EUROPLAN National Conferences

CONFERENCE FINAL REPORT

I. General information

Country	**FRANCE**
Date & place of the National Conference	**PARIS, Hôpital de la Pitié-Salpètrière** **Sept 30, 2010**
Website	**http://www.alliance-maladies-rares.org/**
Organisers	**Alliance Maladies Rares**
Members of the Steering Committee	**Steering committee :** **Catherine Dervieux** **Jeanine Finet** **Jeanne Hérault** **Isabelle Hoareau** **Paulette Morin** **Christel Nourissier** **Bernadette Roussille** **Nathalie Triclin** **Scientific committee :** **Aymeric Audiau Alliance Maladies Rares** **Dr Ségolène Aymé, Orphanet** **Pr Nadia Belmatoug, coordinator reference centre** **Antoine Ferry, Cell Therapies Research and Services** **Pr Nicolas Lévy, GIS Institut des Maladies Rares** **Christel Nourissier, Alliance Maladies Rares, EURORDIS** **Pr Sylvie Odent, coordinator reference centre** **Pr Gil Tchernia, inter-Ministerial coordinator for the second National Plan**

Names and list of Workshops	**Opening** *Viviane VIOLLET, présidente de l'Alliance Maladies Rares* **RARE DISEASES, EUROPE's CHALLENGE** *Christel NOURISSIER, Europlan advisor-EURORDIS* ..... **SESSION 1** How to better evaluate the patient's needs and the impact of the National Plans ?**Err** How to improve knowledge of diseases : databases and registries ?..... **SION 2** How to improve information and training ? ..... **SESSION 3** Research ..... **SESSION 4** Patient empowerment ..... **ROUND TABLE** Diagnosis, care and treatments : how to improve access?..... **Closing the conference** *Viviane VIOLLET*
Chairs of Workshops	**Session 1: Pr Gil Tchernia, inter-Ministerial coordinator for the second National Plan and Olivier Nègre, Alliance Maladies Rares** **Session 2: Ana Rath, scientific director, Orphanet, and Jean Lafond, president cystic fibrosis association** **Session 3: Pr Nicolas Lévy, GIS Institut des Maladies Rares, and Dr Gérard Nguyen, president Rett syndrome Europe** **Session 4: Vololona RABEHARISOA, researcher, Centre de Sociologie de l'Innovation** **ROUND TABLE coordinator: Thomas Sannié, vice-president haemophilia association**
Attachments (programme, list of participants, etc.)	**Minutes of the conference : « Les plans français dans le paysage européen »(in French)** **Conference programme (in French)**

Introduction

The EUROPLAN conference in France has brought together experts involved in the drafting of the second National Plan for rare diseases in 2009/2010, as well as other patient association representatives, members of Alliance Maladies Rares. It was a timely event, as the announcement of the second Plan was delayed until 2011 in France, due to government changes and budget constraints.

Sessions 1 to 4 were opened with presentations, and allowed time for discussion;

1. How to better evaluate the patient's needs and the impact of the plan ? How to improve knowledge of diseases : databases and registries? A pilot experiment using the OrphaCode in the system collecting information in several hospitals with centres of reference and competence was presented. Then a state of the art of existing databases, registers, and outcome indicators opened the discussion on data collection.
2. How to improve information and training? Presentations of pilot trainings of nurses and paramedical professionals, of trainings of centres of reference for and by patient associations, and of the production of European guidelines paved the way for the discussions.
3. Research: A state of the art of research for rare diseases, as well as future perspectives, was presented, followed by bottlenecks for drug development.
4. Patient empowerment: main past achievements of patients associations in France were summed up by a researcher in social sciences and by the president of Alliance Maladies Rares.

Access to diagnosis, care and treatment was discussed in a lively and interactive round table at the end of the day, bringing together the coordinator of a reference centre for developmental malformations, patient representatives, a representative of HAS, the French Health Technology Agency, and the chair of the CEPS, the Economic Committee for Health Products, in charge of pricing and reimbursement of drugs.

II. Main Report

The **Conference Final Report is based on the structure of the National Conference on Rare Diseases (RD), which is common to all EUROPLAN Conferences**.

Main Themes

Theme 1 - Methodology and Governance of a National Plan / Strategy (NP)

Sub-Themes

1. Mapping exercise before developing a National Plan
2. Development and structure of a National Plan / Strategy
3. Governance of a National Plan
4. Monitoring the National Plan
5. Sustainability of the National Plan

1. THE SITUATION BEFORE THE PREPARATION OF THE PLAN

NPRD1 – the National Plan for Rare Diseases n° 1 (2005/2008) – was based on general epidemiological knowledge and on the experience of professionals and associations. Six working parties were formed with all stakeholders involved. It took six months to prepare the Plan, from March until November 2004.

NPRD2 (2010/2014) was preceded by many specific studies : self-evaluations of reference centres[1] 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 performed 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 set up and steered by the High Council for Public Health[2], an independent authority 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, associations, administrations).

[1] In France, centres of expertise are called “reference centres” at national level, and “competence centres” at regional level.

[2] The High Council for Public Health has been set up to provide public authorities with the expertise needed 1) to formulate and evaluate the public health policy, 2) to prevent and manage sanitary risks, in collaboration with the health agencies.

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. Essentially, the issues covered include: epidemiology, screening, care, financial and social coverage, training of professionals, information of patients, drugs and research, national and European partnerships. This evaluation report was then circulated on the Internet site of the ministry. It is available on the site of the European Committee of Experts on Rare Diseases (www.EUCERD.eu/ section: other website documents/country documents). It provides a precise description of the French system and includes the ad hoc qualitative survey mentioned above.

2. ELABORATION AND STRUCTURE OF THE NATIONAL PLAN/STRATEGY

2.1 The Plan 2005/2008

The first four-year Plan (2005/2008) was drawn up and costed very rapidly by a group of experts, professionals and associations. Its objective was to ensure equal access to diagnosis, treatment and care. It comprised 10 areas:

Area 1: Improve the knowledge of rare diseases epidemiology

Area 2: Acknowledge the specificity of rare diseases

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

Area 4: Train health 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 accompaniment needs of patients suffering from rare diseases

Area 9: Promote research on rare diseases

Area 10: Develop national and European partnerships

Costing was presented globally for each research area, and no indicators of follow up were presented.

2.2 The proposed second Plan

In 2008, under the French chair of the European Union, the President of the Republic announced a second Plan. Professor Gil Tchernia, a recognised specialist of sickle cell anaemia, a rare disease, was commissioned in September 2009 by 4 ministers (health, research, and industry, social affairs) to draw up the plan and prepare its implementation together with a project leader in charge of administration and finance. For the implementation, he would be assisted by a Committee for orientation, monitoring and accreditation, representing the administrations, qualified personalities, experts and associations. This committee will in fact be established after the announcement of the Plan.

In order to write the Plan, 7 working groups were set up, comprising experts and professionals (31%), associations (21%), administrations (41%) and representatives of the pharmaceutical industry (7%). The group rapporteurs were high level civil servants from the 4 ministries mentioned. 34 meetings were held between October 2009 and January 2010, involving no less than 184 participants, who based their work on 3 tables:

- Proposals contained in the evaluation report mentioned above
- Proposals from 2 departments of the Health ministry
- Proposals from the associations, in particular those from « AllianceMaladies Rares » and EURORDIS.

As a result of this work, a Plan was proposed and submitted in January 2010 to all the working groups in order to check its coherence and completeness.

The proposals were then submitted for final decision to the directors of ministries involved and to their cabinets (4 meetings), and to the compulsory opinions of the High Council for Public Health and of the National Conference on Health. Subsequently, in July 2010, the draft Plan was delivered to the ministries in the presence of the press.

The leading administration for the Plan (Ministry of Health) then undertook the formatting of the document, to be announced in its final form in the beginning of 2011.

The proposed plan[3] is structured in 7 headings (1 heading for each working group), 25 objectives and 82 proposals for action (see annex 1). Each proposal follows a basic template mentioning : context of the action, motivation, objective and target(s), typology (improvement of an existing action or new action NPRD2), description, phasing (schedule, organisations in charge, process indicators), financial table,

[3] This document, named « Proposals for the National Plan Rare Diseases 2010-2014 » can be accessed on the site of EUCERD

indicators of results, links with existing actions of other public health plans, European and international dimension (see in annex 2 an example of action template). Costs were calculated for each action and no longer for each area.

In parallel, an EXCEL table gave the precise costing of each of the 51 actions that required financial support, and listed the purpose of the funding, the contributors and recipients of funds, the source and nature of funds, the basis for funding in 2010, the target basis for 2015, and the amount of annual funding for one-shot actions and for recurrent actions.

The strategy proposed in the second Plan

The objective is to consolidate, at the end of a period of in principle 5 years, a stable architecture for the treatment of rare diseases in France. The approach is meant to be pragmatic, by offering concrete solutions to patients and professionals. The proposals take into account the specificities of rare diseases, while remaining inserted in the mainstream patient coverage. This strategy should enable to guarantee sustainable implementation.

Build or strengthen the tools of a sustainable policy

A sustainable policy entails the establishment of:

- *A foundation for scientific cooperation.* This will bring together three bodies : the GIS-Institute for Rare Diseases (Scientific interest group), which steers the research policy on rare diseases ; Orphanet, the international web portal for information on rare diseases ; and the national Data Bank of rare diseases, currently created for the collection and processing of data and the acquisition of knowledge. The foundation will organise public/private partnerships.

- *Tools to improve the monitoring of various activities relating to rare diseases.*

  . In the information systems: generalised adoption of the Orphanet nomenclature, inter-operability of the various systems of data collection.
  . In the organisation of care: structuring a limited number of networks, comprising the reference centres, the competence centres, and a novelty: the reference laboratories, renamed « national platforms of reference laboratories for rare diseases »; these entities will disseminate their expertise to external professionals and will be inserted in the European reference networks of centres of expertise.

. In the allocation by the ministry of Health (with funding from sickness insurance) of MIG[4] funds to the reference centres, the competence centres and the reference laboratories: signposting, tracing, sharing, coordinated evaluation of their use.

This challenge is essential: due to the rarity of patients and of experts, the national policy on rare diseases, although clearly funded nation wise, must *in fine* be spelt out at the regional scale.

Propose concrete solutions to the daily problems of patients and professionals

Indeed, one must:
-favour partnerships with the pharmaceutical industry and particularly with SMEs, both for research and in order to ensure the availability of drugs and health products.
-accelerate and simplify procedures for the production of « national protocols for diagnosis and care », and of exemption rules for the ad hoc coverage of drugs and products, in the general framework of coverage of chronic diseases, in order to ensure that patients get reimbursed and taken charge of fairly. The Plan proposes means to improve the financial coverage of complex acts of paramedics and of other professionals, all of whom are inadequately valued at present.
-support patients in complex situations, medical, social and/or administrative, with the assistance of coordinators and mediators. Appropriate facilities will be made available in existing services to enable families and carers to take breaks
-inform patients all along the clinical pathway: recognition of the chronic diseases providing specific coverage[5], inclusion in a research or a therapeutic trial, notification of unwanted effects of drugs, assessment of available services … Systems for feed-back and analysis of difficulties will be put in place, including within the MDPH "Maisons Départementales des Personnes Handicapées" (local unique desks providing orientation, allowances and access to rights, for people with disabilities).
-*improve the information, training and statutory recognition of a number of professions that are essential in the care of rare diseases* (genetic counsellors, bio statisticians and computer engineers, coordinating medical officers…).
It is essential to promote the awareness of medical, paramedical and social professionals, by initial and continuous training, in order to enable them to seek information : the patients must be identified and oriented promptly. Information providers must be known (Orphanet, Maladies Rares (Rare Diseases) Info Service, reference and competence centres, associations of patients…).

[4] In France, public hospitals are funded on the one hand by a system of rate fixing per activity, and on the other hand, up to about 20% by MIG funds (« Mission d'Intérêt Général »). See the next insert.

[5] In France, listed chronic diseases are 100% covered by the National Health Insurance.

-*support patient associations*, essential players of the plan, who must be present at all level: definition of actions to be taken, implementation and evaluation.

THE SYSTEM OF « MIG» (« MISSIONS D'INTERET GENERAL ») IN FRENCH HOSPITALS

Most French hospitals are funded under a system of costing per activity, and also a system of distinct endowment dedicated to perform missions of general interest.

This endowment funds teaching and research activities, referral activities, innovation, and all other missions of general interest, including unlisted acts.

Under the first plan, specific endowments for rare diseases were allocated to the reference centres (40 million Euros renewable each year).

The challenge for the second plan is to evolve from a system of targeted funds by centre to a system of targeted funds by missions:

-clinical research,

-expertise (in particular the production of national protocols for diagnosis and care),

-in depth clinical and biological investigation,

-coordination, animation of the rare diseases networks and international relations (coordination, meetings, colloquia, reimbursement of travel expenses incurred by the various rare diseases centres, participation in conferences and in the preparation of international guidelines,

-collecting data and observations for clinical and biological follow up and for the improvement of knowledge on public health,

-alleviating inadequacies due to the system of costing per activity,

-unlisted acts and laboratory acts on molecular genetics.

The aim is not only to ensure the tracing and signposting of future MIGs of the second plan, but also to re-organise and re-allocate the previous MIG fund.

3. GOVERNANCE

3.1 The governance of the first Plan was carried out by 2 mandated officials at the Ministry of Health, and by a national Committee for Accreditation of Centres of reference, whose task was to advise the minister, at first on the agreement of reference centres, and secondly on the designation of competence

centres by the ministry. The Committee, composed of clinicians, administrators and representatives from associations, met at least 3 times a year. Agreements were decided on the basis of applications submitted in response to calls for projects launched by the Ministry. The decisions were implemented by the services of common law of the administrations. A national task force was set up within the National Health Insurance to coordinate the coverage of rare diseases.

3.2 The proposals of the draft Plan:

- a Committee for Orientation, Monitoring and Accreditation composed of representatives of administrations and agencies and designated members (experts, associations), will provide opinions, monitor the Plan, advise on the accreditation of networks of reference centres, reference laboratories and competence centres.
- An inter-ministerial coordinator, assisted by an operational project leader, will be responsible for the implementation of actions, working in close partnership with all interested parties. He will participate in the Committee for Orientation, Monitoring and Accreditation, sit on the European Committee of Experts on Rare Diseases, and report every 6 months to the administrations and national agencies.
- The Regional Health Agencies will be responsible for the follow up of the funds allocated to institutions and networks, identify unfulfilled medical and social needs, and facilitate the creation of networks and the implementation of programmes for therapeutic education, commission experiments in the mediation/coordination of complex cases and of novel experiments in the support of patients and helpers. These tasks would be listed in the regional health projects.

4. MONITORING THE NATIONAL PLAN

4.1 The first Plan

A monitoring committee was set up, composed of the main partners. In fact, it met only twice and was unable to assemble precise data. The assessment pointed to weaknesses in the monitoring and governance of the plan.

4.2 The proposed second Plan

In addition to the operational project leader mentioned above, the Committee will answer for the monitoring. An interim report will be produced yearly.

Monitoring will use the following tools:

- Process indicators (monitoring the implementation compared to the scheduled phasing of actions)
- Numerous and precise indicators of results for each action

- Impact measurements : in order to assess the global impact of the Plan, 5 surveys « ante and post » are foreseen at the start and termination of the Plan, based on similar methods and samples
    1. Survey « quality of access to care and quality of life » with the patients and their carers
    2. Survey « awareness and care of rare diseases » with a representative panel of health professionals in hospitals, in private practise, and in social areas.
    3. Survey « working conditions » with the professionals of reference centres, competence centres and reference laboratories
    4. Two surveys on the social needs of patients suffering from rare diseases or rare disabilities, and on the capacity of existing services to meet those needs
    5. SUSTAINABILITY OF THE NATIONAL PLAN

As already mentioned above, sustainability is an essential aspect of the strategy proposed in the second plan, as evidenced in particular by the creation of *a foundation for scientific cooperation,* the generalised adoption of the Orphanet nomenclature, and the restructuring of the centres in more coherent networks ; also by the financial measures to be implemented : most of the new funding allocated to the plan will be recurrent, instead of one shot, and the principles defined for signposting and tracing will have to be applied to the MIG on rare diseases[6].

Theme 2 - Definition, codification and inventorying of RD

Sub-Themes

1. Definition of RD
2. Classification and traceability of RDs in the national health system
3. Inventories, registries and lists

1. DEFINITION OF THE RARE DISEASES

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

2. CLASSIFYING AND TRACING RARE DISEASES IN THE NATIONAL HEALTH SYSTEM

[6] See above the insert on MIG

The nomenclature normally used is ICD 10 (in which only 200 to 300 diseases have a specific code). However, the OrphaCode (Orphanet nomenclature) is the one retained in the data banks managed by the Network of Centres for Rare Diseases (CEMARA), which gathers data from 51 reference centres.

In the context of NPRD2, it is foreseen to create a national data Bank that will contain *a minimal data set* to be filled by all data banks (this minimal data set will be used by reference centres, competence centres and reference labs). The idea is not to assemble all the bases in a single one but to gather a minimum amount of common information. In this context, it is necessary to develop the interoperability of information systems and to define formats for exchange.
Furthermore, the OrphaCode will be retained, as of November 2010, for a pilot experiment to be carried out in several centres of reference and competence (as part of the current system used by hospitals to collect information (PMSI). At the present time, it will be applied only in inpatient clinics. [7] At a later date, the OrphaCode should also be used in this system for outpatient clinics.

The benefits brought by the experimental shared medical file, to be set up in France for all patients, will be investigated : possible specifications, pages to register specific requirements for coverage of rare diseases (example : integration and circulation of recommendations and/or emergency personal cards for rare diseases , national protocols for diagnoses and care).

3. INVENTORIES, REGISTERS AND DATABASES

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 under a register, others under a cohort. For others, ad hoc surveys at regular intervals could do.

In France, 4 registers of congenital malformations and 8 registers of Rare Diseases are qualified. The national council of registers, set up during the first Plan Rare Diseases, has launched a new call for qualification of registers in 2010.

In 2009, Orphanet listed 114 registers or data bases of rare diseases in France, some of which are European or international. Their management and implementation procedures are very diverse and in general poorly known. These registers and biobanks are accessible on the Orphanet portal and can be consulted for each disease or gene, entity or funder, and by country.

[7] Proceedings of the Europlan conference available on the site of the Alliance www.alliance-maladies-rares.org

A portal Epidemiology France will be set up to describe the contents of existing data bases on health and cohorts, whether private and public (type of data, co-ordinators addresses, conditions of access).

An interesting idea emerged during the EUROPLAN conference, namely to associate the patients with the collection of data. This is already being experimented, for example on leukodystrophies, with the assistance of a paramedical coordinator, and in the international data base of Rett syndrome.

It is obvious that a real policy of collection and handling of phenotypical, biological and genotypical data will necessitate in France the recruitment of clinical research assistants, who as professionals will also be involved in research activities.

2.1. Information and training

1. How to improve information on available care for RDs in general, for different audiences
2. How to improve access to quality information on RDs
3. How to ensure adequate training of healthcare professionals on RDs

1. HOW TO IMPROVE INFORMATION ON AVAILABLE CARE, FOR DIFFERENT AUDIENCES

The Orphanet portal, www.orphanet.fr, (800 000 pages consulted every month from 200 countries) and the Rare Diseases Info Service (MRIS, tel : O810 63 19 20 and +33 1 56 53 81 36…), provide by telephone (7 000 calls per year) or by mail (info-services@maladiesrares.org) precise and exhaustive information on available facilities : reference centres, competence centres, laboratories, networks, associations…

Orphanet has put on line a number of products to cover the needs of different groups: General Public encyclopaedia, Orphanet Emergencies, a newsletter and the Orphanet bulletin, aimed especially at making available social support better known. Orphanet also circulates the National Protocols of Diagnosis and Care (PNDS) issued by the reference centres under the authority of HAS (Haute Autorité de Santé).

In order to improve the information of the public and of professionals, the draft Plan makes provision for:

- with the general public : a campaign of awareness by the Health ministry, each year during the international Day of rare diseases scheduled on the last day of February, in order to inform on rare diseases and circulate the addresses of Orphanet and MRIS.
- With the professionals: information campaigns, especially in the professional press, to inform on the organisation of care and provide addresses of Orphanet and MRIS.

2. HOW TO IMPROVE ACCESS TO QUALITY INFORMATION ON RARE DISEASES

According to enquiries made during the evaluation of the National Plan 2005-2008, Orphanet is unable to update the information with the speed expected by users and imposed by the progress of knowledge, and secondly, Orphanet remains insufficiently known, while visitors to the site find its portal difficult to navigate.

It is foreseen to :
- Audit the Orphanet site for its user-friendliness and improve it according to the recommendations of the audit.
- Put in place a scientific watch and bring up to date the texts already on line in the Orphanet encyclopaedia.
- Enrich the encyclopaedia of rare diseases by adding on line information on 100 new rare diseases every year. Include information on the impact of these diseases on daily life, in order to enable medical and social professionals to take the best account of the needs of the patients.
- Produce a new « paper » edition of the main available Orphanet data in French (designated networks for diagnosis, treatment, medical and social coverage), easier to use if no access to the web is available.
- Encourage reference centres to set up web sites.
- Put on line the work undertaken at European level (epidemiology, European reference networks of centres of expertise, coding and classification of diseases…), translated and/or adapted in French.
- Carry out every year an enquiry on the frequency of consultations and the satisfaction of users with regard to services offered, in particular the new ones.

3. HOW TO ENSURE ADEQUATE TRAINING OF HEALTH PROFESSIONALS ON RARE DISEASES

All health professionals, doctors, midwives, nurses or paramedics must be made aware of rare diseases during their initial training, as has been done for several years by earmarking two hours in the undergraduate medical studies, and in the new courses of other professionals.

Furthermore, taking into account the scarcity of expertise and experts, it is necessary to encourage:

- The academics specialised in rare diseases to put their courses on line with the assistance of Orphanet. Support from the French-speaking Virtual Medical University could be provided, (an interactive resources centre acting as information and prevention centre for health professionals and the general public).
- The extension to other universities of the optional 30 hours training course on rare diseases proposed every year to 3rd-year students by the Necker-Cochin faculty of medicine, with a participation of representatives from associations.

- The creation of a real grid connecting reference centres, competence centres and regional networks for the training of nurses and paramedics.

Theme 3 - Research on RD

Sub-Themes

1. Mapping of existing research resources, infrastructures and programmes for RDs
2. Needs and priorities for research in the field of RDs
3. Fostering interest and participation of national laboratories and researchers, patients and patient organisations in RD research projects
4. Sustainability of research on RD
5. EU collaboration on research on RD

1. THE EXISTING SITUATION OF RESOURCES, INFRASTRUCTURES AND PROGRAMMES FOR RESEARCH

The situation of research is described and updated in annual reports to the funders by the 2 main organisations in charge: the directorate for hospitals at the Health ministry (Clinical research programme in hospitals) and the GIS Rare Diseases. This research is accessible on the Orphanet portal, by disease or gene, entity or funder, and by country.

2. NEEDS AND PRIORITIES FOR RARE DISEASES RESEARCH

Research is essential, whether basic, clinical or therapeutic. Progress in genetics, immunology, and biochemistry, just to mention those disciplines, has enabled rare diseases research to make considerable progress since 20 years. Recent technologies open up new fields and new lines of investigation.

Research must of necessity be cross disciplinary, involving professionals from different backgrounds as well as patients and families. Researchers need data, so bio-banks and data bases must be available; they also need to study the natural history of diseases, to identify the molecular bases and to select the most relevant models for their physiopathological studies, before embarking on the preclinical studies that are required to approach therapy and design trials.
It is also necessary to prepare the clinical development of drugs – an activity which does not fall within the competence of most doctors and researchers on rare diseases, hence the importance to be given to public/private partnerships.

Human and social sciences are much underfunded in France: an additional effort will be supported under NPRD2. The needs, expectations and satisfaction of patients and families should be better evaluated.

As an example, the reference centre of leukodystrophies uses the knowledge and experience of patients, both of which extend well beyond what a doctor can learn during a single appointment. The same questionnaire has been sent to doctors and families. The replies show that only 10% of the information of use for research is provided by the centres of expertise. Families provide a much larger share of the information, especially on the notion of natural history of the disease. The European project Leukotreat addresses in particular the potential impact of therapies: what do the patients expect from the treatments, how do they, how do their families, cope with them?

In spite of the very high quality of research, industrial development is most difficult in France. Researchers should apply for more patents before publishing, and limit the multiple ownership of such patents.

However, the main challenges in France are those of organisation and funding. The draft Plan aims at :

- *Creating a national body to impulse and advise rare diseases research, by bringing together GIS Rare Diseases (the body that manages most of the system of calls for research proposals), Orphanet (the web based information system) and a National Bank of Data on Rare Diseases : this body would be set up as a foundation for cooperative research (see above).*

The foundation will be able to develop public/private partnerships with industry and associations, to create close links with research centres of excellence, to recruit permanent staff more easily and share managerial staff. It will advise researchers on the administration of projects through a single desk (public-private research, European reference networks of centres of expertise, European projects…).

- *Promoting tools to increase knowledge on rare diseases :*

- Link more strongly around common projects the National platforms of reference laboratories and the research centres.
- Develop high output sequencing centres under these partnerships,
- Support the collecting, conservation, duplication and networking of the biological samples relating to rare diseases, under the European project BBMRI (*Biobanking and Biomolecular Resources Research Infrastructure).*
- Fund the development of animal and cellular models of rare diseases.

- *Promoting therapeutic research (preclinical and phases I/II) for innovative therapies (pharmacological, gene and cell therapies) and existing medications (molecules used without marketing authorisation), through public/private partnerships.*

- *Better evaluating research*
- *Better linking research and industrial development.*

3. HOW TO PROMOTE THE INTEREST AND PARTICIPATION OF LABORATORIES AND RESEARCHERS, OF PATIENTS AND THEIR ORGANISATIONS, IN RESEARCH PROJECTS

The existence of national or international networks is an absolute necessity for the organisation of clinical trials, to address the limited number of patients and the scarcity of expertise. It is essential to access registers or cohorts. One is still far from being able to cover the therapeutic needs of most rare diseases. Due to the limited number of cases, the pharmaceutical industry and biotech companies find it difficult to invest in this field. They produce either new drugs specifically conceived for the treatment of rare diseases (orphan drugs), or molecules already used in the treatment of frequent diseases. Those may have been marketed recently or since a long time. The relevance of the latter molecules for rare diseases treatment should be assessed, possibly resulting in an extension of the marketing authorisation.

Important progress in pharmacological approaches has been made, especially because of a better understanding of physiopathological processes. Thus, various metabolic diseases benefit from alternative enzymatic treatments. Therapeutic research also focuses on innovative therapies (cell therapy, plasma exchanges…). The encouraging results of gene therapy for rare diseases with a genetic origin have opened up a most promising field of research. A combination of several approaches is more and more often considered for the treatment of rare diseases, especially the most severe ones (gene therapy coupled to cell therapy, gene and pharmacological therapy), in order to increase treatment efficiency.

It is therefore necessary to promote clinical and preclinical testing in cooperation with the pharmaceutical industry. In the calls for proposals on clinical research, the type of partnership should be clearly specified. The rationale of the test must be provided by academics. According to the « draft second Plan », project funding will coordinate PHRC funds, calls for projects supported by ANR and privately funded projects, if possible up to about 30 projects every year, with 2/3 of public vs. 1/3 private funding.

4. ENSURING THE SUSTAINABILITY OF FUNDING FOR RESEARCH ON RARE DISEASES

Until now, research was based on 3-year calls for proposals for which the financial provisioning, in practice, was renewed in France year by year. With the foundation for cooperative research, it should be possible to replace this system with a scheme of continuous funding.

The draft Plan will also contribute to the funding and continuity of the E-rare project, aimed at promoting transnational projects, and of the ECRIN project, aimed at facilitating transnational multi-centric clinical trials at European scale.

5. COOPERATION WITH THE EU ON RARE DISEASES RESEARCH

France will continue to support the European project E-Rare (see above). 13 projects were supported between 2006 and 2009 ; at least 3 countries must be involved in each project. Despite the large number and high quality of proposals, only 10% were selected, due to shortage of funds. Such projects, implying that data on patient cohorts and on biological collections be shared, are exemplary of well managed international cooperation.
ANR, the National Research Agency, will support financially the French research teams participating in the projects selected after the E-Rare2 calls of 2010 to 2014. Representatives from Member States should take part in the coordination of « E-rare2 », national budgets should be committed to international cooperation under this scheme, and Member States will have to be associated to strategic decisions for the funding of transnational research on rare diseases. A budget should be earmarked for « E-Rare3 » 2015-2019 and for the coordination of E-rare beyond 2014.

The objective of ECRIN (European Clinical Research Infrastructures Network) is to facilitate multinational clinical studies in Europe. ECRIN fulfils various missions, such as interacting with committees for ethics and relevant authorities, monitoring, pharmacological watch, drug management, management of biological samples, and data processing. Through its network of Clinical Investigation Centres (CIC), France will ensure the continuity of its participation in the ECRIN network, coordinated by INSERM.
France will support the principle of sustainable European funding for structuring activities such as Orphanet, EURORDIS, the European reference networks of centres of expertise, data bases, to be provided by the budget of the European programme of Public Health.

Theme 4 - Standards of care for RDs - Centres of Expertise (CoE)/ European Reference Networks (ERN)

Sub-Themes

1. Identification of national or regional CoE all through the national territory by 2013
2. Sustainability of CoE
3. Participation in ERN
4. How to shorten the route to diagnosis
5. How to offer suitable care and organise adequate healthcare pathways for RD patients
6. How to ensure in CoE multidisciplinary approaches and integration between medical and social levels
7. How to evaluate CoE

4.1. Orphan Drugs (OD)

8. Future of OD
9. Access of RD patients to orphan drugs Pricing and Reimbursement
10. Compassionate use and temporary approval of orphan drugs. Off label use

1. IDENTIFYING THE NATIONAL OR REGIONAL CENTRES OF REFERENCE THROUGHOUT THE COUNTRY IN 2013

The French system is organised nationally:

In 2010, there exist 131 approved centres of reference, listed in 18 groups corresponding to disease types (ex: rare endocrinal diseases or rare diseases of the bones). These centres were accredited following a call for applications issued by the Health ministry to the departments that were already taking care of this category of patients. The national Committee for Accreditation of centres of reference gave its opinion for a period of 5 years, in accordance 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. After 3 years, the centres must undertake a self-evaluation. After 5 years, the High Authority on Health (HAS: French Health Technology Assessment Agency) undertakes an external evaluation, the results of which determine the renewal of the agreement.

Their missions are :

- Appropriate capacities to diagnose, follow up and manage patients with evidence of good outcomes when applicable ;
- Attractiveness measured through the volume of activity which needs to be significantly larger than anticipated from the prevalence of the diseases and the catchment area, the catchment area being the loco-regional area normally served by the hosting hospital for non-rare diseases ;
- Capacity to provide expert advice on diagnosis and management ;
- Capacity to produce and adhere to good practice guidelines and to implement outcome measures and quality control ;
- Demonstration of a multi-disciplinary approach ;
- High level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities ;
- Strong contribution to research ;
- Collaboration with patient groups when they exist

- Close links and collaboration with other expert centres at national and international level and capacity to network.

Subsequently, the associations argued for the need of organisation of care at regional level that had not been foreseen in the draft Plan. A call for applications was published during the last 2 years of the Plan to select 501 competence centres, i.e. hospitals able to carry out the first 3 missions (referral, research, data collection) in liaison with the reference centres, but receiving no dedicated funds for rare diseases, contrarily to the prevailing situation of reference centres. In general, patients are followed daily by a GP or an out-clinic specialist.
During the Europlan conference of 30 September 2010, a group of experts proposed that the expert centres organise also advanced consultations where the patients live.
It will also be important to develop EHealth: i.e. multidisciplinary consultations by telemedicine, videoconferences.

This system of reference centres, competence centres and soon of reference laboratories is clearly identified by the Ministry of health. Orphanet and all the information provided by the associations develop awareness by professionals and patients.

For the period 2011/2012, the draft Plan proposes:
-*to establish clear and coherent networks* (already existing networks of reference and competence centres, to be connected with the laboratories, as described above – PNLRMR-). Their number should be brought down from 65 at present to about 20. Indeed, the existing networks are complex and of very heterogeneous size (for example, the non malignant haematological rare diseases have 7 networks, developmental malformations, only one). Some reference centres cover a single pathology, for others the scope is pluri-thematic. Redundancies exist. Above all, one must ensure that each pathology, even the rarest, is taken care of by a reference centre (who will provide, if needed, a contact with a centre abroad).

-*to include in these networks approved reference laboratories (PNLRMR)* in order to balance the present system, in which the biology component is poorly structured, contrarily to the well organised clinical component.

-*to improve the tracking and contractualisation* of funding of each mission of the centres, including the competence centres.

-*to create a national federation of the networks on rare diseases*, by bringing together the reference centres, the competence centres and the future platforms of reference labs, in order to facilitate inter-centres exchange , in particular by organising every year a conference of the rare diseases networks.

The reference centres lack the means to circulate on their own the expertise to all players (local professionals, care providers, patients): training, therapeutic education, updating directories. The networks should be supported at regional level for these tasks.
-*to synchronise the evaluations* of reference centres, competence centres, reference laboratories, research activities and state of data bases within each network.

2. ENSURING THE LONG-TERM SUSTAINABILITY OF REFERENCE CENTRES

The RC - reference centres - are hospital departments, benefitting from a 5-year agreement by the Ministry of Health for their responsibility on Rare Diseases. After these 5 years, agreement renewal will be subject to an evaluation by HAS. The procedure will be extended to CCs and Rare Diseases laboratories, securing the system. It should be noted however that since the agreement is given to the coordinator of the centre, a problem may arise in the event of transfer or death.

Specific funding from MIG (general interest missions) has been allocated to the RC (up to 40 million for new measures during the first Plan) and renewed during the life time of the agreement. However, funding has not always been proportional to the amount of activity, nor always reached the beneficiaries and has seldom enabled to recruit on indeterminate duration contracts. Yet the main weakness is that much of the staff – ARCs, psychologists, social assistants 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 sanctioned, and categorised 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, knowledge on public health, and compensation of the referral activity). Referral, essential in the RC and CC, should no longer be covered by MIG. It should be handled instead by billing per activity (TAA, tarification à l'activité), provided this remains specific to rare diseases, so as to take into account the complexity, duration and combination of the coverage. The draft Plan makes provision for, and quantifies, these fundings.

3. PARTICIPATION IN EUROPEAN NETWORKS

This activity requires a minimum of funding: coordinating a European network of reference requires a huge amount of time and competence: according to coordinators, it is a task that should be acknowledged and paid at European level.
The production of European recommendations should be exhaustive and practical, and target the whole Rare Diseases issue: diagnosis, treatment and social aspects, in order not only to avoid useless tests and inadequate treatments, but also to prevent complications and inform on risks. Their formulation is

steered by learned societies and medical specialists of the disease: preparation takes a very long time (for example, in the case of lymphangioléiomyomatosis, 5 years were needed to arrive at a consensus). After that, they must be circulated: this is the role of internet sites of the RC, learned societies, Orphanet, the High Authority on Health (publishing them as PNDS), also of associations.
On the other hand, France takes an active part in the European network ENHTA (European Network on Health Technology Assessment).

4. HOW TO CUT SHORT QUEST FOR DIAGNOSIS

Firstly, all professionals and the general population should be kept informed on rare diseases (by the introduction of the notion of doubt: « what if it was a rare disease? », when facing unusual symptoms), and on networks and other existing resources, including at European scale. As mentioned above, this requirement implies :

- To strengthen Orphanet
- To strengthen Rare Diseases Info Service, by networking with other hotlines in Europe and creating a European green number,
- The launching of information campaigns at regular intervals by the Health Ministry.

It is also necessary to:

- Insert clearly the reference laboratories in the pattern of existing resources ;
- Simplify, as indicated above, the organisation of networks (bringing them down to about 20), by linking up all diseases, including the rarest ones, to a centre and letting it interface with centres abroad ;
- Organise and strengthen E Health, particularly telemedicine tools (funding is provided for in the draft plan) ;
- Improve the funding of hospitals, particularly to ensure biological testing free of charge and, whenever necessary, free of charge expedition of samples abroad.

Screening for Rare Diseases is indirectly related to the above topic.

A clear distinction must be made between:

1) The two screening tests proposed to all pregnant women: search for fœtal malformations by sonogram and detection of Down syndrome. A number of rare diseases fall under this category.

2) Neonatal screening (DNN) is currently performed in France for only 5 diseases: 4 on the whole population (PKU, congenital adrenal hyperplasia, hypothyroïdism and cystic fibrosis), and one disease for a targeted population (sickle cell anemia). With the exception of hypothyroïdism, all these diseases

are rare. Neonatal screening is performed with drops of blood deposited on blotting paper after sampling of hair. Organised by AFDPHE (French Association for the Prevention of Children's Disabilities), it was recently codified by a ministerial decree dated 22 January 2010. The emergence of new technologies (in particular mass tandem spectrometry) has enlarged the potential field of application and certain countries already detect at birth up to 30 metabolic diseases.

3) The early detection of deafness or of some congenital heart diseases by specific techniques. Although congenital deafness is frequent (1 per 1000), some rare genetic syndromes have been identified as causes for deafness. It can be detected in newborns with quick, and by now, reliable tests (PEAA and/or OEA). Many countries already undertake this screening, which is currently under evaluation in France for a possible generalisation.

4)The detection of heterozygous carriers for diseases with autosomal recessive transmission :
- It can be a collateral consequence of neonatal screening, the first objective of which is to identify homozygous in order to ensure early coverage. This situation occurs frequently with sickle cell disease and poses the problem of the information to be given to parents.
- It can also be a test on children upon request from the families, or of adults, individuals or couples, i.e. people considered at risk because of their geographic background or previous family history.

5) Upstream of the DNN, the prenatal and pre-implantation diagnoses organised in France under the law of 29 July 1994, are placed under the control of the Agency for biomedicine. Funding is foreseen in the draft plan to develop pre-implantation diagnosis.

The Health Ministry is currently working on improvements to the policy and implementation of screening schemes, beyond those that concern solely the rare diseases. The Ministry has seized HAS, the health technology agency, with a request for its opinion on the extension of neonatal testing. At European level, DG Sanco is currently funding, after a call for tenders, a study on the policies for neonatal screening of rare diseases in Europe, with the aim of issuing recommendations for good practice.

The Monitoring Committee of the Plan will have to decide on the proposals made on all issues relating to rare diseases. Associations of patients and doctors have great expectations in this matter. It will no longer be possible to elude the problem, with its medical, ethical, financial and societal aspects.

5. HOW TO OFFER PROPER CARE AND ORGANISE ADEQUATE HEALTHCARE PATHWAYS

The quality of care provided by centres of expertise is probably adequate, considering the present state of knowledge on rare diseases. It is evaluated periodically.

Much more problematic is daily care, which includes social and disabilities coverage. Health care pathways and daily life of patients suffering from severe and disabling rare diseases is made very difficult, due to:

- Lack of knowledge on rare diseases on the part of professionals,
- Poor awareness of patients and their families on their rights.

This results in administrative quests: finding competent services when they exist, identifying trained health and social professionals, knowing where and how to get financial support. During this quest, many structures and a multiplicity of professionals are consulted in succession: there are no clear definitions of their fields of competence, nor channels for communication or information sharing. The shock resulting from the announcement of the disease is compounded by the lack of a competent, stable and available person whose duty would be to help securing a coordinated and coherent coverage by available medical and/or social services. This appears very necessary to help patients and their relations construct a global individual project for their life.

These diseases are heavy in terms of care, their consequences can be dramatic for families and their social circle; they necessitate adequate connections between doctors (those in the RC and CC, GP, specialists…), health professionals (nurses, physiotherapists, dieticians psychologists …), and social workers (including ergotherapists, assistants at school and at home, family carers…). These specialists should of course be available wherever needed, and adequately trained.

In order to meet the need for improvement in this field, 4 actions were proposed:

1). Enquiries (not intended as prerequisites to other actions). The objective will be to assess the social needs unfulfilled in the regions, by enquiring with all the RC/CC and MDPH (local desks providing orientation, allowances and access to rights for people with disabilities).

2). Experiments on the management of complex cases, with the aim of generalising them.

The RC and CC, their social workers, the GPs, are unable to take on the daily duties of a management and coordination leader: there is ample scope for the involvement of professionals in administrative, medical and social coordination, and in mediation centred on the healthcare pathway and individual life project of patients. The French Association against Myopathies has already put in place a network of social coordinators. A feasibility study on the initiation of this type of activity in different regions could help assess its application to other rare diseases.

ANAP, the national agency supporting health and social services for a better achievement of their tasks, will undertake in 2010/2011 a study on the healthcare pathways of patients and on the « management of complex cases ». An evaluation of the MAIA, - specialised services supporting the autonomy and integration of Alzheimer patients – is also carried out under the Alzheimer Plan. All results will be considered.

Those studies should enable to define one or more schemes for the management of complex cases in the field of rare diseases. These schemes could possibly be common to other fields confronted to the management of complex situations. They will be experimented from 2011/2012 onwards on different regions.

3). *The creation, in connection with the networks for rare diseases, of a system of special fees for complex acts.*

Taking charge of rare pathologies implies sometimes the involvement of health professionals whose out clinic acts are not covered by Sickness Insurance. Such is the case, for example, with dieticians or psychologists.

Furthermore, due to the specificity of rare pathologies, complex acts (by nurses or physiotherapists, for example), may be needed even though their official nomenclature remains unadapted. For such acts, the competences and time needed are not really acknowledged on the official list based on averages.

In order to deal with these situations, it is possible to call in the FNASS (National Fund for Sanitary and Social Action), established with the Sickness Insurance. However access procedures are complicated, not homogeneous in different regions, also under strict conditions of resources and renewal.

The action will consist in clarifying the rules for coverage by FNASS (condition of resources and limitation of renewal possibilities) and harmonising them, in order to fund the prescriptions made by the rare diseases networks, and to do so fairly in the whole country. This coverage could be validated, if required, by a National office for rare diseases, relaying decisions of local Sickness Insurance medical services.

Another objective of the action is to improve the coverage of refundable paramedical acts for complex situations, insufficiently or not evaluated by the official list, and to cover non-refundable paramedical acts, provided they are prescribed by a RC or a CC. A pilot evaluation, currently carried out by the cystic fibrosis association in their reference and competence centres, could be used and adapted to other rare diseases.

4) *Opening adapted units of respite care*

Between 2011 and 2014, places dedicated to Rare Diseases will be created in respite care units, with adapted medical and social care. The aim is to attempt to meet the needs for temporary accompaniment of rare diseases patients and secure periods of rest for carers.

6. HOW TO GUARANTEE PLURIDISCIPLINARY APPROACHES AND THE INTEGRATION OF MEDICAL AND SOCIAL CARE

Pluridisciplinary approaches are mandatory in the RC and CC. However they require the creation of sustainable positions for psychologists and social workers, to be funded under a system of billing by activity adapted to the rare diseases.

Experimenting with the management of complex cases outside hospitals will favour progress toward pluridisciplinarity. GPs can already act as coordinators.

« Patient's knowledge » must also be acknowledged, funded and perfected. Some examples :

- The « sentry patients »programme of the Haemophilia Association relies on patients who are able to feel and transmit the first signs of an hemorrhage, and also to communicate in an adequate vocabulary to other patients ;
- The programmes of therapeutic education.

7. HOW TO EVALUATE THE RC

The HAS, High Authority for Health, an independent health technology agency attached to the ministry of Health, in particular to give agreement to establishments and evaluate practice, is entrusted with the evaluation of the RC : every 3 years, the centres must fill a self-evaluation questionnaire ; every 5 years an external evaluation is carried out by visiting experts, based on terms of reference which take into account the principal missions of the centres (referral, expertise, research and epidemiological watch, organisation and running of the network, linking medical to social care, information and training of health professionals, patients and families). The list is published on the site of HAS ; its latest version is dated 2008, see annex 3.

8. ORPHAN DRUGS AND THEIR FUTURE

The draft Plan insists on the fact that orphan drugs (innovative molecules) are far from representing the essential share of treatments used for rare diseases: currently used drugs, whether recent or not, are

prescribed quite frequently, most of them off label. Non medicinal therapeutic techniques exist also (medical devices, cell therapy, gene therapy…).

Community regulation 141/2000 has given orphan drugs 10-year exclusive rights for marketing 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. Marketing is possible in France under ATU, Temporary Permit to Use. 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 drugs designated as orphan lack transparency.

With regard to other drugs, particularly the many ancient 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. Interruptions in commercialisation can occur, even in the absence of alternative therapies for rare diseases, if prescriptions of these drugs for frequent disorders decline. With regard to this category of drugs, the draft Plan makes proposals to overcome the difficulties described above.

The draft Plan seeks to promote therapeutic research (preclinical and phases I/II), both for applications in innovative therapies (new molecules, gene and cell therapies) and for the use of existing drugs (molecules prescribed without marketing authorisation or having no authorisation). It recommends also contacting a body specialised in financial support, such as the Innobio fund created by the CSIS, Strategic Council of Health Industries, and devoted to the firms implied in the development of health products and biotechnologies. This fund will be able to inject capital in rare disease oriented projects. It should also be stressed that such a fund has to operate on a return on capital basis compatible with the time needed to develop treatments and with the specificities of the rare diseases.

9. ACCESS OF PATIENTS TO ORPHAN DRUGS. PRICING, REIMBURSEMENT

French Plans aim at making access easier, as a result of earlier and more precise diagnoses, as well as adapted prescriptions in the expert centres (RC and CC). There is no financial restriction for patients to access orphan drugs. All orphan drugs are reimbursed without any advance payment: in France, orphan diseases are treated in terms of solidarity. The budget for orphan drugs has increased considerably – mostly due to the rare cancers-. CEP, the Economic Committee for Health Products, fixes the prices for industry. CEPS has recently proposed negotiated prices with payback, offering fixed rate contracts to the firms who commit themselves to commercialising drugs that are accessible for all patients concerned by the treatment.

The provisions of these contracts are entirely unknown by hospitals, doctors or prescribing pharmacists. Receipts are entered into the accounts at the end of the year, and when the fixed amounts are exceeded, the firms return the sums in excess.

In the future, it will probably be necessary to distinguish those orphan drugs that are as profitable as the most gratifying non orphan ones (they amount to two thirds of the total), from those that, while they concern very small populations, are very costly and unprofitable (for instance, the compensators of protein or enzyme deficit). Failing that, the rich orphan drugs will eliminate the poor ones. In spirit, the regulation on orphan drugs is indeed meant to protect and encourage research on orphan drugs and their availability to patients. By reintroducing this separation, and by proposing the suppression of fiscal incentives for the most profitable drugs, CEPS believes it acts in accordance with the spirit of the regulation.

10. COMPASSIONAL USE AND TEMPORARY AUTORISATIONS OF ORPHAN DRUGS. OFF LABEL USE.

Many drugs are used off label in the treatment of rare diseases. Their use in such cases is not always well documented and one cannot exclude a risk for the patients to whom the prescription was given. It is necessary to organise with the RC a survey on the use of drugs, those that have a marketing authorisation and those that are not reimbursed, in order to identify insufficiently documented situations. This survey can be the basis for future actions: studies, coverage by sickness insurance, watch for marketing interruptions. A working group will be set up, composed of representatives from AFSSAPS (National health products agency), LEEM (representing the pharmaceutical industry), the RC and CC.

The system of ATU (temporary authorisations) [8] and of PTT (temporary protocol for treatment) in hospitals is extensively used to treat patients as early as possible. The drugs considered as orphan are often granted ATU either for cohorts or for individuals before they obtain an AMM. Only the ATU given to cohorts must follow a protocol for therapeutic use and information collecting.

The draft plan proposes to take advantage of marketing under ATU to organise with industry the follow up of treated patients, in order to collect data on the tolerance and efficacy in real life of drugs, and thus improve knowledge on these products. Similarly, a register of data on the efficacy and tolerance of drugs used in hospitals should be created as part of temporary protocols of treatment (PTT) for rare diseases, in spite of a more difficult implementation.

[8] This is the possibility, in France, to prescribe a drug that has not received a marketing authorisation at French or European level, in order to treat rare or severe diseases for which adequate treatments do not exist. ATU can be granted to a single patient or to a group of patients. The pharmaceutics firm must demonstrate the presumed efficiency of the drug and commits itself to apply for an AMM within a fixed time.

The granting of an ATU for cohorts by AFSSAPS will be conditional on the obligation to check the patients for tolerance to, and efficiency of, the medication. AFFSAPS will request a similar follow up for the individualised ATU, as soon as the number of patients included in the therapeutic trials exceeds a certain ratio. For PTT, a preliminary round of consultations is needed, to be undertaken by AFSSAPS and INCA (National institute on cancer). In all cases the follow up of patients after marketing authorisation must rely on the network created by DG SANCO joint action.

Several pilot experiments of pharmacovigilance in France have demonstrated the merits of a self-declaration of side effects by patients and their families, for drugs with or without a specific marketing authorisation. The European dimension will enable to broaden the information base.

Theme 5 - Patient Empowerment and Specialised Services

Sub-Themes

1. Involvement of patients and their representatives in decision-making processes in the field of RDs
2. Support to the activities performed by patient organisations
3. Specialised social services: Respite Care Services; Therapeutic Recreational Programmes; Services aimed at the integration of patients in daily life
4. Help Lines

1. INVOLVEMENT OF PATIENTS AND THEIR REPRESENTATIVES IN DECISION PROCESSES IN THE AREA OF RARE DISEASES

The emergence of rare diseases as a problem of public health must be ascribed to the efforts of patients associations. For decades, the associations have promoted the awareness of public opinion and undertaken actions to support and welcome the families and patients. They have set up schemes to inform, exchange and train. They have also developed projects to accompany, educate on therapy, and perform research. They act as relays of public authorities and hospitals (particularly RC) and they are aware of the needs of patients and of their families.

At present, the participation of patients associations in decision bodies is foreseen at various levels. They are often consulted informally. They represented thus 21% of participants in the drafting groups of NPRD2. They are in contact with administrations and all institutions dealing with rare diseases. In this context, their expertise and opinions are taken into account, but they do not take part in decision taking.

Furthermore the associations, on the basis of legal or regulatory texts, participate formally in decisions regarding health: they sit on important national, regional or local bodies, for example the future Committee for the Monitoring of NPRDII, the National Conference on health, the regional conferences, the regional desks for people with disabilities, the managing bodies of public and private health services (boards of administrators, user committees).
In some instances, they also manage the services for patients or disabled persons.
Associations are also very active in the bodies overseeing research and in ethical committees: they can make proposals and be consulted by industry.
The media pay attention to their action, their problems and opinions, and are happy to relay them to the public.

The associations train their members in their role of representatives in various bodies.

The Rare Diseases Platform , inaugurated on 23 October 2001 in Paris, is unique in Europe ; it regroups Alliance Maladies Rares – the National Alliance for Rare Diseases -, EURORDIS, Orphanet, Maladies Rares Info Service-the Rare Diseases hotline, the GIS Research Institute for Rare Diseases, and AFM, the French Association against muscular dystrophies, its main funder.

Confronting the multiplicity and heterogeneity of diseases remains however a real challenge for the federations of associations, so does the transmission of know how. Those are the tasks undertaken by Alliance Maladies Rares, created in 2000, regrouping 201 French patients associations and by EURORDIS, created in 1997, regrouping more than 447 associations in 47 countries.

2. SUPPORT TO ACTIVITIES OF PATIENTS ASSOCIATIONS

Only a few associations, often ancient and well structured, are capable of appealing to public generosity - such as AFM/Téléthon (the French association against muscular dystrophies) -. Most associations, especially those involving few patients, find it difficult to enlist support for their actions and projects. By regrouping them, the existing federations (Alliance Maladies Rares, EURORDIS) favour their restructuration and promote their status in national and international bodies. Orphanet, Maladies Rares Info Service and the federations help raising awareness about their work.

Some of the associations' activities on information/training or accompaniment come under the umbrella of therapeutic education and can be funded accordingly. However, the associations have permanent running costs and undertake many other activities : surveys on patients needs, projects to bring together or accompany patients, mutual support, mediation, drafting and dissemination of documents

for the patients and their families, initiatives for the public (International day for Rare Diseases, Rare Diseases March), awareness raising with the media and authorities, etc.

Whereas Ministry of Health did finance actions of associations during the first Plan, it refers the associations to the federations, because of their increasing number. According to the draft Plan, it is intended that the Ministry will call on the associations to submit innovative projects on training or information, accompaniment, mediation of complex cases, and will earmark additional new funds for them.

3. SPECIALISED SERVICES: RESPITE CARE, THERAPEUTIC RECREATION CAMPS, AND INTEGRATION OF PATIENTS IN THEIR DAILY LIFE.

Respite care will be developed and organised during the second Plan.
The associations have already created and supported a very large number of initiatives outside the remit of the Plan. For instance, AFM's administrative, medical and social coordinators who assist families , or « l'Envol » therapeutic recreation camp for European children, or respite care such as in the Hopital Marin at Hendaye -, or the Intégrascol data base, providing information to facilitate the insertion of children in 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 a closer cooperation between the RC/CC, the MDPH (local desks providing orientation, allowances and access to rights for people with disabilities), and the services.

4. HELP LINES

Since 2001 « Maladies Rares Info Services », the hotline on rare diseases, has served patients, their families, and also the health professionals.

« Maladies Rares Info Services » is supported by AFM, the French association against muscular dystrophies, thanks to the donators of Telethon and INPES, the National Institute of Prevention and Education for Health. Its roles are to listen, inform and orient all persons concerned by rare diseases. The cost of a query is that of a local all.

In the draft Plan, it is suggested to support EURORDIS work, with DG information support, toward the adoption of a single European green number, using a 116 number linking up the European network of help lines: implementation of good practice guidelines, provision of a better service, common annual Caller Profile Analysis (data from all members), matching isolated patients, cost saving technical support.

Horizontal Themes

Theme 6 – Sustainability

This issue has been mentioned above in the relevant paragraphs.

The second Plan intends to include the rare diseases in the provisions of common law. Sustainability will depend on a few legal or regulatory measures, mainly in the area of drugs and also in the granting of the funds necessary to implement the 51 out of 82 measures for which budgets are required.

A total cost of 108, 46 millions Euros over 4 years had been announced for the national plan 2005-2008. Earmarked funds were the addition of one shot and renewable measures. At the end of the plan, the spending was estimated at about 210 millions Euros, of which more than half went to the RC.

The financial provisions of the draft plan have been calculated rigorously. They separate clearly the one shot and the recurrent allocations, and among the latter, they distinguish between actions financed by the recycling/redeploying of funds already in used for rare diseases, and actions necessitating new funds, coming from NPRD2. It defines a precise schedule of annual spending.

Overall, the draft National Plan for Rare Diseases 2010-2014 calls for 42, 7 million Euros of new recurrent funds (State health funds, Health Insurance funds, and social funds) and 20.6 million Euros of one shot measures. In a time of budget constraints, the final decision on appropriation will be taken by the Prime Minister in February 2011.

Moreover, 127.7 million Euros already allocated to some agencies and to hospitals for their reference activity or for laboratory work, can be allocated or redistributed contractually for the benefit of rare diseases.

Theme 7 - Gathering expertise at the EU level

This issue has been mentioned above in the relevant paragraphs.

III. Document history

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