NATIONAL PLAN FOR RARE DISEASES (2011-2014)

"QUALITY OF CARE FOR PATIENTS, RESEARCH AND EUROPE: A STRENGTHENED AMBITION"

Contents

Introduction

A disease is considered rare if it affects less than one in 2 000 people in the general population. Consequently, in France, a rare disease affects less than 30 000 people. According to current estimations, 4 to 6% of the population are affected by a rare disease that is around 3 million people in France and 20 million people in Europe.

More than 7 000 rare diseases are identified today and new ones are regularly described:

- 80% are of genetic origin;
- 65% are serious and incapacitating;
- 50% start before the age of 2 years and are responsible for one-third of deaths in children before 1 year of age, 10% between 1 and 5 years, and 12% between 5 and 15 years.

Background

The first French National Plan for Rare Diseases 2005-2008, called “Ensuring equity in the access to diagnosis, treatment and provision of care”, was launched on 20 November 2004, jointly by the Minister of Health, the Minister of Research and the State Secretary for Disabled People.

It established several principles still valid today:

- rare diseases are a public health issue. For this reason, they were one of the priorities selected out of the five in the Public Health Policy Act, adopted on 9 August 2004;
- rare diseases require that the most vulnerable and least numerous populations always be taken into consideration. They are consequently a central issue and a model for equal access to healthcare and improvement of quality of care and support for patients;
- rare diseases give a central role to patients organisations, which form a community with the healthcare professionals.

The first National Plan achieved significant progress, in particular with regard to:

- access to diagnosis and healthcare, thanks to the creation of centres of expertise labelled for rare diseases:
    - 131 “reference centres” (*centres de référence maladies rares, CRMR*) at national level, which are highly-specialised healthcare providers teams labelled in university hospitals. These centres have received a total €40 million through funding for public interest missions,
    - 501 “regional centres” (*centres de compétences maladies rares, CCMR*), which supplement the actions of the CRMR closer to home for patients;
- information about rare diseases for healthcare professionals, patients, families and the general public, thanks to the development of the Orphanet database and web portal;
- research, thanks to funding for a large number of research projects and closer cooperation between stakeholders, in particular within the “GIS-Institut Maladies rares” (*Groupement d’Intérêt Scientifique-Institut Maladies Rares,* i.e. Rare Diseases Institute-Scientific Interest Consortium);
- development of European cooperation projects, thanks to the action conducted by France through the High Level Group on Health Services and Medical Care, the events organised during the French Presidency of the European Union (EU) and through supporting Orphanet.

The assessment of the first National Plan was carried out by the French High Council on Public Health (*Haut conseil de la santé publique*). In its April 2009 report, it pointed out tracks for improvement, in particular:

- the consolidation of the three flagship achievements of the Plan:

- reference centres: revise the procedures and assessment criteria, better allocate financing, consider a pricing overhaul, develop coordination, and better structure expert laboratory platforms,
- Orphanet: develop the use of the Orphanet nomenclature, the readability of its portal and the information it contains,
- GIS Rare Diseases Institute: bring research forward and create a national structure to drive research on rare diseases;

- the development of actions aimed at:
  - making progress in collecting epidemiological data on rare diseases drawing upon a national databank to be built,
  - simplifying and increasing the production of "national diagnosis and treatment protocols" (*protocoles nationaux de diagnostic et de soins*, PNDS[1]) by the reference centres,
  - developing ties with the professionals of the medical and social field, in particular the "Local-Level Centres for Disabled People" (*Maisons départementales des personnes handicapées*, MDPH).

Developing the second National Plan for Rare Diseases

Following the aforementioned assessment, Prof. Gil Tchernia, mandated by the involved Ministers, formed 7 thematic working groups with nearly 180 people, who met between October 2009 and January 2010. The "Proposals for a Second Rare Disease Plan 2010-2014" was submitted to the Ministers on 21 July 2010.

The second French National Plan for Rare Diseases 2011-2014 was launched by the Ministers on 28 February 2011. It draws upon this preparatory process and carries forth the first National Plan. Its format follows the recommendations of the Genaral Directorate for Health (DGS) as concerns the "recommendations for drafting, monitoring and assessing national public health plans", published in December 2009.

The Plan is the result of an inter-ministerial cooperation, in particular between the Ministry of Health and the Ministry of Higher Education and Research, and the combined and contrasting expertise of all of the Ministry Directorates involved. It was steered by the Ministry of Health and coordinated by the General Directorate for Provision of Healthcare (DGOS), in association with:

- the General Directorate for Health (DGS);
- the Directorate for Social Security (DSS);
- the General Directorate for Research and Innovation (DGRI);
- the General Directorate for Social Cohesion (DGCS);
- the General Directorate for Competitiveness, Industry and Services (DGCIS);
- the Department of European and International Affairs, under the Social Ministries (DAEI).

Meetings held with patients organisations made it possible for them to cooperate closely in the elaboration of the Plan.

The 2011-2014 National Plan for Rare Diseases

The 2nd National Plan for Rare Diseases capitalises on the strengths and progress of the first Plan, and accentuates the commitment to action in the field of rare diseases in three areas of action:

- improving the quality of care for patients with rare diseases;
- developing research on rare diseases;

[1] PNDS are French national practice guidelines for rare diseases.

- increasing European and international cooperation.

The three main areas of the Plan have been expressed in 15 measures, 47 actions and 4 focused actions.

Patient care will be improved through:

- improved access to diagnosis, in particular:
    - bringing forward the assessment procedures and criteria for rare disease reference centres, and optimising their financing procedures,
    - structuring “national networks for rare diseases” (“filières de santé maladies rares”, FSMR) between reference centres, regional centres, diagnosis platforms, and medical and social sectors,
    - organising reference laboratory platforms for diagnosis;
- improved quality of care, in particular:
    - increasing production of “national diagnosis and treatment protocols”,
    - guaranteeing drug-based healthcare suited to each patient, taking into account the progress of research,
    - developing new professions and new care organisations and coordination;
- improving information to patients and healthcare professionals.

The development of research on rare diseases will focus in particular on:

- creating a national structure, the “Foundation for Rare Diseases”, which will make it possible to structure and harmonise the various initiatives underway in the field of research, in connection in particular with the pharmaceutical industry;
- promoting the development of therapeutic trials and clinical and translational therapeutic research.

The amplification of European and international cooperation will encourage:

- promoting expertise-sharing with the European Reference Networks;
- facilitating the design of multinational clinical trials and access to diagnostic tests.

Key Dates

- February 1958: the French Association against Myopathies (AFM) created
- February 1997: Orphanet created
- February 2000: Rare Diseases Alliance created
- October 2001: under the impetus of the AFM, in a building of Broussais Hospital in Paris, the "Rare Diseases Platform" (Plateforme Maladies Rares) is inaugurated by the Delegate Minister of Health
- 9 August 2004: Public Health Policy Act. Rare diseases are selected as one of the five priorities under the law.
- 20 November 2004: the first National Rare Diseases Plan (2005-2008) announced
- 10 October 2008: at the "Europe and Rare Diseases" Symposium, the President of the French Republic commits to ensuring that a plan devised in 2009 be implemented in 2010 for a five-year period
- 8 June 2009: Council Recommendation on an action in the field of rare diseases, published in the Official Journal of the European Union
- 21 July 2010: proposals for the second National Plan for Rare Diseases submitted to the Minister of Health and Sport and the Minister of Higher Education and Research
- 28 February 2011: on International Rare Disease Day, Nora Berra, State Secretary in charge of Health, and Valérie Pécresse, Ministry of Higher Education and Research, present and launch the second National Plan for Rare Diseases (2011-2014)

AREA OF ACTION A: Improving the Quality of Care for Patients

The aim of this first part of the plan is to improve the quality of care for patients, by acting on all its dimensions and building on all the tools or structures that resulted from the first Plan.

The assessment of the first Plan emphasised the significance of the progress achieved, but also the road that lies ahead:

- both the feedback of DHOS and DGS and the observations of the High Council on Public Health encourage measures to strengthen the reference centres, by making the assessment procedures applied to them more operational, coordinating them more, and better tracing the funding allocated to them; this last concern was shared by the National Conference on Healthcare;
- the High Council on Public Health emphasised the progress that remains to be accomplished with regard to patient care, whether to fight against delay for diagnosis or to standardize reimbursement by the public health insurance system.

This first area of action, focused on patient care, has been expressed in 8 measures, 29 actions and 3 focused actions.

The first objective is to bring together the reference centres for rare diseases into national networks and give biological activities their full place alongside clinical activities. The financing and assessment procedures for the reference centres are also to be brought forward, in order to simplify them, better allocate resources taking into account the centres activity, and better report on the use of financing.

This part of the plan aims also at developing telemedicine and Orphanet, and setting up a National Rare Diseases Databank. It aims to improve care for each patient, in particular by increasing the production of “national diagnosis and treatment protocols” (PNDS), guaranteeing patient-appropriate drug-based care, making the necessary interconnections with the initiatives carried out by the medical and social sector, and improving the practices of healthcare professionals.

A-1 Improving Access to Diagnosis and Healthcare for Patients Affected by Rare Diseases

A-1-1 Structuring National Networks for Rare Diseases

In France, the current expertise on rare diseases is within 131 labelled “reference centres” and 501 “regional centres” working in close connection with reference centres. Reference and regional centres cover 18 groups of rare diseases. This layout - a real step forward made possible by the first National Plan - needs to be improved, however. The High Council on Public Health recommends drawing upon the existing spontaneous groupings of reference centres, fostering new multi-player groupings (in “rare diseases reference centres consortia”) and pooling resources in order to share medical, scientific, ethical and administrative issues.

National networks for rare diseases will be organised in 2011.

These “national networks” (“*filières de santé maladies rares”*) will organise the activities and coordination between reference centres and regional centres, diagnostic platforms, technical platforms for medical imaging and functional exploration or any other department involved in care for patients affected by rare diseases. The national networks might be based on the 18 groups of rare diseases usually considered to classify the 131 French reference centres.

Each national network, defined within a group of rare diseases, will make it possible to:

- revise the coordination between the reference centres by pooling coordination and activity resources;
- facilitate identification and orientation within the healthcare system for all rare disease patients and their medical practitioners;
- better coordinate diagnostic, treatment and follow up, and also medical and social care for patients;
- effectively coordinate research action;
- organise the collection of clinical data for epidemiological research purposes and oversee their quality;
- bring resources and expertise together at the national level in order to give them greater visibility at the international level, in particular in the prospect of the future European Reference Networks.

The national networks will, in accordance with the features specific to each, be able to draw upon the public health departments, biostatistics departments, medical and communication technology departments, clinical research units, therapeutic education units and the medical information departments.

The national networks, working in connection with national laboratory platforms for diagnosis (see A-1-2), will have to harmonise the procedures and relations of the reference centres.

The national networks will take care to ensure that the reference and regional centres establish cooperation agreements, where applicable, with national "resource centres for rare disabilities" and with the "local-level centres for the disabled people" (*Maisons départementales des personnes handicapées*, MDPH). A model agreement will be put forth in 2011 by a working group of the Steering Committee of the Rare Diseases Plan (*Comité de suivi et de prospective du plan maladies rares, Cospro*).

The national networks' governance procedures will not be unique, but rather in accordance with the specificities of each, and defined therein by internal regulations.

Action leaders: DGOS, Steering Committee of the Plan.

Co-leaders: DGS, Orphanet, CNSA (*Caisse nationale de solidarité pour l'autonomie*, National Solidarity Fund for Autonomy), DGCS, ARSs (*Agences régionales de santé*, Regional Health Agencies).

Partners: reference centres, national laboratory platforms for diagnosis, learned societies, patients organisations, MDPHs.

Indicators:

- number of reference and regional centres which have become parts of national networks for rare diseases;
- production of the model agreement for cooperation between reference centres and MDPHs;
- number of rare diseases with reference centres in France,
    - including the number of rare diseases benefiting from new reference centres in France;
- number of rare diseases benefiting from reference centres in Europe.

Implementation timeline:

- 2011: identify the possible future national networks for rare diseases, plan the implementation agenda, and create the first national network;
- 2011: produce the model agreement for cooperation between reference centres and MDPHs;
- 2012: complete the creation of the national networks for rare diseases.

A-1-2 Giving biology a full-fledged place alongside clinical care

Currently there are specialised laboratories organised into networks, through the financial support provided by the DGOS to hospital laboratories in order to facilitate genetic diagnosis or conduct complex diagnostic tests for rare diseases. In interaction with the organisation of the reference centres into national networks for rare diseases, it is important that expert-level biology laboratories be better structured so as to improve their consistency with clinical diagnostic approach and clinical research. **For this purpose, reference laboratory platforms dedicated to diagnosis of rare diseases will be identified at the national level**.

This organisation into national platforms including French specialised laboratories will make it possible to:

- achieve, through redistribution, the critical mass needed for effective complex diagnosis;
- optimise the expensive large equipments necessary to perform the biological tests which reference centres henceforth need, in particular NGS technologies.

As with the national networks for rare diseases, this structuring will be designed to put technological and scientific progress to work for the patients and guarantee the quality of the tests performed and their interpretation.

These platforms will be responsible in particular for:

- performing complex diagnostic procedures;
- conducting scientific intelligence activities on new diagnostic options, working in connection with the national networks for rare diseases;
- implementing new technological developments such as NGS technologies;
- contributing to the development of PNDS and the development of decision-making diagnostic trees, in connection with the HAS (*Haute Autorité de Santé*, French National Authority for Health) and the ABM (*Agence de la biomédecine*, French Biomedicine Agency);
- overseeing biological sample archiving and networking, and enriching the existing collections in close contact with the rare disease reference centres;
- taking part in neonatal screening activities and, in some cases, in prenatal diagnosis and pre-implantation diagnosis activities;
- structuring the pooling and harmonisation of diagnostic tests at the European level.

Action leaders: DGOS, Steering Committee of the Plan.

Co-leaders: DGS, HAS, ABM.

Partners: reference centres, learned societies, professional organisations, National Association of Molecular Genetics Practitioners (*Association nationale des praticiens de génétique moléculaire,* ANPGM), Association of French-Language Cytogeneticians (*Associations des cytogénéticiens de langue française*, ACLF), National Commission on Childbirth and on Health of Children (*Commission nationale de la naissance et de la santé de l'enfant),* patients organisations, MDPHs.

Indicators:

- number of national reference diagnosis laboratory platforms created;
- number of rare diseases diagnosed by the national reference diagnosis laboratory platforms;
- number of decision-making diagnostic trees developed.

Implementation timeline:

- 2011: develop procedures for identifying national reference diagnosis laboratory platforms and draft calendar;
- 2012: implement national reference diagnosis laboratory platforms.

A-1-3 Developing NGS approaches within national reference laboratory platforms for diagnosis

CGH (Comparative Genomic Hybridization) and NGS (next-generation sequencing) have recently opened up new possibilities in identifying molecular bases of rare diseases.

- ✓ **NGS**

NGS strategies can now be used to much more quickly identify the mutations that lie behind rare diseases. NGS equipment and information technologies quickly improve the tests speed and the number of analyses that can be carried out in a given amount of time. This costly equipment, which has imperatively to be shared, will modify in depth the genetic diagnosis approach. Within this context, the aim then becomes to ensure that national reference laboratory platforms are able to access NGS equipment.

Specifications describing the conditions for "in-hospital" NGS development (i.e. NGS for "routine diagnosis") will be defined in accordance with technological developments and taking into account the cost of the consumables, reactants and human resources vital to the undertaking (in particular bioinformatics engineering).

- ✓ **CGH (Comparative Genomic Hybridization)**

CGH is a technique used to test all of the genome on DNA chips in order to identify chromosome rearrangements. A review and assessment of the action started in 2008 will help to better structure the offer at the regional level and increase the resources in terms of equipment and qualified staff, in particular in bioinformatics. This organisation will be able to draw upon the existing network dedicated to detecting chromosome micro-adjustments via CGH array, which was established by the DGOS.

This action is aimed at:

- **adapting equipment and laboratories to the needs of the scientific community, with a view towards identifying the rare disease molecular bases and improving diagnosis conditions;**
- **identifying at the national level a limited number of sequencing centres dedicated for rare diseases and integrated into national reference laboratory platforms for diagnosis;**
- **providing equipment and human resources vital to analysing and interpreting the data resulting from NGS.**

Action leader: DGOS.

Co-leaders: DGRI, ABM.

Partners: national reference laboratory platforms for diagnosis, National Association of Molecular Genetics Practitioners

Indicators:

- number of patients for whom the molecular or chromosome base of their disease was identified using NGS approaches;
- number of patients having received genetic analysis using NGS approaches.

Implementation timeline:

- 2011: identify and assess existing equipment and their occupancy rate;
- 2012:
    - o assess the access to existing equipment and explore target infrastructure blueprint,
    - o produce specifications on operating conditions for "in-hospital" NGS development.

A-1-4 Coordinating rare disease structures through a single information system

In order to coordinate the various structures working in the field of rare disease and to foster expertise-sharing, it is important to make harmonised communication tools available to the partners

involved. Currently, the information systems used by the reference centres and regional centres are suited to their specific issues, but are heterogeneous and do not intercommunicate.

This action is aimed at developing and deploying a common information system that can be used to coordinate and enable smoother operations within the future national networks and currently between reference and regional centres. This information system is expected to facilitate sharing and circulation of expertise within rare disease national networks, thereby contributing to better care for patients.

Action leader: DGOS.

Partners: French Agency for Shared Information Systems in Healthcare (*Agence des systèmes d'information partagés de santé*, ASIP), reference centres, regional centres, national networks for rare diseases, National Rare Disease Databank (BNDMR).

Indicator: number of structures connected to the information network.

Implementation timeline: 2012.

Focused Action: The National Rare Disease Databank

The objective is to equip France with a clinical databank that could be used to have a better knowledge on the natural history of rare diseases, document patient care methods and their impact, describe demand for healthcare and the extent to which it is matched by supply in each area, and to produce medico-economic data on rare diseases. This databank could make it possible, for instance, to identify at the national level the patients likely to be eligible for a clinical trial of a new drug or a new medical device, or to match a phenotype profile with data from genomics.

This action is aimed at structuring and financing a National Databank (*Banque nationale de données maladies rares,* BNDMR) containing clinical and subsequently, in all likelihood, biological and therapeutic data on rare diseases. This National Databank will be based on the data collected in the reference and regional centres and in the disease registries.

This National Databank is also destined to be interfaced with the monitoring of specific rare disease cohorts (in particular the cohorts set up by the RADICO project) and with other medical and administrative databases.

In order to structure the BNDMR, the experience gained by the databases put together by the existing network called CEMARA will be taken into account. This network is coordinated by *Hôpital Necker-Enfants Malades* in Paris. It brings together 51 rare diseases reference centres (29 out of Paris and 22 in Paris, including 11 in *Hôpital Necker-Enfants Malades*), 100 regional centres and more than 1 200 professionals who have already collated over 105 000 cases. The experiments carried out by other entities in this field will also be taken into account.

A minimum set of data to be collected will be developed in cooperation with the reference centres, later structured into national networks for rare diseases, INSERM (*Institut national de la santé et de la recherche médicale*, French National Institute of Health and Medical Research) and InVS (*Institut de veille sanitaire*, French Institute for Public Health Surveillance), taking into account the recommendations issued at the European level.

The data export format will be determined so as to be able to supply the BNDMR. The shift toward information system interoperability will make it possible to consider new information exchange modalities. It is during this first stage that the information-gathering policy will be determined jointly with all the stakeholders involved.

A support and methodological advisory unit will be set within the BNDMR up to steer the action. It will determine the charter of working principles that will need to be adopted by all of the professionals sharing in the BNDMR. The charter will describe the rights and responsibilities of all users. Adopting it will be a pre-requisite for access to the protected database. The protection of personal data will be fully-guaranteed and be the focus of a specific prior agreement with the Commission on Information Technology and Liberties (*Commission nationale de l'informatique et des libertés*, CNIL). Alongside this, patients will be provided with due information.

Data collection about rare diseases will be done using the Orphanet nomenclature and take into account recommendations for drawing up and managing databases and registers established by the Rare Disease Task Force run by the DG SANCO, circulated via Orphanet.

In addition to this national database will come monitoring for specific cohorts, drawing upon data collected about selected rare diseases.

Requests that this national database be aligned with other databases, regardless of whether they contain personal information, may be answered in the positive, to the precise extent allowed by the law and with due respect for all of the stakeholders involved, in compliance with the legal and professional ethical framework on data extraction and use.

In order to improve epidemiological data collection, a status report will be produced on the current collection process underway in the reference centres, identifying the stumbling blocks and taking inventory of the information technology equipment available in rare disease consultation departments. Investment resources may be allocated where necessary.

Clinical research assistants will be assigned to database quality control and analysis. Their number will be determined in accordance with the number of data to be collected as the minimum set of data. These professionals will later be pooled within national networks for rare diseases.

The InVS is a natural partner for epidemiological data collection and will be called upon as necessary.

The BNDMR will be a stakeholder in the future Foundation for Rare Diseases. Discussion will be carried out with regard to financing for existing or future registries, with INSERM, InVS and the Foundation for Rare Diseases.

Action leader: DGOS.

Co-leaders: DGS, DGRI.

Partners: ASIP, reference centres and regional centres, CEMARA network, Foundation for Rare Diseases, InVS, INSERM, Orphanet.

Funding: €500 000 in 2010 through renewable hospital credits (public interest mission funding).

Implementation timeline:

- 2011: work begins:
    - assess current status of collection process conducted by reference centres and stumbling blocks;
    - define the minimum set of data to be collected;
    - define data export format;
    - define collection policy.
- 2011-2012:
    - set up support and methodological advisory unit within the BNDMR;
    - develop charter of working principles.

A-1-5 Fostering the development of telemedicine for patients affected by rare diseases

The Decree 2010-1229 of 19 October 2010 on telemedicine serves as a framework for promoting expertise-sharing and dissemination, and enabling diagnosis and treatment for rare disease patients as close to their homes as possible.

The various existing telemedicine procedures can be mobilised for rare diseases, in particular:

- remote consultations, which are designed so that a medical professional can remotely run a check-up on a patient;
- tele-expertise, which is designed so that a medical professional can remotely seek the opinion of one or more medical professionals based on their training or specific expertise.

The National Telemedicine Programme will take into account rare diseases and incorporate the proposals that the ARSs will make in this area.

The structuring of telemedicine activities will require at first establishing an agreement between all the participants, in order to regulate this new care process in terms of both safety and quality, as the Decree on telemedicine specifies.

Action leader: DGOS.

Partners: ASIP, reference centres, regional centres, ARSs, patients organisations.

Indicators:

- number of agreements signed;
- number of reference and regional centres implementing telemedicine procedures.

Implementation timeline: 2013, depending on National Telemedicine Programme.

A-1-6 Improving screening of rare diseases

The first National Plan for Rare Diseases 2005-2008 highlighted the need for progress where screening for rare diseases is concerned.

The issue is different according to the type of screening involved: screening in the general population, neonatal screening and prenatal screening.

Taking into account how diverse they are, screening for rare diseases in the general population is restricted to cascade screening in the families, based on index cases, when dealing with genetic diseases. In practice, it is a matter for the multidisciplinary consultations (declared to the ABM) carried out by professionals in charge of the follow-up of asymptomatic patients, in connection with reference or regional centres for rare diseases.

In contrast, systematic screening in new-borns focuses on specifically-targeted diseases, the diagnosis and treatment of which provide real benefit to the population screened as affected. Based on internationally-recognised assessment criteria and a positive benefit-risk balance (i.e. Wilson and Junger criteria); such screening is enacted by ministerial decision in France. At the current time, the French Neonatal Screening Programme (registered in the French Public Health Code since 2008) requires screening for four diseases in the general population (phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism and cystic fibrosis) and for a fifth one (sickle cell disease) in the population at risk.

Prenatal screening for some diseases has been made possible thanks to technological developments whether in biochemistry, genetics or imaging. This form of screening has been the focus of specific regulation placed under the responsibility of the ABM, which gives the authorisation to the multidisciplinary prenatal diagnosis centres.

The initiatives to be carried out under the current Plan are:

- **extending neonatal screening to diseases other than those currently listed in the French Public Health Code. Preliminary assessment would be entrusted to a new regulatory advisory body;**
- **developing recommendations for risk groups to which prenatal screening would be offered;**
- **supporting pre-implantation genetic diagnosis centres.**

✓ **Extending neonatal screening to diseases other than those currently listed in the French Public Health Code**

The Neonatal Screening Programme is managed by the French Association for Screening and Prevention of Disabilities in Children (*Association française pour le dépistage et la prevention des handicaps de l'enfant*, AFDPHE) and funded by the Social Security System. The indirect costs are little-known, in particular those arising from the involvement of laboratories and clinicians from the university hospitals that are home to the regional associations federated by AFDPHE. Cost assessment is underway and will make it possible to clarify the role and interconnection between the various participants in each region.

In order to investigate requests for new neonatal screening, the *Brodin Report* (report on neonatal screening organisation to the French Minister of Health, coordinated and drafted by Pr Brodin, and published in February 2010) proposes the creation of a "regulatory advisory body", the remit of which would be to conduct the initial investigation on the said requests for new neonatal screening, including those for regional pilot studies, in order to ascertain their potential value. Should the said body issue a positive opinion, an in-depth evaluation study will be entrusted to the HAS before agreement for the implementation of any new neonatal screening programme. The opinion of the ABM will also be asked. Subsequently, the HAS will also carry out an evaluation of the implementation of the authorised programmes.

This "regulatory advisory body" could be placed under the National Commission for Child Birth and Health (founded by Decree 2010-1407 of 12 November 2010) to which the Minister of Health can refer on any matters relating to perinatology and public health programmes or healthcare supply concerning children.

In the meantime, the DGS has called upon the HAS as to the relevance of the launch of neonatal screening based on tandem mass spectrometry (MS/MS) for medium-chain fatty-acid acyl-CoA dehydrogenase (MCAD) deficit and switching to MS/MS to detect phenylketonuria. The HAS is expected to hand in its report in 2011, then to assess extending screening to other types of in-born metabolism errors using MS/MS.

The HAS has been mandated to examine the extension of neonatal screening for sickle cell anaemia in general population, emphasising two aspects: the medical and economic benefit of this extension, and recommendations on information and care for heterozygote patients recognized by the screening and their families. The impact of these recommendations on the organisation and cost of screening will need to be taken into account.

All of the aforementioned recommendations fit into a broader exploration on neonatal screening carried out at the European level, as part of a project funded by the DG SANCO.

✓ **Specify the risk groups to which rare disease screening could be offered at the prenatal stage**

The aim here is to more clearly define which risk groups could be offered prenatal genetic diagnosis and, more rarely, pre-implantation genetic diagnosis. Recommendations could be issued by an independent body, which could be the aforementioned "regulatory advisory body", placed under the National Commission on Child Birth and Health.

As concerns prenatal diagnosis, three medical situations have been identified:

- the first occurs prior to a desired pregnancy. Screening consists in identifying at-risk families, ensuring that they are duly informed and arranging for them to be monitored. This action is directly connected to the implementation of genetic consultations in the reference and regional centres that most often follow these families;
- the second concerns the general population, where screening procedures are being developed (in particular as concerns screening for Down's Syndrome) and offered to pregnant women by their regular physician or the healthcare professionals caring for them during this period. These procedures are based on risk calculations and a threshold from which prenatal diagnosis is offered. They do not currently include screening for rare diseases;
- the third is triggered by the discovery or suspicion of a foetal anomaly. It calls into play the obstetricians' ability to take into account distinctive signals of a specific disease or group of diseases. In ¾ of the time, this situation requires further investigation based on foetal ultrasound.

✓ **Pre-implantation genetic diagnosis (PGD)**

In the specific event where PDG is possible, only the first option, meaning the assessment of foetal risk prior to pregnancy, enables the implementation of PGD. This diagnostic procedure would deserve to be consolidated, in particular in light of the benefits that it offers couples, most often already under the strain of a family illness. The currently-observed implementation timeframes are such that equal access to this type of diagnostic procedure is not possible. Funding (€2.9 million) has been granted in 2010 to three existing PGD centres so that they can respond to demands within reasonable timeframes.

Action leader: DGS.

Co-leaders: DGOS, CNAMTS (French National Health Insurance Fund for Salaried Workers), HAS, ABM, AFDPHE, National Commission on Child Birth and Health; Steering Committee of the Plan, patients organisations.

Partners: national reference diagnosis laboratory platforms.

Indicators:

- number of patients identified by neonatal screening for each disease of the programme;
- number of new types of screening studied;
- number of new types of screening implemented;
- number and type of PGDs available;
- waiting time for PGD;
- number of PGDs carried out.

Focused Action: Due consideration for the needs specific to Overseas France patients

The first National Plan for Rare Diseases granted well-warranted attention to the specific issues raised by rare diseases in French Overseas Departments and Territories. For example, the overseas departments are home to 4 reference centres and 22 regional centres, dedicated primarily to sickle cell anaemia and rare neurological and neuromuscular diseases. The current Plan carries on with this specifically-oriented approach, which has not been criticized by the High Council on Public Health assessment.

Though it has become the most frequent genetic diseases in France, sickle cell anaemia has not received the same attention as other genetic diseases. This focus action is aimed at improving knowledge, screening and care for patients affected by sickle cell anaemia. As this disease affects predominantly populations of African origin and, in particular, those of the West Indies, this action is in connection with the Health Plan for the French Overseas Departments and Territories, published in July 2009.

A special focus is being placed on two selected actions:

- **improving the quality of care provided to overseas patients affected by sickle cell anaemia and other rare diseases;**
- **developing and improving knowledge of the said diseases.** This measure is not specific to sickle cell anaemia and fits in with the more general effort to extend access to databases, as developed by the Plan in the area of research.

In the targeted territories, each of the initiatives detailed below will receive a special attention:

- implementation of PNDSs published by the HAS on sickle cell anaemia in 2010 (called “Major sickle cell anaemia syndrome in adults” and “Major sickle cell anaemia syndromes in children and adolescents”, following the publication in 2008 of PNDS concerning patients affected by major beta-thalassemia). The impact of these PNDSs on patients care will be assessed. The results will be reported to the Steering Committee of the Plan;
- access to care will be facilitated in the French Overseas Departments and Territories, in particular thanks to the development of an appropriate telemedicine programme. The said programme will be based a video-conferencing system for medical purposes, in particular in the West Indies and Guyana, making it possible to provide care to patients affected by complex diseases and alleviate the problems that arise from patients distance from reference and regional centres;
- emphasis will be placed on therapeutic education for patients, making it possible for patients to be part of their care and management process. Development of therapeutic education programmes as formalised by the recent law called “Hospital, Patients, Health and Territories” (published in July 2009) is to be encouraged.

The National Plan for Rare Diseases can build on the reinforcement of screening for sickle cell anaemia-related complications, for which impetus was given previously by the Health Plan for the French Overseas Departments and Territories. New diagnostic resources and human resources have been granted for this purpose (in particular the West Indies and Guyana reference centre has received intracranial echography devices and erythrapheresis devices; Guadeloupe and Martinique centres have received medical and paramedical resources).

The relevant ARSs will report to the Steering Committee on this action.

Furthermore, it should be noted that the HAS will study the relevance of the extension of neonatal screening for sickle anaemia to all newborns in mainland France.

Action leader: DGOS.

Co-leaders: ARSs, DGS.

Partners: HAS, patients organisations.

A-2 Optimising Assessment and Financing Procedures for Rare Disease Reference Centres

A-2-1 Bringing forward the assessment and designation system for reference centres

Over the course of the 2005-2008 National Plan for Rare Diseases, 131 reference centres were designated. The Minister of Health approved the designation proposed by the National Advisory Commission on Labelling. Later, the designated reference centres have been subjected to an external assessment carried out by the HAS after five years, following a self-assessment after three years.

The various appraisal reports carried out on the first Plan reveal a consensus on the need, first of all, to revise and simplify the assessment process for reference centres, secondly to review the designation procedure, taking into account the possible inclusion of the centres in the future national networks. Also to be taken into consideration are the procedures resulting from a change in coordinating physician (due to transfer or retirement) and the emergence of new skills.

The overhaul of the assessment method and the designation procedure will be entrusted, from as early as 2011, to a Permanent Working Group under the Steering Committee of the Plan.

At stake, in particular, in this assessment process is the ability to assess the quality of the clinical benefits provided and to incorporate the quality of care into a continuous improvement approach. Discussion about assessment criteria may take into account factors such as:

- healthcare-related activities actually carried out by the reference centres. Indeed, these activities are not currently fully described. Even if it does call upon “traditional” indicators at times (i.e., outpatient consultations, etc.) - which are only partially suited to rare disease-related activities, this measure is also expected to draw upon systematic information-gathering using the Orphanet nomenclature as a supplementary code to tag rare diseases in the French hospital information system called PMSI (*Programme de médicalisation des systèmes d’information* – Information System Medicalization Programme);
- research activities of the reference centres, measured, for instance, on indicators reflecting scientific publication (SIGAPS, Scientific Publication Query, Management and Analysis System) and participation in clinical trials (SIGREC, Research and Clinical Trial IT and Management System), etc. A centre’s ability to provide care to a patient affected by a rare disease is directly related to its clinical research and innovation capabilities. It is thus important that the research capabilities of the reference centres and specialised laboratories be tied to their overall assessment result;
- revision of the reference centres’ scope of action.

The HAS will be mobilised on these adjustments to the assessment process and will make recommendations on the procedures it entails.

Action leader: DGOS with the Permanent Working Group for reference centre designation under the Steering Committee of the Plan.

Co-leaders: HAS, DGS, ABM.

Partners: DSS, DGRI, reference centres, patients organisations, Agency for the Assessment of Research and Higher Education (*Agence d’évaluation de la recherche et de l’enseignement supérieur*, Aeres).

Indicator: producing the new designation method.

Implementation timeline: 2011-2012.

A-2-2 Better reporting on financing allocated to rare disease reference centres

The aim of this action is to be able to better report on the funding allocated to the reference centres for their missions of expertise, assistance, coordination and research.

On one hand, the "multi-year performance and resource contracts" (*contrats pluriannuels d'objectifs et de moyens*, CPOM) signed by hospitals with the ARSs are expected to better identify the funding dedicated to the rare disease reference centres. On the other hand, the expenses committed by the hospitals will need to become the focus of an appropriate reporting system.

These data will be brought into consideration with the results of the assessment of the reference centres and may entail redistribution of available funding between them.

Action leader: DGOS.

Partners: Technical Agency on Information about Hospitalisation (*Agence technique de l'information sur l'hospitalisation*, ATIH), ARSs, reference centres

Indicator: number of additional clauses to CPOMs concluded between hospitals and ARSs.

Implementation timeline: in accordance with developments of the new assessment and designation procedures.

A-2-3 Giving due consideration to complex and multi-disciplinary visits provided by reference centres for their financing

Healthcare for patients affected by rare diseases requires complex, resource-consuming and multi-disciplinary visits. Yet the current price index of medical procedures inadequately reflects this kind of activities, despite recent developments such as severity indices.

Work is being carried out on complex and multi-disciplinary visits (excluding oncology), as part of the financing campaigns for healthcare establishments. The scope of the 2010/2011 work programme has been focused, with the aim of testing the method, on offsetting the costs in excess generated by healthcare for cystic fibrosis. It appears that the costs in excess come specifically from those multi-disciplinary visits. Consequently, the financing model for such centres could identify and take into account the specific activity related to these "complex" visits. Later, this model could be extended and adapted in structuring the endowments intended to offset the costs in excess for "complex" visits related to other rare diseases.

This action consists of:

- **finalising the current methodological work on complex and multi-disciplinary visits;**
- **auditing the implications of adopting this as standard procedure.**

Action leader: DGOS.

Partners: ATIH, ARSs, reference centres, patients organisations.

Indicator: presentation of proposals to the Steering Committee of the Plan.

Implementation timeline: 2nd Half 2010 until early-2012.

A-3 *Intensifying the Drafting of National Diagnosis and Treatment Protocols*

A-3-1 Establishing a prioritised programme for the elaboration of National Diagnosis and Treatment Protocols (PNDS)

The reference centres are in charge of drafting PNDSs. Implementing the PNDS development method proposed by the HAS during the first Plan implies looking for scientific proof and coordinating all of the parties involved. Two deliverables result from this:

- the PNDS itself, a good practice reference document to be used by the healthcare professionals providing care to patients affected by the rare disease considered,

- and a “list of procedures and services” (*liste d’actes et prestations*, LAP), which includes all of the medical products, procedures and services that appear justified in providing ambulatory care to patients and may be fully reimbursed as related to a long-term and expensive recognized disease. The LAP is drawn up by the HAS from the PNDS.

The national reference laboratory platforms dedicated to rare diseases diagnosis are furthermore in charge of developing decision-making trees describing, for each rare disease and under all circumstances, the tests required to reach the biological diagnosis (see A-1-2). The platforms are supported in this development process by the ABM. The decision-making trees may, where appropriate, be incorporated into the PNDSs.

The PNDSs are intended to improve the quality of care for patients affected by a rare disease. The drugs listed on the LAP may be fully reimbursed by the French Public Health Insurance System, by way of exemption, when used for indications other than those for which they were authorised for market sale, or when they are not reimbursable under common law, provided that they are covered by a ministerial order *(arrêté ministériel)*, as codified under Article L.162-17-2-1 of the French Social Security Code.

The reference centres, which will be structured into national networks for rare diseases, will play a decisive part in improving knowledge and professional practice, by implementing best practices.

The action is aimed at drawing up an annual prioritised list of PNDSs to be developed and the list of existing PNDSs requiring updating.

The HAS will provide methodological support to the reference centres.

Action leader: DGS.

Co-leader: DGOS.

Partners: HAS, reference centres and national networks for rare diseases, DSS, Uncam (*Union nationale des caisses d’assurance maladie*, National Confederation of Public Health Insurance Funds), patients organisations, ABM.

Indicators:

- number of PNDSs in the annual programme;
- number of decision-making trees incorporated into the PNDSs.

Implementation timeline: from 1st Half 2011.

A-3-2 Accelerating the production of National Diagnosis and Treatment Protocols (PNDS)

The PNDSs are good practice reference documents to be used by healthcare professionals.

This action is aimed at defining a simplified method for developing PNDSs, in order to speed up their production. The aim of the action is to develop 200 to 300 PNDSs over the course of the plan’s duration.

The HAS will review the PNDS development method, proposed during the first Plan, working with the reference centres and identifying factors that will simplify the PNDSs production. The following parameters will be taken into account in the new method:

- using the recommendations already developed and currently used by the rare disease reference centres, repositories of expert knowledge and scientific skill;
- incorporating and adapting the recommendations published by foreign experts to the French setting, when appropriate;
- seeking ways to simplify the PNDS updating process, in particular by revising the deadlines it implies.

The PNDSs produced through this effort will be provided via the Orphanet portal, not only for French professionals, but also for all European partners. The LAPs will be made available on the HAS web site.

Action leader: DGS.

Co-leaders: DGOS, Orphanet.

Partners: HAS, Afssaps (*Agence française de sécurité sanitaire des produits de santé*, French Health Products Safety Agency), reference centres and national networks for rare diseases, DSS, Uncam, patients organisations.

Indicators:

- a new PNDS drafting procedure provided by the HAS to the reference centres;
- the number of PNDSs produced per year;
- the number of diseases for which PNDSs are available.

Implementation timeline: from 1st Half 2011 on.

A-4 Guaranteeing the Quality of Drug-Based Care Suited to Each Rare-Disease Patient

By way of introduction, concerning the access to drugs, it is advisable to note that companies producing healthcare products, in particular drugs, intended to treat rare diseases, may apply to use the "Innobio" funds. Innobio is a fund endowed with €139 million, managed by CDC Enterprises. It is jointly underwritten by the world's leading pharmaceutical laboratories (Sanofi Aventis, GSK, Roche, Novartis, Pfizer, Lilly, Ipsen, Takeda, Boehringer-Ingelheim) operating in France. The fund's main objective is to invest directly, in equity and quasi-equity, in firms providing technological and innovative products and services in the field of healthcare. InnoBio is composed of a team of investors specialised in the sector.

A-4-1 Facilitating access to drugs

Rare diseases often require the use of drugs prescribed outsides the indications for which they were authorised for market sale, and of non-reimbursable healthcare products. Article 56 of the Public Health Insurance Financing Act in 2007, codified in Article L.162-17-2-1 of the French Social Security Code, was introduced so that such drugs could be reimbursed by French Public Health Insurance. The said Article has a dual objective:

- authorising reimbursement for drugs prescribed without respecting their marketing authorisation (MA), or non-reimbursable under common law;
- connecting the said authorisation, where necessary, to an obligation for manufacturers to conduct studies with a view toward extending the MA for this purpose, or to organise patient follow-up monitoring.

The HAS and Afssaps have instituted an investigation procedure specific to cases referred to them by the Ministry of Health, under Article 56. The procedure, currently increasing, has turned out to be relatively long and complex. As a result, a number of situations entailed patients to ask for reimbursement directly to the National Task Force on Rare Diseases, placed under the CNAMTS (*Caisse nationale d'assurance maladie des travailleurs salariés*, French National Health Insurance Fund for Salaried Workers). Once it has analysed the situation from the medical standpoint and possibly asked questions to the reference centres, the CNAMTS directs the patients to the French National Fund for Health-related and Social Action (*Fond national d'action sanitaire et sociale*, FNASS) for financial assistance.

As at end-December 2010, less than ten orders had been issued by the ministry under Article L.162-17-2-1 of the French Social Security Code. The number remains low as the procedure is relatively recent, but also because of the very complexity of its implementation by HAS and Afssaps. It emerges that, although the said Article does constitute progress as concerns funding for medical products and drugs required by patients affected by rare diseases, this assistance cannot be used in certain situations, in particular when the absence of published data on the benefits and risks of the drug does not allow the Afssaps to express its opinion on the essential nature of the said drug for the treatment of patients. This observation has been a move to improve the investigation

procedure implemented by HAS and Afssaps, so that, while remaining demanding, it becomes more productive.

The development of a prioritised programme for investigating requests for the reimbursement of drugs prescribed without respecting their MA and other non-reimbursable products, following consultation of the reference centres and national networks for rare diseases, will make it possible to draw up a list of products likely to be reimbursed under Article 56.

The prioritisation will make it possible to identify:

- the treatments for which there exist clinical data enabling the HAS and Afssaps to issue an opinion on their indispensable nature, thereby substantiating reimbursement by way of exemption;
- as to drugs used without compelling clinical data, the importance of the need (as perceived by physicians and patients) and the rationale as to benefit expected, resulting in a list of drugs presumed indispensable. This category must thereafter become part of the drugs on which it is important to increase knowledge (see A-4-4) through studies financed by the relevant industrial stakeholder where patented products are concerned, and by other sources of financing where older products are concerned. Prioritisation of the drugs and their indications is an indispensable prerequisite to begin collating clinical data.

This action comes alongside the production of PNDSs, one of the aims of which is to produce a census of the drugs and other healthcare products used in treating diseases (collated in the LAP).

Action leader: DGS.

Co-leader: DSS.

Partners: Afssaps, HAS, reference centres and national networks for rare diseases, Uncam, patients organisations.

Indicator: production of a prioritised programme.

A-4-2 Preventing the discontinuation of commercialisation

Article L. 5124-6 of the Public Health Code provides that a firm must inform Afssaps at least 6 months prior to the planned or foreseeable date on which commercialisation is to be discontinued, when the drug is used for a severe disease with no therapeutic alternative.

This action is aimed at increasing the timeframe from 6 months to one year, when dealing with drugs used in therapeutic care for patients with rare diseases and set up an intelligence system to monitor market withdrawal on the said products.

Action leader: DGS.

Co-leader: DSS.

Partners: Afssaps, HAS, reference centres and national networks for rare diseases, Uncam, patients organisations.

A-4-3 Facilitating conditions for the delivery of experimental drugs

Experimental drugs cannot, under the current regulations, be issued by dispensing chemists, thus making it necessary for patients included in clinical trials to obtain them from hospitals, even when developments in the treatment of a rare disease match a new indication of a drug already approved for market release and publicly-commercialised.

This action is aimed at enabling dispensing chemists to deliver experimental drugs to patients affected by rare diseases, when this makes it possible to simplify or improve the organisation of care or quality of service provided to a patient. In this case, an agreement concluded with the dispensing chemist sets out the responsibilities bearing upon the latter, in order to guarantee the quality and safety of pharmaceutical delivery.

The Public Health Code will need to be modified in order that dispensing chemists are able to deliver experimental drugs in specific situations, provided that they have been approved for market sale and are not listed as being reserved for hospital use alone. This modification is to be made without impairment of the existing law as regards the financing, by the promoter, of all clinical trial expenses, including the cost of the drug and, where applicable, compensation for officinal distribution. This modification will apply to Article L 5125-1 of the Public Health Code.

The DGS and Afssaps will need to carry out a specific discussion process on the package labelling for these drugs.

Action leader: DGS.

Co-leader: DSS.

Partners: Afssaps, reference centres and national networks for rare diseases, Uncam, patients organisations.

A-4-4 Improving understanding of the use of drugs

The various undertakings that will be carried out under the present Plan are:

- **firstly, identifying the uses outsides MA and planning for data collection;**
- **secondly, securing the conditions for drugs to be prescribed to hospitalised patients.**

✓ Identifying uses outsides MA and planning for data collection

This action is aimed at identifying the uses of drugs outsides their MA and of non-reimbursable products used in treating rare diseases, and planning for data collection on drug efficacy and tolerance when used in the context of temporary use permits (*autorisation temporaires d'utilisation,* ATU) and temporary therapeutic protocols (*protocoles thérapeutiques temporaires,* PTT).

Many drugs are used to treat rare diseases in situations for which they have not been approved for market sale. This use is not always well-documented and a risk cannot be precluded for the patients to whom they have been prescribed. Such use outsides MA along with the use of non-reimbursable products needs to be identified, through a joint effort with the reference centres, in order to bring to light yet-insufficiently documented situations. This identification process will then serve as a foundation for the studies to be carried out, and also possibly for intelligence activities on market withdrawals. A working group composed of representatives from Afssaps, LEEM (*Les entreprises du medicament,* French pharmaceutical industry association), reference and regional centres, patients organisations and other bodies, will be created for this purpose. It will carry out the identification of uses outsides MA, but also perform analysis of the national and international orphan drug market, thanks to the support of LEEM and Afssaps. DREES (*Direction de la recherche, des études, de l'évaluation et des statistiques,* Directorate of Research, Studies, Assessment and Statistics, in Ministry of Health) and CEPS (*Comité économique des produits de santé*, Economic Committee on Healthcare Products) will be mobilised to whatever extent needed. The working group will report annually to the Steering Committee of the Plan.

Furthermore, orphan drugs are often covered by a cohort-based or nominative ATU prior to approval for market sale. Other drugs are used to treat rare diseases, sometimes for years, under nominative ATUs. Only cohort-based ATUs are subject to a therapeutic use protocol requirement, including information-gathering, currently limited to monitoring of side effects. Data available to the health authorities on drugs used in the treatment of rare diseases are limited, due to the low number of patients. The opportunity thus needs to be taken, when drugs under ATU used in the treatment of such diseases are considered for market release, to compel manufacturers, without prejudice to the clinical trials required for market approval, to also monitor the rare disease patients treated, in order to collect data not only on tolerance, but also on efficacy in real-life conditions and data on product use procedures and the characteristics of the treated population. This information will enrich current knowledge of the products used. Products granted a cohort-based ATU by Afssaps will also entail mandatory patient monitoring, focused on tolerance and efficacy. Afssaps will request comparable monitoring for nominative ATUs.

Taking the same perspective, data collection on the tolerance and efficacy of drugs not recorded on the "usual hospital list" and used outsides MA under PTT to treat a rare disease could be instituted. This would require prior exploration by Afssaps.

The group of drugs identified as requiring more data collection needs to be extended to include those used outsides MA (in hospitals or community use) without sufficient clinical data as pointed out in the prioritisation action described in A-4-1.

Action leader: DGS.

Co-leaders: DSS, DGOS.

Partners: Afssaps, HAS, reference centre and national networks for rare diseases, DREES, patients' organisations.

- ✓ **Securing the conditions within the field of rare diseases for drugs to be prescribed to hospitalised patients**

Article L.162-22-7 of the French Public health insurance Code was modified by the Public Health Insurance Financing Act of 2009, in order to provide that financing for drugs referred to as orphan and recorded on the "non-usual hospital list" is subject to approval of the initial prescription by the reference centres and possibly the regional centres competent with respect to the rare disease addressed.

The "template" proper usage contract found in the appendix to Decree 2005-1023 of 24 August 2005 as modified furthermore provides, in its second chapter, that the initial prescription of a drug referred to as orphan by the EMA - aside from the specific instance of specialities benefiting from an ATU granted Afssaps, pursuant to Section B of Article L.5121-12 of the Public Health Code – requires a positive opinion from a reference centre competent with respect to the rare disease addressed, where such a centre exists, or from one of its regional centres.

Action is recommended to ensure that innovative and costly drugs, regardless of whether they are referred to as orphan drugs, when used in the treatment of rare diseases, be prescribed with due care when administered to hospitalised patients. This applies in particular to drugs authorised before EC Regulation 141/2000 of the European Parliament and Council of 16 December 1999 on orphan drugs came into effect. Ultimately, considering the experience gained in the hospital setting, a study will be carried out in order to determine the feasibility of extending this system to out-patients. Likewise, based upon this experience, the possibility of extending the first-time prescription system to the most complex and/or costly diagnostic tests will be considered.

Article L. 162-22-7 of the Public Health Code and appendix to Decree 2005-1023 of 24 August 2005 as modified will be adjusted to enable this.

Action leader: DGS.

Co-leaders: DSS, DGOS.

Partners: Afssaps, reference centres and national networks for rare diseases.

A-5 Developing Ties between Professionals Involved in Patient Care and in Support

The first Rare Diseases Plan and the Disabilities Act of 2005 are contemporaries. The Rare Diseases Reference Centres and the MDPH developed in parallel, but the interactions between them began only recently, to a variable extent depending on the region concerned. These interactions need to be taken into consideration as a matter of standard procedure.

Not all rare diseases result in "rare disabilities"[2]. When rare diseases have debilitating consequences, the medical-social institutional offering established under common law should be able to offer an appropriate solution.

Some rare diseases give rise to "rare disabilities" (for instance, they account for 82% of actively-treated deaf-blind and deaf-visually impaired children and adults at the "Resource Centre" for rare disabilities in Poitiers). The National Organisation Plan for Rare Disabilities published in 2009 aims at consolidating, developing and making accessible the rare multi-disciplinary expertise required to assess and support individuals and families in their daily lives, at home or in institutions. One of its principles is building up a medical-social response structure for rare disabilities, incorporating the interconnection between rare diseases and rare disabilities where they exist.

The possible areas of synergy possible between the two plans are: familiarity with rare disease situations and information provision to families and professionals, connections between reference/resource centres and medical and medical-social expertise, and response and support to assistance providers.

A-5-1 Promoting the use of complex-case managers or re-entry technicians

The aim here is to foster the creation of an integrated structure including healthcare, social care and medical-social care, so as to better coordinate care and living pathways, in particular in the most complex situations. Thus, the care and living pathways for people affected by rare diseases is marked by the contribution of many structures and multiple professionals.

Such diseases, which entail intensive treatment and heavily impact both families and society, require an interconnection between medical professionals (reference centres and regional centres, in-hospitals and community physicians, etc.), paramedical professionals (nurses, physical therapists, ergotherapists, dieticians, etc.), medical-social workers (psychologists, social workers, helpers, family helpers, etc.), and the various competent institutions at regional or local level (MDPH, CPAM[3], CCAS[4], etc.).

The social responsibilities of regional centres, in connection with their reference centres, are important in informing and coordinating healthcare pathways within the course of the life of persons living with a disability due to a rare disease. This was underlined in particular in the assessment of the first plan.

As to the most complex support situations (including patients living with a complex or rare disability due to rare disease), **an action-assessment study aimed at identifying the specific pathway coordination needs and testing the response procedures required could be carried out at the level of 2 to 3 regions.** The regional level stands out as the best choice, considering the complex situations involving reference centres and regional centres. The study would thus involve the relevant MDPHs or medical-social support services for adults (SAMSAH). It would make it possible to identify needs in terms of pathway support continuity, in order to round out, adjust and bring forward the social and medical-social services offering under common law. Moreover, in most reference centres, in particular paediatric centres, nurses or social workers play a coordination role de facto.

This action is also aimed at promoting, in the long run, this type of skill, for which a specific training offer is under preparation, either as part of an inter-university degree programme developed within a network, or as part of training programmes certified to grant Master's-level degrees.

[2] In France, a "rare disability" is defined as the coexistence of a combination of severe deficiencies (vision or hearing disability, dysphasia, severe epilepsy etc.), a prevalence of no more than 1 in 10 000 people, needs for complex care and rarity of competent professionals. A specificc plan ("National Organisation Plan for Rare Disabilities") aimed at « rare disabilities » was adopted on 27 October 2009 for the period 2009-2013. Rare diseases may cause rare disabilities, but also non-rare diseases.

[3] Health Insurance Fund at the local level

[4] Municipal Social Action Centre

Action leaders:

- promotion of integrated organisations: DGOS, DGCS, CNSA ;
- training: DGOS.

Partners: DGCS, MESR, CNSA, MDPHs, reference centres, patients organisations.

Implementation timeline: from 2012.

A-5-2 Improving and disseminating knowledge about the consequences of rare diseases in terms of disabilities and impact on the schooling and quality of living of the affected persons

This action is aimed at increasing and structuring the scientific production of information on rare disabilities and rare diseases, and their consequences in terms of disabilities (rare or otherwise), in order to better understand and provide care for the specific disabilities generated by rare diseases.

This action will be carried out in six progressive stages:

1. indexing the rare diseases in terms of disability, using the International Classification of Functioning, Disability and Health (ICF);
2. creating information sheets on rare disabilities and available care for such disabilities;
3. enriching the Orphanet patient encyclopaedia with information about the functional limitations and restrictions on being part in society generated by each rare disease;
4. incorporating an information section on rare disabilities on the Orphanet site, regardless of whether they are due to rare disease;
5. increasing the number of information sheets dedicated to rare diseases in the Integrascol portal[5];
6. including a “rare diseases” section in the training offered across the region by the National Agency for the Assessment and Quality of Social and Medical-Social Establishments and Services (ANESM), so as to spread best practices to medical-social structures.

Action leaders: DGCS, CNSA, DGS.

Co-leader: DGOS.

Partners: Orphanet, ANESM, CNSA, National Higher Training and Research Institute for Young People with Disabilities and Special Education (INSHEA), patients organisations.

Indicators:

- number of rare diseases listed with ICF;
- number of Orphanet encyclopaedia fact sheets filled out;
- number of rare disease fact sheets in the Integrascol database;
- number of rare disability fact sheets produced and disseminated.

Implementation timeline: already initiated in 2010; implementation: 1st Quarter 2012 to 2014.

A-5-3 Developing organisation modes to respond to the need for respite care for patients with rare diseases or their assistance providers

The aim here is, first, to gain a better understanding of the social and medical-social support needs of patients affected by a rare disease and, secondly, to create greater opportunity for them and their assistance providers to benefit from respite options.

[5] Information Portal for Teacher and Education Professionals working with Ill and/or Disabled Children

The first step in this process will be to gain a more precise understanding of the social and medical-social needs of patients affected by a rare disease and the capacity to respond to those needs in the region, which is not currently possible using the information systems in place.

Efforts will thus be needed in order to improve the understanding of stakeholders in the region.

- ✓ A survey led by the DGOS and CNSA, working in connection with the DGCS, addressed at rare disease reference centres, will be launched in order to identify the best action plans to step up cooperation between national rare disability resource centres and rare disease reference centres. This survey will need to involve the MDPHs as well. It ties into Action 1, under Objective 12/4 of the 2009-2013 National Plan for Rare Disabilities adopted by the Ministers in charge of Disabled Persons in November 2009.

This survey will also be the setting chosen to promote ownership in the national networks for rare diseases with respect to the new medical certificate intended for the MDPHs.

Upon completion of this survey, a good practice guide will be produced, working in step with the rare disease reference centres and rare disability national resource centres. This effort will need to take into account the fact sheets produced in connection with Orphanet (see A-5-2, and in particular the fact sheets for rare diseases, enriched with information about functional care and rare disability fact sheets). They may also give rise to a biennial conference involving the rare disease reference centres and the national resource centres for rare disabilities.

- ✓ This survey may be supplemented by information parsed from the existing database of grievances collated from users living with a disability and addressed to the MDPHs. The user satisfaction questionnaire sent out under that system consists of 35 questions, a number of which may more specifically concern people with a rare disease.

A group derived from the monitoring group dedicated to the “user satisfaction measurement” approach may be involved in processing this data regarding respondents with a rare disease.

During the second stage, it follows naturally from the common law principle that places of respite should be developed for individuals living with a disability or impaired self-sufficiency that a specific respite offer should be developed for persons with a rare disease and their assistance providers. This will require, as part of the work carried out on the regional healthcare project and the development of regional master plans, incorporating this aspect into the needs inventory.

The development of a respite offer will necessarily draw upon several areas:

- adapting the projects currently existing in the region in order to take into account the specific needs of individuals affected by a rare disease and their assistance providers;
- training for professionals;
- where applicable, the 2008-2012 Multi-Year Programme to create new places and thereby support disabled patients throughout their lives, under which it is provided that the temporary medical care offer be expanded. Out of the 590 places still to receive funding between 2011 and 2014, a 50 places target could be dedicated to 5 to 6 temporary medical care units in order to cover, at the inter-regional level, the temporary support needs expressed by the patients and their assistance providers. These places will need to be planned and approved pursuant to common law;
- in all events, a coordination and support effort by the healthcare sector will be needed in the medical-social area.

Action leaders: DGCS, CNSA.

Co-leaders: DGOS, DGS.

Partners: patients organisations, reference centres, rare disability resource centres, MDPHs, ARS.

Indicator: number of respite places available to patients affected by a rare disease, specifically opened through project creation or adaptation.

Implementation timeline: 2012-2014.

A-5-4 Defining a risk prevention and support system specifically geared toward assistance providers

- ✓ **Defining a reference base listing the prevention and support requirements of assistance providers**

The role of assistance providers when rare diseases are involved differs from that of a chronic illness setting, in that the complexity of the care required makes numerous appointments a necessity, in particular appointments far from the home.

This is an area in which associations have the perspective and concrete experience that make it possible to effectively identify the support which carers need.

Support for family members caring for persons affected by debilitating disease is one of the DGCS's priorities. This entails, first of all, ensuring that services and professionals capable of providing support and care are available, and furthermore that they meet the necessary proximity, continuity, flexibility, quality and cost criteria. In this sense, when diagnosing needs and planning the services to be offered as well as subsequent adjustments therein, the requirements and expectations of care providers are also to be taken into account. It is the responsibility of the ARSs to devise "regional medical-social organisation plans", addressing the issue through two systems: planning for the development of day and temporary stay spots; and the development of respite platforms and carer support.

As regards financing, the ARSs will become the secondary order issuers to the CNSA on Section IV funding not covered by national-level agreements. They will thus, in connection with the "regional directorates for youth, sport and social cohesion" (DRJCS) and the general councils, steer the regional deployment plan for a coordinated set of training and professionalization actions geared at employees of establishments and services operating directly with individuals who have become disabled due to a rare disease, modernisation and structuring actions for home assistance services and support and training actions for carers (Art 78, 2011 LFSS).

The Steering Committee of the Plan and the patients organisations will thus be entrusted with responsibility for defining a reference base on the prevention and support needs of patient care providers.

Action leader: Steering Committee of the Plan.

Co-leaders: DGCS, CNSA, DGOS, ARSs.

Partners: Patients organisations.

Indicator: successful production of reference base by the Steering Committee Working Group.

Implementation timeline: 2012.

A-6 Improving Healthcare Professionals Practices

A-6-1 Assessing the contributions of new professions to rare disease

From as early as the first plan, the importance of new responsibilities had become clear, sometimes forming entirely new professions, such as advisors in genetics, or other areas such as biostatisticians and healthcare coordinators. For certain professionals, this translated into the inevitable need to develop new areas of expertise or delegate certain tasks. The lack of a civil service corps specific to the hospital sector did not hinder the recruitment or, more frequently, the identification of professionals capable of taking on the relevant responsibilities, though the setting varied considerably from one establishment to the next.

The action is aimed at taking stock of these new professions and/or new skills, and in-depth analysis of the benefits provided. This action will need to be carried out in close conjunction with that pertaining to complex disease managers or re-entry technicians.

Action leader: DGOS.

Partners: DREES, DGCS, representatives of healthcare professionals, patients organisations.

Implementation timeline: 1st Half 2012.

A-6-2 Building knowledge in healthcare and social sector professionals about rare diseases

- ✓ **Initial training for healthcare professionals about rare diseases and orphan drugs**

Under the first Rare Diseases Plan, the theme of rare diseases had been incorporated into the exam preparation programme for the nationwide graduation and ranking exam taken by all medical school students. In addition, optional "rare disease" modules, which make it possible to effectively highlight the multi-disciplinary aspect of care, have been developed in certain medical schools. Each so-called "rare" health issue is addressed in the paramedical training institutes, as part of the coursework on the broad disciplines to which the disease treated belongs. While this topic is not necessarily the focus of a distinct teaching unit as such, the issue of rare diseases is potentially addressed in its specificity within public health teaching and in each paramedical training institute.

This action is aimed at:

- **producing a circular addressed to all paramedical training institutes in order to reiterate that the public health teaching modules must be regularly adjusted and take into account the major priorities of public health, in particular as materialised by the plans underway;**
- **adopting the same approach to medical and pharmaceutical training, during the revision of legislation on training content with a view toward integrating the Bachelor-Master-Doctorate (LMD) degree course. The public health modules will similarly need to adapt to national priorities, without entailing constant changes to the curricula.**

These adjustments, purely instructional in nature, are in line with the total instructional independence granted to the university Training and Research Units (UFR) in healthcare.

Action leader: DGOS.

Co-leader: DGS.

Partners: ARSs, DGCS, higher education, schools of medicine, training institutes, professional schools, training bodies, rare disease reference centres.

Indicators:

- number of medical schools offering education on rare diseases;
- number of schools/training bodies with plans to provide reference points on rare diseases.

Implementation timeline: 1st Half 2011.

- ✓ **Raising awareness in social work professionals about rare diseases and orphan drugs**

It is important to complete the action carried out under the 2009-2013 National Organisation Plan for Rare Disabilities which is aimed at making information about the consequences of disabilities due to rare diseases available to families, professionals and teachers.

The aim is to develop information during initial training for future social work professionals.

The national strategic objectives for social sector training, currently being finalised, will make mention of the importance of training bodies' (whether initial or continuing training) taking into account the resource or reference centres (autism, rare diseases, etc.) toward the implementation of such training in actual teaching. The benefit of multi-professional modules must be emphasised. The reference bases on initial training are sufficiently broad in scope that the employment situation of social workers can be adapted through continuing training, in agreement with the employers. The framework agreements concluded in 2008 between the State, CNSA and accredited fund collecting and distributing agencies with responsibility for continuing training are all factors conducive to continuing training on rare diseases for professionals of the medical-social services.

This action will need to be interconnected with the action conducted under the 2009-2013 National Organisation Plan for Rare Disabilities, which states the aspiration to hold each two years a

conference supported by the CNSA to gather the national resource centres on rare disabilities and relevant rare disease reference centres in order to pool their knowledge and experience gained over the course of their missions.

Action leader: DGCS.

A-6-3 Making use of continuing vocational development to update the knowledge of healthcare professionals about rare diseases

Article 59 of the 21 July 2009 Law called "Hospital, Patients, Health and Territories" establishes the requirement to ensure continuing vocational development for each professional. National strategic objectives on continuing vocational development are set out by the Minister of Health, based on proposals specified by the professionals themselves.

This action is aimed at encouraging the development of systems and programmes specific to continuing vocational development for the healthcare professionals involved in care for rare diseases.

Action leader: DGOS.

Co-leader: DGS.

Partners: ARSs, higher education, schools of medicine, training institutes, professional schools, training bodies, rare disease reference centres.

Implementation timeline: 1st Half 2012.

A-6-4 Developing and disseminating good practice recommendations on emergency situations resulting from rare diseases

The "Healthcare and Emergency Cards" and "Orphanet Emergency" fact sheets are two supplementary tools for improving emergency care for patients affected by a rare disease.

The healthcare and emergency cards are developed under the aegis of the DGS by the reference centres and patient associations. They contain the patients' personal medical information as filled out by the physician from the rare diseases reference centre following the patient. As such, they are a key component of healthcare coordination. They also contain more general information about care (in French and in English) for use by the professionals, as well as an information section on the said rare disease for non-professionals (the patient, the family, the teaching personnel, etc.). Between 2006 and 2009, 22 such cards were disseminated via the reference centres and patients associations.

The assessment, carried out in 2010, shows that the cards could be simplified, in which case they could also be issued in larger numbers and produced in conjunction with the "Orphanet Emergency" fact sheets.

The "Orphanet Emergency" fact sheets are produced for emergency care professionals. They are drafted by the reference centres and supplemented by the patients associations, under the coordination of Orphanet. A steering committee identified an initial list of rare diseases for which fact sheets are necessary. Production of these fact sheets began in late-2007. To date, 35 fact sheets are online in French on the Orphanet site.

This action is aimed at:

- **increasing the number of diseases for which the healthcare and emergency cards and "Orphanet Emergency" fact sheets are available;**
- **organising joint production of cards and fact sheets;**
- **optimising the cards distribution channel.**

Ultimately, the possible integration of the aforementioned information into each patient's personal medical records is to be considered.

Action leader: DGS.

Co-leader: DGOS.

Partners: Orphanet, HAS, reference centres and national networks for rare diseases, ABM, patients organisations.

Indicator: number of new diseases covered by a card or an equivalent, and by an “Orphanet Emergency” fact sheet.

Implementation timeline: from as early as 1st Half 2011.

A-6-5 Promoting the production of digital teaching modules

A federation of higher education establishments joined forces to form a national public interest consortium in 2003. Its purpose is to implement information and communications technologies in medical schools, for both initial and continuing training. Its main responsibilities are to produce document resources for use as a supplement to the courses provided to medical school students. More than thirty digital campuses specific to the field are open online.

This action is aimed at encouraging universities with specialist expertise on rare diseases to response to the consortium’s call for projects in order to produce digital teaching modules about rare diseases for specialist physicians and to promote them.

Action leader: DGS.

Partners: Inter-University Federation for French-Language Virtual Medical Instruction, rare disease reference centres, Orphanet, the National Conference of Deans of Schools of Medicine, and the Conference of University Presidents.

A-7 Making Information Accessible and Disseminating It

A-7-1 Organising an annual national communication initiative on rare diseases

As a supplement to the communication initiatives carried out by rare disease associations including the Telethon, **the aim is to develop a national communication initiative that can fit into the European Day for Rare Diseases (now international) on 28 or 29 February each year.**

It is designed in particular to:

- create awareness of rare diseases and care orginisation;
- promoting the activities of Orphanet and "Maladies Rares Info Services", resource structures to disseminate information about rare diseases in France;
- promoting healthcare cards and emergency fact sheets as well.

Action leader: Ministry of Health (Directorate for information)

Co-leaders: DGS, DGOS.

Partners: Orphanet, “Maladies Rares Info Services”, reference centres, patients organisations.

Implementation timeline: 28 February 2011, then annually on 28 or 29 February.

A-7-2 Promoting “Maladies Rares Info Services" as the single telephone information helpline on rare diseases

“Maladies Rares Info Services" is a personalised information helpline about rare diseases, offered by phone (0810 63 19 20, price of a local call from a landline) and by e-mail, via its website www.maladiesraresinfo.org. It takes part in the project to reorganise remote healthcare assistance, which is aimed at optimising the accessibility and quality of the service provided to the public, by sharing certain tools. It makes it possible to provide information tailored to the demand and situation of patients and their families, by recording their needs and expectations. It draws upon the “Rare Diseases Platform” (see C-1-3) and is also supported by the French Association against Myopathies (AFM).

This action is aimed at promoting the system as a reference information helpline and encouraging its participation in the European project on Telephone assistance services for rare diseases.

The current financing provided by INPES (*Institut national de promotion et d'éducation pour la santé*, French Institute for Health Promotion and Health Education) could change in order to guarantee continued accessibility and the quality of services provided.

Action leader: DGS.

Partners: INPES, "Maladies Rares Info Services", patients organisations.

Indicator: number of calls to "Maladies Rares Info Services" per year.

Implementation timeline: 1st Half 2012.

A-7-3 Disseminating information to patients and primary care physicians

The healthcare and social care systems, services and assistance, financial aid and reimbursements provided to patients, in particular those affected by rare diseases, require an information provision effort.

The actions to be carried out include:

- **stepping up the provision of information to primary care physicians and raising their awareness about the organisation instituted in France under the first National Plan for Rare Diseases;**
- **stepping up the provision of information to patients affected by rare diseases.**

✓ Stepping up the provision of information to primary care physicians and raising their awareness about the organisation instituted in France under the first National Plan

This action is aimed at disseminating information suited to general practitioners about the issue of rare diseases and the organisation already in place, in particular when one of their patients has been diagnosed with a rare disease.

Information sharing needs to promote standard procedure between the physician from the reference centre and the primary care physician, in particular when the former draws up the initial protocol and the second extends it to allow the patient to benefit from specific rights provided under national public health assurance fund in case of long-term chronic health condition (ALD, *Affection de longue durée*).

This information from the reference centre to the primary care physician will have to be supported by general information documents such as:

- the name of his counterparts at the reference centres;
- the healthcare and emergency card or "Orphanet Emergency" fact sheets;
- the PNDS and/or other recommendations.

Furthermore, the aim is to raise awareness in primary care physicians about existing resources, in particular the "Rare Diseases Unit" at the CNAMTS and the "Aid and Services for patients affected by rare diseases" book published by Orphanet.

Action leader: DGS.

Partners: Orphanet, reference centres, patients organisations, continuing vocational development bodies.

Implementation timeline: action initiated in 2010.

✓ Stepping up information to patients affected by rare disease

There is already a great deal of information aimed at patients, whether from associations, Orphanet or about financing (see the French Public Health Insurance System's website Ameli).

Orphanet's patient encyclopaedia currently covers some one hundred rare diseases. It records over 40,000 document downloads per month. Yet the information effort needs to be kept up: it helps relieve patients' isolation, puts them in a position to better manage their disease and relations with healthcare professionals and can have a positive effect on diagnostic delay.

For the patients, the aim is to:

- provide them and their families with clear and straight-forward information describing the aid and programmes existent, by extending the Orphanet patient encyclopaedia written in partnership with the reference centres and patients associations;
- make them familiar with the resources to which they can address their questions about rights and aid, or which they can view online, in particular by updating and disseminating the Orphanet's book "Aid and Services for patients affected by rare diseases".

Action leader: DGS.

Co-leaders: DGCS, DSS, CNSA.

Partners: Orphanet, patients organisations, rare disease reference centres, MDPHs, French Public Health Insurance Systems.

A-8 Orphanet: An Information and Research Tool

A-8-1 Gradually integrating the Orphanet nomenclature into the existing French databases

This action is aimed at:

- **completing the nomenclature used for PMSI, drawing upon that of Orphanet;**
- **developing the identification of rare diseases in the various healthcare information systems;**
- **using the data gathered through this process in the said computerised information systems in order to document the mortality and morbidity of rare diseases (hospitalisation, drugs, etc.).**

✓ Completing the nomenclature used for PMSI to code rare diseases

The aim here is to use the Orphanet nomenclature to improve general understanding of patients' care pathway.

Until such time as ICD-11 comes into being (see C1-1 Supporting the Identification of Rare Diseases), it is proposed that a form be adopted to supplement the PMSI information gathering form ("fichcomp file"), in order to inform the diagnostic process when a rare disease patient receives care, regardless of the conditions and cause of care. Initially, the area explored would include short-duration hospital care (in medical, surgical, obstetric departments) in hospitals with reference and regional centres.

The "fichcomp file" contains several information areas. One of them deals with "diagnostic analysis for survey purposes". The "survey" area would be used to collect "rare disease" information in the form of four variables, which the establishments are already accustomed to providing. These include:

- the FINESS number (establishment's legal code);
- the type of service provided (using code 99 for the rare disease survey);
- the number identifying the stay (this number is already listed on the outgoing standardised summary, and is thus customarily provided);
- the diagnostic code using the Orphanet nomenclature.

Action leader: DGOS.

Co-leaders: ATIH, Orphanet.

- ✓ **Developing the identification of rare diseases in the various healthcare information systems**

The aim here is not only to take into account the Orphanet nomenclature for the BNDMR, as well as for the PMSI data, as well as those of the CepiDC (Centre for Epidemiology on the Medical Causes of Death), Public Health Insurance System and medical-social databanks.

Action Leader: DGOS, DG.

Co-leaders: ATIH, Orphanet.

Partners: BNDMR, UNCAM (National Confederation of Public Health Insurance Funds), CNSA, CepiDc, InVS.

- ✓ **Using the data gathered through this process in the said computerised information systems in order to document the mortality and morbidity of rare diseases (hospitalisation, drugs, etc.)**

The aforementioned rare disease identification initiatives will make it possible to continue work on the production of rare disease indicators, and in particular to inform the indicators on the 2004 Public Health Policy Act.

Action leader: DGS, DGOS.

Partners: CepiDc, InVS, DREES, ATIH, Orphanet, UNCAM (National Confederation of Public Health Insurance Funds), CNSA, BNDMR.

A-8-2 Developing Orphanet's content and ergonomics

Orphanet, a INSERM's service unit, is the reference portal for documentation and information about rare diseases and orphan drugs, whether in France or in Europe, and increasingly at the international level. It is the focus of a joint effort on the part of all 27 EU Member States.

This action is aimed at:

- **continuing to enrich the database (Orphanet professional and patient encyclopaedias, information about professionals and associations, etc.);**
- **improving the accessibility of the latest data on rare diseases for patients, the general public, healthcare professionals, researchers, industrial stakeholders and decision-makers;**
- **making the Orphanet nomenclature freely available;**
- **including an information section in Orphanet about rare disabilities, regardless of whether they are due to rare diseases.**

Preparations for a new edition of the Orphanet directory, aimed at hospital wards, maternal and child welfare and independent practitioners will begin.

Action leader: DGS.

Co-leaders: DGRI, DGCS.

Partners: DGOS, DAEI, UE, CNSA.

Indicators:
- number of articles published online at the Orphanet website;
- number of booklets published and/or updated by Orphanet.

Implementation timeline: 1st Half 2011.

Focused Action: Supporting the Action of Rare Disease Patients Organisations

The organisations for patients affected by a rare disease have managed to secure a place for rare diseases as a public health issue. They started out by raising awareness in the general public, carrying out support and information initiatives for families and patients, set up information, sharing and training systems, and put together support, therapeutic education and research projects.

Today, these organisations are partners to the public authorities and hospital establishments (reference centres, in particular).

Taking into account the number of organisations involved, priority is given to support for the federations. However, it is possible to identify innovative projects that are in need of support (needs assessment surveys, mediation activities, drafting and dissemination of documents for use by patients and their families, participation in patient education projects or support actions under the 21 July 2009 Law “Hospital, Patients, Health and Territories”) and to allocate them financing on the basis of calls for projects, carried out by the DGS.

Action leader: DGS.

Partners: reference centres, “Rare Disease Platform” participants, Cospro.

Indicators:

- number of national meetings;;
- number of innovative projects selected;
- number of international meetings
- initiatives carried out by patients organisations (under agreements with DGS).

Implementation timeline: initiatives initiated from as early as 2010.

AREA OF ACTION B. Developing Research on Rare Diseases

The essential issues at stake in the research to be carried out during the 2011-2014 Rare Diseases Plan include: creating a structure that can be used to coordinate research on rare diseases; drawing upon relevant databases; saving and gradually putting to use the tissue, cell or DNA banks which exist; fostering the development of cell and animal models for rare disease; improving the access of research teams to technological platforms; and developing public-private partnerships, in particular for therapeutic research.

As pertains to the "Developing Research" area of the second National Plan, it should be underscored that most financing remains conditional on the selection of research teams following their response to specific calls for projects.

This area will be executed through the 4 measures listed below, in turn detailed into 10 actions:

- creating a national structure for giving impetus to research, in interface with public and private stakeholders;
- promoting tools that can be used to increase knowledge of rare diseases;
- promoting the development of therapeutic trials;
- fostering clinical and translational therapeutic research.

B-1 Creating a National Structure to Give Impetus to Research, Interfacing with Public and Private stakeholders

One difficulty found in research on rare diseases is due to the small number of dedicated federating structures and their lack of coordination. The result of this situation is a lack of visibility as to potential financing sources, whether for a disease or a given group of diseases, or for an innovative approach. Furthermore, this gives rise to difficulties in accessing the technological platforms in particular, when they are increasingly vital to competitive research. This stems from the fact that today's new research approaches require special expertise and equipment, which can sometimes only be gained via national platforms.

B-1-1 Assuring the transition of the Rare Diseases Institute-Scientific Interest Consortium into a "Foundation for Rare Diseases" housed in a "Healthcare" Scientific Cooperation Foundation

This partnership-based foundation will mobilise all stakeholders (public, industrial, associations) within a coordination structure that will make it possible to set out shared strategic thrusts. The structure will be responsible for such aspects as ensuring the continuity the action already being run by the Rare Diseases Institute-Scientific Interest Consortium (*GIS-Institut Maladies Rares,* GIS-IMR) and accelerate these efforts. The GIS-IMR, working with its institutional partners, previously established and managed a range of annual calls for bids, aimed at research on rare diseases. It initiated "cross-cutting" action aimed at assisting the rare diseases research community to gain access to technological platforms, and is coordinating the call for bids "E-rare" funded, via the French National Research Agency (*Agence national de la recherche,* ANR), by the EU Member States taking part in the initiative. However, the interface between industry and the academic stakeholders in the field of rare disease needs to be improved, following the efforts underway (LEEM, competitive clusters, Healthcare Industries Strategic Board, LIR, etc.). The creation of a "Foundation for Rare Diseases" will make it possible to coordinate the development of tools and services aimed at improving knowledge in the field of rare diseases and speeding up the development of therapies.

Focused action: The Foundation for Rare Diseases

The “Foundation for Rare Diseases” will be housed within an umbrella scientific cooperation foundation dedicated to “Healthcare”. The housed Foundation will be created by an agreement signed by the umbrella foundation for “Healthcare” and one or more founders of the Foundation for Rare Diseases. The Agreement makes provisions in particular on the purpose of the housed Foundation, its name, structure and functioning, relations with the umbrella foundation and rules for wind-down.

The housed foundation will be structured around a decision-making body, including representatives of founders, as well as qualified personalities appointed by the latter. It may also include other parties subject to the rules set out by the umbrella foundation and the founders’ wishes. The decision-making body will include one representative of the umbrella foundation, responsible for ensuring that there is due compliance with the agreement. One or more advisory bodies may also be created.

The prime purpose of creating a Foundation for Rare Diseases is to structure and harmonise the different initiatives undertaken in the field of research on rare diseases, by coordinating and inter-connecting the missions of the GIS-IMR, the BNDMR and Orphanet. The Foundation’s aim is to develop and federate the expertise instituted through the currently-existing structures dedicated to databases for (clinical and therapeutic) research purposes and for information (the Orphanet portal). Other specific structures are destined to join the foundation, such as OrphanDev, a structured focused on methodological and regulatory assistance in designing and coordinating clinical trials on rare diseases. Furthermore, the Foundation will be responsible for identifying research needs dedicated to the human and social sciences in the field of rare diseases and provide incentive measures for the relevant teams in the area, in order to structure the said research in connection with patients associations and the social and human sciences community.

The Foundation will also be responsible for ensuring that progress in research, which remains relatively fragmented and laborious, is quickly transferred to the patients. Once the various players involved in research on rare diseases are coordinated within a foundation structure, real added value will be able to emerge, with the flow of a “continuum” of expertise vital to the development of research on such diseases. This continuum will be required to incorporate action ranging from fundamental and clinical research to assistance in designing and carrying out clinical trials. The creation of the Foundation will also be an asset in terms of “readability”, in particular for industrial partners. The Foundation will also aim to develop information about rare diseases, research underway in France, Europe and internationally, as well as on financing opportunities.

Such a structure will obviously contribute to building recognition for and promoting the varied and complementary types of existent expertise, a pre-requisite for effective and competitive research.

This will be made possible thanks to the support and backing of the various public research bodies already involved in research on rare diseases, and in particular INSERM, CNRS (*Centre national de la recherche scientifique*, National Centre for Scientific Research), universities and hospitals. The Foundation will serve as a “national contact point” for all researchers, healthcare professionals, industrial players and, of course, patients associations involved (first and foremost, the AFM and the French Rare Diseases Alliance). Through its project federating, facilitating and financing action, and through its visibility across the nation and Europe, the Foundation’s objective will be to strive to secure over the long term the research resources to fight against rare diseases, and will make it possible to very concretely establish rare diseases as a full-fledged public health issue.

In conclusion, the Foundation for Rare Diseases will be responsible for: bringing together and federating research skills, facilitating access to national technological platforms, creating synergies that foster the emergence of appropriate therapies, developing partnerships with industry, and financing projects in connection with the resource agencies, national research structures in place (ANR) and DGOS as for the PHRC (*Programme hospitalier de recherche clinique*, Hospital Clinical Research Programme). The Foundation’s responsibilities will proceed in coordination with the actions set out below (B-2), some of which it will lead.

Action leaders: the Foundation for Rare Diseases will enjoy the backing of themed multi-body institutes (ITMO), the National Alliance for Life Sciences and Health (AVIESAN) and in particular the Institute for Genetics, Genomics and Bioinformatics and Institute for Cellular Biology, Evolution and Development.

Partners: the founding members of the Foundation, currently being defined (INSERM, CNRS, AFM, the French Rare Diseases Alliance, universities, CHU, competitive clusters, industrial stakeholders, etc.).

Indicators:

- creation of the Foundation;
- establishment of governance;
- definition of a five-year strategic plan.

Implementation timeline: creation of Foundation for Rare Diseases planned for 2011

B-2 Promoting the Tools Conducive to Greater Understanding of Rare Diseases and Incorporating a Minimum Funding Level for Research on Rare Diseases into ANR Programmes

The scientific community has underscored the importance of ensuring that the ANR's programmes guarantee a minimum funding level for rare diseases. It has also determined a number of priorities, namely: structuring biological sample archiving, developing animal and cell models, and supporting interaction between research and hospital platforms by improving access to national technological research platforms for research projects on rare diseases.

B-2-1 Guaranteeing a minimum funding level for research on rare diseases in ANR programmes

Over the course of the first Rare Diseases Plan, the existence of special calls for projects, managed by the GIS-IMR and ANR (2004-2008), considerably fostered the development of fundamental research, improved relations between clinicians and researchers, and clearly-readable quality levels in French research teams working on this topic from the perspective of international onlookers. This excellence is confirmed by the fact that the transformation of the special call for projects (GENOPATH), in 2008, into a call for projects on rare diseases and frequent diseases did not lead to a decrease in the subsidies allocated to rare diseases; financing for research projects on rare diseases increased, to the contrary. In 2010, the rare diseases teams took part in a "blank-slate" call for tenders and, though it is too early to confirm this trend, it is likely that the quality of the teams selected will once again guarantee a positive trend in terms of financing. Nonetheless, it is very important that a minimum level of funding dedicated to rare diseases be secured in ANR programmes and to annually review the funds allocated to this focus area. This undertaking will make it possible to very clearly show the benefit of research on rare diseases at the national government level and stimulate industrials and private partners to become involved.

Action leaders: ANR, in connection with AVIESAN and the Foundation for Rare Diseases.

Indicators:

- number of projects submitted;
- number of projects financed.

Implementation timeline: ANR 2011 call for projects.

B-2-2 Optimising data collection and biological sample archiving, drawing upon existing collections

The availability of patient cohort data and related biological collections is fundamental to all research on rare diseases as well as to therapeutic trials. This information is currently very widely-scattered across a variety of structures and coordination has turned out essential. Collections need to be managed in line with the existing regulations, with a quality assurance approach for sample management, storage and distribution. One of the aims is to make these collections available for subsequent analysis (microchips, NGS, functional analysis, etc.). It is important to ensure that they can be securely maintained over the long term. A connection with the national network of "biological resource centres" (CRB) needs to be carried out in order to optimise the procedures.

Action leaders: INSERM with the relevant ITMOs, in connection with the Foundation for Rare Diseases

Indicator: number and quality of samples taken and available for genotyping studies

Implementation timeline: BNDMR involvement in Rare Diseases Foundation activities in 2011

B-2-3 Developing cell and animal models

Preclinical studies adapted to the therapeutic strategy being developed must without exception be carried out prior to clinical trials in order to assess the efficacy and possible toxicity of the compounds or biotherapies being considered. The resulting experimental data must be in compliance with standards compatible with those of the regulatory authorities when reviewing applications for clinical trial approval. Cell models may, in particular, be created from human stem cells. Animal models must be able to be generated as new genes are identified and new physiopathological avenues in rare diseases come to light. The animals must remain accessible to the experimenter and be protected from possible pathogens and risks inherent in certain biotherapies. The GIS-IMR has, since 2003, run calls for projects on access to murine models, which will need to be coordinated by the future Foundation for Rare Diseases along with the other calls for tender. The development of these models needs to be encouraged and sped up, and national research infrastructures for functional exploration need to develop their services and technologies in order to be able to address this need.

Action leaders: Foundation for Rare Diseases in connection with AVIESAN, through the relevant ITMOs.

Indicators:

- number of projects submitted;
- number of projects financed.

Implementation timeline: calls for projects launched in 2011.

B-2-4 Fostering access to sequencing platforms for research teams

It is important that ties between the national reference laboratory platforms for diagnosis (see Action A-1-2) and the research platforms be strengthened. The related coordination effort could be carried out through the Foundation for Rare Diseases. It will also be necessary to facilitate the access of research teams to NGS platforms (“exome sequencing”-type projects, for instance); this type of project could be covered by European and/or private service providers. At the current time, the most expensive equipment and related staff are mobilised primarily for studies on frequent diseases. Projects concerning rare diseases must also have access to and benefit from these technological facilities.

Action leaders: Foundation for Rare Diseases, in connection with ANR and AVIESAN

Indicators:

- number of projects submitted;
- number of projects financed.

Implementation timeline: calls for projects launched in 2011.

B-3 Promoting the Development of Therapeutic Trials

B-3-1 Developing therapeutic research (pre-clinical and Phases I/II) in cooperation with the pharmaceutical industry

Therapeutic research on rare diseases is limited by the low number of patients affected. Access to registries and national or even international cohorts are essential if clinical trials are considered. In addition, the small number of affected patients limits the interest of industrial stakeholders in such diseases. It is essential to be able to use new drugs specifically designed to treat rare diseases (orphan drugs) and drugs available in treating frequent diseases (the indications of which may deserve to be reviewed so as to later be approved for broader market use) regardless of how long they have been available for sale. Major progresses in pharmacological approaches have been made possible in this manner, in particular thanks to a better understanding of physiopathological mechanisms. Namely, a variety of metabolic diseases benefit from substitute enzyme treatments.

Therapeutic research can also be carried out under non-drug programmes (cell therapy, plasma exchanges, etc.) and engineering programmes using innovative technologies. The encouraging results of gene therapy in treating rare diseases of genetic origin have opened up a very promising field of investigation. More and more frequently, a combination of various approaches is considered in treating rare diseases, in particular the most severe (gene therapy combined with cell therapy, gene therapy and pharmacological therapy), in order to improve therapeutic efficacy. It is thus vital that the number of trials relating to innovative therapies and more traditional therapeutic paths (molecules used in non-AMM indications or without AMM). The Foundation for Rare Diseases will help involve industrial partners and thereby fund such trials. The Foundation will also make it possible to foster cooperation with the AFM already financing trials.

It is essential that a continuum be achieved between fundamental research to "proof of concept" and on to clinical research, whether within the projects themselves or as concerns their funding, in particular in the intermediate stages, covering bioproduction, toxicity studies and pre-clinical approvals. The DGOS finances therapeutic studies via the PHRC, but ANR/PHRC interactions need to be stepped up, in particular to secure the connection between fundamental research and clinical trials. Such interaction is essential in the field of rare diseases, so as to enable early trials on biotherapy, innovative therapy or drugs in non-AMM indication.

It is proposed that the Interministerial Group for Research and Innovation (GIMRI), which is to be set up at the Ministry of Research in 2011, arrange, along with the ANR and DGOS and drawing upon international benchmarking, a clarification effort so as to prevent ambiguity or flaws in the project financing system. This will make it possible to optimise the use of the funds granted, guaranteeing that they have enabled financing for the best projects and that the full range of disciplines to be mobilised is effectively covered.

Action leaders: Foundation for Rare Diseases in connection with ANR, DGOS and AVIESAN.

Partner: AFM.

Indicator: number of Phase I/II pre-clinical and clinical trials funded.

B-4 Fostering Translational Research

While the first National Rare Diseases Plan did foster ties between fundamental scientists and clinicians, interaction between the two needs to be optimised in order to improve the essential "continuum" between fundamental and clinical research.

B-4-1 Identifying the clinical investigation centres involved in therapeutic trials on rare diseases, fostering relations with the reference centres

The Clinical Investigation Centres (*Centres d'investigation Clinique*, CICs) are clinical research infrastructures made available to investigators (biologists, researchers and clinicians), based in the university hospitals in order to foster the development of excellence in translational research. Action must be taken to facilitate interaction between the reference and regional centres and the CICs, under specific therapeutic protocols and as part of a possible partnership with industrial stakeholders, in order to secure technical support and share skills.

Action leaders: INSERM and DGOS in connection with the Foundation for Rare Diseases

B-4-2 Developing research projects on rare diseases in the human and social sciences

The current understanding of quality of living in patients affected by rare disease is limited. This information is important for patients, but also in terms of public health, so as to estimate the impact of these diseases on the everyday lives of patients and those around them, and from the economic standpoint. Yet rare diseases are little-known or not known at all to the social science research teams already in place. The reference centres are all located in university hospital complexes, interfacing with other university teams. The hospital wards are often called upon to host various

students for internships, from universities or healthcare observatories. It must be possible to interest young researchers in rare diseases.

The Foundation for Rare Diseases also needs to foster inter-disciplinary collaboration (epidemiology, sociology, psychology, healthcare economics, etc.), by encouraging university teams from the reference centres to become involved in the studies, in partnership with specialised teams. It is planned the Foundation will post a list of the research structures working in the field for this purpose.

This action is aimed in particular at offering research fellowships (Master's, PhD and post-doctoral) for work carried out jointly by the reference centres and social sciences teams. This action is also aimed at promoting and triggering dialogue between the scientific communities (biomedical and social and human sciences), in order to stir the development of research joint programmes.

Action leaders: Foundations for Rare Diseases in connection with AVIESAN, in particular the Public Health ITMO, the National Alliance for the Human and Social Sciences (ATHENA) and DGS.

Partners: patients organisations.

B-4-3 Developing within the Foundation a blog to enable swift interaction between experts

The therapeutic trials underway, in particular those dealing with existing drugs for non-AMM use, are not adequately inventoried and the trials with negative results are not always submitted or accepted for publication. As a result, much valuable information is lost to the scientific and medical community, in particular as concerns side effects or the efficacy of potential therapy. In addition, information sharing between the national and European expert centres working on the same diseases is sometimes inadequate in this field. The creation of a blog, coordinated by the Foundation for Rare Diseases, will make it possible for physicians to quickly report their experimental findings on the potential benefits or risks of a therapeutic approach to the scientific community.

Action leader: Foundation for rare Diseases

Co-leader: Afssaps.

Partners: patients organisations.

Appendix: Research News (*Investissements d'Avenir*)
Fostering the Development of Patient Cohorts: the RADICO (*RAre DIsease COhorts*) Project

Research in the field of rare diseases implies a multi-disciplinary approach involving clinicians and clinical, genetic, physiopathological, therapeutic and human and social science research teams, as well as patients associations. The very large number of such diseases (several thousand), their heterogeneity, the difficulties inherent in gathering phenotype information and biological material (due to the rarity of these diseases, the scattering of information, the uneven resources currently dedicated to each disease) and the limited investments made by drug industry skateholders in this field make a specific effort to be carried out over the long term and coordinated action a vital necessity.

The RADICO project was selected subsequent to the call for cohort projects "*Investissements d'Avenir"*. The main purpose of this programme, which considerably builds structure at the national level, is to form rare disease patients cohorts (in the epidemiological sense of the term). The project, which is expected to include over 250,000 patients in France, is based on the creation of a rare diseases platform designed to unite existing strengths on the field: 131 reference centres, 501 regional centres, molecular diagnosis laboratories, CRBs in connection with research laboratories, technological platforms and patient associations. This platform, which will in particular be responsible for collecting the data necessary for epidemiological and public health studies, is expected to stimulate the emergence of clinical and translational research programmes in the field of rare diseases, all the while anticipating future needs, such as the integration of data from "omics" approaches and systems biology.

Action leaders: INSERM with the relevant ITMOs, in connection with the Foundation for Rare Diseases

Indicators:
- institution of patients cohort coordination;
- inclusion of first patient;
- number of patients included and monitored in the cohorts, number and quality of samples taken and available for genotyping studies

Implementation timeline: BNDMR involvement in the Foundation for Rare Diseases in 2011 and implementation of the RADICO project platform thereafter.

AREA OF ACTION C. Amplifying European and International Cooperation

Due to the limited number of patients for each rare disease and the rarity of expertise itself, France has always pleaded for a European approach to this issue.

A number of pioneering initiatives have been taken by the French authorities at the level of the EU:

- regarding orphan drugs: under its previous Presidency of the European Union in 2000, Regulation 141/2000 dated 16/12/1999 of the European Parliament and Council on Orphan Drugs was launched;
- increasing information about rare diseases, via the development of the Orphanet database;
- support for cooperation between Member States as regards financing for research on rare diseases, through the ERA-NET project, "E-Rare";
- the "European Reference Networks" on rare diseases where France used to run the European Commission's working group;
- the European clinical research infrastructure "ECRIN", (*European Clinical Research Infrastructures Network),* which benefits first and foremost rare diseases, by supporting multinational clinical studies, initiated and coordinated by France;

The European Commission's European policy has recently been shaped by:

- the European Commission's final communication COMM (2008) 679 of 11 November 2008 on "Rare Diseases: Europe's Challenge" (COM 2008 679) which sets out a Community strategy designed to assist Member States in the fields of diagnosis, treatment and care for the EU's 36 million citizens affected by such diseases;
- the Council Recommendation on an action in the field of rare diseases of 8 June 2009;
- the creation of the European Union Committee of Experts on Rare Diseases (EUCERD), which met for the first time in December 2010;
- the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare (approved by the European Parliament on 19 January 2011) applies both to rare diseases and the European Reference Networks.

France supports the objectives of the communication, "Rare Diseases: Europe's Challenge" and intends to play an active part in the EUCERD.

Moreover, in 1997, four French associations (AFM-Téléthon, Vaincre la mucoviscidose, Aides, Ligue nationale contre le cancer) were founding members of the European Organisation for Rare Diseases, "EURORDIS - *Rare Diseases Europe*", to which over 430 patients organisations belonged across 43 countries in 2011.

European cooperation must contribute to bringing together the expertise, experience and limited resources available for rare diseases. It must facilitate contact between patients and professionals from the different Member States, knowledge- and information-sharing, as well as coordination, by networking the various countries' expertise centres and the use of "online health" technologies.

For over 10 years, France's policy on rare diseases has been based on European and international cooperation. It intends to continue on this path in the years to come.

This part of the Plan will be executed in three measures, in turn detailed in 8 actions.

C-1 Promoting the Sharing of Expertise at the International Level via European Reference Networks

C-1-1 Supporting the development of rare disease coding in all information systems

This action is aimed at giving visibility to rare diseases in the healthcare information systems of Member States by promoting an appropriate coding system (Orphanet nomenclature) and the production of common indicators.

Rare diseases cannot be traced in national healthcare information systems, due to the lack of specific codes for most of them. Orphanet has developed a specific coding system combined with a polyhierarchy code structure. This system serves as the model for developing the next version of the WHO International Classification of Diseases scheduled to be issued in 2014 (ICD-11). Furthermore, the Orphanet nomenclature is interfaced with other international coding systems, such as SNOMED-CT, MeSH and MedDRA.

France, thanks to its first National Plan, has enabled the development of a rare disease coding system of international standard. The aim now is to establish it in France's healthcare information systems, as well as to promote its adoption internationally, in particular in the other EU Member States, until the adoption of ICD-11, which is expected to include a code for all rare diseases.

To achieve this, a free download service specific to the Orphanet nomenclature and related codes in other international nomenclatures will be launched, in order to ensure optimal dissemination in a user-friendly manner.

Action leader: Orphanet.

Co-leaders: DGS, DAEI.

Partners: reference centres.

Indicators:

- number of countries using the Orphanet nomenclature in their information systems;
- number of nomenclature downloads, including all institutions.

Implementation timeline: 2011.

C-1-2 Promoting improved communication, information-dissemination and expertise-sharing across Europe and internationally

The Orphanet portal is an information dissemination tool, used in France as well as in over 30 European countries. The Orphanet portal is intended to become international in scope, to optimise the initial investments released by France so that as many users as possible could benefit. This will require promoting translation of the site, the disease database and the encyclopaedia into new languages, beyond the five languages currently available, through agreements with countries wishing to offer their citizens information in their national language(s). This will also come through the extension of information collection on expert services (consultation, diagnosis laboratories, registries, bio-banks, clinical trials, patients organisations) and on new countries, beyond the current 36 countries participating.

The benefit and feasibility of a European toll-free number dedicated to rare diseases will be considered with the support of INPES, DGS, European Commission and Eurordis.

The experience-sharing activities between patient associations in Europe and the South, structured into association federations by disease or into rare disease alliances, need to be supported.

The same applies to collaboration between teaching staffs at the European level.

Lastly, efforts will need to be made to enable, to the greatest extent possible, the participation of French national networks for rare diseases and European association federations in the European Reference Networks of centres of expertise and/or contribute to their creation and development, and help the French experts wishing to form such networks to develop their projects and manage them. Expertise-sharing will be facilitated through the development of ICT tools (information and communication technologies).

Action leader: DGS.

Co-leaders: DGOS, Orphanet, European Commission, INPES.

Partners: reference centres and national networks for rare diseases, patients organisations.

Indicators:

- number of European countries using the toll-free number (116) and number of calls shared by "Maladies Rares Info Services" with other countries;
- number of French national networks and associations involved in European Reference Networks;
- number of online rare disease patient communities.

Implementation timeline: 2011.

C-1-3 Continuing support for the operation and international renown of the "Rare Diseases Platform"

The "Rare Diseases Platform" was created under the impetus of the AFM in order to foster interaction between patients associations, healthcare professionals and public stakeholders. It combines in one building: Eurordis, the French Rare Diseases Alliance, AFM, Orphanet, "Maladies Rares Info Services" and the GIS-IMR (in the future, the Foundation for Rare Diseases). The various components of the platform are independent, both in legal status and financial resources, but the synergies generated by their physical combination have made it possible to reciprocally become more familiar with their respective actions and enabled the emergence of a shared dynamic. The main provider of funds for the Rare Diseases Platform and its various players is AFM (except for Orphanet).

The aim of the action is to continue to provide support to a structure that has demonstrated its efficacy at the national level, as well as its added value at the European and international levels.

An action plan designed to strengthen the synergies, international renown and service offering at the Platform level, for all rare disease stakeholders will need to be discussed consistent with the funding provided.

Action leader: DGS.

Partners: French Rare Diseases Alliance, AFM, Foundation for Rare Diseases, "Maladies Rares Info Services", INSERM, Orphanet, Eurordis, European Commission.

Implementation timeline: 2011.

C-2 Improving Capacity to Carry out Multinational Clinical Trials, Access to the Diagnostic Tests Available at the European Level and Test Quality Control

C-2-1 Consolidating ECRIN as a tool for developing observational and interventional studies

ECRIN (*European Clinical Research Infrastructures Network*) is the European clinical research infrastructure designed to facilitate multinational clinical studies, which is of particular importance with rare diseases, enabling recruitment at the EU level. ECRIN is one of the infrastructures on the European research infrastructure roadmap outlined in the ESFRI (*European Strategy Forum on Research Infrastructures*) and, following funding of the 7th Framework Programme for Research and Development (FP7), will in 2011 take on the shape of an international organisation with ERIC (*European Research Infrastructure Consortium*) status, the long-term future of which is guaranteed by the financial contributions of its Member States. Orphanet and Eurordis are historical partners of ECRIN, including in this new development stage.

ECRIN is based on the interconnection of national clinical research network coordinating bodies (in France, the network of CICs). It currently covers 14 countries (most in Western Europe) and is extending gradually toward Central European countries.

This action is aimed at assessing the contribution of the ECRIN system to research on rare diseases.

The action is composed of the following stages:

- assessing the opportunities to step up the contribution of ECRIN in the field of rare diseases, in particular through its contribution to the structuring of clinical research on rare diseases at the European level;
- stepping up support to ECRIN;
- producing an annual activity report for ECRIN on its action in the field of rare diseases.

The Healthcare Priority under the FP7 now makes it possible to fund multinational academic clinical trials, and ECRIN's participation can be an asset in such projects.

Action leader: DGRI.

Co-leader: DAEI.

Partners: networks of CICs, Orphandev-Eurobiomed, DGCIS, DGS, DGOS, patients organisations, reference centres and national networks for rare diseases, researchers, pharmaceutical industry, competitiveness hubs, LEEM.

Indicators: they will be defined in connection with the ECRIN's annual activity report.

Implementation timeline: 2012 to 2014.

C-2-2 Pooling and standardising diagnostic test practices at the European level

Biological diagnosis of rare diseases is often based on tests carried out by a very small number of laboratories in Europe, thus requiring cross-border cooperation. This situation undeniably creates problems as regards financing for the tests carried out, medical liability and compliance with national regulations, which continue diverging considerably in Europe.

At the European level, European laboratory networks have developed to stabilise the external quality control tools and structure (e.g.: the "EuroGenTest" network, which currently structures cooperation in performing quality control checks on tests with a genetic component).

This action is aimed at bringing together and structuring into a community system expertise developed at the level of each country in the field of rare diseases, so that all of the tests required for diagnosis and monitoring available in Europe can be offered, and so that the said tests can be carried out under optimal conditions, with concern for quality of their results and rationalised healthcare expenditure.

The national reference laboratory platforms for diagnosis and Orphanet are the main players in finalising and updating the decision-making trees used across all required media, and widespread dissemination thereof.

This action is composed of the following steps:

- supporting the development of the Orphanet-EuroGenTest database, which provides access to information about European expertise and quality standards in the laboratories carrying out tests for rare diseases;
- identifying the foreign reference laboratories with which to work in cooperation for exploration that cannot be carried out in France;
- promoting the formation of a European working group on regulatory issues connected with the practice of cross-border biology within the EUCERD.

Action leader: DGRI**.**

Co-leader: DGOS.

Partners: ABM, HAS, reference centres, national reference laboratory platforms for diagnosis, patients organisations, Orphanet-EuroGenTest, EUCERD.

Indicators:

- number of decision-making trees published;
- number of partnerships with foreign reference laboratories.

Implementation timeline: 2011.

C-3 Improving Access to Diagnosis, Healthcare and Patient Care, Research and Information on Rare Diseases, by Structuring European and International Cooperation

The initiatives developed in this measure fall in step with the revised texts on pharmacovigilance published in the Official Journal of European Union on 31/12/2010.

C-3-1 Continuing and improving support for the collection, archiving, duplication and networking of biological samples

The biological collections maintained by the various structures continue to be very widely-scattered. It is vital that patient samples be grouped together so as to create collections of biological samples related to rare diseases. At the French level, the coordination of CRBs accessible to research, the harmonisation of procedures and the standardisation of storage techniques is coordinated within the CRBs national network, supported by INSERM. This network forms the French component of the European "*Biobanking and Biomolecular Resources Research Infrastructure*" (BBMRI) Project.

The collection, archiving, duplication and networking of biological samples relating to rare diseases not only form the foundation for the studies aimed at identifying their cellular and/or molecular bases, but can also sometimes make it possible to identify patients who can benefit from inclusion in specific therapeutic trials.

The CRBs thus emerge as important in the field of rare diseases and thus must be able to rely on a structure that enables medical diagnosis and scientific research.

The aim of this action is thus to continue to provide support to the CRBs (existing and to come), guarantee the security of "rare diseases" collections, and enable their structuring in CRBs national networks specialised in rare diseases, with a view toward shared management of organisational and legal aspects.

This action falls in step with both the CRBs' national network project and the European plan to institute a biobank and bimolecular resource infrastructure (BBMRI), coordinated by Austria, for which INSERM serves as leader on the French side. This project will make it possible to share expertise and knowledge, harmonise quality practices in collection, storage and analysis, in particular IT-related, and define an ethical and financial reference framework.

It should be noted that the future BNDMR will be able to benefit from the harmonisation of practices and methodological, technical, legal and regulatory recommendations on the collection of biological rare disease samples discussed in the working groups set up these past 3 years by BBMRI.

This action is composed of the following stages:

- defining the specifications for the CRBs and the 4 to 6 storage centres that will be part of the national reference laboratory platforms for diagnosis, in agreement with the BBMRI specifications and the CRBs national network;
- assessing needs and securing financial support (to be specified) for the operation and networking of the CRBs, in the rare diseases sector.

Action leaders: DGRI and DGOS.

Partners: learned societies, Steering Committee of the Plan, national networks for rare diseases, patients organisations.

Indicators:

- number of recommendations for the implementation of the diagnostic tests published;
- number of partnerships with foreign reference laboratories.

Implementation timeline: 2011 and 2012.

C-3-2 Assisting and supporting the research role of rare disease reference centres, including at the European level

Assessment of the 2005-2008 National Plan showed that certain reference centres had substantive experience with computerised monitoring of patient cohorts, therapeutic trials and connections with fundamental research. However, the necessity has emerged for a research support and training structure on rare diseases, providing advice on the elaboration and implementation of public or private research projects, including European projects;

Action leader: DGRI and Foundations for Rare Diseases.

Co-leader: DAEI.

Partners: reference centres.

Indicator: number of requests addressed for advice or assistance to the support and training structure in charge of rare diseases.

Implementation timeline: from 2011.

C-3-3 Contributing to the funding and long-term consolidation of the E-Rare Project

Cross-border research about rare diseases is currently conducted at the EU level thanks to funding for collaborative and multi-disciplinary research projects provided under the “Healthcare” axis of FP7 and ERA-Net “E-Rare” (FP6).

The ERA-Net “E-Rare” initiative is coordinated by France (INSERM – GIS IMR) and brings together 8 European partners (Germany, Belgium, Spain, France, Italy, Israel, the Netherlands and Turkey). The E-Rare-2 Project (2010-2014) will include 4 additional partners (Austria, Greece, Poland and Portugal).

“E-Rare” is a European initiative under which French researchers can develop partnerships through trans-national research projects on rare diseases, and promote them at the EU level. Since 2007, E-Rare is an essential tool for the creation of themed rare disease networks at the European level.

The objectives of this action are thus to:

- **support, through the ANR, funding for French research teams involved in the research projects launched by E-Rare-2;**
- **ensure stakeholder participation in European meetings contributing to the definition of research policies on rare diseases;**
- **promoting the E-Rare network to the EUCERD.**

Looking ahead to FP8, this action could also include the promotion of a third E-Rare project (2015-2019).

Action leaders: DGRI, ANR.

Co-leader: DGS.

Partners: DGOS, AVIESAN, national networks for rare diseases, academic researchers, industrial stakeholders, patients organisations.

Indicators:

- number of projects selected/year;
- number of projects involving French researchers/total number of projects funded;
- total amount of funding granted to national teams/total budget.

Implementation timeline: from 2011.

GOVERNANCE OF THE PLAN

The 2011-2014 French National Rare Diseases Plan is monitored in accordance with the procedures outlined in the "Recommendations for the Development, Monitoring and Assessment of Public Health Plans" issued by the General Directorate for Health (December 2009), and adapted to its specificities. It takes into account the assessment findings relevant to the previous plan, in particular the "Assessment of the 2005-2008 National Rare Diseases Plan", issued by the French High Council on Public Health (HCSP).

Monitoring takes place primarily through:

- a Steering Committee, chaired by the Director General in charge of Healthcare Provision, which has been put in charge of strategic steering of the Plan;
- a Secretary General in charge of implementing the Plan;
- interaction with the ARSs.

1. The Steering Committee

This committee has a major part to play in strategic decision-making assistance. It follows the implementation of the measures and actions set out in the Plan and, where necessary, propose adjustments to the Plan during the course of execution. By no means immutable, the measures and actions described in the Plan may to the contrary be modified when necessary, hence the necessity for a precise reporting on the monitoring results to an authority with the power to decide on such changes.

1.1 Missions

The Steering Committee is the body:

1°) to which monitoring results of the implementation of the Plan are presented. Results must be presented at least twice annually, not only to ensure due execution of the measures set out in the Plan, but also in order that proposals for possible adjustments be made during the course of the Plan, when necessary;

2°) vested with the authority to propose structural policy orientations to the Ministries.

More specifically, the Steering Committee is responsible for:

- monitoring the implementation of the French Second National Rare Diseases Plan and the programmes resulting from it;
- establishing the "permanent working group" in charge of proposing a new labelling methodology for reference centres
- establishing working groups on the following themes:
    - determining the number and scope of the future national networks for rare diseases,
    - national reference laboratory platforms for diagnosis,
    - data available on orphan drugs;
- establishing any other working group, as required by ongoing developments;
- proposing to Ministers corrective measures and actions that become necessary as the Plan is executed or in light of the planned mid-term assessment report. The relevant measures might address, for instance, the care strategy for patients affected by rare diseases, as well as the structuring of their care pathway, or the strengthening of research, training, information or epidemiological surveillance;
- proposing themes on which the High Council on Public Health (HCSP), the National Institute for Health and Medical Research (INSERM) and the National Authority for Health (HAS) could called upon to provide their expertise on steering the care system for patients with rare diseases;

- conducting surveillance work on new diagnosis and prevention methods, as well as on patient treatment and care.

1.2 Organisation

The chair of this inter-ministerial committee is entrusted to the **Director General for Healthcare Provision,** who must have the power to mobilise all of the national administrations and national and regional agencies involved in implementing the measures set out under the Plan. He is replaced by the **Director General for Health** whenever necessary.

Two scientific vice-presidents, respectively in charge of Research and Health, have been appointed. They guarantee that the initiatives carried out in their respective areas of responsibility are effectively coordinated and consistent with one another. They can ask the chair to include any points they see as of particular importance on the Committee's agenda.

The scientific vice-president in charge of Health:

- works in close coordination with the vice-president in charge of Research and the Secretary General of the Plan;
- reports on his/her action to the Committee;
- guarantees the scientific quality of the actions carried out in Health area under the Plan.

The scientific vice-president in charge of Health is responsible for:

- providing his/her expertise on specific health issues and, in particular, those relating to the quality of care for patients affected by rare diseases;
- managing the work of the Committee on the quality of care for patients affected by rare diseases and any working group the Committee may entrust to him/her.

In particular, the vice-president steers the working group on the "Labelling Methodology for Reference Centres". This working group is a permanent body operating throughout the plan's duration. It meets regularly, at least 4 times per year. Its purpose is to:

- make proposals to the Committee so as to improve the assessment procedure currently entrusted to the HAS, in coordination with the AERES;
- draw upon the results of the assessment steered by HAS to propose recommendations regarding reference centre labelling.

The scientific vice-president in charge of Research:

- works in close coordination with the vice-president in charge of Health and the Secretary General of the Plan;
- reports on his/her action to the Committee;
- guarantees the scientific quality of the actions carried out in Research arera under the Plan.

The scientific vice-president in charge of Research is responsible for:

- ensuring strategic consistency between Research actions of the Plan;
- ensuring smooth coordination between the research stakeholders working on rare diseases (Foundation for Rare Diseases, AVIESAN, ANR and others), taking into account new knowledge and organisation at the national, European and international levels;
- refining assessment of research activity carried out by the reference centres.

1.3 Composition of the Committee

The broad composition of the Committee was designed to ensure that all rare diseases stakeholders are adequately represented:

- patients associations;
- professionals who are part of patient care and research;
- health agencies, scientific authorities and research organisations;
- administrative directorates of the involved Ministries.

2. Secretary General

The Secretary General's mandate is set out in an inter-ministerial engagement letter. He/She works in close cooperation with the President of the Steering Committee and the scientific vice-presidents in charge of "Health" and "Research", to whom he reports.

His/her responsibilities include:

- monitoring and operationally implementing the measures and actions set out in the Plan (at the national and regional level);
- consolidating France's exemplary role in the field of rare diseases with the European authorities;
- identifying the difficulties associated with implementing measures under the Plan and proposing initiatives to remedy them;
- contributing to drafting the plan's annual report;
- ensuring that information is communicated and exchanged with representatives from Ministries, authorities (health agencies, HAS, INSERM, etc.), professionals and associations representing patients by meeting them regularly.

For this purpose:

- he/she has access to all information of use to his/her mission;
- he/she takes the appropriate initiatives for due implementation of the plan;
- he/she participates in and reports to the Steering Committee, to which he/she can propose to organise specific working groups.

The Secretary General fulfils his/her missions with the help of a dedicated team in the Division "Steering of Healthcare Performance" under the General Directorate for Healthcare Provision (DGOS). Working meetings are held regularly between the Secretary General and this operational team. Financial monitoring for the Plan is also the responsibility of the said Division. In this Division, the "Healthcare Quality and Safety" Office (PF2) is allocated a part-time plan manager and a 60%-time project manager, both dedicated solely to the National Rare Diseases Plan.

3. Regional Health Agencies (ARSs)

The structures created under the two successive National Plans, like the reference centres or national reference laboratory platforms, are not intended primarily for the purpose of covering the territory effectively, but rather fostering excellence and recognised expertise at the national, European and international levels.

At the same time, the National Plans are designed to facilitate access to healthcare and harmonise care provision, which has a particular importance in regional steering. Moreover, the future national networks formed by reference centres will be responsible for establishing close ties with all the structures in the medical and social sector which, like the Local-Level Centres for Disabled People (*Maisons Départementales des Personnes Handicapées*, MDPH), are all anchored territorially.

The responsibilities assigned to the ARSs were defined to foster:

- a better matching between the medical-social care supply and the needs of patients affected by rare diseases outside the healthcare field;
- a better support for patients affected by rare diseases and a better coordination of the professionals from the various sectors acting around them.

While these issues are not specific to rare diseases, they do take on particular importance in light of the serial misdiagnosis or diagnostic delays too often suffered by the patients, and the difficulties that arise in administrative procedures and in directing both the patients and their family to the appropriate structures or care providers, when the said diseases are so complex and rare.

The ARSs are also responsible for supporting implementation and monitoring of:

- therapeutic education programmes developed by the reference centres;
- telemedicine programmes;

- generally speaking, national health policy objectives.

Toward this end, specific missions relating to rare diseases will be identified by each ARS. Each ARS will take care to:

- identify an operational project leader so as to guarantee quality discussion with the national level, in particular in establishing the various regional initiatives, monitoring the objectives assigned to the structures, and coordinating between the healthcare and medical-social sectors;
- provide a rapid and appropriate response to the possible difficulties that can arise in implementing the said initiatives at the local level, in particular on financial coverage for care, where relations with the network of Local Public Health Insurance Offices are of major importance;
- facilitate interaction with the reference centres and the regional centres or other healthcare professionals involved.

In order to take into account the various types of ARS structuring, the responsibilities relating to rare diseases, which are ultimately to be entrusted more to medical personnel, can be pooled with the response to needs identified in other types of care for rare and complex diseases (rare cancers, CVA in children, early Alzheimer's Disease, etc.).

The ARSs will be made aware of the specific problems in care or interconnection between health and medical-social sectors, which professionals dealing with patients affected by rare diseases can face. The ARSs will work, in connection with the patients associations and professionals, to provide them with appropriate solutions, within the scope of their general responsibilities. Current pilot experiments, such as the Regional Information and Orientation Platform " PRIOR" - the aim of which is to support patients affected by rare diseases along their healthcare pathway, to help families and patients, and to inform the medical and medico-social community – may help ARSs finding regional solutions for rare diseases.

LIST OF ACRONYMS

ABM	French Biomedicine Agency
DNA	Deoxyribonucleic acid
AERES	Agency for the Assessment of Research and Higher Education
AFDPHE	French Association for Screening and Prevention of Child Disabilities
AFM	French Association against Myopathies
AFSSAPS	French Health Products Safety Agency
ALD	Long-term chronic health condition
AMM	Marketing authorisation
AMR	Rare Diseases Alliance
ANESM	National Agency for the Assessment and Quality of Social and Medical-Social Establishments and Services
ANPGM	National Association of Molecular Genetics Practitioners
ANR	National Agency for Research
APHP	Public Hospitals of Paris
ARC	Clinical research assistant
ARS	Regional Health Agency
ASIP	Agency for Shared Healthcare Information Systems
ATHENA	National Alliance for Human and Social Sciences
ATIH	Technical Information Agency about Hospitalisation
ATU	Temporary use authorisation
AVIESAN	National Alliance for Life Sciences and Health
BBMRI	*Biobanking and Biomolecular Resources Research Infrastructure*
BNDMR	National Rare Diseases Databank
CCAS	Municipal social action centre
CepiDC	Centre for Epidemiology on the Medical Causes of Death
CEPS	Economic Committee on Healthcare Products
CGH	Comparative Genomic Hybridization
CHU	University Hospital
CIC	Clinical Investigation Centre
CIF	*International Classification on Functioning, Disabilities and Health*
CNAMTS	French National Health Insurance Fund for Salaried Worker
CNIL	Commission on Information Technology and Liberties
CNRS	National Centre for Scientific Research
CNSA	National Solidarity Fund for Autonomy
CPAM	Local Public Health Insurance Funds
CRB	Biological Resource Centre
DAEI	Directorate of European and International Affairs (under French Social Ministries)
DG SANCO	*Directorate General of Health and Consumer Protection, under the European Commission*
DGCIS	Directorate General for Competitiveness, Industry and Services (under French Ministry of Industry)

DGCS	General Directorate for Social Cohesion (under French Ministry of Social Affairs)
DGOS	General Directorate for Healthcare Provision (under Ministry of Health)
DGRI	General Directorate for Research and Innovation (under French Ministry of Higher Education and Research)
DGS	General Directorate of Health (under French Ministry of Health)
DICOM	Delegation on Information and Communication (under French Social Ministries))
DOM	Overseas Administrative Unit
DPI	Pre-implantation Diagnosis
DREES	Directorate of Research, Studies, Assessment and Statistics (under French Ministry of Health)
DSS	Directorate of Social Security (under French Ministry of Health)
ECRIN	*European Clinical Research Infrastructures Network*
ESFRI	*European Strategy Forum on Research Infrastructures*
EUCERD	*European Union Committee of Experts on Rare Diseases*
EURORDIS	*European Organisation for Rare Diseases*
FNASS	National Health and Social Fund
GIS-IMR	Rare Diseases Institute-Scientific Interest Consortium
HAS	French National Authority for Health
ICD-10	Version 10 of the International Classification of Diseases
ICD-11	Version 11 of the International Classification of Diseases
INPES	French Institute for Health Promotion and Health Education
INSERM	French National Institute of Health and Medical Research
INVS	French Institute for Public Health Surveillance
ITMO	Thematic Institutes at INSERM
ITMO-SP	Thematic Institute on Public Health at INSERM
LAP	List of procedures and services
LEEM	French pharmaceutical industry association
LFSS	Public Health Insurance Financing Act
LIR	International research laboratories
MDPH	Local-Level Centres for Disabled People (local-level services for evaluation of loss of autonomy and special benefits allowance for disabled people)
MESR	French Ministry of Higher Education and Research
WHO	World Health Organization
Orphanet	Information portal on rare diseases and orphan drugs
FP7	Framework Programme on Research and Development
PHRC	Hospital Clinical Research Programme
PMSI	Information System Medicalization Programme
PNDS	National Diagnosis and Treatment Protocol for Rare Disease
PTT	Temporary Treatment Protocol
SAMSAH	Medical-social Support Services for Adults
SIGAPS	Scientific Publication Query, Management and Analysis System
SIGREC	Research and Clinical Trial IT and Management System
UNCAM	National Confederation of Public Health Insurance Funds