow up of the measures decided under the Plan 2011/2014. The presentation of measures should take place at least twice a year. In addition to providing information on the progress of the plan, it provides an opportunity to suggest adaptations as the need arises;

- the body empowered to propose structural orientations to the ministers.

The scientific vice-president « health » of the COSPRO

She is responsible for the quality of the actions on health. Her mission is to steer the work of the Committee on the quality of care of patients, and of any working group that the committee entrusts to him. In particular, he chairs the working group « methodology of accreditation of reference centres ». This working group is permanent over the whole duration of the plan; it meets regularly, at least 4 times a year.

The mandate of the group is:

- to propose to the committee ways of adapting the evaluation procedure which is entrusted at present to the High Authority for Health (HAS) in coordination with the Agency for evaluation of research and higher education:

- based on the results of the evaluation made by the HAS, to specify the requirements for the accreditation of RC.

The scientific vice-president « research » of the COSPRO

She guarantees the scientific quality of research actions under the plan. She ensures the strategic coherence of research activities, the coordination of organisations involved in research (Foundation Rare Diseases, national Alliance for life sciences and health, national research Agency and others), in conformity with the evolution of knowledge, the evaluation of research activities of RC and the organisation of research on a national, European and international scale.

The secretary general

The mandate of the secretary general is set down in an inter-ministerial letter of assignment. S/he cooperates with the president and the scientific vice-presidents for « science » and « research » to:

- monitor and implement the operational and financial measures of the Plan (at national and regional level);

- plead with the European authorities the exemplary role of France on the rare diseases issue;

- identify the difficulties in the implementation of the Plan and propose solutions to overcome them;

- contribute to the preparation of the annual interim report on the Plan;

- ensure the communication and exchange of information with the representatives of ministries, institutions (health agencies, HAS, INSERM), professionals and patient organisations, by convening them regularly.

The secretary general is assisted by a dedicated team, positioned within the general Directorate for the organisation of care.

The Regional Health Agencies (ARS)

The specific arrangements for Rare Diseases developed in the national Plan (Reference Centres, or national platforms of laboratories), are not primarily dictated by territorial specificities, but are based first on excellency, on an expertise acknowledged nationally and internationally.

Nevertheless, in the national Plan, the facilitation and harmonisation of access to care are objectives of special importance for the requirements of regional management. Furthermore, the networks of RC for rare diseases are expected to create close links with medico-social institutions. Like the departmental institutions for disabled persons, the latter are anchored territorially.

By their terms of reference, the Regional Health Agencies are in a position to seek:

- the compliance of offered medico-social services with the requirements of non-sanitary care;

- the adequate social support for patients and the coordination of the various specialists of the sanitary and medico-social fields.

The ARS are also expected to support the implementation and monitoring of:

- the programmes of therapeutic education of patients (ETP) prepared by the rare diseases RC;

- the programmes of telemedicine;

- and more generally, the objectives of the national strategy for health.

In order to meet these goals, the missions relating to rare diseases should be identified within each ARS.

1.5 DIFFUSION AND COMMUNICATION CENTERED ON THE NATIONAL PLAN

The Plan was announced and explained on 28 February 2011 at an important press conference of the health and research ministers. The media and professional press covered the conference extensively. The Plan was presented at professional exhibits and mentioned in the guidelines circulated in 2011 by the health ministry for the elaboration of the regional scheme of organisation of care.

The Rare Diseases Alliance, with its 200 patient organisations, relayed the information with written and electronic documents and regional fora.

The annual international Rare Diseases Days of February provide an opportunity to mobilise the media. The rare diseases walk in Paris, taking place in December every year under the auspices of Telethon, is mediatised, especially on TV, for an important public fund-raising event (around 80 million euros in 2013).

However, while the public is aware of the existence of rare diseases, the Plan remains little known. According to a recent study, 15% of GPs know of it, and yet 63% of them are aware of the existence of Reference Centres.

The annual satisfaction enquiry of « Maladies Rares Info Services » (the French Rare Diseases Helpline) shows that only one tenth of the patients and their families know of the Plan.

What do these data mean? They tend to show that the availability of resources specifically devoted to rare diseases is unknown.

It is to be deplored that RARE DISEASES and the Plan are not included in a systematic and multiannual strategy of communication of the health ministry, based especially on the expertise of the staff of the Rare Diseases Alliance.

1.6 MONITORING AND EVALUATION OF THE NATIONAL PLAN

1.6.1 The Committee for Monitoring and Orientation - COSPRO; its crucial role

The Committee was set up on 19 may 2011 and met on 24 January 2012, 19 March 2013, 19 November 2013 and 11 February 2014, chaired by the general director for the offer of health services at the ministry of health. It serves as a focal point for assessments and exchange of views, especially with the patient organisations.

The vice-presidents « health » and « research » have been very active in monitoring the progress of measures. For each measure of the plan, lists of indicators appear as boxes to be filled and there is an implementation schedule.

Half-way through the Plan, no evaluation has been undertaken but the project team of the health ministry organised a one-day information meeting on 19 December 2012 with the medical coordinators of the RC for Rare Diseases, the managers of genetics laboratories and platforms concerned, the general directors of the academic hospitals concerned, the general directors of regional health agencies and the leaders of patient organisations involved in the monitoring of the Plan. The meeting was a great success.

A call for proposals on the creation of networks was issued and produced 32 answers.

1.6.2 Review of actions undertaken at the date of 31 December 2013

During the 3 years 2011/2013, 41 actions out of 45, the 4 focus of which 2 are the statements of objectives of the corresponding actions (National data Bank on Rare Diseases and Rare Diseases Foundation), and the project Rare Diseases Cohorts (RaDiCo), were under way.

- **One action is over:** creation of the Rare Diseases Foundation

- **One action is cancelled:** purposeless blog (Action B.4-3)

- **Two actions have been merged:** those relating to high speed sequencing (Actions A.1-2 and 3)

- **Four actions could not be launched:** on telemedicine, and on drugs in expectation of the future national law on public health (A.4-3)

- **Seventeen actions, one focus and one annex are severely delayed:** Screening (Action A.1-6), Funding (A.2-2), PNDS (A.3-1 and 2), Medico-social (A.5-1 to 4), Training (A.6-2 to 3, A.6-4, A.6-5 and A.7-3), « overseas » Focus, CIC (B.4-1), International (C.1-3), Diagnostic tests (C.2-2), RaDiCo project.

Such a « quantitative »assessment should however be viewed with caution. Indeed, if a number of actions could not be initiated or are severely delayed, the reasons are manifold: problems of management, or abundance of obstacles in the areas of law (law on drugs of December 2011), regulations, organisation or human resources. The initial schedules were ambitious but the necessary arrangements, especially the creation of « working groups » to reflect on various issues, often cause delays. This is true with all public health plans.

1.6.3 State of progress for each major measure; main files treated or currently in progress

1.6.3.1 Improve the quality of patient care (Area A)

Organisation of the health system; monitoring and evaluation (Measure A.1, 2 and 3)

- *Structuring the health system for rare diseases.*

In 2011, a working group led by Pr. Sabine Sarnacki, vice-president « health », issued specifications for the organisation of the networks, outlining their role, tasks and principles of governance. It also proposed the corresponding call for tenders, subsequently endorsed by COSPRO in March 2013.

The call was launched on 29 July 2013, setting the deadline for the submission of proposals for 27 September 2013, later extended to 25 October 2013. The permanent group in charge of evaluating the proposals was established on 18 December 2013 and formalises the **health networks for rare diseases** during the first quarter of 2014.

- *Development of high speed approaches*

A working group led by Pr. Gossens addressed the development of these new technologies, particularly to identify at national level a precise number of sequencing centres for rare diseases. Thanks to a grant of 9 600 000 euros, these centres received equipment for high speed sequencing. The performance of sequencers was thus raised to modern standards, having gained in precision, speed and numbers of diagnoses.

Furthermore, reflections were initiated at the end of 2012 to identify a very high speed French chain of genomic sequencing. A working paper was produced in 2013 by Pr. Nicolas Lévy, assisted by Pr. Thierry Frébourg and Pr. Jean-Louis Mandel. This activity is on-going in the form of consultations with various partners (National Alliance for Life Sciences, Rare Diseases Foundation, General Directorate for the offer of care), in order to validate a strategy for the organisation and funding of the project, and thus to restore the position of France which had declined significantly in this field, by comparison with other European countries.

- *Creation of a national data bank on rare diseases*

The objectives are to provide France with a bank of clinical data to enable progress on epidemiology, to document methods of care and their impact, to describe the request for care and its level of adequacy with the corresponding offer and to produce medico-economic knowledge on rare diseases.

A working group was established in 2011, coordinated by Pr. Paul Landais. An important step forward consisted in defining the minimal data set of information. This is a key element to allow the interoperability of data sets under a legal framework ensuring the protection and confidentiality of data. A steering committee was established on 17 September 2013 to follow the operational development of the data bank over the years and to define the policy for data collection and treatment.

- *Evolution of the system of evaluation and accreditation of RC*

A working group « methodology, evaluation, accreditation » was established in September 2011 with Pr. Sabine Sarnacki. A new directory for evaluation was validated by the assembly of the High Health Authority in 2013.

A numerical model of the future Annual Activity Report of the RC is being finalised, to be circulated in 2014. The procedure for the succession of RCs' Directors has been reviewed and published in an instruction dated 29 July 2013.

The working group met for the last time on 11 September 2013, and its files have since then been handed over to the permanent group.

- *Production of the national protocol for diagnosis and care*

The High Health Authority published in December 2012 a simplified method for the drafting of national protocols by the RC. This method has not yet enabled a significant increase of their production. A first prioritisation of themes was made in 2012, to be taken up again after the creation of the health networks.

- *Medicinal care (Measure A-4)*

An overview of actions listed in NPRD 2 (2011-2014) was presented to COSPRO on 19 September 2013. Several measures will be proposed under the future national health law (creation of a mechanism to detect interruptions in commercialisation, easing of the conditions of distribution of experimental drugs, validation of primo-prescription by RC of non-orphan drugs prescribed for rare diseases).

It was proposed to establish two working groups:

- A first group to analyse the national and international market of orphan drugs, in cooperation with the national Agency for drug safety and the drug industry;

- A second group to analyse transitory measures to be taken before obtaining a temporary recommendation of use.

- *Medico-social coverage (Measure A-5)*

A first assessment was made at the COSPRO meeting of 19 November 2013. These actions may not have been treated under NPRD 2, but they were undertaken in a more transversal context, since similar problems of coverage exist for other pathologies (cancers, Alzheimer…).

Future discussions will have to take into account this dimension and the role of the Regional Health Agencies, described in the chapter on governance.

- *Training/information (Measures A-6, 7 and 8)*

The aim of these measures is to improve the practice of health professionals by promoting their information and that of the patients. A few enquiries have shown the need for a continuation of efforts in this area: the percentage of diagnostic delays is still too high, a large number of GPs are unfamiliar with rare diseases and on how to treat them.

Although each RC performs training activities (not always optimised) and in spite of the very important role of patient organisations, of the Rare Disease Foundation and of Orphanet, it is necessary to undertake in 2014 an overall assessment of these various actions.

1.6.3.2 Develop research on the rare diseases (Area B)

This area includes **4 measures and 9 actions.**

Developing research is essential in this field, since a number of rare diseases still cannot be diagnosed.

- *Creation of the Rare Diseases Foundation*

The Foundation was created in 2011 to coordinate the development of tools and services aimed at improving knowledge on the rare diseases, and to accelerate the development of therapies.

The assessment of actions implemented by the Foundation in 2011, 2012 and 2013 has revealed the excellence of its activity and involvement. 6 out of the 9 actions of this area are steered by the Foundation.

One action deserving to be highlighted is the development of research projects in human and social sciences. The first call for proposals was issued in 2012 and the first results were discussed at a conference organised by the Rare Diseases Platform in December 2013.

- *Promote the development of therapeutic trials*

The development of therapeutic trials is a national and international priority. Participants in this research must be able to find ad hoc financing programmes and the system of calls for projects must be clarified for the applicants. The classical stages of the elaboration of a treatment are: study of the physiopathology of the disorder in order to identify therapeutic pathways, pre-clinical phases based especially on models, and finally clinical trials on man. In France, funding opportunities in this context are offered by the National agency for research (ANR) and two programmes: Hospital programmes for clinical research (PHRC) and Translational research programmes in the field of health (PRTS).

The NPRD 2 has devoted a lot of efforts to set up the PRTS in order to make concrete the continuum of research, by reinforcing the status of translational research in the Calls for Proposals of the general directorate of offer for care of the Ministry of Health.

The first PRTS campaign received a grant of 12 million euros for the year 2013. A research group composed of all actors or institutions participating in these actions was reactivated at the end of 2013.

1.6.3.3 Amplify European and international co-operations (Area C).

This area includes 3 measures and 8 actions.

Some of these actions are the continuation of actions undertaken at national scale: coding of acts, circulation of expertise and of information, etc.

Others are more specific: for example, the European Clinical Research Infrastructure Network (ECRIN), which was granted the status “European Research Infrastructure Consortium” (ERIC) at the end of 2013.

This area should integrate in the 2014 programme other actions pertaining especially to current European projects and programmes and to the implication of France.

1.6.4 An ambitious work programme for 2014

1.6.4.1 Concrete actions, under way and in some cases, implemented now in the form of annual programmes. They have to be monitored or even evaluated.

Areas B and C are the most concerned. For area B, one notes: the creation of the Rare Diseases Foundation, to be adequately monitored; the publication of calls for projects for clinical research (PHRC), translational research (PRTS), in human, social and basic sciences.

The objective is now to monitor the results of the Calls for Projects and the presence of the rare diseases in these calls.

For area C: an action aimed at obtaining the ERIC status for the ECRIN and E-Rare projects.

1.6.4.2 Well advanced actions, to be finalised in 2014

- First of all, the official creation of health networks, with their funding. Also, the definition of a monitoring and evaluation procedure of these health networks.

- Validation of the new accreditation procedure. This entails: issuing annual activity reports in mid-May 2014, formalising the self-evaluation benchmark (HAS site), formalising the validation procedure by the permanent group and the president of COSPRO

- Creating the national Data Bank

- Conclusions of the two working groups on drugs

- Evaluation of the high speed sequencers (acquired in 2001/2002) of the genetics laboratories, and the necessary upgrading of some of them.

1.6.4.3 Topics to be followed more in depth

In area A, the programme for each main field of action includes:

- Developing high speed approaches and particularly the establishment of a very high speed national platform. Discussions are on-going.

- Preparing a programme for the drafting of national protocols of diagnosis and care. This will be one of the criteria used in the evaluation of health networks.

- All actions relating to information and training.

- Actions to develop links between care and social support for those living with rare diseases.

In some of their aspects, these themes are identical to those of other plans. They should lead to discussions in common and enable to capitalise on measures already in place or on current experiments.

Some orientations arising from the discussions of 19 November 2013: need to plan at the scale of the territory; improve the knowledge of medico-social aspects of care; work on cross-cutting; address the training of various actors; integrate tele-expertise.

In area C:

Measure 1 consists in « promoting the sharing of expertise at international scale through the European reference networks ». This measure and its three actions are essentially implemented by Orphanet and the Rare Diseases Foundation. It represents a major challenge for Orphanet, the Foundation and their status in Europe.

Taking into account ongoing European projects and the creation of the working group following the EUCERD recommendations of 31 January 2013 on ERNs, it will be important to define very soon a strategy.

1.6.4.4 Actions to be integrated, but not explicitly mentioned in NPRD 2

The transposition of the European regulation on cross-border care and the creation of European reference networks must be integrated in the 2014 programme. Discussions will also be initiated with the Regional health agencies on the tasks listed in their mandates.

1.7 SUSTAINABILITY OF THE NATIONAL PLAN

This issue is central for the strategy of the second National Plan for Rare Diseases, as shown particularly by the creation of the Rare Diseases Foundation, the adoption of the Orphanet nomenclature, the creation of the national Data Bank on Rare Diseases and the restructuring of centres in more coherent and rational health networks.

Terms of reference of the health networks have been drawn up, together with a model of annual activity report for the RC, comprising a section on finance and a section on activity.

THEME 2 – DEFINITION, CODING AND REGISTRATION OF RARE DISEASES

2.1 DEFINITION

The French definition retains the European threshold of prevalence: less than one individual out of 2000.

2.2 CLASSIFYING AND TRACING RARE DISEASES IN THE NATIONAL HEALTH SYSTEM

The nomenclature normally used is ICD-10 (in which only 200 to 300 diseases have a specific code). However, the Orphanet code is the one retained in the national data bank for rare diseases managed by the Network of Centres for Rare Diseases - CEMARA - which collects at present the data from the RC.

In the context of NPRD 2, a national data bank is currently being developed, that will contain *a minimal data set* to be filled by all data banks (this minimal data set will be binding on the suppliers of applications in trades relevant to rare diseases : RC , CC and reference labs). The idea is not to bring together all the data bases in a single one but to gather a minimum of common information at one location. In this context, it is necessary to develop the interoperability of information systems and to define formats for exchange. The minimal data set has been endorsed by the ministry of Health, and the steering committee of the data bank was established in November 2013.

The Orphanet code was introduced as of November 2012 in the current system used by hospitals to collect information on their medical activities. At the present time, it is applied only to clinical care prescribed in the RC and CC (« file of diagnostic information for enquiries »). Recommendations for coding are currently being drafted by the data bank.

2.3 INVENTORIES, REGISTERS AND DATA BASES

It is essential to be informed adequately on the evolution of patients suffering from rare diseases. Depending on the clinical aspects and on the impact and prevalence of different diseases, the requirements for the collection of clinical, biological and genetic data are different: some patients may be listed in a register, others in a cohort. For others, ad hoc surveys at regular intervals could do.

In France, 5 registers of congenital malformations and 11 registers of Rare Diseases are qualified. The national committee of registers was suppressed by decree on 23 May 2013, resulting *de facto* in the dissolution of the national committee of rare disease registers created during the first national plan for rare diseases (2005-2008).

The national Institute of sanitary watch, the national Institute of health and medical research, and the national Institute for cancer are committed to setting up a **Committee for the evaluation of registers.** This Committee will evaluate the registers against their terms of reference for research and surveillance, and propose priorities for the policy of registers in response to epidemiological needs.

In 2013, Orphanet recorded 130 registers or data bases of rare diseases in France, some of which are European or international. Their management and implementation vary greatly and in general, are poorly known. These registers and bio-banks are accessible on the Orphanet portal and can be consulted by disease or gene, by institution or funder, and by country.

A portal Epidemiology France has been installed by the Alliance for Life Sciences and proposes an on-line catalogue of the main data bases on health of French source, that could be of use for the progress of research and expertise in public health. Each data base in the catalogue is described according to its main features: objectives, themes, populations covered, nature of the information collected, conditions of access, manager…

Furthermore, the RaDiCo project (Rare Disease Cohorts), funded by the research Ministry until December 2019 under the « Cohorts » programme of investments for the future managed by the National Agency for Research (ANR), is moving ahead. Its aim is to provide France with large instruments for epidemiology in order to better understand the determinants of health and optimise medical practice and public health policies. The main objective of RaDiCo is to collect, with a long term view, extensive phenotypic data on rare diseases for clinical and epidemiological research in connection with translational and basic research. The nature of such data can be diverse: anatomical (medical imaging), biochemical, molecular, etc. A first call for projects was launched in February 2014.

An interesting idea emerged during the EUROPLAN conference: involving patients in data collection.

This is being experimented in Leukodystrophy disorder with the assistance of a paramedical coordinator, and in the international data base of the Rett syndrome.

A concrete policy for the collection of phenotypic, biological and genotypic data will certainly necessitate in France the recruitment of research associates or technicians, i.e. professionals who are also active on the research front.

2.4 INFORMING DIFFERENT SECTORS OF THE PUBLIC ON THE AVAILABILITY OF CARE IN THE TREATMENT OF RARE DISEASES

2.4.1 The existing systems

The website of the health Ministry offers a lot of information on the policy and systems relating to the Rare Diseases. However, for the general public, the reference portal on rare diseases and orphan drugs is Orphanet, a service of INSERM (National Institute for Health and Medical Research) managed by a consortium of about 40 countries and funded in part by the health ministry and the European Commission. Its objective is to contribute to the improvement of diagnosis, coverage and treatment of rare diseases.

Orphanet proposes a number of services free of charge and freely accessible in 7 languages, for the benefit of professionals and the general public:

- An inventory of rare diseases and a classification following the expert classifications published;

- A professional encyclopaedia of the rare diseases in French and in English, to be gradually translated in the other languages of the site;

- An encyclopaedia in French for the general public, comprising since end 2013 specific data on the disabilities caused by rare diseases, in the context of a collaboration with the National solidarity fund for autonomy ;

- Recommendations in French for situations of emergency, translated gradually in the other languages of the site;

- An inventory of orphan drugs at all stages of their development;

- A directory of specialised resources, informing on expert centres, diagnosis labs, on-going research projects, clinical trials, registers, networks, technological platforms and patients patient organisations, with regard to the rare diseases in the countries of the Orphanet consortium.

- A help-desk to diagnosis, enabling investigation by signs and symptoms.

- A directory of professionals and institutions.

In 2011, Orphanet developed a second site, Orphadata, enabling to download a body of data on rare diseases and orphan drugs. The data proposed are partly extracted from those stored in Orphanet. The site is updated every month, with a mention of the date of the previous update. It is exclusively in English, but the data are accessible in six languages (English, French, German, Italian, Portuguese and Spanish).

- an inventory of the rare diseases, with their OMIM, ICD-10 number and the genes associated in HGNC, OMIM, UniProtKB and Genatlas ;

- Orphanet's classification of rare diseases;

- epidemiological data on rare diseases in Europe (prevalence, average age of occurrence, average age on death), taken from the literature;

- a list of signs and symptoms associated with each disease, with their frequency class;

- and since 2014 an ontology of the rare diseases.

Orphanet developed in 2013 a mobile application, free of charge, on iOS and Android http://www.orpha.net/consor/www/cgi-bin/Education_MediaEvents.php?lng=FR

Orphanet also publishes a newsletter in the form of a bi-monthly electronic letter of information, Orphanews, which gives in French, English and Italian the most recent scientific and political news on the rare diseases and orphan drugs. A collection of synthesis reports on transversal topics, the Orphanet notebooks ("Cahiers d'Orphanet"), can be downloaded on the site.

Moreover, the 202 patient organisations of the Rare Diseases Alliance, with its 18 regional desks, are an important source of information on the system of care. The same with the RC: in addition to informing on care, they disseminate information on the overall system.

The National French Helpline on Rare Diseases (Maladies Rares Info Services) also contributes extensively (more than one third of the answers provided) to directing patients and their families towards expert centres and specialised medical services.

2.4.2 Proposals for improvement

Many opportunities for improvement exist. The ministry can be requested to act more proactively on *Rare Disease Day.* It should also be possible to develop a strategy for improving information targeting professionals, with the help of stakeholders of the *Platform of Rare Diseases* and their networks. It also seems necessary to review the initial training and existing university degrees relating to the diseases.

It is also essential to assess the current actions on DPC (Continuous Professional Development).

Furthermore, as indicated in the national Plan, one should encourage academics specialised in rare diseases to put their teaching on line (French-speaking virtual medical University). And finally, one should continue to work on the creation of a European hot line.

2.5 LISTENING AND HELP LINES

2.5.1 The fundamental role of the National French Helpline for Rare Diseases

There exists a national French Helpline for Rare Diseases: "Maladies Rares Info Services" or **MRIS**. In addition, some of the patient organisations provide help and assistance on the telephone to the patients and families who contact them.

The French Helpline, MRIS, is an organisation created in 2001 and supported by the French Association on Muscular Dystrophies (AFM – TELETHON) and the ministry of health. The helpline provides assistance and replies to the queries by telephone, e-mail and chat. The helpline's telephone number is included –in fact free of charge – in the packages for cell-phones and fixed telephones that the great majority of callers subscribe to nowadays. Its cost, excluding the package, is that of a « standardised » call, i.e. the lowest usual rate.

Patients and their families need simple and clear information in order to understand the disease. They also need to be directed to medical services specialised in their pathology or to services providing social care. They also want to break their isolation by meeting other persons concerned.

Each query receives a clear reply adapted to the situation of the person. MRIS is the first national helpline in the field of health to have been certified ISO 9001, a norm for quality management.

The professional team is specialised in rare diseases. In 2012, MRIS answered 5190 calls, mails and chats.

Half of the users are patients, about 40% are close relations of patients. Out of the 10% of remaining queries, almost half are from professionals of the health and social sectors.

In half of the cases, information and explanations on the disease are given on the phone. Over one third of the queries result in directing to an expert medical service. One user out of five is directed to an association in order to break his/her isolation. A fourth type of service informs the callers about services of daily life and social assistance. Its proportion is on constant increase from year to year. And finally, support to patients remains an important task of the service.

Furthermore, the helpline has created and runs a Forum on rare diseases, where patients can share their information and experiences. The Forum attracts a lot of interest from patients. For on-line communities, it provides new ways of information-sharing. Its success illustrates the complementarity of resources available to patients and their families.

2.5.2 MRIS, an efficient service that should be reinforced

How satisfied are the users?

From the annual satisfaction enquiry (2013):

- 87.5% of callers accessed the service after a single attempt;

- 96.5% of users felt their request had been understood;

- 83% of users obtained the information they were seeking;

- 84% felt they received efficient or rather efficient help;

- 84% of internet users found the site user-friendly or rather user-friendly;

- 95% of internet users thought the messages and on line information of the Forum interesting.

To complement the national French helpline for rare diseases, France strongly wishes that a single European number be put in place (116 number) throughout Europe, and is willing to contribute to this action. The benefits would be two-fold: offer high added-value service to European citizens and enhance the visibility of the Rare Diseases cause, across borders and for the benefit of citizens.

2.6 TRAINING OF HEALTH PROFESSIONALS

2.6.1 The need for training in the area of Rare Diseases.

At the time of the first Plan on Rare Diseases (2005-2008), the theme « Rare Diseases » had been introduced in the programme of the national classifying test (ECN) for medical students, and specific modules had been set up in some universities and in the institutes of paramedical training.

This trend has been increasing since 2012 and 2013:

- NPRD 2 (2011-2014) is clearly mentioned in the DGOS instruction of 9 august 2012 on the implementation of public health plans in the programmes of initial training for paramedical professions;

- the reference to public health plans was introduced for those professions of which the diplomas have been modified. Indeed, many professions are involved in the treatment of rare diseases patients: nurses, physiotherapists, occupational therapists, speech therapists. However, we have at our disposal no overall view of the initial training of doctors on rare diseases. Isn't that one of the challenges of years to come in this field?

With regard to complementary and continuous training, university or inter-university degrees exist, that are open to health and social professionals, especially on problems of deficiency and disability. The continuous professional development, mandatory each year for all health professionals, medical and paramedics, doctors especially, includes sometimes modules dealing with rare diseases. However, these trainings, being very decentralised, are not inventoried at national scale.

At present, the decree of 26 February 2013 lists the national orientations for continuous professional development. Although quite wide-ranging, they already include such actions:

- Orientation 1: improve the coverage of patients, in particular for chronic diseases, health pathways and screening actions.

- Orientation 2: improve relations between professionals and patients, particularly on the theme : « improvement of the quality of care of fragile or disabled persons ».

Bearing in mind the rarity of expertise and of experts, one should encourage furthermore:

- academics specialised in rare diseases to put their courses on line, in cooperation with Orphanet, by using the French speaking Virtual Medical University, i.e. an interactive centre of resources for health professionals which is intended as a centre of information and prevention for health professionals and for the public.

- the extension to other universities of the optional training module on rare diseases, proposed each year to 3rd year students of the Necker-Cochin medical school with the participation of patient organisations.

- the creation of a real grid of RC (reference centres, CC (competence centres) and regional networks for the training of nurses and paramedics.

2.6.2 Focus on the Inter University Degree (DIU) promoted by the Rare Diseases Foundation

The Foundation for Rare Diseases is promoting training for research on rare diseases, in order to complement existing schemes of training that are generally devoted to groups of pathologies or to specialities.

This training is intended for professionals and focuses on research and the development of treatments for rare diseases. The format chosen is that of the "inter-university degree". The targeted public is diverse, being composed especially of doctors, researchers, pharmacists, advisers in genetics, clinical research associates, nurses, all paramedics, psychologists, researchers in human and social sciences, representatives of authorities and of the pharmaceutical industry…

The programme that is elaborated for the year 2014 consists of 9 modules:

- General module on rare diseases
- Context of diagnosis and various therapeutic approaches
- Biotechnologies and bioinformatics applied to rare diseases
- Data bases, cohorts and registers
- Translational research: from pre-clinical development to clinical trials
- Regulatory framework for orphan drugs
- Innovation and proof of concept: transfer and optimisation of the results of research
- Medico-economic potentials and strategies
- Ethics and research in human and social sciences applied to rare diseases.

THEME 3 – RESEARCH ON THE RARE DISEASES

3.1 THE EXISTING SITUATION OF RESOURCES, INFRASTRUCTURES AND RESEARCH PROGRAMMES

Research on rare diseases mobilises a number of teams in universities and hospitals. In support to these teams, specialised technological platforms offer the technical services needed to carry out various research programmes (technologies for high speed genetic sequencing, technologies for high speed screening of molecules potentially active in therapeutics, platform for the development of experimental models,…).

Reference centres for rare diseases (131 RC and 501 CC), accredited in the context of NPRD 1 (2005-2008), are major actors of research in university hospitals: their research is carried out in parallel with their activity on treatments. In doing so, they are backed up by university labs, national research institutes (INSERM, CNRS).

The portal Orphanet (http://www.orpha.net/) informs on the various on-going research projects. The search engine enables selection by disease or gene, by institution or funder, by country or type of project, thus complementing the information available on site https://clinicaltrials.gov which registers on-going clinical trials, including in the area of rare diseases.

Furthermore, Research is funded by the Health Ministry and the Ministry of Higher Education and Research, also by private sources such as those proposed by the Rare Diseases Foundation via dedicated calls for projects, or those made available through industrial or associative partnerships. Research teams are thus able to submit projects to the programmes of the National Agency for Research (ANR), the Hospital Programme of Clinical Research (PHRC), or again the Programme of Translational Research on Health (PRTS). Only a few of these programmes guarantee a minimal amount of funding for rare diseases.

Lastly, a number of other portals inform on opportunities for the funding of research, some being specific to rare diseases (http://fondation-maladiesrares.org/types-de-recherche), some not (http://www.girci-est.fr/thesaurus/).

3.2 RESEARCH PROGRAMMES ON THE RARE DISEASES, AND MEANS TO MANAGE THE FUNDING OF RESEARCH

NPRD 2 (2011-2014) makes research on rare diseases a major challenge and devotes to it one of its main themes, with a focus on « developing research ». Four priorities are targeted:

- create a national structure to impulse research: the Rare Diseases Foundation

- promote tools to increase knowledge on the rare diseases

- promote the development of therapeutic trials

- favour translational clinical and therapeutic research

The latter three measures are facilitated by the overall activity of the Foundation and by the launching of two national programmes: **RaDiCo (Rare Diseases Cohorts)** managed by the Ministry of Higher Education and Research, and the programme of **the National Data Bank on Rare Diseases**, managed by the Health Ministry.

3.2.1 The Rare Diseases Foundation

Conceived as a national structure for the coordination and fostering of research, the Rare Diseases Foundation is one of the prominent features of the theme « Research » of NPRD 2. A private non-profit body for scientific cooperation, the Foundation was created on 7 February 2012 by a decree of the Ministry for Higher Education and Research. This unique model of scientific cooperation arose from a decision of its five founding members: AFM-Telethon, the French Rare Diseases Alliance, INSERM, the Conference of General Directors of University Hospitals (« *Collèges hospitaliers Universitaires* ») and the Conference of University Presidents. The task of the Foundation is to federate competences and create synergies for the emergence of new therapies.

The Foundation is an accelerator of projects, a facilitator of partnerships, a federator in the area of rare diseases.

Since there is a strong risk of dispersion of research efforts (multiplicity of diseases, scarcity of expertise, small number of patients for each disease...), it is essential to create links between researchers and staff in charge of care. Within 2 years, more than 2000 meetings and 3 colloquia gathering 450 professionals were organised (http://fondation-maladiesrares.org/nos-realisations.) Strengthening these links contributes to:

- the understanding of rare diseases. The Foundation facilitates access to the technological resources needed to understand rare diseases (high speed sequencing, creation and investigation of animal models). The research projects are selected according to their scientific excellence, as a result of calls for projects. About one hundred projects were thus supported in 2 years.

- the development of new treatments. By publishing calls for projects, the Foundation facilitates access to screening techniques in order to identify new potential molecules for treatments (15 preselected proposals). Furthermore, it detects and accompanies promising projects at various stages of their therapeutic development (80 candidate drugs detected).

- improving the lives of patients. The Foundation, acting in partnership with the national solidarity fund for autonomy (CNSA) and the General Directorate for Health (DGS) of the Ministry of Health, has issued two calls for projects to support joint research activities between doctors, researchers in human and social sciences and patient organisations. The objective is to evaluate the impact of rare diseases on patients and their families, and to suggest practical adaptations. 17 projects were thus funded, based on their scientific merits.

3.2.2 The RaDiCo Programme

The aim of the RaDiCo programme *(Rare Diseases Cohorts)* is to develop a common platform to assist in the formation and/or the monitoring of rare diseases cohorts in France. The project is funded by the Research Ministry until December 2019. It was selected in 2011 following the call for « Cohorts » projects of the « Investments for the Future of the Great Loan » managed by the National Agency for Research.

The objective of this call for projects was to provide France with large instruments in epidemiology so as to better understand the determining factors of health, optimise medical practice and public health policies.

Cohorts are instruments open to federative research projects in the context of public, private, associative or industrial partnerships. Their purpose is prevention and the improvement of practice in diagnosis and therapy.

RaDiCo relies on the network of the 131 RC and 501 CC both covering 18 large groups of rare diseases, 54 university hospitals' laboratories of molecular diagnosis, centres of biological resources, research labs and registers of rare diseases and on patient organisations as well.

The challenges to be met are due especially to the dispersion of the many teams concerned (for care and research), the disparity of allotted means depending on which rare diseases are considered, and the disparity of existing information systems (clinical and biological).

The main objective of RaDiCo is to collect, with a long term view, extensive phenotype data for purposes of clinical and epidemiological research, in connection with basic and translational research. Subsidiary objectives are to establish phenotype/genotype correlations, make progress in the knowledge of physiopathological processes, validate/discover new therapeutic pathways in cooperation with industrial partners.

RaDiCo has issued in January 2014 its first call for « cohort » projects. The deadline for submissions was set for 31 May 2014: http://www.radico.fr/fr/appels-a-projets-cohorte-offres-radico/appel-a-projets-cohorte-en-cours).

3.2.3 Data collection: the National bank of Data on Rare Diseases (BNDMR)

The National Bank of Data on Rare Diseases (http://www.bndmr.fr/) was created to meet the need for clinical data on rare diseases. The expected benefits in the long term are to improve knowledge on the natural history of diseases, to document methods of care and their impacts, to describe the request for care and evaluate the adequacy of the corresponding offer and to produce medico-economic knowledge on rare diseases. BNDMR is intended to interface with the RaDiCo programme, in particular to identify at national level patients who could be eligible for the clinical trial of a new drug or medical procedure.

The first stage in the development of the data bank consisted in defining the minimum data set, i.e. a common base for all rare diseases and all the staff in charge of care. This stage was essential to guarantee the quality and exploitability of the data collected.

The data are collected under the responsibility of RCs and CCs for rare diseases, particularly from their available files and data bases. Prior to this, it is essential to make the information systems interoperable, so as to facilitate data exchange. Connectors are being developed to automatise data collection and avoid double entries.

In order to assist professionals in the use of Orpha codes, the national data bank has created a tool to help coding rare diseases, named LORD (Linking Opendate for Rare Diseases; http://lord.bndmr.fr/)

3.3 ENSURING THE SUSTAINABILITY OF RESEARCH ON RARE DISEASES

Public health plans such as the two French NPRDs are essential in that they impulse a global momentum and lead to a federation of initiatives. They include provision for governance and monitoring. These steps forward were made possible by the mobilisation and support from all parties involved with rare diseases (patient organisations, doctors, researchers, institutions). Research on rare diseases is one of the three priorities of the NPRD 2011-2014.

Since rare diseases should benefit from the excellency of the health and research systems provided under common law, since research on rare diseases brings benefits to the whole scientific community, and even more so, can be applied to frequent diseases, since French scientific excellence nourishes this research, and because much remains to be done, efforts must be made sustainable and even be strengthened over the next years. Research must remain a priority and be treated as a matter of national emergency!

To achieve this goal, funding remains a crucial issue. The earmarking of funds and their proper use could be optimised. Moreover, the means allotted to research (programmes, teams, organisations) are inadequate. Guaranteeing a minimum amount for rare diseases in the programmes of the National Agency for Health would certainly help to keep French scientific excellence at a high level of competitiveness.

Ensuring the sustainability of actions such as those of the Rare Diseases Foundation is a major issue, especially with regard to its funding.

3.4 NEEDS AND PRIORITIES FOR RARE DISEASES RESEARCH

Significant progress has been made in the field of rare diseases research. However, much remains to be done and a few priorities emerge.

Access of research teams to advanced technology should be made easier, especially for high speed sequencing, the creation of animal models, the omics approaches…

One should take advantage of the excellent proximity of basic and clinical research in France. It is essential to acquire means for translational research, with regard both to funding and organisation. New economic models will have to be invented in order to optimise efforts for a better exploitation of results. Public-private partnerships should be encouraged in order to speed up research and improve the « return on investment ». Academics cannot bear the whole burden of a translational programme, even less so its regulatory aspects.

Patient organisations too have an essential place in research programmes. They have a very important role to play on ethical aspects, in the spreading of information, or in documenting the natural history of the diseases and the experience of those who have to live with them. In this respect, human, social and medico-economic sciences are still largely unexplored. The area of rare diseases is conducive to interdisciplinary research projects.

NPRD 2 (2011-2014) has moreover stressed the importance of research on human/social sciences in the treatment of rare diseases. Just understanding the causes and biological processes of rare diseases does not ensure optimal coverage. Knowledge on the life courses of patients remains too limited, and too few research projects are devoted to them. By studying the impacts of rare diseases on various aspects of the lives of patients and their families, one could improve the conditions of diagnosis and the procedures of treatment and care.

In order to support this major theme of research, the Rare Diseases Foundation launched 2 calls for projects in 2012 and 2013. These calls were supported by the national solidarity fund for autonomy (CNSA) and the General Directorate for Health (DGS). Their aim is to increase knowledge on the individual and social

consequences of living with a rare disease, particularly in terms of limitation of activities and integration in the society. The results will be better care and social support in all aspects of the life and health pathways of the patients.

As stressed in NPRD 2, these calls for projects are also aimed at stimulating the cooperation between researchers in human and social sciences, experts in medical care (RC and CC), experts in social and medico-social services, and patient organisations. Finally, the results will enlighten public policies on the disparities faced by the patients in their attempts to access appropriate care.

Three topics were addressed in these two calls for projects:

- The care pathway and life course: seeking a diagnosis, announcement of the disease, disability, medical treatment, social support of the person and his family;

- The new technologies in genetics: consequences on information, legal protection, new practices, costs of care;

- The educational, social and professional course of patients.

The two calls for projects mobilised 450 teams of clinicians and researchers, and 112 organisations of patients. 157 letters of intent were submitted, illustrating the need for research in this area. After evaluation and selection, 17 projects were funded under the two calls, involving 76 teams of clinicians and researchers, and 20 patient organisations.

Economic and social sciences, together with the ethical implications of rare diseases, are interdisciplinary fields that could be investigated more fully. Lastly, the emphasis given to research in human and social sciences in the European calls for projects, should not be neglected and must be borne in mind.

In conclusion, important priorities of public health remain to be formulated, either in a new rare diseases Plan or in the continuation of the on-going Plan, or as components of a strategy of significant support for these rare diseases.

3.5 STIMULATING THE INTEREST AND PARTICIPATION OF LABORATORIES AND RESEARCHERS, PATIENTS AND ORGANISATIONS, IN RESEARCH PROJECTS

Research on rare diseases runs into various obstacles that hinder innovation. In practice, it suffers from the scarcity of expertise, the small number of patients, their geographical dispersion, and sometimes even a lack of clinical consistency for a given disease.

Furthermore, although the world ranking of French research is high, the conversion rate into concrete projects of translational research remains too low. And finally, in spite of the existence of incentives, owing to the rarity of cases and the existence of technological and regulatory risks, industry invests too little in rare diseases research.

In view of this situation, it is mandatory to make research on rare diseases more attractive for all: researchers, industry and patients.

3.5.1 Promoting Public-Private partnerships

Translational research is absolutely necessary to speed up the transition from basic to clinical research, but it will become possible only in partnership with the industry. Hence, in order to optimise each research project, it is essential to share a common language and form dynamic teams in which each competence has been clearly identified with its role in the project. Financial constraints must be taken into account in the long term, with a budget for the maturation and optimisation of results, without neglecting or underestimating neither the

existence of Directives nor the issue of intellectual property which will have to be addressed at very early stages.

The culture of optimisation of results should form a integral part of every translational research project, implying win-win strategies for public-private partnerships where each partner finds its place.

3.5.2 Favouring the participation of patients and their patient organisations in research

This is a fundamental point. A few approaches could be attempted:

- Effective participation of patient organisations in future health networks;

- Inform on results of research;

- Improve the communication between stakeholders: regular meetings;

- Favour international co-operations;

- And above all, **education** of professionals (researchers, clinicians, patient organisations) on issues relating to rare diseases.

Encouraging patients and patient organisations to participate in research will help promote TRUST, ATTENTION and RESPECT.

3.6 EUROPEAN COOPERATIONS IN RARE DISEASES RESEARCH

3.6.1 The European programme E-Rare

The objective of E-Rare is to finance translational research through annual calls for projects. E-Rare partners are ministries and funding agencies in Europe and in the world, which combine their support for research in order to favour the emergence of transnational cooperations. In France, the National Agency for Research (ANR) funds the French teams of selected transnational projects. E-Rare was coordinated until 2014 by INSERM.

Two calls for projects were issued during the first E-Rare programme: in 2007, the first call involved six funding agencies and 13 projects were supported; in 2009, 16 projects were funded under the second call. France was present in all selected projects of the first call and in 11 out of 16 projects selected after the second call.

The second phase of the programme (E-Rare 2 – 2010-2014) brought together 18 ministries and funding agencies from 15 countries.

France participated in the three calls of this second phase, published in 2011, 2012 and 2013. French teams participated in the 13 projects funded in 2011, in 7 out of the 11 projects of 2012 and in 9 of the projects funded in 2013.

In December 2013, the consortium issued its joint annual call 2014 on « innovative therapeutic approaches for rare diseases » with a budget of 13 M euros[2]. In 2014, the agencies and ministries partners in E-Rare proposed a follow up project to the European Commission in the context of the Horizon 2020 programme. If the project is selected, E-Rare should start early in 2015, coordinated by ANR.

For more information: http://www.erare.eu/

[2] Evaluations are still on-going at the time of writing this document

3.6.2 ECRIN (European Clinical Research Infrastructures Network) – European infrastructure for clinical research

The objective of ECRIN is to promote and facilitate multinational clinical studies on a European scale. ECRIN connects national networks of centres of clinical investigation or units of clinical research, located at present in Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Spain, Sweden, Switzerland and United Kingdom. It will gradually involve other European countries. ECRIN is a distributed infrastructure, based on competence centres which are able to provide integrated services for the continuation of clinical studies in Europe, mainly for academic sponsors.

By relying on its network of national correspondents, ECRIN facilitates clinical research in Europe by:

- providing information and consultations on regulatory and ethical requirements, insurance, costs and funding, selection of centres in the member states;

- proposing decentralised services to carry out studies (ethical and regulatory submissions, monitoring, watch, etc.);

- coordinating the access to clinical research centres/units or groups of clinical studies.

In France, the national network of clinical investigation centres (CIC) and its thematic networks participate in the ECRIN network. The ECRIN correspondent is hosted by INSERM, within the department coordinating the CIC and the centre for Clinical research of the Public Health Institute of INSERM. The ECRIN correspondent relies on these two structures to fulfil his tasks of information and support for multinational studies, whether the sponsor is based in France or abroad.

For more information: http://www.ecrin.org/

3.6.3 International Rare Diseases Research Consortium (IRDiRC)

The objective of IRDiRC is to coordinate international collaborative efforts in order to accelerate the development of diagnostic tests and therapies for rare diseases. The two main objectives of the international Consortium until 2020 are to develop:

- 200 new therapies,

- the means to diagnose most rare diseases.

Launched by the European Commission and the NIH in 2011, the IRDiRC consortium comprises 41 members (funding agencies, research organisations, patient organisations and pharma industries) supporting rare diseases research on four continents. IRDiRC members invest a minimum of 10 million euros over 5 years in research projects and programmes contributing to the IRDiRC objectives.

The IRDiRC structure consists of three scientific committees and several working groups. The scientific committees address three transversal topics: diagnostics, therapies, interdisciplinary. Each scientific committee is composed of about 15 members, achieving a well-balanced expertise and representation of academic institutions, patient organisations, pharmaceutical industry and regulatory bodies. They advise the Executive Committee on research priorities and on the scientific progress made under IRDiRC.

In France, the following organisations are members of the IRDiRC Executive Committee: AFM-Telethon, ANR (National Agency for Research), Rare Diseases Foundation and Lysogene.

For more information: http://www.irdirc.org/

3.6.4 European research infrastructure for rare diseases

Horizon 2020 (started in 2014), is the Research and Innovation programme of the European Commission and therefore, a major financial instrument for funding Research and Innovation in Europe. The 2014 call for projects invites the research community to develop a research infrastructure for rare diseases at European scale. The infrastructure will integrate enough information and data on patients to enable the etiological study of the diseases, a monitoring of the epidemiology, the development of tools for diagnosis and of therapeutic options. The objective is to bring together, to integrate on a European scale and to open up the main national and regional research infrastructures to all European researchers, from academia and/or industry, by ensuring their optimal utilisation and common development.

THEME 4. PATIENTS CARE IN RARE DISEASES, REFERENCE CENTRES, HEALTH SYSTEMS, EUROPEAN REFERENCE CENTRES

4.1. IDENTIFICATION OF THE REFERENCE CENTRES (RC) AND COMPETENCE CENTRES (CC)

The French system is organised nationally:

In 2010, 131 **Reference Centres** have been approved, listed in 18 groups corresponding to disease types (ex: rare endocrine diseases or rare diseases of the bone). These centres were accredited following a call for applications issued by the Health ministry to the University Hospitals that were already taking care of this category of diseases. The national committee for accreditation of RCs gave its opinion for accreditation in compliance with the European criteria listed by the « High Level Group of Standard of Care » to define the missions of an expert centre. Accreditation of these centres was based on what existed and on volunteering. The designation is valid for 5 years. After 3 years, the centres must undertake a self-evaluation. After 5 years, the High Authority on Health (French Health Technology Assessment Agency) undertakes an external evaluation, the results of which determine the renewal of the agreement.

Their missions are:

- referral (diagnosis, consultations, one-day (or more) admission in hospitals, remote advice …)

- data collection for clinical follow up, research and knowledge in public health

- research

- expertise (in particular the drafting of national protocols for diagnoses and care, “PNDS”)

- in-depth clinical investigations

- coordination and management of the system

- international relations

Subsequently, the patient organisations argued for an organisation of care at local level that had not been foreseen in the drafting of the first Plan (2005-2008). A call for applications was published during the last 2 years of the first Plan to select 502 **Competence Centres** (CC), i.e. hospitals able to carry out the first 3 missions (referral, research, data collection) in liaison with the RC, but receiving no dedicated funds for rare diseases, contrarily to the prevailing situation of the RC. In general, patients are followed daily by a GP or an out-clinic specialist.

It is also deemed important to develop e-Health, i.e. multidisciplinary consultations by telemedicine, videoconferences.

This system of RC, CC and soon of **reference laboratories** is clearly identified by administrations. Professionals and patients are made aware of it, thanks to Orphanet and to all the information provided by patient organisations.

4.2 MISSIONS AND MODES OF OPERATION OF THE REFERENCE CENTRES AND COMPETENCE CENTRES

NPRD 1 2005-2008 has better structured the provision of specialised care for rare diseases as well as its user-friendliness for the patients and the different actors in the healthcare sector.

The Plan describes successive steps leading to these objectives:

- acknowledgment of the structures of scientific/clinical excellence for rare diseases, by granting accreditation to RCs for one (or a group of) rare disease(s);

- gradual building up, around these RC, of a specialised scheme to improve access to diagnosis and better quality of care, through the identification of regional or interregional CC for those rare diseases.

The Reference Centres (RC) for rare diseases

131 RC have been accredited and funded up to 40 million euros as components of “General Interest Missions” (MIG). They bring together highly specialised university hospital teams.

A RC for rare diseases has two essential roles:

- **expertise** on a disease or a group of diseases for which it has developed specific and acknowledged competences;

- **referral**, by which the centre, confronted with the rarity of the pathology covered and the small number of specialised teams, is able to exert its attraction (interregional, national or international) beyond its local base.

Points to remember:

RCs have 6 missions:

- they facilitate diagnosis and define a strategy of therapeutic/psychological care and social support;

- they define and circulate protocols of care, in cooperation with the High Authority for Health (HAS) and the national union of medical insurance offices (UNCAM);

- they coordinate research work and take part in epidemiological surveillance, in cooperation with the national institute of sanitary surveillance (InVS);

- they participate in initiatives for the training and information of healthcare professionals, patients and their families, in cooperation with the national institute of prevention and education for health (INPES);

- they run and coordinate the networks of health and medico-social correspondents;

- they are privileged contacts for authorities and patient organisations.

Reference Centres for rare diseases are designated according to a national procedure of accreditation. This is based on an independent expertise and on precise specifications. The label “RC” is conferred by the Health ministry, for a period of 5 years.

4.3 THE HEALTH NETWORKS OF RARE DISEASES

The first national plan for rare diseases 2005-2008 has allowed improving access to diagnosis and care for rare diseases patients, as a result of the creation of 131 certified RCs. The plan was completed with the identification of 502 CC attached to the RC, offering assistance for proximity medical care.

The evaluation of this first plan has stressed the merits of the system together with the need to develop pooling and complementarities between the RCs and the other actors of care and research. The High Council of Public Health has recommended to favour large groupings (for instance, anomalies of growth, metabolic diseases, etc.) as well as to federate the RCs of different regions dealing with the same disorders. Similarly, in the article 12 of Directive 2011/24/EU of the European Parliament and of the Council of 9 march 2011 on "the application of patients' rights in cross-border health care", it is specified that the European Commission helps Member States create European Reference Networks (ERNs) between healthcare providers and expert centres in Member States, particularly in the area of rare diseases.

The first action mentioned in NPRD 2 2011-2014 is to build health networks of rare diseases. The health network should cover a wide and coherent range of rare diseases, whether they are closely related by their symptoms, consequences or coverage, or affect a single organ or system. The network deals above all with known rare diseases, and also with not yet confirmed diseases or syndromes. Nevertheless, these networks are not meant to replace the RC nor the CC in the treatment of rare disease patients.

Generally speaking, these rare diseases networks have two objectives. First of all, they will improve user-friendliness in order to reduce diagnostic delays and provide timely treatments. They will do this by making it easier for all patients and GPs to navigate in the health system, particularly if no RC exists for the identified or suspected disease, or if several RCs exist with comparable areas of competence.

The health networks will also bridge gaps and create a continuum between the various actors, those involved in medical care, in diagnostic innovations, in therapeutic R&D and in the medico-social sector.

This mode of structuration is not meant to insulate networks from each other, in a way that would contradict the multisystemic features and consequences of many rare diseases and the necessary complementarity of research activities. As far as needed, a RC continues to interact with another RC belonging to another health network, and all the health networks cooperate together.

By structuring the health networks of rare diseases, one seeks to improve global coverage of patients. NPRD 2 intends to « structure rare diseases networks » in order to manage and coordinate RC and CC, consultations and genetics labs, the various technical services and any other structure for a comprehensive offer for care to rare diseases patients.

The aim of each network built around a coherent group of rare diseases must be to coordinate the RC by pooling their means of management ; to help all patients and their GPs find their way in the system of care ; to strengthen the coordination of care in terms of diagnosis, treatment and medico-social care ; to organise the collection of good-quality clinical data for follow up and research ; to impulse and coordinate research actions ; to bring together resources and expertise at national level in order to increase their international visibility, particularly with the aim of facilitating their integration in future European reference networks.

It is however essential to stress once more the major role of patient organisations. Their participation and investment in these networks are of crucial importance. The instruction of the Health ministry specifies expressly that rare diseases patient organisations should be partners of the rare diseases health system. Indeed,

they will be associated with the governance and the work. The instruction also specifies that the extent to which patient organisations are involved in the networks will be a decisive criterion in the allocation of projects.

More generally, these health networks will also provide opportunities to implement some actions or proposals formulated during the French EUROPLAN Conference of 13th January 2014.

- A representative from AFM (the French neuromuscular dystrophy association) suggested to increase the number of persons acting as advisors for health pathways, and to extend their role to advise also on life courses, especially with regard to the rights of accessing to specialised social support;

- It will be necessary to pay attention to the future place of patient organisations in the governance of the system. This can be checked during the annual evaluation of health networks. Conversely, the patient organisations must bring a positive contribution to the work of the very dedicated doctors who run the health networks. Some doctors - who are still somewhat reluctant - should at last commit themselves to exchanging with patient organisations.

- Encourage health networks to introduce common tools, for example for the therapeutic education of the patient.

- Accompany the structuration of genetics laboratories. The geographical distribution of these labs should converge with that of networks. Beyond that, the funding problem hampers considerably the rise of genetics. It is necessary to clarify the funding channels so as to enable geneticists to play fully their role in the rare diseases sector.

- Let the networks promote the European Reference Networks: a network would not necessarily act as coordinator as initially envisaged, but could mandate its RC to take a particularly active part within a European Reference Network.

4.4 GUIDELINES FOR GOOD PRACTICE

The drafting by experts of **national protocols for diagnoses and treatments (PNDS)** was first provided for in NPRD 1 and confirmed in NPRD 2 using a method proposed by the French High Authority for Health (HAS).

The objective of a PNDS is to make explicit to professionals the best available methods for diagnosis and therapeutic care and the treatment course of a patient affected by a given rare disease. The ultimate aim is to optimise and harmonise the treatment and follow up of the disease throughout the country.

These PNDS can be used as reference by the GP (the doctor whose name is given to the medical insurance office by the patient) in consultation with the specialist. This will happen especially when the protocol of treatment is drafted to accompany a request for exemption of co-payment in the case of an unlisted disease in the list of 30 chronic illnesses recognised by the French healthcare system.

The French High Authority for Health (HAS) published in December 2012 a simplified method of PNDS drafting by the RC. This method has not yet resulted in a significant increase of the production of these PNDS. A first prioritisation of themes was made in 2012. It will be reviewed once the health networks have been created.

4.5 FIGHTING AGAINST DIAGNOSTIC DELAYS AND IMPROVING SCREENING POLICIES

The initial step is to inform professionals and the population, first on the rare diseases (by introducing the notion of doubt: « and what if it is a rare disease? »), and secondly on the system of health networks and other existing resources, including at European level. As explained above, this implies: to reinforce Orphanet; to

reinforce the French helpline for rare diseases in parallel with other hotlines and by introducing a European “116” number; periodical campaigns of information by the Ministry of Health.

It is also necessary to:

- mention clearly the reference labs in the list of existing resources;

- simplify, as mentioned above, the structure of networks (down to about 20), by registering all diseases, including the rarest, in a centre able to interface with centres abroad, should the need arise;

- organise and reinforce the tools of telemedicine (dedicated funds are provided for in the plan);

- increase the funding of hospitals in order to make biological tests free of charge and cover the shipping costs of samples abroad whenever necessary.

There is an indirect connection between this theme and the issue of screening of rare diseases. One should clearly distinguish between the following categories of tests:

1) The two screening tests proposed to pregnant women: search for birth defects by echography and screening for some aneuploidies such as Down's Syndrome. Some rare diseases fall under this category.

2) Newborn screening is applied at present in France for only 5 diseases: 4 for the bulk of the population (phenylketonuria, Congenital Adrenal Hyperplasia (CAH), hypothyroidism and cystic fibrosis), and one for a targeted population (sickle cell anaemia). All these diseases, except hypothyroidism, are rare. Screening is performed with drops of blood deposited on blotting paper after capillary sampling. Organised by AFDPHE (French Association for the Prevention of Children Disabilities), it was recently codified by a ministerial decree of 22 January 2010. The progress of new technologies (in particular tandem mass spectrometry) has broadened the potential field of investigation and in some countries, screening of up to 30 metabolic diseases is already performed at birth.

3) The early detection of deafness or some congenital heart diseases, by specific technologies. Congenital deafness is frequent (1 out of 1000) but some of its causes are common with those of rare genetic syndromes. It can be detected at the neonatal stage with fast tests, now made reliable (Auditory evoked potential and/or Otoacoustic emission, OAE). This screening is already performed in many countries, and is at present the subject of a study in France in view of its possible generalisation.

4) The screening of heterozygotes autosomal recessive disorders:

. can be a collateral consequence of newborn screening, the first objective of which is to identify homozygotes in order to treat them at an early stage. This situation often occurs in cases of sickle cell anaemia and raises the question of the information to be delivered to parents.

. it can also consist in screening of children at the request of the family, or of adults, individuals or couples, considered to be at risk in view of their geographic origin or family antecedents.

5) Provision for funds is made in the Plan to develop Pre-implantation genetic diagnosis.

The ministry of Health is currently seeking to improve the policy and implementation of screening procedures. The ministry has requested HAS for an opinion on the extension of newborn screening. DG Sanco of the European Commission, following a call for tenders, is funding a study on policies of newborn screening of rare diseases in Europe, the objective being to formulate recommendations for good practice.

The Committee for monitoring the national plan will have to give its opinion on the proposals made on all matters dealing with rare diseases. In the area of screening, patient organisations and doctors have great

expectations. It will not be possible to elude for a very long time this medical, ethical, financial and social problem.

4.6 ENSURING THE LONG TERM SUSTAINABILITY OF REFERENCE CENTRES

The RC – Reference Centres – are hospital units, benefitting from a 5-year accreditation by the Ministry of Health. After these 5 years, the renewal of accreditation will be subject to evaluation by HAS. If this procedure is extended to CC – Competence Centres - and to Rare Diseases laboratories, the system will gain in administrative stability. It should be noted however that the coordinator of the Reference Centre is the holder of the label "RC", which might lead to some problems if the coordinator leaves the RC.

Specific funding from MIG (general interest missions) has been allocated to RCs (up to 40 million for new measures during the first RD plan) and renewed during the life time of the accreditation. However, funding has not always been proportional to the amount of activity, nor has it always reached the beneficiaries, and it has seldom enabled to recruit staff with a long term contract. Yet the main weakness is that much of the staff – clinical research associates, psychologists, social workers and even some medical staff – is on short term contracts.

It is therefore necessary to review the funding allocations, ensure that they can be tracked and earmarked, and allocated by activity: expertise, in depth clinical investigation, coordination, organisation of the network and international relations, clinical research, collection of data and of observations for clinical follow up and knowledge on public health, and compensation of the referral activity. Referrals, being essential in RCs and CCs should no longer be covered by MIG. It should be handled instead by billing per activity, provided this remains specific to rare diseases, so as to take into account the complexity, duration and interdisciplinarity of the provision of care. The Plan makes provision for, and quantifies these fundings.

4.7 PARTICIPATION IN EUROPEAN NETWORKS

The new call for European projects, hopefully to be more sustainable, will be launched in 2015. The French networks will have to find their place in this new context. Clearly, these networks must promote the European reference networks: a given network would not necessarily act as coordinator as initially envisaged, but could appoint one of its RC to take an especially active part within a European structure.

4.8 EVALUATION AND SUSTAINABILITY OF REFERENCE CENTRES

HAS (the French Health Technology Assessment Agency) is as an independent agency acting in liaison with the minister of Health, particularly to certify establishments and evaluate health practices. HAS is commissioned to undertake the evaluation of RCs: every 3 years, centres must fill in a questionnaire of self-evaluation; every 5 years an external evaluation is carried out by visiting experts, based on terms of reference which take into account the main missions of the centres (referral, expertise, research and epidemiological surveillance, structuration and management of the system of sanitary and medico-social care, information and training of health professionals, patients and families). The most recent version of these terms of reference is published on the website of HAS, annex 3.

A working group « methodology, evaluation, accreditation » was established in September 2011, chaired by Pr. Sabine Sarnacki. New terms of reference were validated by the college of HAS in 2013. A digital template of the future Annual Activity Report of RCs has been finalised to be widely available in 2014. The procedure for the replacement of RC managers has been reviewed and is spelt out in an instruction dated 29 July 2013.

The last meeting of this group took place on 11 September 2013. The permanent group has now taken charge of these files.

THEME 5. DRUGS AND THERAPIES FOR RARE DISEASES

5.1 ORPHAN DRUGS

5.1.1 Orphan drugs in the Rare Diseases Plans

In the first two NPRD, no measures specifically targeted the development of orphan drugs. However, a better organisation of research on rare diseases will result in a multiplication of new therapeutic approaches. Are additional incentives needed at national level to stimulate the development of orphan drugs?

The plans insisted on the fact that orphan drugs (innovative molecules) are far from representing the essential components of treatments used for rare diseases: currently the drugs (recent or not) that are the most often prescribed, are **off label**. Non medicinal therapeutic techniques also exist such as medical devices, cell therapy, gene therapy….

The European Regulation 141/2000 has given orphan drugs a 10-year EU market exclusivity and has authorised national subsidies. However, the regulation falls short of solving all problems. Some phases of drug development are not covered by subsidies, and the existing subsidies are not known enough.

In France, when a drug, notably an orphan drug, has not yet received its marketing authorisation, this drug can be prescribed under exceptional circumstances in the case of severe and life threatening diseases. This system of compassionate use is called **ATU** (“authorisation temporaire d’utilisation”). Although of unquestionable benefit to patients, ATU does not include an obligation to collect data on the efficiency of treatments. In France, the market and costing of orphan drugs lack transparency.

With regard to other drugs, particularly the many “old” molecules used off label, clinical development is confronted to many difficulties and to a lack of motivation on the part of industry ; hence, at times, a problem of safety and efficiency of use. Interruption in manufacturing/ selling a drug can occur, even in the absence of alternative therapies for rare diseases, if prescriptions of this drug for frequent disorders decline. With regard to this category of drugs, the Plan makes proposals to overcome the difficulties described above.

5.1.2 Developing orphan drugs: yes but how?

First question: are additional incentives needed at national level to stimulate the development of orphan drugs?

Three approaches exist. The first one is to develop incentives, mainly on organisational matters, facilitate public-private and private-private partnerships, accelerate procedures for the evaluation of drugs, develop data bases and registers, particularly in order to enable pharma companies to follow good practice.

Secondly, in contrast to the situation in the USA where 85% of drugs for rare diseases are produced by small or very small companies, the majority of drugs in France come from big companies. It is a major challenge for the French economy and employment.

Thirdly, the ministry of Economy is not mentioned in the national rare diseases plan, and this is an important point to consider. The problems of international pharmaceutical companies are not the same as those of small-very small companies. The latter has to convince their parent companies of the steady attitude of France regarding matters of regulations and the priority given to rare diseases. Transparency must also be ensured.

5.2 PATIENTS' ACCESS TO TREATMENTS FOR RARE DISEASES

This is a major issue. Facilitating the earliest possible access of patients to new treatments is a real challenge. The process is however complex and the introduction of medico-economic criteria could have some disturbing aspects. Hence the question: are national procedures of access to the market and of pricing adapted to the specificities of rare diseases? And, *in fine,* what are those specificities and how could one improve and speed up procedures?

Clearly, one has to take into account the very great disparity of rare diseases. For 2.8% of them, the prevalence ranges from one case in two thousand to one in ten thousand, i.e. 6 000 to 30 000 patients in France. For 5.5%, the prevalence is 600 to 6 000 in France, for 27.8% it is between 6 and 600 000 patients in France and for 63.9%, between zero and five patients in France.

All these diseases, therefore, cannot be treated in the same manner. The entry into force in October 2013 of the decree introducing a new medico-economic step in the evaluation of drugs, is at the same time a good and bad news. While the culture in France is not to set a threshold to treat a patient, one needs to remain careful. It is also necessary to take into account the specificities of rare diseases, especially for the distribution of drugs; they are reserved in retrocession for hospitals and rarely available in pharmacies. The *conditional pricing* and the *conditional market access* should take more into account the data of the plans for management of risks, adapted to the national situation.

5.3 COMPASSIONAL USE AND TEMPORARY AUTORISATION

5.3.1 ATU, essential authorisations for the treatment of rare diseases

The system of ATU (as explained above) is extensively used to treat patients as early as possible. The drugs designated as orphan are often granted ATU either for cohorts or for individuals before they obtain a Marketing Authorisation (MA). Only the ATU given to cohorts must follow a protocol for therapeutic use and data collection.

The ATU is an exceptional procedure, effective in France since 1994[3], to make available some drugs that have not received a MA. The objective is to enable early access to new treatments in circumstances of real interest for public health, i.e. for patients affected by serious pathologies and facing a therapeutic dead end. This is exactly the situation faced by rare diseases patients.

The ATUs have been granted very frequently since 1994 and have enabled in practice to treat several tens of thousands of patients every year, several months before the approval of a Marketing Authorisation. They are crucial for rare diseases patients. One should particularly stress the importance of individual ATU for treatments. This system is essential for patients whose health or situation excludes them from being fitted in existing categories.[4] This type of ATU is vital because it allows *in fine* to place off-label drugs at the disposal of people who have no therapeutic alternative.

However, the Mediator scandal and the law of 29 December 2011 on drugs have changed the picture. The legislator wishes to legislate in order to correct a number of weaknesses observed in the former ATU regulation. The legislator wishes furthermore to obtain a better balance between ATU for cohorts and individual ATU, the latter being much more frequent.

[3] Art. L5121-12 of CSP. See also Art. 26 of the **Law n°2011-2012 of 29 december 2011**

[4] The pharmaceutical industry often excludes these persons from the clinical trials on the ground that their participation could « question » or « weaken » the results.

For this reason, in order to protect the patients, the legislator considered it important to control more tightly the legitimacy of requests for ATU (especially the individual ones), the delays granted to companies to apply for MA and their compliance with these delays.

However, regulating the ATU does raise questions for the patients. For instance, when seeking the safety of patients, one should not end up, *in fine,* by blocking the access to treatments. It is therefore imperative to find a balance between the requirements for safety in the use of drugs and the need of patients to access innovative drugs.

Broadly speaking, ATU can be: - « for cohorts » when applied to a group of patients. – « individual » when delivered only to a single patient at the request and under the responsibility of a prescribing doctor.

NB: individual ATU is often given during phase II of the clinical trials. In the case of cohorts, it is granted during phase III.

Lastly, it should be noted that drugs benefitting from an ATU are delivered by the pharmacist in hospital or by a doctor affiliated to the hospital or a pharmacist who has signed up an agreement with the hospital

ATU for « cohorts » are granted for groups of patients. They concern drugs of which the efficiency and safety are strongly assumed after completion of the therapeutic trial undertaken to support a request for Marketing Authorisation (MA). An ATU is requested to the laboratory holding the manufacturing rights of the drug and delivered following the opinion of the MA Commission of "ANSM", the French agency for the safety of medicine and health products. An ATU is valid for one year, renewable. The ATU for cohorts is subject to the signature, between ANSM and the holder of the manufacturing rights, of a protocol of therapeutic use and data collection. An ATU is granted subject to the condition that the company has applied for Marketing Authorisation or commits itself to applying in a given time.

5.3.2 Authorisations that must be defended

The law of 29 December 2011 seems quite adequate in addressing the ATU. Its impact on patients, especially those with rare diseases, is expected to be positive. Patients will benefit from better evaluated treatments, particularly in the case of cohorts. In the long term, they will have at their disposal a drug with a marketing authorisation. Patients will also be better followed, because the companies concerned have an obligation of systematic and reinforced monitoring. The system will provide an incentive to undertake clinical trials in the country, not at the detriment of patients. Furthermore, « compassionate » access to drugs, or the individual derogatory ATU, will be kept for patients whose vital prognosis is poor in the short term and for drugs no longer commercialised. In this way, treatments can be continued even in situations of off-labelling of the drug. It is however essential to always remain cautious in order to prevent public authorities from questioning the ATU system.

5.4 REIMBURSEMENT OF OFF-LABEL DRUGS, RECOMMENDATIONS FOR TEMPORARY USE (RTU) IN THE TREATMENT OF RARE DISEASES

5.4.1 New regulations for off-label prescriptions and for RTU

An off-label use of drug means that the drug has been prescribed for an in indication different from the one stated on its label. In principle, only with a Marketing Authorisation (MA), the *sine qua non* condition for commercial use, can the drug be made available. Furthermore, the MA is valid only for the « therapeutic indications » listing the conditions of use (dosage, targeted population).

However, these indications or conditions of use are not always exhaustive, because they depend on the way pharma companies formulate their requests. In the absence of such requests, they are not mentioned in the MA. A given drug can therefore be efficient for a pathology that is not covered by the MA.

In fine, if the indications and conditions of use are too restrictive, the prescriber is sometimes faced with a therapeutic dead-end. He may then have to prescribe a drug off-label, i.e. outside the scope of its indications or conditions of use.

Although doctors have to follow the indications of the MA, off-label prescriptions are not illegal. In fact, they represent today 15 to 20% of total prescriptions, and furthermore, they are well justified on medical grounds.

Until now, neither the legislation nor the regulations have forbidden that practice. However, following the Mediator scandal that created an atmosphere of generalised suspicion on off-label prescription, the law of 29 December 2011 and the decrees of 9 may 2012 focus on a better definition of the legal framework of these prescriptions.

So, at present, a drug can be prescribed off-label if there exists no alternative drug benefitting from an ATU for individuals or cohorts, provided that:

- ANSM has made a recommendation of temporary use (RTU) on the indications or conditions of use;

- or the prescriber, having in mind the progress of science, believes this drug is essential to improve or stabilise the clinical state of the patient.

However, prescribers are from now on under the obligation to inform the patient:

- that the drug is not prescribed in conformity with its MA and there is no adequate alternative;

- of the risks incurred, the constraints and benefits expected from the drug;

- of the conditions of coverage by the medical insurance of the prescribed drug.

NB : the prescriber must furthermore add on the prescription the mention: «off-label prescription», since the healthcare services and national healthcare insurance absolutely need this mention to identify the prescription.

5.4.2 Off-label drugs prescribed for rare diseases

It appears that more than 500 drugs, due to the lack of therapeutic alternatives, are prescribed off label. The law of 29 December 2011 has created the system of RTU (Temporary Recommendation for Use) in order to regulate and make secure a minority of these uses. For other off-label uses, the prospects are very uncertain. Can one make safe and regulate for all patients the access to treatments prescribed to-day off-label? Should one create new regulations? What would be the role of reference centres?

In fact, further to the law of 29 December 2011, no RTU has yet been issued, even though a number of files are under study. In practice, its use is restricted to a minority of situations. ANSM, has thus specified that RTU would be reserved for situations in which public health is at stake, essentially to cover the patient's situation. This raises a very acute problem for an adequate coverage of rare diseases: more than 500 cases of off-label use were identified through a survey from ANSM. The challenge is to be inventive and propose other solutions for all other situations.

5.5 PHARMACOVIGILANCE

5.5.1 Patients and their patient organisations can declare undesired effects

According to the code of public health, the aims of pharmacovigilance are to survey, evaluate, prevent and manage the risk of undesired effects in the use of drugs and products. It seeks therefore to guarantee the safety of use of drugs. It is chiefly based on the reporting of undesired effects.

At present, authorities have opened the possibility for patients and/or patient organisations to declare directly the undesired effects of a drug, without directly contacting a physician. They can fill in a form to be found on ANSM's website and to be sent to their Regional Centre for Pharmacovigilance. The objective here is to enlarge the information base and detect signals in addition to those reported by health professionals, by involving all actors of the system and making it more transparent. This measure complies with the French public health regulation and with the new European regulation derived from a regulation and a directive of the European Parliament and of the Council dated 15 December 2010.

The opening of the national system of pharmacovigilance to patients follows several experiments carried out by ANSM in recent years, in cooperation with the patient organisations. These pilot phases have demonstrated the interest taken by patients in this field, and their degree of involvement.

5.5.2 Possible evolutions

One has to note today the inadequacy of communication and information to health professionals, patients and patient organisations. Although we observe a more than 50% increase of alerts by patients, the share of these alerts is still marginal with respect to that of other actors. Thus, medical studies should devote more time to pharmacology, prescription and pharmacovigilance, and also to training as a component of continuous professional development.

It is also essential to improve the initial and continuous training of medical doctors to facilitate a better prescription and use of drugs. Similarly, the information for doctors should be conceived by professionals and mobilise learned societies as well as the patient organisations, considered as unavoidable partners.

Lastly, with regard to alerts by patients, it seems essential that the forms for the declaration of undesired effects be translated and made available in English, so as to enable foreigners to notify these effects. An electronic version would enable to expand the system and increase its efficiency.

THEME 6. SOCIAL SERVICES IN THE AREA OF RARE DISEASES

6.1 SPECIALISED SOCIAL SERVICES: RESPITE CARE, ADAPTED THERAPEUTIC RECREATION CENTRES, SERVICES FOR THE INTEGRATION OF PATIENTS INTO SOCIETY

The NPRD 2 (2011-2014) foresees more places in respite care centres for people living with a rare disease. Besides, the patient organisations have already created and supported a very large number of initiatives outside the remit of the Plan. Examples include: AFM's social coordinators who assist families, adapted Therapeutic Recreation centres such as « l'Envol » for European children, respite care centres such as the one in the Hendaye Hospital (Hôpital Marin d'Hendaye), and the "Intégrascol" data base, providing information to facilitate the integration of children at school.

Existing social services will be better adapted to the needs of rare diseases patients and of their families thanks to adequate training of staff and to closer cooperation between the Reference Centres/Competence Centres

and the departmental house for the disabled (MDPH, providing information, allowances and access to rights for people with disabilities) as well as other medico-social services.

6.2 THE SCOPE OF THE RARE DISEASES HEALTH NETWORKS

One of the measures of NPRD 2 has clearly the ambition to « develop links between the actors of care and social services».

The **Health Networks of Rare Diseases** will further support social services. These networks are getting organised to adapt themselves to the specificities of the diseases on which they operate.

The French Alliance recommends that the potential for social support provided by the RC/CC be adequately taken into account in the evaluation of health networks. Social support includes therapeutic training for medico-social coverage. The Alliance also recommends taking into account the role and place of patient organisations, since they should be approached not only at the time of evaluation of the networks, but also at the stage of their elaboration.

6.3 INTEGRATION OF THE RARE DISEASES ISSUE IN THE CONSTRUCTION OF THE NEW SCHEME ON RARE DISABILITIES

In France, rare diseases and rare disabilities are considered separately. There is the 2nd National Plan for Rare Diseases (2011-2014) as well as a National Scheme for Rare Disabilities (2009-2013).

However, rare diseases and rare disabilities have much in common. It is estimated that 65% of the rare diseases generate multiple disabilities. The rarity and complexity of the patient's symptoms often result in a wrong diagnosis and inappropriate assessment of the social support needed by the patients. Hence, the need for gathering specialised medical expertise into organised health networks at national level.

The healthcare professionals are often unfamiliar with both rare diseases and rare disabilities: GPs are poorly informed on rare diseases; professionals of the medico-social sector ignore the specificities of rare disabilities.

Rare disabilities and rare diseases have been brought together in the more general context of the national disability acts, in particular the Act of 2005 that created the **local houses for the disabled (MDPH)**, guaranteeing access to everyone.

The first mission of the National Scheme is to adapt the environment as much as possible, but people with disabilities need individual solutions, implying evaluations by the local houses and proposals for individual or group compensation. Complex situations beyond the application of common law require a specific organisation.

The national scheme for rare disabilities has been implemented from 2009 to 2013. In 2014, the national solidarity fund for autonomy (CNSA) has reviewed and prepared a second scheme for rare disabilities. On this subject, let us remark that the formulation « rare disability » may not be very well chosen: the notion of rare disease refers to prevalence, while "rare disability" is rather a complex situation, not always provoked by a disease. A more or less rare disease can occur simultaneously with an accident of life. Rare disability is characterised above all by the complexity of its coverage, care and social support. People living with a rare disability and their family often find difficult to access relevant resources.

The CNSA promotes social support and the Directorate for social cohesion manages it at national scale. A scheme under common law brings together the local houses for the disabled, the Health Regional Agencies, medico-social services, four centres of national resources for rare disabilities and a national coordinating group.

The EUROPLAN conference has raised the problem of information of professionals and of the public on rare diseases and rare disabilities. Orphanet, in partnership with CNSA, has issued booklets to inform on the rights of disabled people in France.

The encyclopaedia of Orphanet is being revised to integrate the notion of "disability": the first fifteen updated files are available on the website. They have been produced as a result of a collaboration between hospital professionals and professionals in the field of disability management. Indexing the functional consequences of rare diseases is also under way.

6.4 THE INTERNATIONAL DIMENSION

We can note here the work carried out within the Joint Action of the European Committee of Experts on Rare Diseases (EUCERD), Work Package 6, on "Specialised Social Services and Integration of Rare Diseases into Social Policies and Services", co-funded by the European Commission, the CNSA and the Fund Lea Rose.

Reminder: the French plan calls for developing links between actors of care and those of social support/ aid. The Action "A-5-3" promotes the development of organisational models to meet the respite needs of rare diseases patients and/or their helpers/carers. Thus, "the development of an offer of respite care will, by necessity, be based on several requirements:

- adaptation of projects currently developed in regions in order to take account of the specific requirements of rare diseases patients or their helpers;

- training of professionals;

- When appropriate, the multi-annual programme 2008-2012 for the creation of life-long stays in specialised centres for disabled people, foresees the development of temporary stays in nursing homes or specialised centres. Out of the 590 places in homes/ centres that remain to be funded from 2011 to 2014, 50 could be reserved for 5 or 6 units of temporary stays to cover the needs for temporary care, respite of the patients and their carers, across the regions. These places will have to be programmed and authorised in compliance with common law.

- In all cases, this will necessitate an activity of coordination and support of the medico-social sector by the healthcare sector.

The problems to be faced in order to access social services are clear. One has to face a lack of policies for universal and systematic access. National Plans can help advocate for the need of a legal and more systematic frame.

As regards the lack of information and knowledge on rare diseases and on the specific needs of patients and their families, one should prepare the social services and professionals in charge of people living with rare diseases (good practice for the social services) and make them aware of the tools and systems available for the training of social workers. The adaptation of on-going projects and the training of professionals (NPRD 2, A-5-3), also encourage multidisciplinary cooperation between Reference Centres and social services, coordination and support of the medico-social sector by the healthcare sector.

The identification and mapping of adapted social services to rare disease patients in Europe correspond to one of the deliverables of the Work Package 6 on social policies within the EUCERD Joint Action. So far, 64 services have been identified in 20 countries: Therapeutic Recreation Centres, Respite Care Centres, adapted housing services and Centres of Resources. This mapping does not aim to be exhaustive, but it shows the specificities of some countries. Case studies have also been carried out following on-site visits to specialised social services for

rare diseases/ disabilities. This helps generate ideas. Clearly, while we have a lot to show to European countries, they can in turn teach us a lot. In 2014, the team of the Work Package 6 focused on the training of social workers and collected information throughout Europe. In 2015, the team will be working on the integration of rare diseases into social policies and social services. *In fine,* a report will be produced on the principles to be followed in the social coverage of rare diseases.

ANNEXE I – PROGRAMME IN FRENCH

CONFERENCE EUROPLAN
13 Janvier 2014, Paris

SESSION PLENIERE

- Le mot du comité d'organisation EUROPLAN II de l'Alliance Maladies Rares.
  9h30-9h40 **Nathalie TRICLIN**, *Présidente du comité d'organisation EUROPLAN II, Vice-présidente de l'Alliance Maladies Rares*

- Ouverture :
  9h40-9h55 **Jean DEBEAUPUIS**, *Directeur général de la DGOS*
  9h55-10h15 **Alain DONNART**, *Président de l'Alliance Maladies Rares*

- La France, inspiration des plans maladies rares en Europe, les enjeux de l'articulation du plan français avec les Etats Membres et la stratégie européenne.
  10-15-10h45 **Yann LE CAM**, *Directeur général d'EURORDIS*

- **Etat des lieux des principales réalisations et de l'axe 3 du second Plan National Maladies Rares français :**
  10h45-11h05 **Dominique PETON-KLEIN**, *Secrétaire général du PNMR II*

- **Maladies rares et politiques publiques, stratégie nationale ou PNMR III ?**
  11h05-11h30 **Table ronde :**

  Viviane VIOLLET - Yann LE CAM - Christophe DUGUET - Jean DEBEAUPUIS - Dominique PETON-KLEIN

Echange avec la salle de 11h30 à 12h00

SESSIONS PAR GROUPE

- **Discussion par thème en 6 groupes**
  13h30-15h30

1. Information et formation, soins transfrontaliers
2. Définition, codification et inventaire des maladies rares / bases de données
3. Recherche
4. Filières : centres d'expertise, réseaux européens de référence, et dépistage néonatal
5. Médicaments et thérapies pour les maladies rares
6. Parcours de santé, parcours de vie pour les maladies rares

- **Restitution en plénière**
- **Conclusion :**
  Nathalie TRICLIN, *Présidente du comité d'organisation EUROPLAN II, Vice-présidente de l'Alliance Maladies Rares*
  Alain DONNART, *Président de l'Alliance Maladies Rares*

ANNNEXE II – LIST OF PARTICIPANTS

Last name	First name	Organisation	Stakeholder Group
AGNERAY	Laurent	AFMHRC	Patient organisation
AILLEAUME	Martine	Insuffisance surrénalienne	Patient organisation
AIRIAU	Jean Luc	CADASIL France	Patient organisation
ALLANT	Martine	AMRO FRANCE HHT	Patient organisation
ANTOUN	Zeina	Laboratoire GlaxoSmithKline	Industry
AREJULA	Peggy	association Gêneris	Patient organisation
ARVEILER	Benoît	Praticien hospitalier génétique moléculaire	Healthcare Professional
ASSELINO	Meryl	Alliance Maladies Rares	Patient representative
AUDIAU	Aymeric	FAHRES Centre de Ressources Handicaps Rares composante Épilepsie Sévère	Social service
AUDOLLENT	Clotilde	Fondation maladies rares	Foundation
AUDOUZE-CHAUD	Anne	Association Ichtyose France	Patient organisation
AYME	Ségolène	Inserm US14 - Orphanet	Academia
BADER-MEUNIER	Brigitte	Hôpital Necker, APHP	Healthcare Professional
BAILLEUL	Florian	ASBH	Patient organisation
BAILLY	Dominique	AFSO	Patient organisation
BALEYDIER	Claudie	Alliance Maladies Rares	Patient organisation
BEGHDAD	Zakia	AFSED	Patient organisation
BELHAIT	Salah	Particulier	Patient organisation
BELLENGUEZ	Martine	Association GENIRIS	Patient organisation
BELOT	Alexandre	Hospices Civils de Lyon	Healthcare Professional
BENDAHAN	David	CRMBM UMR CNRS 7339	Academia
BERNARD	Jacques	MRIS et Association François Aupetit	Patient organisation
BERNASCONI	Antoine	ORPHAN EUROPE	Industry
BERRUE GAILLARD	Helène	Alliance Maladies Rares	Patient organisation
BERTHOLET -THOMAS	Aurélia	Centre de référence des maladies rénales rares, Bron	Healthcare Professional
BERTHOU	René	Alliance Maladies Rares	Patient organisation
BICHET	Marie Pierre	AFMF	Patient organisation
BIGER	Chantal	GENIRIS	Patient organisation
BIHOUE	Nicolas	Faculté de médecine Angers	Healthcare Professional
BLOCH	Gilles	Fondation maladies rares	Foundation
BLOCH	Juliette	CNSA	Social service

BOISSONNAS	Jean	Retraité de la Commission Européenne, participant libre (invité)	
BOLLAERT	Béatrice	hôpital Necker enfants malades APHP	Healthcare Professional
BOMMÉ	Marie-Christine	Association française du syndrome de Smith Magenis: ASM 17 France	Patient organisation
BONNEAU	Dominique	Plate-forme régionale d'information et d'orientatio pour les maladies rares (Prior) des CHU Angers, Nantes	Social service
BOTTARELLI	Valentina	EURORDIS	Patient organisation
BOUCHAIB	Malika	ASSOCIATION BARDET-BIEDL	Patient organisation
BOURGOIN	Faustine	Association française du syndrome d'Angelman	Patient organisation
BOURLIER	Mireille	Association Neurofibromatoses et Recklinghausen	Patient organisation
BRISSOT	Pierre	Centre de Référence des Surcharges en Fer Rar d'Origine Génétique	Healthcare Professional
BUISSON	Marie-Christine	AIMK TARLOV	Patient organisation
BURGLEN	Lydie	centre de référence Malformations, maladies congénitales du cervelet, Hôpital Trousseau, Paris	Healthcare Professional
CAMBON-THOMSEN	Anne	INSERM	Academia
CARBONEL	Sylvie	Association Huntington Espoir Grand Est	Patient organisation
CARETTE	Marie-France	Hôpital TENON - APHP -	Healthcare Professional
CARLIER	Frédéric	PSP	Patient organisation
CARTIER	Nathalie	INSERM	Academia
CASTELLA	Sylvie	Association Huntington Espoir Grand Est	Patient organisation
CASTRO	Raquel	EURORDIS	Patient organisation
CAUBIT	Anne	LFB	Industry
CHABRIAT	Hugues	Centre de référence maladies rares - CERVCO	Healthcare Professional
CHANUDET – VAN DEN BRINK	Estelle	Fondation maladies rares	Foundation
CHARRIERES	Sandrine	LFB	Industry
CHOQUET	Rémy	Banque nationale de données maladies rares	Academia
CLAUSON	Pascal	IRSAM	Healthcare Professional
COLINOT	Magali	PRIOR MALADIES RARES	Patient representative
COQUENTIF	Sophie	reconnaissance handicapée et ayant maladie rare; sociétaire de Groupama	Foundation
CORDEAU	Elisabeth	IRSAM	Healthcare Professional
COTTET	Christian	AFM-Téléthon	Patient organisation
COTTON	Liliane	AMR / Unapei	Patient organisation
CREUZET	Sophie	CNRS Institut de Neurobiologie	Academia
DAHAN	Muriel	Association HPN FRANCE/APLASIE MÉDULLAIRE	Patient organisation

DANG	Thi My Lan	SHIRE	Industry
DARMOUNI	Caroline	APPT	Patient organisation
DAVID-MARESCOT	Catherine	ARMK (Association de soutien à la recherche et aux personnes concernées par la maladie de Kennedy)	Patient organisation
De la MORLAIS	Marie Christine	ASTB	Patient organisation
De LARY de LATOUR	Thibault	Alexion	Industry
De NARBONNE	Laurent	BioEquity Partners	Industry
DEAN	Laurence	Shire France	Industry
DEBEAUPUIS	Jean	Ministry of Health	Ministry
DELAUNAY	Stéphanie	Association Française des Syndromes de Marfan apparentés	Patient organisation
DELEUZE	Christian	GENZYME	Industry
DELFORGE	Thomas	AMRO FRANCE HHT	Patient organisation
DEPUY	Martine	AIRSS (Association pour l'Information et la Recherche sur le Syndrome Sapho)	Patient organisation
DERVIEUX	Catherine	Williams-France	Patient organisation
DESCHAMPS	Nicole	Association surrénales	Patient organisation
DESIR-PARSEILLE	Diana	Fondation maladies rares	Foundation
DESSAULLE	Marie-Sophie	ARS Pays de la Loire	Hospital administration
DEVEZE	Michel	AMADYS	Patient organisation
DEYBACH	Jean-Charles	Centre de référence des porphyries	Healthcare Professional
DOLLFUS	Hélène	Centre de référence affections rares en génétique ophtalmologique CARGO, Strasbourg	Healthcare Professional
DOMENIGHETTI	Laëtitia	Association Les Feux Follets. (Phénylcétonurie)	Patient organisation
DOMY	Philippe	directeur général du centre hospitalier universitaire de Montpellier (Hérault)	healthcare Professional
DONNART	Alain	Alliance Maladies Rares	Patient organisation
DOSQUET	Patrice	Ministry of Health	Ministry
DROUVOT	Valérie	Ministere des affaires sociales et de la santé	Ministry
DUBOIS	Jean Michel	Association Neurofibromatoses et Recklinghausen	Patient organisation
DUFRESNE	Chantal	AFA	Patient organisation
DUGUE	Ginette	Association HPN FRANCE	Patient organisation
DUGUET	Christophe	AFM-Téléthon	Patient organisation
DUONG	Francine	association CMT-France	Patient organisation
DUPONT	Ludovic	Fondation maladies rares	Foundation
ELKOUBI	Roland	AMRO-FRANCE	Patient organisation
EWENCZYK	Claire	CR maladies Rares neurogénétique, Pr Brice, Paris	Healthcare Professional
FALAISE	Xavier	AFM TELETHON	Patient organisation

FARRUGIA	Agnes	Pfizer France	Industry
FATALOT	Eric	LABORATOIRE PHARMACEUTIQUE	Industry
FAVRESSE	Roseline	Fondation maladies rares	Foundation
FELIX	Christelle	Flam France	Patient organisation
FERRY	Antoine	Laboratoire CTRS	Academia
FERY-LEMONNIER	Elisabeth	Conseiller général des établissements de santé	Ministry
FIEVET	Claude	HTAP France	Patient organisation
FINET	Jeannine	Association "Surrénales"	Patient organisation
FLOC'HLAY	Annie	Conseil Général Val d'Oise	Policy maker
FONTAINE	Alain	Alliance Maladies Rares	Patient organisation
FORGET	Sylvain	Nassyane	Industry
FRANCKHAUSER	Nathalie	AFSO	Patient organisation
GANCEL	Dominique	Association Generation 22	Patient organisation
GARCELON	Nicolas	Institut Imagine	Academia
GARCIA	Alain	Ministry of Health	Ministry
GIAI	Ghislaine	Association Française de Narcolepsie-Cataplexie Hypersomnies Rares	Patient organisation
GIMENES	Paul	Alliance Maladies Rares	Patient organisation
GINALDI	Natalia	ALCAP	
GIRAULT	Chloe	APHP PITIE SALPETRIERE	Healthcare Professional
GIRAULT	Marie Joëlle	Pharmacien	Pharmacist
GODARD	Dominique	ASSOCIATION DES SCLERODERMIQUES DE FRANCE	Patient organisation
GORRY	Philippe	Université de Bordeaux Faculté d'Economie, CNRS UMR 5113	Academia
GOULET	Véronique	INSTITUT DE VEILLE SANITAIRE	Public health administration
GRANDET	Christian	ASSOCIATION CAVERNOMES CEREBRAUX	Patient organisation
GROSJEAN	Virginie	Association IRIS	Patient organisation
GUILLOU	Marie	Genodermatoses Network	Healthcare Professional
HAFFNER	François	A.S.B.H	Patient organisation
HANRIAT	Philippe	ASSOCIATION STRÜMPELL-LORRAIN (ASL/HSP-FRANCE)	Patient organisation
HERASSE	Muriel	Alliance maladies rares	Patient organisation
HERMANS	Aurélie	ARS	Hospital administration
HERVE	Dominique	Centre de reference maladies rares - CERVCO	Healthcare Professional
HEUYER	Thomas	MRIS	Social service
HOUYEZ	François	EURORDIS	Patient organisation

HUART	Guillaume	Institut Imagine	Academia
HUBERT	Céline	Fondation maladies rares	Foundation
HUGUES	Danièle	APPT	Patient organisation
JABRI	Myriam	Pfizer	Industry
JAN	Nicolas	Fondation maladies rares	Foundation
JANEL	Nathalie	Université Paris Diderot	Academia
JEDEON	Katia	Centre de Référence des maladies rares de la face de la cavité buccale MAFACE Hôpital Rothschild	Healthcare Professional
JODAR	Nelly	APPT Association des Personnes de Petite Taille	Patient representative
JOUAN-FLAHAULT	Chrystel	LEEM	Industry
JOUANNE	Béatrice	Genespoir, association française des albinismes	Patient organisation
JOURDAN	Brigitte	ABQTL	Patient organisation
JULKOWSKA	Daria	Fondation maladies rares	Foundation
KHALFA	abdelhak	association AMANI de lutte contre les anémies héréditaires, Algerie	Patient representative
KREMP	Odile	INSERM US14- ORPHANET	Academia
KUPPERSCHMITT	Josette	Association AIMK Tarlov	Patient organisation
KURTZ	Annie	CADASIL France	Patient organisation
LAGARDE	Jérôme	Programme RADICO	Academia
LAGOUTTE	Marie-Emmeline	FOP France	Patient organisation
LAGOUTTE	Antoine	FOP FRANCE	Patient organisation
LANDAIS	Paul	Programme RADICO	Academia
LAPOINTE	Anne-Sophie	Alliance Maladies Rares	Patient organisation
LAPORTE	Denise	Association Française du syndrome d'Angelman	Patient organisation
LASBLEIS	Bertrand	Association Bardet-Biedl	Patient organisation
LASSALE	Catherine	LEEM	Industry
LAURENT-GELY	Sandrine	Association Française du Syndrome de Marfan apparentés	Patient organisation
LE BERRE	Dominique	Alliance Maladies Rares délégation Pays de la Loire ASTB	Patient organisation
LE CAM	Yann	EURORDIS	Patient organisation
LE HEIGET	Odile	HPN	Patient organisation
LE HENAFF	Yannick	Université de Rouen	Academia
LE STRAT	Mary	FFAMH	Patient organisation
LEVY	Nicolas	Fondation maladies rares	Foundation
LIBANY	Martine	Cmt France	Patient organisation

LOCHU	Marie	E3M (Entraide aux Malades atteints de Myofasciite à macrophages)	Patient organisation
LORDIER BRAULT	Agnès	Ministère de la Santé DGOS	Ministry
LORENCE	Annie	ANSM	Public health administration
LUIGI	Emmanuel	Ministry of Health	Ministry
MANARINCHI	Dominique	Directeur général ANSM	Healthcare Professional
MANENT	Patty	Fondation Voir et Entendre	Patient organisation
MARGAIL	Florence	Réseau VADLR	Healthcare Professional
MARRE	Francis	Les Enfants du Jardin	Patient organisation
MARTIN	Gwénaël	AFAF	Patient organisation
MATHON	Dominique	Centre de ressource Handicap Rare La Pépinière	Social service
MEDDAD	Faiza	association algérienne du syndrome de Williams Beuren	Patient organisation
MESLARD	Nicole	MDPH 95 PÖLE ENFANT	Patient organisation
MICALLEF	Joelle	ORPHANDEV CIC-CPCET	Industry
MILOR	Evelyne	AGENCE REGIONALE DE SANTE DU LIMOUSIN	Hospital administration
MINH MUZEAUX	Sophie	Hôpital Pitié Salpêtrière - Centre de Référence po les Maladies Cardiaques Héréditaires	Healthcare Professional
MIRLAND	Sandrine	ASSOCIATION TREMPLIN SYNDROMES DE PIERRE ROBIN	Patient organisation
MOIGNE	Edith	UVTD	Industry
MONNIER	Véronique	Université Paris Diderot	Academia
MONTAUBAN	Vincent	Shire	Industry
MONTFORT	Danielle	AMADYS	Patient organisation
MOREL	Caroline	Eurobiomed	Industry
MORIN	Paulette	Association Française des Syndromes de Marfan apparentés	Patient organisation
MORINI	Marianne	ALCIMED	Industry
MOUNIER	Françoise	Association Syndrome de Brugada	Patient organisation
NEGRE	Olivier	ALLIANCE MALADIES RARES	Patient organisation
NEUHAUS	Françoise	GENERATION 22	Patient organisation
NICOLAS	Anne-Claire	Les Feux Follets	Patient organisation
NOURISSIER	Christel	EURORDIS	Patient organisation
OLYMPIE	Alain	Association François Aupetit	Patient organisation
PARET	Stéphanie	AFMHRC	Patient organisation
PARKER	Samantha	Orphan Europe	Industry
PECKER	Françoise	AFMHRC	Patient organisation

PELLET	Françoise	ASSOCIATION FRANCAISE DU GOUGEROT SJOGREN	Patient organisation
PENHALEUX	Nadège	ALCIMED	Industry
PERROLET	Camille	ARMK	Patient organisation
PERROT	Marie-Suzanne	Association Nationale des Cardiaques Congénitaux	Patient organisation
PERSOZ	Charles	INSERM	Academia
PETIT LE BACLE	Colette	Association des familles de victimes de papillomatose respiratoire	Patient organisation
PETITET	Sébastien	Chiesi	Industry
PETON-KLEIN	Dominique	Ministry of Health	Ministry
PINEAU	Nicolas	Fondation maladies rares	Foundation
PINEAU	Brigitte	FFAMH	Patient organisation
PITOIS	Joelle	Association d'information et de prévention de drépanocytose	Patient organisation
PIVETEAU	Denis	Secrétaire général des ministères sociaux, Conseiller d'Etat	Ministry
POHER	Muriel	UNAPEI	Patient organisation
POINTAUX	Estelle	Association IRIS	Patient organisation
POPESCU	Marius	PC PAL	Patient organisation
PRESTEL	Anna	CHU DE RENNES	Healthcare Professional
PRESTINI	Mireille	CNSA	Social service
PUJOL	Emmanuelle	maladies rares info services	Social service
RAVAGNAN	Luigi	Fondation maladies rares	Foundation
RAYNAUD	Catherine	Pfizer	Industry
RIGAL	Loïc	Institut Droit et Santé	Academia
RIGOUX	Priska	INSERM U933 Programme RaDiCo	Academia
RIVIERE	Marianne	AFL+	Patient organisation
ROINET-TOURNAY	Marie	Alliance Maladies Rares	Patient organisation
ROLLAND	Francis	ARMK	Patient organisation
ROSSIGNOL	Karine	Institut Imagine	Academia
ROUSSILLE	Bernadette	Alliance maladies rares	Patient organisation
RUDELLE	Nathalie	Association scléreuse tubéreuse de Bourneville	Patient organisation
SABATIER	Annick	Association Bardet-Biedl	Patient organisation
SAIDE	Jean	Association Française du Gougerot Sjögren	Patient organisation
SARDA	Pierre	Réseau VADLR	Healthcare Professional
SARNACKI	Sabine	Centre de référence malformations Ano-rectales pelviennes MAREP, Paris	Healthcare Professional
SARRE	Evelyne	AGENCE REGIONALE DE SANTE DU LIMOUSIN	Hospital administration

SENECAT	Juliette	EURORDIS	Patient organisation
SIAHMED	Hamid	CHU de Limoges	Healthcare Professional
TELLIER	Zéra	LFB Biomédicaments	Industry
THEVENOT	Alice	KLS-France	Patient organisation
TRANCHAND	Audrey	Fondation maladies rares	Foundation
TRICLIN	Nathalie	Alliance Maladies Rares	Patient organisation
TRICOIRE	Hervé	CNRS/ Université Paris Diderot	Academia
TROCELLO	Jean-Marc	Hôpital Lariboisière, CNR Wilson	Healthcare Professional
TRUCHET	Marie	Pfizer	Industry
VALLAT	Jean-Michel	Centre de référence "neuropathies périphériques rares" CHU Limoges	Healthcare Professional
VARNET-THUAULT	Isabelle	Alliance Maladies Rares Champagne Ardenne	Patient representative
VICARD	Christine	Maladies rares info services	Social service
VIENS	Gérard	AFSA	Patient organisation
VIOLLET	Viviane	Alliance Maladies Rares	Patient organisation
VOLF	Ginette	Lupus France	Patient organisation
WAHLE	Véronique	Association FLAM	Patient organisation
WARZEE	Jean-Pierre	Géniris	Patient organisation
WEINBACH	Jérôme	Programme RADICO	Academia
WEINMAN	Ariane	EURORDIS	Patient organisation
WENZEL	Carolin	Centre de référence Epilepsies rares, Hôpital Necker, Paris	Healthcare Professional
WESTERLOPPE	Jérémie	Celgene	Industry
ZWAENEPOEL	Ingrid	Fondation maladies rares	Foundation
ZINDY	Pierre-Joachim	Fondation maladies rares	Foundation