



**RECOMMENDATIONS  
FOR THE DEVELOPMENT OF NATIONAL PLANS FOR RARE DISEASES  
GUIDANCE DOCUMENT**

**Final Draft  
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## RECOMMENDATIONS FOR THE DEVELOPMENT OF NATIONAL PLANS FOR RARE DISEASES GUIDANCE DOCUMENT

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## PART I - INTRODUCTION

### 1. Background on Rare Diseases

#### **Council Recommendation (2009/C 151/02)**

*“Rare diseases are a threat to the health of EU citizens, in so far as they are life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Despite their rarity, there are so many different types of rare diseases that millions of people are affected.”*

1. Rare diseases are life threatening or chronically debilitating conditions affecting no more than 5 in 10 000 people. The field of rare diseases is vast and complex and characterized by specific problems and needs which have been reported and explained in several important European documents, such as the *“Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions” on Rare Diseases: Europe’s Challenges*, published the 11 Nov 2008, and the *Council Recommendation of 8 June 2009 on an action in the field of rare diseases*.

In particular these documents have underlined the facts that:

- although every single disease is rare, it is estimated that between 5000 and 8000 rare diseases have been described, affecting about 6% to 8% of the population in the course of their lives, for a total number of people ranging between 27 and 36 million in the EU. About 80% of rare diseases have a genetic origin. The life expectancy of patients with rare diseases is significantly reduced. Many of these conditions are complex, severe, degenerative and chronically debilitating, whilst others are compatible with a normal life, if diagnosed in time and managed properly;
- rare diseases affect physical and/or mental abilities, behavioural and sensorial capacities, and generate disabilities. Several disabilities often coexist, with many functional consequences. These disabilities might be a source of discrimination and reduce educational, professional and social opportunities;
- health professionals often have insufficient knowledge of rare diseases, which may delay the diagnosis and the provision of appropriate care;
- early diagnosis and follow-up require expert medical competence. However, if diseases are rare, experts are rare as well;
- due to the situation of scarce visibility to most health care systems, diagnostic delay, and inappropriate treatment, patients with rare diseases are subjected to isolation and social exclusion.

2. EU member states have in place genetic services and health policies for disability and for the medical and social need of children. Patients with rare diseases may have in some cases the characteristics (e.g. severity, clinical complexity) to benefit from the provisions by these services and policies. However, the aforementioned European documents indicate that the lack of initiatives and health policies specifically targeted to

rare diseases result in delayed diagnosis and difficult access to treatment and care. This leads to additional physical, psychological and intellectual impairment, lack of prevention and inadequate social services or even harmful treatment.

3. The focus on rare diseases and the recognition of the fact that rare diseases have common issues in a public health perspective and require specifically targeted policies is a relatively new achievement in most EU member states. There is at present great variability among countries about the type of services provided to rare disease patients and the accessibility to these services. This is due to the fact that some countries started studying and implementing measures some years ago, other countries started the process only very recently, and other countries have not started yet. This gives a varied panorama in terms of how patients with rare diseases can be diagnosed and followed, with great inequalities across Europe. Citizens from different member states and even from different regions in the same member state have, at present, unequal access to expert services, drugs especially developed for rare diseases, the so called orphan drugs, diagnosis and rehabilitation. Moreover, most member states share common problems of lack of knowledge and expertise in this field.

4. The work done in the past years at European level in the field of rare diseases and the experience of those countries, where public health initiatives for rare diseases exist, have shown that a global and specific national approach and European collaboration and common development of solutions are the key elements to improve health care (and social care) of patients with rare diseases. The creation of specific plans or strategies at national level has been seen as a high priority in both the aforementioned Commission Communication and Council Recommendation and such importance has been confirmed by the Impact Assessment Working Staff Document accompanying the Council Recommendation document: *'within the member states, there is fragmentation of the limited resources available for rare diseases, thus it is essential to have a specific plan to concentrate and make efficient use of these resources* (SEC(2008) 2713 final, 11.11.2008 - <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=SEC:2008:2713:FIN:EN:DOC>).

## 2. Background on the EUROPLAN Project

5. The European Project for Rare Diseases National Plans Development (EUROPLAN), a three-year project of the Programme of Community action in the field of Public Health (2003 - 2008) has the task to elaborate documents to facilitate the establishment and implementation of National Plans or Strategies, as stated in the Council Recommendation of the 8<sup>th</sup> of June 2009 on an action in the field of rare diseases. Such plans or strategies are recommended to be established and implemented “*preferably by the end of 2013*”. The health authorities of the 27 EU member states (MS) signed the document, stating their willingness to fulfil this deadline.

6. Thirty partners from different countries and the European patients’ umbrella organization EURORDIS participate in EUROPLAN, with the coordination of the National Centre for Rare Diseases, Italian National Institute of Health (Istituto Superiore di Sanità, Italy). The project ensures an inclusive and broad engagement of stakeholders, including health care authorities and health care policy makers, health care professionals, researchers and patients.

7. A core group of EUROPLAN partners prepared the first draft of this document, which has been extensively discussed in several meetings with different stakeholders involved in the field of rare diseases. The final draft modified according to the inputs received in these meetings has been submitted to an informal consultation of experts from the EU health authorities. The final draft is being revised according to the comments received and the resulting final document will be agreed at a workshop with the health authorities (to be held in Krakow on 13 May 2010). The final document will be presented at conferences organized by EURORDIS in Bulgaria, Croatia, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands, Romania, Spain, Sweden, United Kingdom, and possibly also in Poland. During these National Conferences, local stakeholders will discuss the EUROPLAN recommendations and the main elements of the EU strategy on rare diseases, with the aim to assess their transferability in their respective Countries. The comments arising in the conferences will be recorded and attached as annexes to the final document.

## 3. What does ‘Recommendations’ mean in the context of this document

8. The Council Recommendation of 8<sup>th</sup> of June 2009 on action in the field of rare diseases states that EUROPLAN has the task to develop ‘guidelines and recommendations’. During the meetings for the preparation of the present document there has been vivid discussion on the meaning of the word ‘Recommendations’ in this context. It has been agreed that Recommendations are to be meant as ‘guidance’ for the development of National Plans and Strategies, implementing the contents of the main European documents on rare diseases and in particular the aforementioned Council Recommendation. Great importance has also been given to their use as a ‘toolbox’, in relation to the fact that the EUROPLAN recommendations provide a set of ‘tools and examples’ of how activities for rare diseases can be organized at national (and European) level. In fact, the actions

recommended in this document will be implemented and developed differently in different member states, based on the organisation of the national health and social system, on the population size of the country, on the availability of expertise in the field of rare diseases, on the integration with already existing initiatives and on budget issues.

9. We are aware of the fact that several countries have already a tradition of good practices in specific health policy aspects of rare diseases and, in other countries, National Plans or Strategies are being prepared at the same time as we are writing the present document. The EUROPLAN Recommendations do not aim at substituting the initiatives that exist or are spontaneously arising in those countries, but rather at providing instruments for a reflection on the key elements of action for rare diseases that have been identified in several years of European work and reported in the European documents as the most relevant to improve the situation for rare diseases in a country.

10. In accordance with the general aims of EUROPLAN, the present document containing EUROPLAN Recommendations is intended as a tool to guide national efforts for rare diseases and to make them compatible with a common strategy at European level, facilitating the coherence of national initiatives with the main issues and good practices identified in this field, and preparing the ground for possible synergies and cooperative approaches as desirable to improve the provision of health care to rare disease patients in the EU member states.

11. The target users of the present document are policy makers and other stakeholders involved in planning interventions or, more specifically, plans or strategies for rare diseases in their own country.

#### 4. EUROPLAN definition of National Plans and Strategies

12. A National Plan or Strategy can be defined as *a set of integrated and comprehensive health and social policy actions for rare diseases, to be developed and implemented at national level, and characterized by identified objectives to be achieved within a specified timeframe*. The allocation of appropriate resources (e.g. human, financial, infrastructural) for the development of the National Plan or Strategy and its monitoring and evaluation are of special value to ensure the efficacy of the plan or strategy.

The aforementioned definition of a national plan or strategy includes two main concepts of the Council Recommendations of the 8<sup>th</sup> of June 2009 on an action in the field of rare diseases.

*Integrated* refers to the fact that strategies should be developed in a way to identify complementarities, maximize synergies and avoid duplications.

*Comprehensive* refers to the fact that the actions foreseen in the plan should fulfil the main patients' needs (e.g. quality of care but also social services). In order to appropriately address patients' needs, a plan or strategy, which aims at achieving maximum impact from the planned actions, cannot be limited to one single area, as several areas are linked and support each other.



## **PART II – DESCRIPTION OF AREAS, ACTIONS AND EUROPLAN RECOMMENDATIONS**

13. In this part of the document, the areas and actions published in the Council Recommendations are discussed based on the experience in health care planning for rare diseases of the EUROPLAN core group and the experts participating in the different meetings and consultations organised by the EUROPLAN project.

14. To facilitate legibility of the actions recommended by EUROPLAN, this document follows the same structure of the Council recommendations:

**Area 1. PLANS AND STRATEGIES IN THE FIELD OF RARE DISEASES**

**Area 2. ADEQUATE DEFINITION, CODIFICATION AND INVENTORYING OF RARE DISEASES**

**Area 3. RESEARCH ON RARE DISEASES**

**Area 4. CENTRES OF EXPERTISE AND EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES**

**Area 5. GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL**

**Area 6. EMPOWERMENT OF PATIENT ORGANISATIONS**

**Area 7. SUSTAINABILITY**

**PART II****Area 1. PLANS AND STRATEGIES IN THE FIELD OF RARE DISEASES****Council Recommendation (2009/C 151/02)**

1. Establish and implement plans or strategies for rare diseases at the appropriate level or explore appropriate measures for rare diseases in other public health strategies, in order to aim to ensure that patients with rare diseases have access to high-quality care, including diagnostics, treatments, habilitation for those living with the disease and, if possible, effective orphan drugs, and in particular:

(a) elaborate and adopt a plan or strategy as soon as possible, preferably by the end of 2013 at the latest, aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems;

b) take action to integrate current and future initiatives at local, regional and national levels into their plans or strategies for a comprehensive approach;

(c) define a limited number of priority actions within their plans or strategies, with objectives and follow-up mechanisms;

(d) take note of the development of guidelines and recommendations for the elaboration of national action for rare diseases by relevant authorities at national level in the framework of the ongoing European project for rare diseases national plans development (EUROPLAN) selected for funding over the period 2008-2011 in the first programme of Community action in the field of public health

**1.1 Introduction**

15. The process for designing a National Plan or Strategy for rare diseases may be significantly different among member states. This is because the circumstances and the level of experience on rare diseases can be very different. Some member states already developed their second plan (e.g. France), other countries have just limited knowledge about the situation of people living with a rare disease in their territory. Still, following the Council Recommendations, each member state should (preferably by the end of 2013) establish and implement plans or strategies for rare diseases at the appropriate level. The aim is to ensure that all patients with a rare disease in Europe have equal access to high-quality care, including diagnostics, treatments and rehabilitation.

## 1.2 The development of a national plan

16. On the basis of existing experiences and on the consultation of the expert stakeholders during the meetings of EUROPLAN, several elements have been identified as important for the success of the development of a National Plan or Strategy for rare diseases. Positive factors are the creation and increase of awareness, involvement of different stakeholders during the development and the implementation of the plan; the assessment of the bottlenecks in the care of people with a rare disease, of the main patients' needs and of possible solutions. Negative factors, which can limit solutions, may be related to the availability of expertise and resources in a country, the small population size, but also the features of the health system.

17. In order to develop a National Plan or Strategy for rare diseases, during the European Conference on National Strategies on Rare Diseases on the 18<sup>th</sup> of November 2008 co-organized by the French Ministry of Health, EURORDIS and EUROPLAN under the French Presidency, the following actions have been identified and agreed:

- a) assessment of the needs of people with a rare disease living in the country, the need for resources, the existing provisions in the national health and social care, and the possible solutions;
- b) creation of a mechanism supporting the national plan or strategy in the country and drafting of the plan;
- c) draft a Plan or Strategy, with definition of general objectives and areas
- d) identification (ensuing from the results of the assessments indicated in item a) of this list), within the specific areas, of initiatives and actions to put into force within a specified timeframe;
- e) ensure the sustainability, transfer and integration of the actions foreseen by the national plan or strategy into the general health system of the country;
- f) monitor the implementation, evaluate the results and revise the plan accordingly.

## 1.3 Setting-up\_a mechanism for the governance of the National Plan or Strategy

18. Devising and putting in place a mechanism of governance (e.g. interdisciplinary panel or committee) is very helpful for the development as well as for the implementation of a National Plan or Strategy.

The identification and involvement of different actors/stakeholders, including national/regional/local authorities, learned societies, clinicians, hospital managers, patients' organizations representatives, etc., who participate in the planning and implementation of the National Plan or Strategy has shown surplus value in the different member states (e.g. Belgium, Italy, Portugal, The Netherlands). Due to the diversity of rare diseases, it can be helpful to collect the opinion from the various stakeholders about priority actions for a National Plan or Strategy. This is a method to stimulate the exchange of experience and knowledge and simultaneously create joint responsibility and ownership on the issue of improving the situation of people with a rare disease in the country. Finally, a group of dedicated people may help to facilitate and stimulate the increase of knowledge about rare diseases in general within the country.

In Belgium as well as in the Netherlands a multidisciplinary Steering Committee on rare diseases and Orphan Drugs exists. Both committees are independent. Members are representatives of patient organisations, physicians, researchers, pharmacists, representatives of pharmaceutical industry, health care insurers and governmental advisory boards. They have a permanent scientific secretariat and are a central contact point for all relevant stakeholders in their own country and abroad.

#### 1.4. Awareness raising

19. Awareness can be created in different ways, and it is often the effect of advocacy from patients' groups. The organization of conferences, events, involvement of the media (e.g. the Telethon marathons on television) and other known ways of eliciting awareness in other fields can be applied to the field of rare diseases. An example of successful awareness-raising activity is provided by the Rare Diseases Day. In order to encourage the progress of the development of a national plan, the health policy makers should raise awareness amongst 'people in charge' (e.g. policy makers in health and other sectors, and departments, notably Social affairs and Research, regional and local authorities, but also hospital managers or professional groups).

##### **CREATING AWARENESS: THE EXAMPLE OF THE RARE DISEASES DAY**

The Rare Disease Day was initiated by EURORDIS for the first time on the 29<sup>th</sup> of February 2008.

In 2009, 19 national alliances organised a day at local level; 600 patient groups participated in Europe and 30 countries were involved in total. The target audiences of the day were policy makers (health authorities, national and European parliamentarians) as well as the general public, media, health professionals, academics and researchers.

A website was created for the event, and other web-based platforms such as Facebook and You-Tube were used to promote the Rare Disease Day. 21.000 visits were made to [www.rarediseaseday.com](http://www.rarediseaseday.com) in few days that year. Media coverage of the day was strong with over 1500 media articles. The 2<sup>nd</sup> Rare Disease Day also spread outside Europe with the participation of the USA, Canada, Argentina, Colombia, Australia, Taiwan and China.

A dinner debate was held at the European Parliament and was attended by policy-makers at the European Commission, patient advocates, parliamentarians and the representatives of the biopharmaceutical industry. The Rare Disease Day 2009 also saw lobbying action at national level (Spain, UK, USA, China), and provided the momentum in pushing for national plans and strategies (Belgium, Spain, Portugal, Bulgaria, Ireland, Czech Republic), and for Centres of Expertise (Netherlands, Denmark), and in the construction of emerging national alliances (Switzerland, Australia).

The Rare Disease Day also provided a focus for fund raising – this year's Telethon in Catalonia was dedicated to rare diseases. Rare Disease Day also played an important role in raising awareness amongst the general public (this was helped through VIP and celebrity patronage this year) to inform, educate and involve the public in the issues surrounding rare diseases.

#### 1.5 Assessing patients' needs

20. Due to the specific situation and problems of rare diseases in a public health perspective, assessing unfulfilled needs as well as reporting on the existing provisions in the national health and social systems could require slightly different formats and methodology. Collection of the following information may be relevant in the preparatory phase of developing a national plan or strategy for rare diseases:

- analysis on unmet or unsatisfied needs of patients and their families with a rare disease in the country (e.g. dimension of the problems, descriptive

- epidemiology figures);
- inventory of existing health care resources and of services and policies directed to, or from which rare diseases patients can benefit (e.g. in the fields of disability, child healthcare, reimbursement, epidemiological surveillance, psychological and social care, etc.);
- available options for improving health and social care of people affected by rare diseases at national level.

In the box an example of the evaluation of the patients' needs is given.

**“MABNAHMEN ZUR VERBESSERUNG DER GESUNDHEITLICHEN SITUATION VON MENSCHEN MIT SELTENEN ERKRANKUNGEN IN DEUTSCHLAND“**

This study has been published in August 2009 by the German Federal Ministry of Health. This study was done to analyse the situation of people with a rare disease in Germany and to see if there were aspects which could be implemented by a National Action Plan for rare diseases. The structured interviews, questionnaires and focus groups gave insight in the lack of information about rare diseases in the country and the fact that there was diagnose delay with rare diseases. It also became clear that there are limited possibilities for therapy and there was a need for centres of expertise or a better coordinating of care (shared care concept). To improve this, the German government concludes that a national action plan for rare disease could be helpful.

### 1.6 Small population countries

21. During one of the meetings of EUROPLAN, specific problems were presented for developing health care policies for rare diseases in small population countries:

- lack of awareness due to the extremely low numbers (rare is rarer in small countries);
- lack of experts and centres of expertise (specialised health care professionals);
- lack of possibility of providing expert services in the country for many rare diseases;
- lack of sufficient resources and/or critical mass to perform research on rare diseases.

22. For these reasons, the need for international cooperation (European networks for diagnosis and international laboratory networks, identification of centres/laboratories in neighbouring countries, participation in European consortia, project and networks), which is important for all countries, is vital for small countries. The specific situation of small countries will obviously influence the way a National Plan or Strategy for rare diseases is formulated in the country. Actions developed within collaborative frameworks with neighbouring or other countries and within the European context will be favoured, rather than the national self-provision of health care for patients with rare diseases. Examples of international cooperation are illustrated in the following boxes.

**Central European countries plan extensive co-operation for rare diseases**

Leading experts from six Central European countries - Austria, Czech Republic, Germany, Hungary, Italy and Slovenia - discussed the possibilities for improving cross-border co-operation in the field of rare diseases at an informal meeting in Salzburg. The meeting, organised by the European Health Forum Gastein (EHFG), took place on 24 and 25 August 2009 as a follow-up of a similar meeting of a year earlier with several EU health ministers in Salzburg. The possibilities for the practical implementation of the close co-operation sought in

this specialised area of medicine were discussed at the expert level.

**Rapsody Project (<http://www.rapsodyonline.eu/>)**

Rare diseases may appear to be rare, but all together they affect a high number of people. Due to low case numbers per disease in individual countries, intensive international cooperation is vital. Countries involved in this project hope to set up centres of competence for 16 rare diseases; exchange information about procedures and services for rare disease patients across Europe; compare services in different countries; identify the best procedures and to support, or initiate, the development of new services (via websites, databases, care institutions and programmes).

Participating countries: Czech Republic, Denmark, France, Germany, Hungary, Italy, Luxembourg, Spain, Sweden, The Netherlands, Portugal, Great Britain.

### 1.7. Areas and actions of a National Plan or Strategy

23. Existing national plans (Bulgaria, France, Greece, Portugal, Spain) identify general objectives and specific areas and where initiatives are needed. The specific areas are similar across the existing plans, reflecting the fact that rare diseases share common needs in different European countries.

The main areas identified include in most cases: recognition of the specificity of rare diseases; information for the patients and the society; improved access to medical care (centres of expertise); timely and appropriate diagnosis; improved treatment and access to the required medicines (e.g. orphan drugs); research; training of health professionals; patients' empowerment; improvement of healthcare and specialised social services. These areas are in line with the Council Recommendations.

24. The Council also recommends to define "a limited number of priority actions within their plan or strategies, with objectives and follow up mechanisms". The currently endorsed National Plans indicate a number of specific areas and objectives between 5 and 10. Of course, the dimension and commitment of these plans cannot be compared by numbers, since the objectives and approaches are set with different levels of complexity and are built on different conditions of the health care systems.

25. Prioritizing areas, objectives and actions is in the competences of the National Authorities and can be carried out only on the basis of the assessment of the specific health and socio-economic conditions of the country. However, the general objectives of a National Plan or Strategy are based on the general overarching values of universality, access to good quality care, equity and solidarity.

**THE BULGARIAN NATIONAL PLAN ON RARE DISEASES 2009-2013**

<http://www.raredis.org/pub/events/NPRD.pdf>

On 27th of November 2008, the Bulgarian Council of Ministers adopted the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009-2013). The plan consists of the following 9 priorities:

1. Collecting epidemiological data for the rare diseases in Bulgaria by creation of a national register.
2. Improvement of the prevention of the genetic rare diseases by enlarging the current screening programmes.
3. Improvement of the prevention and diagnostics of the genetic rare diseases by introducing new genetic tests, decentralisation of the laboratory activities and easier access to medical genetic counselling.

4. Integrative approach to the prevention, diagnostics, medical treatment and social integration of patients and their families.
  5. Promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases.
  6. Feasibility study on the necessity, possibility and criteria for creation of a referent centre for rare diseases of functional type.
  7. Organising a national campaign for informing the society about rare diseases and their prevention.
  8. Support and collaboration with NGOs and patient associations for rare diseases.
  9. Collaboration with the other EU members.
- The total budget of the plan is 22 103 098 BGN (=11,306,974 EUR)

#### **THE FRENCH NATIONAL PLAN 2004-2008**

It is the first one to be elaborated and the only one that has undergone an external evaluation up to date, was structured around ten strategic priorities:

1. Increase knowledge of the epidemiology of rare diseases;
2. Recognize the specificity of rare diseases;
3. Develop information for patients, health professional and the general public;
4. Train professionals to better identify rare diseases;
5. Organize screenings and access to diagnostic tests;
6. Improve access to treatment and the quality of health care provision for patients;
7. Continue efforts in favour of orphan drugs;
8. Respond to the specific needs of accompaniment of people suffering from rare diseases and develop support for patients' associations;
9. Promote research and innovation on rare diseases, notably for treatments;
10. Develop national and European partnerships in the domain of rare diseases.

#### **THE GREEK NATIONAL PLAN FOR RARE DISEASES (2008-2012)**

It defined eight strategic priorities.

1. Acknowledge the specificity of rare diseases (registration on the list of chronic long-term disorders).
2. Increase the knowledge of the epidemiology of rare diseases and generation of a registry for rare diseases.
3. Develop information for patients, health professionals and the general public concerning rare diseases.
4. Upgrade services for diagnosis, therapy and rehabilitation of rare disease patients (train health care professionals to better identify the diseases and improve access to the health care system and to quality health care).
5. Organize screening and access to diagnostic tests.
6. Promote research and innovation regarding rare diseases and most specifically effective new therapies.
7. Respond to the specific needs of people living with rare diseases.
8. Generation of an integrated platform for action in the field of rare diseases at a National level and development of European partnerships.

#### **THE PORTUGUESE NATIONAL PLAN FOR RARE DISEASES**

On the 12<sup>th</sup> of November, 2008, the Portuguese Minister of Health approved the National Plan for Rare Diseases for Portugal. The web information in Portuguese language can be found at: [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/portugal.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/portugal.pdf).

Two are the main objectives of the National Plan: 1) To create and improve the national measures in order to satisfy the necessities of people with rare diseases (RD) and their families of medical services and care; 2) To improve the quality and the equity of the provided health care measures of to people with RD.

These objectives will be achieved by

- 1) creation of reference centres for RD;
- 2) To improve the access of people with RD to the adequate care;
- 3) To improve the knowledge on RD;
- 4) To promote the innovations in the treatment of RD and accessibility to orphan drugs;
- 5) To assure cooperation on national and international level, including the countries from EU and the

Community of countries with Portuguese official language.

The National Plan on RD is (NPRD) compatible with the National Plan of Health within the frame of 2010. It encloses an initial period of implementation (2008-2010) and period of consolidation (2010 and 2015).

The main strategies of the NPRD are grouped in 3 main axes: a) strategies of intervention; b) education and training strategies in RD; and c) collection and analysis of the information. The plan also details 15 actions for evaluation.

#### THE SPANISH STRATEGY FOR RARE DISEASES

On the 3<sup>rd</sup> of June 2009, Spain has adopted, under consensus among the Ministry of Health and Social Policy, Autonomous Communities and Scientific and Patient Associations, the Strategy for Rare Diseases of the NHS. Both the Strategy for Rare Diseases of NHS and other autonomous community's actions are horizontally targeted to every RD. This is available on-line (in Spanish) at:

<http://www.msc.es/organizacion/sns/planCalidadSNS/docs/enfermedadesRaras.pdf>.

The elements defined in the Spanish strategy follow the recommendations delineated by the European Council Recommendation on an Action in the Field of Rare Diseases.

The Spanish Strategy for Rare Diseases of NHS includes the following strategic aspects:

1. Information on RD (specific information on the disease and on the available care resources).
2. Prevention and early detection of RD.
3. Health care (coordination among health care different levels).
4. Therapies: orphan drugs, adjuvant drugs and medical devices, advanced therapies and rehabilitation.
5. Social and health care.
6. Research.
7. Education and training.

According to FEDER, the Strategy is not mandatory. It is a legal framework for a group of recommendations for Regional Health Administrations, which have the competence on Health and social issues. It is based on the Spanish Senate RD Working group Report, published in the Official Newsletter, February 23th 2007. In short, the Senate required the Government to develop and Action Plan on RD, with clear objectives, deadlines and specific budget and a RD Information and Coordination Entity. At regional level, specific initiatives related to RD are implemented.

### 1.8 Target population of the National Plan for rare diseases

26. 20. The European policies do not distinguish between the around 8000 different rare diseases in terms of health care needs and rights; in fact, rare diseases are defined in the EU as life-threatening or chronically debilitating diseases, including those of genetic origin, with a prevalence of no more than 5 in 10.000 and a high level of complexity. Thus, many types of diseases are included, e.g. genetic diseases, rare cancers, auto-immune diseases, congenital malformations, which may be already the subject of specific policies. In other situations, the policy makers can find it appropriate and ethical to extend the care improvements stimulated by the rare diseases needs to other (not rare) health conditions.

27. Therefore, for the purposes of the national health and social care provision, it can be useful to define the target population in greater details, according to the needs of the health system and the socio-political and health context in the country. This is currently being done in different ways in some national plans already developed in European countries.

the **Bulgarian National Plan (2009-2013)** defines its target groups as:

Patients with rare diseases (about 6% of the country's population); Families in risk of giving birth to a child with genetic problems; Families with reproductive problems; Pregnant women; All newborns. The rationale

for this definition is that all these groups can benefit from the activation or strengthening of genetic testing in prenatal, neonatal and selective (for at-risk groups) screening programmes, as well as of awareness campaigns.

In the **Portuguese National Plan** the target population is *'individuals of either gender, in any moment of their life, affected by a Rare Disease, considered in the context of their families and the community at large, and independently from their disability level.'* Such a definition underlines the fact that the plan or strategy is targeted to all patients with a rare disease.

### 1.9 Dissemination of the information on National Plans and Strategies

28. The dissemination of information on the National Plan or Strategy in development or adoption in the country should also be part of the strategy to ensure effective impact on rare diseases patients' behaviour and the health system performance. During the procedural steps of the EUROPLAN project, it has been agreed that the National Plan or Strategy should be public (i.e. published) in all its parts, including all specific actions, relative timelines and the results of its evaluation, when performed. An effective dissemination of complete and detailed information on the plan or strategy helps ensuring a higher efficacy of the actions foreseen in the plan. The dissemination of the plan at European level, with the preparation of a summary in English, has also been considered very important to stimulate spontaneous International cooperation.

### 1.10 Sustainability and duration of the National Plans and Strategies

29. In order to integrate the National Plan or Strategy into the general health system and improve its sustainability, whenever possible, the activities necessary to implement it should be assigned to existing structures of the health and social security system, and should complement, as far as possible, existing provisions for the delivery of specific health and social services. When a new structure or body is to be created, its composition, mandate and organisational relationships with other relevant institutional bodies are to be analysed and defined.

30. To ensure that the National Plan or Strategy results in a sustained impact on the delivery of health care after its conclusion, it is important to set out provisions for the integration of the actions foreseen in the national plan or strategy into the general health system of the country.

31. The life-span of the existing National Plans or Strategies is variable, with an average duration between 3 and 5 years, but sometimes no specific timeframe is set at all. The optimal duration of actions in the Plan is related to the way each specific health system works. However, there has been consensus on the fact that a National Plan or Strategy for rare diseases, similarly to other public health plans, should have a limited and well-defined duration, with an intermediate and final evaluation and, where necessary, a re-definition of objectives.

### 1.11 Monitoring

32. From the consensus reached in the EUROPLAN meetings, it is advisable:
- to have a mechanism for monitoring the Plan or Strategy at regular intervals, the single initiatives in each specific areas and their accomplishment of targets and deadlines;
  - as the experience of the French National Plan Evaluation suggests, a minimum mandatory number of meetings per year of the members belonging to the governance mechanism (e.g. interdisciplinary panel or committee) is recommended. The regularity of these meetings has emerged as added value;
  - the elaboration of a report is recommendable and preferably disseminated within the 'Rare disease community' (e.g. national patients and healthcare organisations, policy makers, etc.).
33. The choice of the institutions measuring the indicators is crucial for the success and efficiency of the process, as well as to reduce the burden of the activities. Indeed, it is important that data on an indicator is collected by a structure/institution which is interested, for its nature, in the information yielded by that indicator: this will ensure the necessary attention, continuity, technical competence and background organization.
34. The EU Council, with their Recommendations, invites the European Commission *"To produce, by the end of 2013 and in order to allow proposals in any possible future programme of Community action in the field of health, an implementation report on this recommendation addressed to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions and based on the information provided by the Member States, which should consider the extent to which the proposed measures are working effectively and the need for further action to improve the lives of patients affected by rare diseases and those of their families."* and *"To inform the Council of the follow-up to the Commission Communication on rare diseases on a regular basis."* Therefore, besides the national purposes and aims for monitoring the implementation of a national plan, it is necessary to consider that some indicators are to be assessed for the purposes of providing the European Commission with the data on the implementation of the national plan or strategy, necessary to prepare the report requested by the EU Council. A coherent set of indicators, with definitions ensuring the comparability of indicator data from all EU member states is therefore necessary.
35. In the framework of the EUROPLAN project a list of indicators has been prepared, based on the main areas and on some possible actions in such areas. The indicators have been chosen to be able to monitor the actions recommended, to be adaptable to the different national situations, and taking into account more general documents on the development of health indicators for rare diseases (e.g. Rare Diseases Task Force, RDTF). A separate EUROPLAN Document deals with the list of indicators, describing the methodology for their selection and their characteristics. The indicators proposed by EUROPLAN are, in most cases, process indicators, as they are expected to monitor the phases of development and implementation of the National Plan or Strategy, and a limited number of outcome indicators in the domain of health services.

36. Health outcome indicators are also necessary to monitor the epidemiological situation of rare diseases. For the purpose of defining a common set of health indicators for rare diseases, some debate has started at European level by the RDTF (and likely will be taken over by its successor the EU Committee of Experts on Rare Diseases - EuCERD).

#### 1.12 Evaluation and audit

37. Evaluation and audit of a National Plan and initiatives are advisable. To this purpose, suggestions and recommendations developed in the framework of the EUROPLAN project include:

- the most appropriate evaluation is external (audit), i.e. performed by a group of experts external to the mechanism (e.g., panel, committee) and bodies participating in the development, implementation of the National Plan or Strategy;
- the indicators developed in EUROPLAN constitute an important basis for evaluating the process of action planning and the implementation, and for evaluating some of its outcomes, even though obviously more indicators will be needed for evaluating those specific initiatives not foreseen by the EUROPLAN indicators or by the EUROPLAN Recommendations.

38. In addition to more standardized evaluation tools, the patients' and other citizens' view is important to assess the success of a National Plan or Strategy for rare diseases and it is worthwhile to explore the most appropriate tools for considering them. Some soft outcomes such as patients' satisfaction have been used as evaluation tools. Despite the limitations of such approach (not quantitative, not standardized, etc.), such evaluation has been proven to be useful in the first evaluation process of the French National Plan. See box on the evaluation of patients experience and satisfaction in the French National Plan.

#### **EVALUATION OF PATIENTS' EXPERIENCE AND SATISFACTION**

Within the evaluation of the French National Plan interviews with patients and their families revealed that the majority of them were not aware of the existence of the Plan. However, they had perceived improvements in the received health care, particularly through the creation of centres of reference (which in many cases started a virtuous circle leading to e.g. reimbursement of Orphan Drugs and better assistance at home).

Specific needs of the Rare diseases community came out from these interviews, which will help stirring the actions in the future French NP and which can be useful to take into account in other countries. In particular, the passage from childhood to adulthood was indicated by the patients and parents as an area where more attention is needed by the health care providers; furthermore it was noted that there is no sufficient provision of psychological assistance to the patients and families, in particular to the siblings, and of sufficient training to the general practitioners, who are those responsible of the care of rare diseases patients on a daily basis.

### 1.13. EUROPLAN Recommendations on Area 1: Plans and strategies in the field of rare diseases

- *Rare diseases are recognized as a priority in the public health area because of their specific needs.*
- *Initiatives are stimulated to raise awareness about the dimension of the problem and create joint responsibility.*
- *A mechanism (e.g. interdisciplinary panel, committee) including relevant stakeholders is established to assist the development and implementation of the National Plan or Strategy.*
- *An inventory of existing healthcare resource, services and policies is made including those directly addressing rare diseases as well as those from which rare disease patients may benefit (e.g. in the fields of disability, child healthcare, reimbursement, epidemiological surveillance, psychological and social care, etc.).*
- *Unfulfilled needs of patients are assessed.*
- *Available options for improving health and social care of people affected by rare diseases at national level are evaluated.*
- *European collaboration and the European documents in the field of rare diseases are taken into account in the development of the National Plan or Strategy.*
- *The National Plan or Strategy is elaborated with well described objectives to be achieved within a specific timeframe of limited duration. The general objectives of a National Plan or Strategy are based on the general overarching values of universality, access to good quality care, equity and solidarity.*
- *The policy decisions of the National Plan or Strategy are integrated, i.e. structured maximizing synergies and avoiding duplications with existing functions and structures of the health care system of the country.*
- *The policy decisions of the National Plan or Strategy are comprehensive, addressing not only health care needs, but also the other important needs of patients with rare diseases and their families, such as social needs.*
- *Specific areas are indicated, with priority given to those areas where major needs have been identified in the member state.*
- *The allocation of appropriate resources, consistent with own decision-making processes, is important to ensure the feasibility of the actions in the planned time.*

- *Information on the National Plan or Strategy is made accessible to the public and it is disseminated to patients' groups, health professionals' societies, general public and media, making the plan also be known at European level.*
- *Measures are taken to ensure the sustainability, transfer and integration of the actions foreseen by the national plan or strategy into the general health system of the country.*
- *The National Plan or Strategy has a duration of three – five years.*
- *The National Plan or Strategy is monitored at regular intervals using, as far as possible, EUROPLAN indicators. An intermediate deadline is established, after which, an evaluation process is undertaken and possible corrective measures are adopted.*
- *The implementation of the actions and their achievements are assessed.*
- *An external audit or evaluation of the National Plan or Strategy is carried out taking into account also patients' and citizens' views.*

## Area 2. ADEQUATE DEFINITION, CODIFICATION AND INVENTORYING OF RARE DISEASES

### Council Recommendation (2009/C 151/02)

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| <p>2. Use for the purposes of Community-level policy work a common definition of rare disease as a disease affecting no more than 5 per 10 000 persons.</p> <p>3. Aim to ensure that rare diseases are adequately coded and traceable in all health information systems, encouraging an adequate recognition of the disease in the national healthcare and reimbursement systems based on the ICD while respecting national procedures.</p> <p>4. Contribute actively to the development of the EU</p> | <p>easily accessible and dynamic inventory of rare diseases based on the Orphanet network and other existing networks as referred to in the Commission Communication on rare diseases.</p> <p>5. Consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance.</p> |
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### 2.1. Introduction

39. Several EU Countries have no special provisions for rare diseases as a group of conditions requiring specific initiatives. Countries like Sweden and UK rely very much on a “horizontal” model of high quality care and on the principle of health equity to ensure appropriate care to patients with rare diseases. However, due to the rarity and variety of these diseases, they are difficult to diagnose and record with the current practices of any health care system. Therefore, a special effort is needed to improve the identification and traceability of rare diseases. At single member state level a classification of appropriately coded rare diseases may be needed for guiding reimbursement policies and for improving traceability of rare diseases in the health care information system. Monitoring of health care initiatives for rare diseases is essential for the fact that, at present, many sources of indicators for such diseases, such as hospital and mortality certificates, are lacking the codification and classification of rare diseases. Although the national prerogatives in adopting the own health service organization must be acknowledged, it is important that a common, European and international, coding of rare diseases is adopted to facilitate all those activities for which the EU collaboration is necessary to face effectively the challenges posed by rare diseases, e.g. collection of epidemiological information, healthcare provision and development of registers of patients.

## 2.2. Coding and Classification of rare diseases

40. One of the main problems in planning health care for rare diseases is that the burden of most of them is invisible to the health systems, due to misclassification and the lack of appropriate coding. For this reason, codification is a central topic in the European initiatives for rare diseases. Specific actions have been taken in the past years by the Rare Disease Task Force (RDTF) leading to the creation of a working group for the classification of rare diseases in conjunction with the World Health Organization (WHO), in the framework of the revision of the 10<sup>th</sup> version of International Classification of Diseases, which has been launched by the WHO in 2007. The Chair of the EU Rare Diseases Task Force has been appointed Chair of the Topic Advisory Group (TAG) on Rare Diseases in order to provide proposals for codification and classification of rare diseases. ICD 11 is planned to become operative in 2015 and will provide a tool to trace rare diseases in the health information systems. Due to the remarkable changes in the coding of rare diseases, which will appear in ICD11, it is necessary that an appropriate and specific training is foreseen for the health care professionals. Before ICD 11 comes into force, the Orphanet classification (Orpha Code) provides a code which is largely in line with the future ICD11.

### **IMPROVE CODING RARE DISEASES ON EUROPEAN LEVEL**

The Working Group (WG) of the Rare Disease Taskforce on Coding, classification and data confidentiality collaborates closely with the WHO on its International Classification of Diseases and will contribute to the revision of the ICD-10 considering all existing classifications to ensure transparency. In this WG besides Orphanet, UKGTN (UK), NIH, EUROCAT, DIMDI (Germany), CINEAS (NL) and the Italian WG (see box below) are participating.

### **THE ITALIAN WORKING GROUP FOR CODING AND CLASSIFICATION OF RARE DISEASES**

In order to improve the classification of rare diseases and to codify them to the highest degree of accuracy, completeness and consistency, the Italian Working Group (WG), coordinated by the National Centre for Rare Diseases (CNMR) of the Italian National Institute of Health (Istituto Superiore di Sanità, Italy) has been established. The aims of this WG are the following: to evaluate the accuracy of rare diseases code on the ICD 10 and ICD 9 CM classification system; to harmonize the terminology of rare diseases; to develop coding procedures; to identify problem areas regarding coding process.

This WG is constituted by different members : national experts on coding of mortality data (Italian Institute of Statistics - ISTAT), hospital discharge data (Ministry of Health), rare tumours data, congenital malformation data; regional representatives involved in activities related to rare diseases: Apulia, Latium Lombardy, Piedmont, Tuscany and Veneto. A web-based system, prepared by the CNMR, is used to facilitate the exchange within the experts WG. This working group participates also to the TAG coding activities

### 2.3. Inventory

41. To learn more about rare diseases, the existence of an accurate inventory of rare diseases, regularly updated, by prevalence, mechanism, clinical features and aetiology would allow maximizing awareness and provides documentary support to health care providers, patients and researchers. However, in today's daily practice these inventories are scantily used. Therefore, it is necessary to promote the use of inventories for epidemiologic and public health purposes, while improving the collection and management of existing data. Important documentary references in this context is the ORPHANET<sup>1</sup> inventory.

### 2.4. Epidemiology, registries and surveillance

42. Epidemiological assessment of rare diseases is difficult due to the described problems of coding and classification, which make it difficult tracing rare diseases in the health care systems, as shown also from the experience of the first term of the French National Plan. The importance of a sound data base about prevalence of rare diseases, as it can result from an EU-wide data collection, for the appropriate planning and management of specialised national health services and possibly their collaboration and networking among EU member states, calls for the member states to start developing solutions for tracing rare diseases, combining national efforts with the European dimension.

43. A working group of the Rare Disease Task Force (RDTF) has the task of studying the state and the development of health and health care indicators for rare diseases, including epidemiology indicators. The 2008 report of this working group contains agreed reflections and indications of relevant epidemiologic data in the field of rare diseases with the current limitation of data collection at national and international level. This report and similar agreed strategies on this topic constitute a good consultation tool in order to have more insight in the difficulties and possible solutions for some aspects of the epidemiology of rare diseases.

44. Initiatives, such as working groups, focusing on the assessment of the added value of data mobilization and cross-referencing of existing databases for epidemiology and public health purposes related to rare diseases may be useful.

#### 2.4.1. Registries

45. Disease-specific registries or registries for groups of rare diseases are an effective way to assess health care needs as well as to generate research in several areas, including epidemiology; often, they are the only existing source of scientific/clinical and epidemiologic information on rare diseases. The added value of registries has been extensively assessed and established in the past years from the work of the RDTF and strongly supported in the Council Recommendations. Member states can put several initiatives into action in the domain of registries and of their uses for epidemiology and

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<sup>1</sup> (<http://www.orpha.net>)

public health purposes, according to their needs, the situation in the country, and keeping in mind the inputs and recommendations issued at European level by expert groups and by scientific societies.

#### **THE NATIONAL REGISTRY OF RARE DISEASES IN ITALY**

In 2001, the Ministry of Health issued a Decree (DM 279/2001)<sup>2</sup> establishing the national network for rare diseases and cost exemptions for related health service provisions. The main aim of this Decree was to set rules for cost exemptions for services included in the Essential Care Levels and to identify specific protective measures for rare disease patients. To address this aim, the Decree established a national network of Centres for the prevention, surveillance, diagnosis and care of rare diseases. With reference to surveillance, a national registry of rare diseases was established at National Centre for Rare Diseases (Italian National Institute of Health), receiving epidemiological, clinical and other data from regional and multiregional registries. The Registry collects data on 284 single and 47 groups of rare diseases included in the Decree. The list of rare diseases is waiting to be extended with an additional 109 conditions. Up to now this registry covers more than 80% of the national territory and is able to provide incidence of rare diseases, information on health migration of patients, and other information useful for public health purposes.

#### **THE SPANISH RARE DISEASES REGISTRY**

The Spanish Rare Diseases Registry and Specimens Bank was created in June 2005, through a Ministry Order establishing that the Rare Diseases Research Institute is its responsible organism. It is a nation-wide registry, and it has high level of security measures corresponding to databases with personal health data, which are considered sensitive and should be protected. The aims of the registry are the improvement of the knowledge on rare diseases and epidemiology in Spain, promotion of research on rare diseases, provision of information for the decision-making process on public health and policies, and collaboration on orphan drugs research.

The registry is nourished by patients who directly ask for their inclusion as well as by researchers interested in the diverse rare diseases, and also by Spanish autonomic regions cooperating with the registry.

#### **THIRTY YEARS OF HEMOPHILIA TREATMENT IN THE NETHERLANDS, 1972-2001**

In the Netherlands a series of five postal surveys have been performed from 1972 onwards. In April 2001, questionnaires were sent to all known Dutch haemophilic patients, with a response of 70%. As a result of the survey during all these years, changes in both the medical situation and social functioning of haemophilic patients in the Netherlands could be well described. It turned out that patients with severe haemophilia (not affected by hepatitis C or HIV) had a life expectancy of 71 years, which was still slightly lower than the life expectancy of the Dutch male population of 76 years. Moreover, changes in treatment were reflected by an increase in the use of prophylaxis; especially in children. The occurrence of haemorrhages has gradually decreased. Hospital admissions decreased from 47% of all patients in 1972 to 18% in 2001. (HIN-5, I. Plug LUMC Leiden, The Netherlands).

46. Provided that the organization of surveillance is very difficult and there are not yet agreements on the best dimension (e.g. for which types of rare diseases surveillance would be more important and/or feasible) and methods for performing epidemiologic surveillance of rare diseases, much of the work is nowadays in progress at European level<sup>3,4</sup>. It can be useful, when addressing this topic, to keep in mind as references the documents produced by these and other initiatives at national and international level,

<sup>2</sup> Ministerial Decree 18 May 2001, n. 279. Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell'articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998, n. 124. (published in GU n. 160 del 12-7-2001- Suppl. Ordinario n.180/L).

<sup>3</sup> Orphanet Report Series (2009): Patient Registries in Europe October 2009. Available on line at:

<sup>4</sup> EPPOSI (2009): Workshop On Patients' Registries For Rare Disorders - Need for Data Collection to Increase Knowledge on Rare Disorders and Optimize Disease Management and Care

where methods, consensus and criteria for the choices of rare diseases to be monitored are described, adapting such criteria to the specific national situation.

Initiatives at national level for integrating the use of administrative, demographic and health care data in the field of rare diseases (such as mobilize, cross reference and compare existing databases; create working groups for assessing the value of such data for the use in epidemiology and public health) should be promoted.

## 2.5. EUROPLAN recommendations on area 2: Adequate definition, coding and inventorying of rare diseases

- *The European definition of rare diseases is adopted in order to facilitate transnational cooperation and community level actions (e.g.: collaboration in diagnosis and health care; registration activities).*
- *The use of a common EU inventory of rare diseases (Orphanet) is promoted in the national health care services and collaboration is carried out to keep it updated.*
- *Coding of rare diseases is promoted, encouraging their traceability in the national health system.*
- *Cross-referencing rare diseases is carried out across the different classification systems adopted in the country, ensuring coordination and coherence with European initiatives, such as the reference to the Orpha-code.*
- *The collaboration in the ICD10 revision process is ensured and ICD-11 is adopted as soon as it becomes available.*
- *Healthcare professionals are appropriately trained in coding rare diseases.*
- *Initiatives are promoted at national level for the integrated use of administrative, demographic and health care data sources to improve the management of rare diseases.*
- *National/regional registries of rare diseases are promoted and supported for public health purposes under the management of the health authorities or other stakeholders. Public/academia partnerships for the establishment and maintenance of registries are stimulated.*
- *Participation of existing registries and centres of expertise in European registries is fostered.*
- *Collaboration at European level is ensured for assessing and agreeing on ethical and legal issues (ownership, intellectual property, personal data protection, etc.), scope and use of European/national registries and funding aspects, which can hamper the functioning of many European registries.*
- *Instruments are identified for combining EU and national funding for registries.*

### Area 3. RESEARCH ON RARE DISEASES

#### **Council Recommendation (2009/C 151/02)**

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| <p>6. Identify ongoing research and research resources in the national and Community frameworks in order to establish the state of the art, assess the research landscape in the area of rare diseases, and improve the coordination of Community, national and regional programmes for rare diseases research.</p> <p>7. Identify needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them, and promote interdisciplinary cooperative approaches to be complementarily addressed through national and Community programmes.</p> | <p>8. Foster the participation of national researchers in research projects on rare diseases funded at all appropriate levels, including the Community level.</p> <p>9. Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.</p> <p>10. Facilitate, together with the Commission, the development of research cooperation with third countries active in research on rare diseases and more generally with regard to the exchange of information and the sharing of expertise.</p> |
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#### 3.1. Introduction

47. Research on rare diseases is scarce and scattered throughout the EU. The recent methodological and scientific advancements provide new and powerful approaches that can be used to reveal the mechanisms of many rare disorders. However, various reasons make research on rare diseases difficult to conduct, namely: the high number and wide variety of the diseases, the lack of suitable experimental models for most rare diseases, the poorly defined endpoints, the small number of patients and, above all, limited resources. Such difficulties are especially relevant to development of translational research, which, indeed, is necessary to bridge the gap between basic research and therapy development. Clinical studies on rare diseases, which are of high added value, may also need complex collaboration among EU Countries since patients enrolled and data collected in a single country may not have sufficient statistical power to draw conclusions on the efficacy of the treatment under investigation. Finally, public health and social studies on rare diseases and patients' needs are limited since these issues have received attention only recently. In conclusion, there is a strong need of fostering collaborative programs on all fields of research on rare diseases, from fundamental/basic through to social research, at national, European and international level.

#### 3.2. Fundamental research

48. Fundamental research is mainly not labelled as rare disease research and therefore it is usually supported through current financing channels for biomedical research. Within this broad framework, fundamental research may provide important new knowledge into the pathogenesis of rare diseases; in addition, it provide inputs to translational research and the development of new diagnostic tools and therapies (e.g. enzyme replacement therapy).

### 3.3. Translational and clinical research

49. Most pharmaceutical companies are reluctant to invest in developing medicinal products for rare diseases because of the limited market for each individual disease. Moreover, clinical studies with newly developed drugs but also with well established drugs used in new combinations, are rarely supported by public bodies. Programmes to foster clinical research should consider that the development of a new therapeutic use of an already established drug would be often more cost-effective than that of a new drug. One of many examples is the recent successful improvement in childhood cancer survival, now more than 75% in some European countries, which to a large part has been achieved by clinical trials using already established drugs.

50. The difficulty to perform clinical trials is one important and often limiting step in providing therapies for rare diseases. The Clinical Trials Directive 2001/20/EC of the European Parliament established rigorous quality and ethical criteria for the development of drugs, thus achieving a major progress in protecting the rights of the patients involved in the clinical trials. A large proportion of clinical trials for rare diseases is performed by small actors with limited resources, such as academic clinical researchers or small and medium enterprises; therefore, administrative and/or financial support to these actors should be envisaged, in order to facilitate studies on new rare disease therapies.

Multinational clinical research is hampered by the fragmentation of health and legislative systems in Europe. **The European Clinical Research Infrastructures Network (ECRIN)** is a sustainable, not-for-profit infrastructure supporting multinational clinical research projects in Europe, funded by the FP7 Programme. ECRIN provides information, consulting and services to investigators and sponsors in the preparation and in the conduct of multinational clinical studies, for any category of clinical research and in any disease area. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.  
[www.ecrin.org](http://www.ecrin.org)

51. Clinical trials are also an important area of collaborative action for member states. International collaboration strengthens the study power, hence improving the potential to assess the treatment efficacy for rare diseases. Collaboration is required among member states also in order to facilitate the design of clinical trials, such as studying possibilities to harmonize ethical, legal and consensus issues, as well as to set specific tools for assessing the added value of orphan drugs.

52. It is advisable to set instruments and measures (e.g. centres) to facilitate planning and performing clinical trials for rare diseases; this can include the provision of scientific, clinical, statistical, ethical and regulatory expertise to such actors as academia and small and medium enterprises. A consistent and efficient support to clinical trials on rare diseases would ultimately benefit orphan drug development also at EU level, increasing the amount and quality of dossiers presented for evaluation to the European Medicine Agency (EMA) and the Committee for Orphan Medical Products (COMP).

53. Overall, interdisciplinary approaches to research are necessary to generate new effective therapies for diseases which often affect several organs and or systems. An

effective causal therapy is often not available and can only be developed if the disease pathogenesis is understood. However, so far this has been possible for few rare diseases. Networking of the different expertises relevant to rare diseases is therefore particularly important and it should be proactively promoted.

Two different approaches to multidisciplinary collaboration in research are presented in the following boxes.

**European partnership for research on rare diseases: E-RARE**

E-Rare (ERA-Net for research programs on rare diseases) is a network of ten partners – public bodies, ministries and research management organizations – from eight countries, responsible for the development and management of national/regional research programs on rare diseases. E-Rare is supported by the European Commission under the Sixth Framework Program ERA-Net scheme for a 4-year period (from June 1st 2006). The aim of E-Rare is to foster research on rare diseases in Europe: to set up sustained and long lasting cooperation between MS partners, to coordinate national research programs in order to overcome the fragmentation of research on rare diseases and promote interdisciplinary approaches, to harmonize and develop synergies among the national and/or regional research programs of the participating countries, to develop common research policy on rare diseases and to sustain a favourable competitive position with regard to research on rare diseases in other regions of the globe such as North America and Asia. E-Rare launched a first joint call for proposals in 2007 and the second in 2009.

[www.e-rare.eu](http://www.e-rare.eu)

**German Federal Ministry of Education and Research (BMBF)**

Close networking of the different working groups on rare diseases is particularly important. The BMBF (Federal Ministry of Education and research) has therefore funded the establishment of ten disease-specific networks with a total of €31 million. The objective of the start-up funding was to pool national capacities in research and care in order to create the conditions for specific diagnosis, systematic research, optimal information transfer and competent patient care. The funding of the individual networks has been provided for an initial period of three years since 2003. After a successful interim evaluation, nine of the networks for rare diseases were being funded for another two years until 2008 [www.bmbm.de](http://www.bmbm.de)

### 3.4. EUROPLAN recommendations on Area 3: Research on Rare diseases

- *Specific national research programs for rare diseases (basic, translational, clinical, public health and social research) are established and supported with dedicated funds, preferably for a long period. Research projects on rare diseases should be made identifiable and traceable within broader national research programs.*
- *Specific provisions are included in the national plans or strategies to promote appropriate agreements between Health, Research and Social Ministries/Departments for improving knowledge on different aspects of rare diseases.*
- *National networks are promoted to foster research on rare diseases. Special attention is given to translational research in order to facilitate the application of new knowledge into rare disease treatment. Compilation and updating of a directory of teams carrying out research on rare diseases should be endorsed when feasible.*
- *Proper initiatives are developed to foster participation in cooperative international research initiatives on rare diseases, including the EU framework program and E-RARE.*
- *Specific technological platforms and infrastructures for rare disease research are established and supported.*
- *Multi-centre national and trans-national studies are promoted, in order to reach a critical mass of patients for clinical trials and to exploit international expertise.*
- *Instruments and measures (e.g. centres) are set up to support clinical research on rare diseases.*
- *Specific programs are launched for funding and/or recruitment of young scientists on rare diseases research projects.*

#### Area 4. CENTRES OF EXPERTISE AND EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES

##### Council Recommendation (2009/C 151/02)

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| <p>11. Identify appropriate centres of expertise throughout their national territory by the end of 2013, and consider supporting their creation.</p> <p>12. Foster the participation of centres of expertise in European reference networks respecting the national competences and rules with regard to their authorisation or recognition.</p> <p>13. Organise healthcare pathways for patients suffering from rare diseases through the establishment of cooperation with relevant experts and exchange of professionals and expertise within the country or from abroad when necessary.</p> | <p>14. Support the use of information and communication technologies such as telemedicine where it is necessary to ensure distant access to the specific healthcare needed.</p> <p>15. Include, in their plans or strategies, the necessary conditions for the diffusion and mobility of expertise and knowledge in order to facilitate the treatment of patients in their proximity.</p> <p>16. Encourage centres of expertise to be based on a multidisciplinary approach to care when addressing rare diseases.</p> |
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#### 4.1. Introduction

54. The establishment of centres of expertise at national or regional level is an important instrument for the provision of health care to rare disease patients. Designation of centres of expertise allows the formal set up of a national framework of healthcare centres, which are acknowledged for their specific expertise in diagnosis and treatment of specific rare diseases. They allow the process of definition of health care pathways, of collaboration and coordination for diagnosis and care, streamlining the patients to the most appropriate centres for their disease and enabling healthcare managers to identify where to allocate specific resources.

55. In the first term of the French national plan the creation of centres of expertise has proven to have a positive impact on patients' satisfaction, and to lead, in the opinion of patients, to better treatment and reimbursement mechanisms and better connection with home care and other services for those attending the centres.

#### 4.2. Definition of centres of expertise

56. While the procedures and the criteria for the designation of centres of expertise are in the national competence, it is important to recall the declaration elaborated by EURORDIS, an important European patients' association<sup>5</sup>.

EURORDIS' "**Declaration of Common Principles on Centres of Expertise and European Reference Networks**" ([http://www.eurordis.org/sites/default/files/publications/Declaration\\_Centres%20of%20Expertise-nov08.pdf](http://www.eurordis.org/sites/default/files/publications/Declaration_Centres%20of%20Expertise-nov08.pdf)) represents a bottom-up approach to the development of a common concept of CE.

<sup>5</sup> EURORDIS (2008): "Declaration of Common Principles on Centres of Expertise and European Reference Networks" Available on line at: ([http://www.eurordis.org/sites/default/files/publications/Declaration\\_Centres%20of%20Expertise-nov08.pdf](http://www.eurordis.org/sites/default/files/publications/Declaration_Centres%20of%20Expertise-nov08.pdf))

It describes the basic key principles of CE and aims to ensure that patients have access to equal care and services wherever they living in Europe through CE that shall facilitate the coordination of the multidisciplinary management of rare diseases, provide accurate diagnosis, facilitate access to social assistance, coordinate research activities and infrastructures, share their knowledge at the national and European levels, and last but not least, make patients feel welcome and safe, including them in their management and evaluation.

The adoption of the Declaration followed a two-year inclusive reflection process to develop common principles on CE and ERN and was eventually voted on and adopted in May 2008 at the Annual Membership Meeting of EURORDIS. The process began in April 2006, at the Membership Meeting in Berlin, dedicated to “Centres of Reference or Rare Diseases: How can we make it happen?”. Since that time, EURORDIS’ national alliances and their members have worked together to promote the need for specialised, multidisciplinary health services for rare disease patients and facilitate the development of common concepts, common language and common strategies.

In the context of the EC-funded Rare Disease Patient Solidarity project (RAPSODY) 270 patient representatives, health care professionals and decision-makers have participated in one-day national workshops in 11 EU member states following the same methodology and agenda; 80 representatives from 11 countries participated in a two-days European Workshop of synthesis in Prague in July 2007; the final synthesis was presented at the European Conference on rare diseases 2007, in Lisbon.

#### 4.3. Identification and designation of centres of expertise

57. Most of the European countries do not have at present centres of expertise for rare diseases and where they exist, there are remarkable differences in their organization and position in the national health system (national, regional), focus (only research, only clinical research; multidisciplinary, dealing with one or more rare disease or with a specific group of diseases) and sources of funding. Also procedures for the definition, designation and evaluation of centres of expertise are different (see boxes).

From the experience of the few member states where centres of expertise exist, it is clear that specific funding is deemed necessary to ensure long-term sustainability of such centres. Long-term sustainability is needed for the benefit of the patients, and ensures hoarding of the knowledge and experience developed in the centre as well as the continuity of care. In addition centres of expertise are often called to bear special costs and administrative efforts due to the complexity of rare diseases and the high costs of treatments.

##### **IDENTIFICATION AND DESIGNATION OF CENTRES OF EXPERTISE**

Denmark: the selection is done by the National Board of Health after consultation of the learned societies, the administrations and patient organizations.

France: the potential centres of expertise apply annually through a competitive call for proposals. As of 2008, 132 centres of expertise have been established, each of which designated for five years, with a mid-term self evaluation after three years and an external evaluation after five years. The limitation of this method is that in the first rounds it led to the selection of centres which were fast aware of the call, leaving outside centres that might have been more qualified but did not know about the call.

Italy: the centres of expertise are designated at regional level by regional health authorities.

UK: the centres are commissioned by 10 bodies in England (the specialized commissioning groups) each responsible for a population of about 5 million people.

##### **EVALUATION OF CENTRES OF EXPERTISE**

Denmark: In 2003 Rare Disorders Denmark, the Danish national rare disease alliance, carried out a survey among 900 rare diseases patients to investigate their overall satisfaction with the care received in centres of expertise. Only 33% of rare diseases patients reported being treated at a centres of expertise, however those receiving care at a centres of expertise were more satisfied with their treatment overall.

France: The centres of expertise have an self-evaluation after three years and external evaluation after five years.

UK: Monitoring of clinical outcomes has a great importance in the evaluation of centres providing specialised care. Outcomes of surgery (e.g., portoenterostomy for biliary atresia) and other interventions (e.g., interventional radiology for malformation of the Vein of Galen, or gene therapy for immunodeficiency disorder) are monitored for all patients treated – a 100% consecutive case series.

There is however difficulty in defining appropriate outcomes for some rare and untreatable disorders (e.g., epidermolysis bullosa and Alstrom syndrome).

For the diagnostic services, e.g., primary ciliary dyskinesia) emphasis is placed on external inspection and accreditation and external quality assurance systems

In Spain, Royal Decree 1302/2006 of 10 November, which establishes the conditions regarding the **procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish NHS**, refers to rare diseases by defining the characteristics that must be met by pathologies or groups of diagnosed or treated by means of techniques, technologies or procedures included in the Spanish National Health System's common services portfolio. Royal Decree defines what is understood by Reference Centre, Service or Unit of the Spanish NHS and establishes the conditions regarding the procedure for the designation and accreditation of CSUR. The entire procedure for the designation of CSUR is formulated through the CSUR Designation Committee of the Spanish NHS, which was created in the aforementioned Royal Decree and which reports and submits proposals to the Interterritorial Council where all the Regional Ministers are involved.

The tasks of the Designation Committee are: to study the needs and propose the pathologies or the diagnostic or therapeutic techniques, technologies and procedures for which a CSUR needs to be designated; to propose the procedure for the designation and accreditation of a CSUR and to report on it; to assess the designation applications received and make designation proposals to the Interterritorial Council; to study and propose the renewal/revocation of the designation of CSUR; and to establish the procedure for the referral of users. Each of the different areas is being developed by groups of experts appointed by the Autonomous Communities, scientific societies and the Ministry of Health and Social Policy. Once the criteria has been agreed a period of CSUR application is opened, and the respective Autonomous Communities can present their proposals through the Designation Committee. Once they have been admitted for processing, the applications are sent to the Spanish NHS Quality Agency for the start of the audit and accreditation process.

After the respective accreditation reports have been received, the said Committee studies them together with the other information on each file and submits its proposals for designation, or not designated, to the Interterritorial Council. The Ministry of Health and Social Policy, at the suggestion of the Designation Committee and with the prior consent of the Interterritorial Council, decides on the designation of the CSUR for a maximum period of 5 years. Before that period has terminated the designation will have to be renewed, provided that, after a re-evaluation by the Spanish NHS Quality Agency.

<http://www.msc.es/profesionales/CentrosDeReferencia/home.htm>

#### 4.4. Healthcare Pathways

58. Clinical or healthcare pathways are structured, multidisciplinary plans of care designed to support the implementation of guidelines and protocols. They are designed to support clinical management, resource management, clinical audit and also financial management, with the obvious advantage of applying the same, high quality standard to the provision of health care in a particular disease.

**GuíaSalud** is a National Health System (NHS) programme in Spain, for development of products based on scientific evidence to assist health professionals in decision-making. Since its first steps, in mid-2002 until now, it has been characterised in framework changes within the quality of the NHS Plan. It involves health professionals and patients in definition and development of clinical guidelines. <http://www.guiasalud.es/home.asp>

59. Guidelines are extremely scarce in the field of rare diseases. This reflects a lack of expertise in the medical community and the insufficient knowledge and evidence, but also a lack of attention to the subject by the health care system. Clinical guidelines for rare diseases are extremely needed in order to improve the diagnostic ability of doctors but also to disseminate quality clinical practices and guide the everyday health management of patients with rare diseases, who have often high levels of co-morbidity and complications, some of which are difficult to identify and treat ('rare in the rare'). The definition of quality guidelines and best practices is dealt with in Area 5.

60. The importance of a transnational approach to health care pathways is great in all medical fields and vital in the field of rare diseases, because of the frequent lack of expertise at national level. Thus, health care pathways would be particularly valid when based on sufficient quality evidence, successful protocols and expert consensus and also on wide collaborative networks of centres of expertise. Such pathways should include measures to provide adequate social care and psychological support to patients and their families whenever possible.

#### 4.5. Networking

61. Networking of centres of expertise in different member states is to be sought by means of appropriate collaboration agreements and frameworks. Spontaneous referral to centres of expertise is facilitated by the communication of the designed centres to a common European inventory of rare disease resources, and therefore the updating of the Orphanet inventory is to be ensured.

Substantial improvements and extensions of the activities based on networking are expected from the application of new information and communication technologies and especially those developed specifically for e-Health. On-line and electronic tools are very efficient and should be a strong part of the EU strategy on rare diseases. They can save the life of persons with rare diseases in emergency situations.

**THE ITALIAN NETWORK ON RARE DISEASES**

In 2001, the Ministry of Health issued a Decree (DM 279/2001) establishing the national network for rare diseases and cost exemptions for related health service provisions. The main aim of this Decree was to set rules for cost exemptions for services included in the Essential Care Levels (LEA: Livelli Essenziali di Assistenza) and to identify specific protective measures for rare disease patients. To address this aim, the Decree established the national network of Centres for the prevention, surveillance, diagnosis and care of rare diseases.

The Italian health care system has delegated the responsibility for the provision of health services to the regional health authorities. Based on a decision from the State-Regions Conference, a permanent inter-regional technical group, made of Regional Representatives, the Ministry of Health and the National Institute of Health) was established in 2002. Their mandate is to ensure the coordination and monitoring of health care activities regarding rare diseases, with the aim of optimising the operation of the Regional networks and safeguarding the principle of equity in healthcare for all citizens. Each Region identified its own Centres of Expertise for rare diseases to be part of the National Network for Rare Diseases. The Regional Centres were identified among those possessing documented experience in diagnostic or specific therapeutic activities and endowed with adequate structures and complementary services (emergency services and services for biochemical and genetic-molecular diagnosis). Moreover, by virtue of their competences, four Regions (Marches, Piedmont, Tuscany and Aosta Valley) adopted a list of rare diseases that was more extensive than the one established at the national level, and two Regions (Tuscany and Veneto) have recently decided to undertake population wide newborn screening that has been expanded to cover more than 20 rare diseases. Regional activities that address rare diseases have received 30 Million Euro in financial support based on the Financial Law 2007.

62. The Communication from the Commission to the European Economic and Social Committee and the Committee of the regions on Rare Diseases states that e-Health can contribute in a number of different ways to this area, in particular through:

- Electronic online-services developed by several EU funded projects, are a clear demonstration of how Information and Communication Technology (ICT) can contribute to putting patients in contact with other patients and developing patient communities, to sharing databases between research groups, to collecting data for clinical research, to registering patients willing to participate in clinical research, and to submitting cases to experts which improve the quality of diagnoses and treatment;
- Telemedicine, the provision of healthcare services at a distance through ICT, is another useful tool. It can, for instance, enable to bring highly specialised expertise on rare diseases to ordinary clinics and practices, such as a second opinion from a centre of excellence;

Recent information on this topic can be found in the outcome of the Ministerial conference at the base of the Prague Declaration on e-Health, signed on the 20<sup>th</sup> of February 2009 ().

#### 4.6. Diagnosis

63. A timely and appropriate diagnosis is one of the central calls of patients affected by rare diseases. Experiences collected among patients testify that the diagnostic delay in the field of rare diseases is common and bears dramatic consequences (see box EURORDISCARE2). Diagnosis is at the basis of appropriate health care and of the possibility of getting a treatment, and several bottlenecks have been identified in the pathway leading to diagnosis of a rare disease: from the lack of recognition of an unusual pattern of symptoms, the lack of appropriate referral to an expert centre by health professionals, to the scarce availability of diagnostic tests. It is therefore an area where appropriate health

care policies can make real changes, fostering the diagnostic capabilities of centres and taking advantage of the scientific advancements in the fields of genetics, biochemistry and other disciplines, in order to reduce the burden imposed to the patients and the health care system by late diagnosis and misdiagnosis.

Many genetic tests are more and more available and used for diagnosis of rare diseases. The quality of genetic testing and other diagnostic tests has to be ensured, and participation in external quality control schemes should be promoted at national and international level. Moreover, the use of genetic counselling has to be promoted.

#### **THE VOICE OF 12.000 PATIENTS: RESULTS OF PATIENTS' SURVEYS ON DIAGNOSIS DELAY (EURORDISCARE2)**

The Eurordis Care programme survey was conducted between 2003 and 2006 in order to describe the experiences of patients' regarding diagnosis in 16 European countries and on 8 different rare diseases: 1) Prader-Willy Syndrome; 2) Marfan syndrome; 3) Crohn's disease; 4) Duchenne muscular dystrophy, 5) tuberous sclerosis; 6) cystic fibrosis; Fragile X syndrome; 8) Ehlers-Danlos syndrome.

Key findings of the EurordisCare2 Survey on delays in, and conditions surrounding the announcement of diagnosis include:

25% of patients reported waiting between 5 and 30 years from the time of first symptoms to a confirmatory diagnosis of their disease;

40% of patients were initially misdiagnosed leading to severe consequences such as inappropriate medical interventions, including surgery and psychological treatment;

25% of patients had to travel to a different region to obtain a diagnosis and 2% had to travel to a different country;

In 33% of cases, the diagnosis was announced in unsatisfactory terms or conditions. In 12.5% of cases, it was announced in unacceptable ones.

The genetic nature of the disease was not communicated to the patient or family in 25% of cases. This is paradoxical, given the genetic origin of most rare diseases, Genetic counselling was only provided in 50% of cases.

Even with some methodological limitations (e.g. in some cases the diagnosis is almost entirely based on symptoms which are non specific, or different degrees of severity of the disease exist and milder forms can be easily missed, or the diagnosis is difficult to confirm), these results provide a very interesting overview of the state of diagnosis for rare diseases in Europe.

64. Information, development of guidelines and training of healthcare professionals play a crucial role among the areas leading to the improvement of diagnosis. Similarly, Centres of expertise have a central role in enhancing the diagnosis capacity in the field of rare diseases, and their participation in European networks constitutes an added value.

#### **THE DYSCERNE NETWORK**

The **DYSCERNE** network, coordinated by the University of Manchester, is a proper example of how to improve the diagnosis of rare dysmorphic diseases using images exchange. These aims will be achieved by:

- The creation of a European network of existing centres of expertise in dysmorphology.
- Development of a web-based dysmorphology diagnostic system (DDS)
- Development and wide dissemination of clinical management guidelines for selected dysmorphic conditions.

The project is a partnership between six existing centres of expertise in dysmorphology from; Belgium, France, Italy, Netherlands, Poland and the UK. <http://www.dyscerne.org/>

#### 4.7. Screening

65. While lack of specialist knowledge on rare diseases can often result in symptoms

being misread, some rare diseases can, nowadays, be included in screening programs. Screening programs are very powerful to detect rare diseases for which appropriate diagnostic tests are available. The highest value of a screening is shown in case that it detects the conditions before its clinical manifestation and when treatment can be started in time to prevent the onset of symptoms. However screening can have several other applications in prevention. The number of diseases which can be detected is continuously increasing, thanks to new technologies and to the development of mass spectrometry techniques. However, wide application of population screening programs is hampered by ethical and economic considerations. In order to implement screening programs it is important to establish an efficient collaboration between relevant hospital departments and screening laboratories and ensure that appropriate performance is monitored and quality assurance schemes are in place.

66. Cooperation among member states may be of advantage in carrying out screening programmes, e.g. in case that tests are necessary in selected conditions only or for confirmatory purposes or in case that the test is routinely available in few countries only. The priority actions to facilitate cooperation and equal access to screening and early treatment to all EU citizens are described in area 5.

#### **EUROGENTEST**

EuroGentest is an EU-funded Network of Excellence (NoE) with 5 Units looking at all aspects of genetic testing: (i) Quality Management; (ii) Information Databases; (iii) Public Health; (iv) New Technologies; (v) Education. Through a series of initiatives EuroGentest encourages the harmonization of standards and practice in all these areas throughout the EU and beyond ([www.eurogentest.org](http://www.eurogentest.org)).

#### **THE EUROPEAN MOLECULAR GENETICS QUALITY NETWORK (EMQN)**

EMQN is a not-for-profit organisation promoting quality in molecular genetic testing through the provision of external quality assessment (proficiency testing schemes) and the organisation of best practice meetings and publication of guidelines (<http://www.emqn.org/emqn/>).

#### **NATIONAL EXTERNAL QUALITY CONTROL SCHEMES IN ITALY**

Since 2001, national external quality control schemes for genetic tests are organised by the National Centre for Rare Diseases (Istituto Superiore di Sanità) in Italy. Up to now, 95 laboratories using genetic tests for molecular as well as cytogenetic diagnosis are monitored ([www.iss.it/cnmr](http://www.iss.it/cnmr)).

#### **THE CZECH DATABASE OF CYTOGENETIC AND DNA LABORATORIES**

In the Czech Republic, there are over 70 molecular genetic laboratories.. Together, they offer diagnostic tests for more than 492 different rare disorders. Neonatal screening is routinely performed in the country for PKU, congenital adrenal hyperplasia (CAH) and congenital hypothyroidism. From October 1/2009 neonatal screening has been expanded by 13 other metabolic disorders and cystic fibrosis (IRT/DNA protocol). It is commendable that there are clinical genetics services throughout the entire country, with every major district having such services, both at private and/or state based levels. Genetic services are carried out in compliance with all international professional standards and are fully covered by the national health insurance system (<http://www.uhkt.cz/nrl/db>).

## 4.8. Rehabilitation

67. For a number of rare diseases leading to the development of disabilities, it is necessary that a rehabilitation process is put in place in order for the affected patients to be enabled to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. For patients with rare diseases, rehabilitation needs arise which require ad hoc training of paramedical professionals. Centres of expertise are therefore the most appropriate place for ensuring the proper training of paramedical specialists and coordinating the exchange of good practices. The extra effort needed to treat people with rare diseases should be properly compensated. A special compensation for paramedical treatment of rare disease patients has been recognized in the 2<sup>nd</sup> French National Plan on Rare Disease.

A specific coding is needed and must be incorporated into the health systems to ensure that this additional effort is captured, recognised and properly resourced. Alternatively, professionals providing rehabilitation treatment may find themselves in a position to have to reject rare disease patients.

#### **4.9. EUROPLAN recommendations on Area 4: Centres of Expertise and European Reference Networks for rare diseases.**

- *Transparent mechanisms of designation of centres of expertise are established ensuring their quality, efficiency and long term sustainability .*
- *Healthcare pathways are defined and adopted, based on best practices and expertise at national and international level.*
- *A national directory of Centres of expertise operating in the national territory is compiled, kept updated and published at national level as well as in a common European Inventory (Orphanet).*
- *Centres able to provide quality diagnosis and care are identified in neighbouring or other countries, where patients or biological samples can be referred to, and networking is promoted.*
- *Travelling of biological samples, radiologic images, other diagnostic materials, and e-tools for tele-expertise is supported.*
- *A national framework is ensured on rare diseases screening options and policies.*
- *Proper performance of newborn screenings prescribed in the country is monitored with appropriate indicators.*
- *Accessibility to genetic counselling is promoted.*
- *The quality of genetic testing and other diagnostic tests is ensured, including participation in external quality control schemes at national and international level.*
- *Collaboration with the EU inventory of the national provision of testing for rare diseases (genetic, biochemical, enzymatic, tissue/cell identification, clinical) published both at national level and on Orpha.net is ensured.*
- *Centers of expertise provide proper training to paramedical specialists; paramedical good practices are coordinated, in order to serve the specific rehabilitation needs of rare diseases patients.*
- *An ad hoc coding must be incorporated into the national health system to recognize and appropriately resource the special rehabilitation treatments necessary for people affected by rare diseases.*

## Area 5. GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL

### **Council Recommendation (2009/C 151/02)**

17. Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support:

(a) the sharing of best practices on diagnostic tools and medical care as well as education and social care in the field of rare diseases;

(b) adequate education and training for all health professionals to make them aware of the existence of these diseases and of resources available for their care;

(c) the development of medical training in fields relevant to the diagnosis and management of rare diseases, such as genetics, immunology, neurology, oncology or paediatrics;

(d) the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences;

(e) the sharing member states' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge and expertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients.

### 5.1. Introduction

68. The training of professionals and development and exchange of best practices and education are a high priority in the field of rare diseases and are main determinants for a timely and appropriate diagnosis and a high quality of care.

### 5.2. Information, education and training of health professionals

69. The adoption of appropriate initiatives for training and education of health professionals is an important instrument to improve diagnosis and quality of care. The need for training does not refer only to clinical capacity, but also to the ability to communicate with patients. Indeed, patients' associations have identified gaps in the way information is provided by health professionals to patients at several stages, such as the communication of diagnosis; the reception in emergency situations; the care provided throughout the illness to help social inclusion; periods of disease aggravation and at the end of life. Moreover, it has been remarked that most health professionals do not have adequate information on clinical and organizational aspects (e.g. diagnostic strategies, referral of patients, etc.), which may cause dangerous delays in the provision of adequate care. The provision of accurate information in a format adapted to the needs of professionals is a key element to improve diagnosis and care in the field of rare diseases. For this reason, in 1997, supported by the European Commission and institutions from all member states (see box) the European portal of rare diseases and orphan drugs, Orphanet, was established.

### **THE ORPHANET DATABASE FOR RARE DISEASES**

Since 2000, the Orphanet database has been providing information about over 5000 rare diseases in six different languages. It provides (i) a comprehensive encyclopaedia about rare diseases; (ii) a directory of professional services in 35 countries; (iii) a directory of European centres of reference, of ongoing clinical trials, and of available guidelines; (iv) a database for orphan drugs providing information on their stage of development and availability in EU countries; and a range of other services for specific categories of

stakeholders, including (v) a facility to retrieve diagnoses through symptoms and signs and (vi) a library of recommendations for emergency situations. The portal also provides reports on epidemiology data, and gives direct access to other relevant websites and published articles. It serves as a repository for clinical guidelines, also. The Rare Disease Task Force has established a bi-monthly newsletter, Orphanews, which constitutes an important tool for disseminating information on health and research policies at International and national level, on new scientific facts, on courses and conferences. [www.orpha.net](http://www.orpha.net)

70. Training and education of professionals can be targeted in different ways according to the role they play in rare disease care; all health care professionals should be made aware of the existence of rare diseases, the difficulty of diagnosis, the specific organization of the health service to assure appropriate care and of the needs of rare disease patients.

Several actions in this area are advisable, on the basis of existing experiences, such as:

- improve communication on the available sources of information about rare diseases, e.g. several national / regional databases, as well as Orphanet database;
- support the training of medical students in the field of rare diseases (e.g. the introduction, in the curricula of the medical degree courses, of a specific module on the features of rare diseases and the specific organizations put in place to speed up diagnosis and facilitate patients' access to quality expertise);
- provide training of health professionals on rare diseases in general (e.g., main characteristics of rare diseases due to the rarity, specific medical and psycho-social needs of persons with a rare disease);
- provide specifically targeted training to general practitioners (e.g. in order to cover the daily care needs of patients with rare diseases);
- develop medical training in fields relevant to the diagnosis and management of rare diseases (e.g., genetics, immunology, neurology, oncology, paediatrics);
- support the training of new professions which could help improve the care of patients and their families;
- promote the exchange and sharing of expertise and of knowledge between centres within the country and in other countries;
- develop and disseminate evidence-based and internationally agreed guidelines and best practices on rare diseases;
- promote harmonisation of qualification for medical specialties relevant in the field of rare diseases, in order to ensure that all medical professionals involved in the field receive the same level of adequate training.

**HARMONISE QUALIFICATIONS FOR CLINICAL GENETICS AS MEDICAL SPECIALTY ADOPTED BY THE EUROPEAN UNION OF MEDICAL SPECIALISTS**

The European Union of Medical Specialists (UEMS), a non-profit organisation founded in 1958 to determine high quality standards by harmonising specialist training for European physicians, represents some 1.5 million European medical specialists in 38 specialist sections throughout 35 national member associations. In April, the UEMS Council adopted the text entitled Description of Clinical Genetics as a Medical Specialty in EU: Aims and objectives for specialist training. The document, which defines educational goals for a specialisation in genetic medicine, has been endorsed by the European Society of Human Genetics, the UEMS Multidisciplinary Joint Committee for Clinical Genetics, and the UEMS Specialist Sections & European Boards. This is good news for rare disease patients in countries where clinical genetics is not yet recognized. It will stimulate equal provision of genetic services across Europe.

**PARAMEDICAL TRAINING IN THE 2ND FRENCH NATIONAL PLAN ON RARE DISEASE**

In France, in the context of a restructuration of Centres of Expertise being proposed for the second National Plan for Rare Diseases (as described in the above box "Identification and Designation of Centres of Expertise"), 20 to 30 nation-wide networks specialised in spreading expertise, information and training, including therapeutic training, will link the Centres of Expertise. These networks will be responsible, amongst other, to train paramedical health professionals and to exchange their best practices, taking as an example the already existing networks for cystic fibrosis and development anomalies in the region of Montpellier. It is also envisaged that the greater complexity of the treatments provided to rare disease patients by the medical and paramedical staff will be adequately reflected in the fees applied to those treatments.

### 5.3. Neonatal screening

71. The use of organized neonatal population screening or of targeted screenings depends on public health systems and social issues which may vary in different countries, such as the different geographic patterns of distribution of certain diseases or the distribution in specific groups of population at high risk.

72. Regarding neonatal screening practices, significant differences exist within European countries, e.g. the number of rare diseases screened may range from 2 to 25. The need of pooling data from national screening programs and evaluating the outcomes of different screening policies has stimulated DG Public Health to launch a call for tender in July 2009 for the evaluation of the current situation of newborn screening practices in the EU member states.

73. On these premises, it is important that a national plan or strategy for rare diseases:

- takes into consideration to contribute to the European evaluation of the existing neonatal screening programs;
- monitor changes in the population which can justify the provision of targeted screening practices.

### 5.4. Clinical guidelines

74. In the field of clinical guidelines, evidence-based guidelines are the gold standard because modern medical practice requires that any recommendation should have a clear scientific and clinical justification. The availability of evidence-based guidelines in the field of rare diseases is extremely scarce, due to the lack of evidence-based, controlled studies,

which can be partly overcome pulling clinical research resources together through collaboration in international networks. When there is insufficient quality evidence usually a consensus is reached from a number of experts in the field. The international dimension is extremely important in the field of guidelines for rare diseases, due to the rarity of experts in each specific rare disease/group of diseases.

75. The elaboration of new guidelines can be promoted in different ways, such as:
- stimulating the national guidelines creating mechanisms (when applicable) to analyse the main areas/diseases where guidelines are needed and act accordingly;
  - stimulating the national scientific societies and other experts to promote the topic at national and international level and to organize working groups;
  - launching specific calls and support projects;
  - promoting the adoption and/or adaptation of clinical guidelines produced by other member states or other International bodies for rare diseases not covered by national guidelines.

**THE NATIONAL GUIDELINES OF THE FRENCH NATIONAL AUTHORITY FOR HEALTH**

In the framework of the first **French national plan for rare diseases (2004-2008)** 27 practice guidelines have been issued through the HAS (French national Authority for Health). Even though this is a good result, the evaluation of the French national plan has underlined the fact that such a process is lengthy and costly, and international collaboration and a European dimension for such creation has been suggested as more effective

**THE NATIONAL GUIDELINES SYSTEM (SNLG - WWW.PNLG.IT) OF ITALIAN NATIONAL INSTITUTE OF HEALTH (ISTITUTO SUPERIORE DI SANITÀ, ISS)**

It produces and disseminates evidence-based guidelines for clinical practice following a detailed methodology. In this context, guidelines for specific rare diseases (e.g. alternating hemiplegia) have been elaborated by experts with the co-ordination of the National Centre for Rare Diseases ([www.pnlg.it/lgmr#](http://www.pnlg.it/lgmr#)).

### 5.5. Access to orphan drugs

76. The adoption of the regulation (EC) No. 141/2000 on orphan medicinal products provided the guidelines and criteria for designation as 'orphan medicinal products', i.e. those medicinal products which are meant for the diagnosis, prevention or treatment of rare conditions.

77. Despite the incentives for development and marketing of orphan medicinal products provided by the regulation (EC) No. 141/2000, the availability of orphan drugs within the European countries and their access of citizens are very variable and unsatisfactory. The reasons are different and multiple, laying, in some cases, in the fact that companies do not market the drug in some countries (because of scarce market value, e.g. in small countries), or, in other cases, in the national procedures for reimbursement or criteria for special access to drugs. A recent study has been published by the London-based Office of Health Economics investigating pricing and reimbursing schemes and specific orphan drugs policies in some European countries (see box).

**ACCESS MECHANISMS FOR ORPHAN DRUGS: A COMPARATIVE STUDY OF SELECTED EUROPEAN**

**COUNTRIES**

The report (November 2009) has been compiled by the Office of Health Economics that compares the pricing and reimbursement schemes and specific orphan drug policies of France, Germany, Italy, the Netherlands, Spain, Sweden and the UK. Via a review of existing literature, consultation with national experts and an examination of data on the coverage decisions taken concerning the first 43 orphan medicinal products (OMP) that the European Medicines Agency authorised following the adoption of EU Regulation EC 141/2000 on orphan medicinal products, certain conclusions were able to be drawn.

The study reveals the conflict between regulations geared towards accelerating orphan medicinal products to the marketplace and Health Technology Assessment policies that can effectively hinder access to such products. The report concludes with:

- More cooperation and networking at the European and international level are required in order to develop more reliable evidence after marketing authorization.
- It is crucial that all key stakeholders, including clinicians, are involved in the development of Europe-wide registries and processes for data collection around treatment pathways.
- To address the potential conflicts between data requirements for licensing and for reimbursement purposes, an early engagement between licensing bodies, HTA bodies and companies should be facilitated in order to identify the potential evidence issues and to explore possible ways forward.
- In many cases there is no “second chance” to conduct an additional clinical study if the available data prove inadequate due to the limited number of patients and ethical considerations of further randomization.
- It might be appropriate to develop common guidelines for setting an “acceptable minimum dataset” for licensing and reimbursement to be considered as a benchmark by developers/manufacturers and decision-makers at the European level.

Access Mechanisms for Orphan Drugs: A Comparative Study of Selected EU Countries can be consulted on [www.OHE.org](http://www.OHE.org)

78. Although the EU approved more than 60 orphan drugs and assigned more than 600 orphan designations (2001-2010), a specific treatment is not available for most rare diseases. Since it has been estimated that between 5000 and 8000 different rare diseases exist, the unsatisfactory situation of the available treatments is evident.

European and national initiatives in the field of rare diseases are therefore necessary to foster basic biomedical research and translational research for the development of orphan drugs and other effective treatments for rare diseases. It should be noted that the likelihood for a patient with a rare disease to obtain a new therapy (with an orphan drug) increases when more biomedical scientific research has been published about the disease. The development of the drug itself relates not only with the level of research and scientific output, but also with the stimulation of pharmaceutical innovation and with the country expenditure in research and development. According to various sources, the development of drugs is risky and costly, especially for a small market. The discussion on the development of orphan drugs in the near future is likely to focus more on costs and availability in relation to the benefit for patients.

**IMPROVING ACCESS TO ORPHAN DRUGS TO ALL PATIENTS AFFECTED IN EU**

In the framework of the EU Pharmaceutical Forum, a three-year process launched in 2005 by the EU Commissioners for Enterprise and Health, the Forum’s Working Group on Pricing developed and adopted a document on “Improving Access to Orphan Drugs to all patients affected in EU” ([http://ec.europa.eu/pharmaforum/docs/pricing\\_orphans\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/pricing_orphans_en.pdf)).

The paper is the result of a process involving representatives of all 27 EU member states, the European Commission, the industry’s trade associations EFPIA and EuropaBio, EURORDIS.

The documents aims at setting up guiding principles to identify the main bottlenecks related to development of orphan drugs, assessment, pricing and reimbursement practices by companies and by national authorities

and awareness raising. It then puts forward some ideas that should be explored in order to ensure timely and equitable access for all EU citizens to orphan medicines, namely: 1) Establish early dialogue between companies and pricing and reimbursement authorities, including clinical value assessment authorities regarding orphan medicines in the pipeline and the future needs for these medicines; 2) Exchange of knowledge amongst member states and European authorities on the scientific assessment of the clinical added value of orphan medicines; 3) Promotion of the initial uptake of orphan medicines through conditional pricing and reimbursement decisions; 4) Building EU-level awareness and expertise on orphan diseases.

79. In terms of assessment of the clinical added value of orphan drugs, it is important to highlight that much of the groundwork is done by the European Medicines Agency (EMA). In order to receive a marketing authorisation as an official “orphan” medicine, the treatment has to prove that (i) it treats a rare, serious and life-threatening or debilitating disease; that (ii) there is no satisfactory existing treatment; (iii) that it offers significant benefit to patients. As such, an EMA marketing authorization already provides the basis for a clinical added value of an orphan medicinal product. It has been suggested to establish a clinical added value working party.

#### **THE ASSESSMENT OF THE CLINICAL ADDED VALUE ON ORPHAN DRUGS (CAVOD)**

The patient group EURORDIS and other stakeholders, such as the industry platforms EuropaBio, European Biopharmaceutical Enterprises (EBE) and European Federation of Pharmaceutical Industries and Association (EFPIA), are proposing to create a Working Party for the assessment of the Clinical Added Value on Orphan Drugs (CAVOD) and to locate this Working Party where the relevant knowledge and expertise on Orphan Drugs is gathered, namely at the European Medicines Agency (EMA).

The Working Party on the CAVOD would produce: 1) Scientific Common Assessment Reports (CARs) on the CAVOD to provide a non-binding basis for the national level to take appropriate, well-informed decisions on pricing and reimbursement within the legal timeframe, based on expert opinions that will support and speed-up national decisions; 2) The Annex to the CARs on CAVOD to provide a non-binding basis for agreement on the post-marketing studies required by member states. This approach will support the promotion of conditional pricing and reimbursement which can be reviewed in the following years based on data generated to better define the place of the medicine in the therapeutic strategy of the rare condition in real life setting.

80. In addition, several European legislation initiatives in the field of medicinal products are being developed that may influence the situation of orphan drugs, such as the implementation of the Clinical Trials Directive, the Advanced Therapies Regulation, the decision to make public parts of the EudraCT, the clinical trial database. The impact assessment of the Clinical trials regulation (which will be released in 2010) may shed some light on the status of the development of orphan medicinal products.

#### **AUTHORIZATION FOR TEMPORARY USE (ATU)**

French ATU System has the purpose to make new promising drugs (not yet approved in France, or approved abroad) earlier accessible for patients in France. As a result of this ATU system 70% of the orphan drugs were available for patients 29 months earlier (before market authorization). The criteria are: the new promising drug is meant for the treatment, prevention or diagnose of a rare or serious disease; there is no satisfactory alternative available; efficacy and safety are presumed; the authorization for temporary use is for limited time.

## 5.6. EUROPLAN recommendations on Area 5: Gathering the expertise on rare diseases at European level

- *The use of international global information websites and data repositories for rare diseases is supported.*
- *Help lines for health professionals are supported.*
- *Awareness of the academy is raised on rare diseases, with particular attention to those lacking treatment.*
- *Information for health professionals is made available for joining European Reference Networks.*
- *The curriculum of the medical degree course includes an education package on rare diseases and on the relevant, specific provisions in the healthcare services.*
- *Training of medical doctors, scientists and new healthcare professionals in the field of rare diseases is supported.*
- *Specifically targeted training to general practitioners is provided.*
- *The exchange and sharing of expertise and knowledge between centres within the country and abroad is promoted.*
- *Collaboration is ensured in the European evaluation of the existing screening programs.*
- *The development and dissemination of evidence-based and internationally agreed guidelines and best practices on rare diseases is promoted.*
- *An inventory of the accessibility to orphan drugs, including reimbursement issues, is implemented.*
- *Dissemination of the information about orphan drugs, e.g. EMA decisions, is ensured in the most effective way, to avoid delays of the orphan drug accessibility.*
- *Provisions are set out for the off-label use of approved medicinal products for application to rare diseases; the use of drugs still under clinical trial is facilitated; measures of compassionate provision of orphan drugs are considered.*
- *Participation is ensured in actions promoting the marketing authorization of orphan drugs in all EU Countries; initiatives are taken for a common pricing mechanism.*
- *Patients' access to treatment of authorised orphan drugs is recorded at national or EU*

*level.*

- *The list of on-going clinical trials on Orphan Medicinal Products included in the European database for clinical trials on Orphan Medicinal Products (EUDRA) is made public in order to improve quality of clinical trials through a higher number of patients and more reliable data.*

## Area 6. EMPOWERMENT OF PATIENT ORGANISATIONS

### **Council Recommendation (2009/C 151/02)**

18. Consult patients and patients' representatives on the policies in the field of rare diseases and facilitate patient access to updated information on rare diseases.

patient organisations, such as awareness-raising, capacity-building and training, exchange of information and best practices, networking and outreach to very isolated patients.

19. Promote the activities performed by

### 6.1. Introduction

81. Empowerment is the process of increasing the capacity of individuals or groups to make informed choices and to transform those choices into actions and outcomes. As a result of empowerment, patients with rare diseases have in many cases played an active and instrumental role in determining research projects and shaping health care policy. In addition, empowerment may result in better management of the daily needs of patients and better compliance with care protocols, in coping with the associated psychological conditions and in improving the social inclusion. Promotion of education and of work participation are also important actions to foster the psychological development of rare disease patients and their families.

### 6.2. Information to the public and patients

82. Due to the large number of different rare diseases there are over 1700 different patients' organizations in Europe. They play an important role in offering information and assistance to patients, raising funds for research and lobbying for better quality of care and of treatment. Many of these people (patients and relatives) are organized into national alliances/umbrella and/or affiliated to European umbrella organisations, the most important of which is, by far, EURORDIS (see box). The participation of EURORDIS in shaping the European policies for rare disease and the contribution given to the general advancement of the rare disease field in several areas represent a clear success of the patients' empowerment process.

#### **THE EUROPEAN UMBRELLA ORGANISATION FOR RARE DISEASES (EURORDIS)**

The website of the European umbrella organisation for rare diseases, EURORDIS ([www.eurordis.org](http://www.eurordis.org)), in 6 languages (English, French, German, Spanish, Italian, Portuguese) is a very valuable source of information on EU and national Policies, on orphan paediatric and advanced therapies and drugs, on patients' stories etc. The monthly e-Newsletter of EURORDIS published also in 6 languages provides news and in-depth analysis, links to blogs and forums for discussions.

83. Patients with rare diseases and their families experience major difficulties in finding information on their disease (especially in their own language), regarding its clinical features, measures for social and economic assistance and location of the centres providing appropriate expertise and care. The provision of accurate information in a format adapted to the needs of patients is an important instrument frequently used by patients to fulfil

their information needs.

84. Disease-specific websites about patients' associations, networks of reference, registries or specific activities on rare diseases are very important sources of information frequently used by patients. Among the initiatives for the provision of general and specific information on rare diseases, an essential role is played by the telephone help lines. Established by patients' organizations or governmental institutions, they contribute to inform, guide and support patients, families and healthcare professionals.

Help lines usually offer:

1. information about a specific or a group of rare diseases or rare disease-related topic, in order to compensate the frequent critical lack of information. This service is essential, when other possible means do not exist or cannot provide suitable information, thus preventing the isolation of patients, and overcoming the digital divide, which is essential to reach more vulnerable people.
2. psychological support to the patient and practical-logistics support regarding services offered in the country.

85. Help lines should be included in the context of a National Plan or Strategy for rare diseases, as a useful tool to:

- provide quality information customised to the individual needs;
- provide support and orientate patients towards Centres of Expertise;
- provide information on access to orphan drugs and to special provisions to accelerate and facilitate access to existing drugs;
- provide information on ongoing clinical trials and researches;
- provide information on genetic testing, genetic counselling, neonatal screening;
- provide access to existing patient organisations and online communities;
- provide support to very isolated patients and facilitate communication with other similar patients and inclusion in communities, including virtual communities;
- participate in the European Network of telephone help lines, (see box below) where common approaches to the daily management of them are proposed;
- support the establishment of a single European telephone number for rare diseases.

#### **THE NETWORK OF RARE DISEASE HELP LINES**

The Network of Rare Disease Help Lines was created in the context of the European Rhapsody Project (Rare Disease Solidarity Project).

The main objectives of the network are:

- increase the quality of service provided by rare disease help lines across Europe by sharing expertise and creating a common approach;
- provide support to help line services across Europe (advocacy – communication – technical tools – training and support);
- improve the visibility of help line services at European and national level;
- increase funding opportunities for members services and the network itself;
- implement a membership policy that is as inclusive and representative as possible while still ensuring that standards of excellence are part of the admission procedure.

#### **THE ITALIAN RARE DISEASE HELP LINE**

In Italy, there are several institutional (national and regional) help lines as well as many others supported by patients' groups. The institutional national helpline is a public service (800 896949) established at the

National Centre for Rare Diseases (Italian National Institute of Health).

A multidisciplinary team (psychologists, sociologist and medical doctors) trained on telephone counselling, public health policies and management of rare diseases is involved. The main aim of the service is provide information to patients and to health operators on rare diseases, centres for their diagnosis and care, clinical trials, availability of orphan drugs, etc.

86. Based on the information needs of patients and health professionals, information which is particularly relevant and usually difficult to find in the field of rare diseases are those related to organization of care and specialised services, to orphan drugs and other treatments, ongoing experimental trials, rehabilitation and social services, administrative and legal information on access to care, right to reimbursement and other benefits provided by the public services.

87. Websites providing 'global information' on rare diseases and other information tools at national level are going to be more effective when containing links to international information portals and institutions to facilitate access to additional information resources, such as the EU Public Health website and in particular the section on rare diseases; the EMA website; EURORDIS and ORPHANET websites; and any other relevant website for rare diseases, in addition to specific information on national and regional initiatives.

#### **THE BULGARIAN ASSOCIATION FOR PROMOTION OF EDUCATION AND SCIENCE (BAPES)**

The Bulgarian Association for Promotion of Education and Science (BAPES) established in 2004 the "Information Centre for Rare Diseases and Orphan Drugs" (ICRDOD) as a main project. It is the first and unique Eastern European information and educational service, dedicated to all people, associations and medical professionals, interested in rare diseases and orphan drugs. ICRDOD maintains a website ([www.raredis.org](http://www.raredis.org)) and provides free-of-charge information on rare diseases to people and their families, but also to health professionals and patient organisations. All medical and health information, provided and hosted on the site is given by medically trained and qualified professionals. The information provided on this site is designed to support, not replace, the relationship that exists between a patient/site visitor and his/her doctor. Sources of information that the centre uses to respond include MEDLINE, OMIM, ORPHANET, specialised medical literature, and other internet sources/databases. The information is provided in English and Bulgarian languages. Those requesting information can do so using the multilingual site of the information centre, email, fax or helpline.

#### **INFORMATION WEB SITES IN ITALY**

In Italy, information on rare diseases and orphan drugs is provided by institutional as well as patients' websites. At national level, the website of National Centre for Rare Diseases ([www.iss.it/cnmr](http://www.iss.it/cnmr)) provides validated information on centres for diagnosis and management of rare diseases; genetic tests quality assessment; patients' groups etc.; registries; guidelines; narrative medicine; orphan drugs; news, etc. At regional level, there are institutional websites, examples are in Lombardy (<http://malattierare.marionegri.it/>); Piedmont ([www.malattierarepiemonte.it](http://www.malattierarepiemonte.it)) and Veneto (<http://malattierare.regione.veneto.it>).

### 6.3. Specialised social services

88. Specialised social services are instrumental to the empowerment of people living with rare diseases and improve wellbeing and health. For people living with a rare, chronic and debilitating disease, care should not only be restricted to medical and paramedical aspects, but should also take into account social inclusion and psychological or educational

development. Online communities are vital for establishing contacts among extremely isolated patients. Therapeutic recreational programmes encourage personal development. Respite care services give family members and carers downtime opportunities.

89. Respite care services have been devised to assist on a temporary basis people who normally live at home, so that their carers benefit of a pause from care giving. One of the important purposes of respite care services is to give family members time and temporary relief from the stress they may experience while providing extra care for a family member affected by a rare disease. Several different approaches and services exist in offering respite care: centre-based respite care (day-centre); residential based respite care and home care.

90. Therapeutic recreational programmes are formally or informally organised recreation activities (e.g. summer camps, *ad hoc* trips) which have been planned taking into account the specific needs of children or young adults with rare diseases. Activities are centred on fun, leisure and entertainment. They may include regular or *ad hoc* activities.

91. Examples of social services to integrate patients in their daily life and support their psychological and educational development are:

- a) educational support for patients, relatives and caregivers;
- b) individual support at school at different schooling level, for both pupils with rare diseases and teachers, including disease-specific good practices;
- c) promotional activities aimed to foster higher education for people with rare diseases;
- d) supporting mechanisms to enter and stay in school and participate in work life for people with disabilities.

#### **THE DISEASE PATIENT SOLIDARITY PROJECT (PROJECT RAPSODY)**

The objectives of the European Commission funded Rare Disease Patient Solidarity project (Acronym : RAPSODY) are to improve access to, and quality of, fundamental services primarily for patients, families and patients organisations, but also for health professionals. RAPSODY run from 2006 to 2008, was managed by the patient organisation EURORDIS and involving 10 partners. As a development of the services included in RAPSODY, European networks of respite care centres, of therapeutic recreation programmes and help lines were created and are currently managed by EURORDIS. On [www.rapsodyonline.eu](http://www.rapsodyonline.eu) an overview of respite care services, therapeutic recreation programmes, leisure and call centres within Europe is given.

#### **STATE REFERENCE CENTRE FOR RARE DISEASES PATIENTS AND THEIR FAMILIES (CREER)**

State Reference Centre for Rare Diseases Patients and their Families (CREER) in Burgos (Spain) is in charge of promoting the coordination between health and social care services. Moreover, it should act as a driving force behind the cooperation between the different services and units with responsibilities in the fulfilment of the needs of people with rare diseases and of their families, and also between the public sector and the associative movement. Its main role consists of integrating into a single strategy the assistance foreseen by the system for the equalisation of opportunities for people with disabilities. To achieve that mission it will use its functions in the areas of the management of information and publications, the training of specialists, as well as the promotion of actions in the field of innovation, development and technical aid services.

[http://www.imserso.es/creer\\_01](http://www.imserso.es/creer_01)

#### **ÅGRENSKA (www.agrenska.se)**

Ågrenska is a Swedish NGO which organizes activities with a holistic perspective for children, youths and

adults with disabilities, their families and concerned professionals. The aim is to function as a creative and supportive environment between needs and knowledge.

Ågrenska facilitates the individual's possibility to cope with everyday life and to live an independent life. This is accomplished by arranging a variety of programs, such as family sojourns, courses for professionals and respite service.

#### 6.4. EUROPLAN recommendations on Area 6: Empowerment of patients

- *Advocacy of patients' needs by patients' associations is recognized as an important element in defining policies on rare diseases; the organization of a national umbrella organization that represents the interests of all rare diseases patients is encouraged.*
- *The patients' organizations are involved in decisions making processes in the field of rare diseases.*
- *Valid information on rare diseases is produced and made available at national level in a format adapted to the needs of patients and their families. Information to patients is available at the EURORDIS website in five languages, till now; information given at Orphanet websites is also translated into several EU languages.*
- *Specialised social services are supported for people living with a chronically debilitating rare disease and their family carers.*
- *Specialised social services are established to facilitate integration of patients at schools and workplaces.*
- *A directory of centres providing specialized social services, including those offered by patients' associations, is compiled, kept updated and communicated to national, regional and patients' websites and included in the Rapsody network.*
- *National help lines for patients are supported, advertised and linked to the Network of Rare Disease Help lines (Rapsody Project).*
- *Information and education material is developed for specific target groups (e.g. teachers, social workers, etc.).*
- *Facilitate the activities aiming at patients' empowerment carried out by patients' associations.*

## Area 7. SUSTAINABILITY

### **Council Recommendation (2009/C 151/02)**

*20. Together with the Commission, aim to ensure, through appropriate funding and cooperation mechanisms, the long-term sustainability of infrastructures developed in the field of information, research and healthcare for rare diseases.*

#### 7.1. Introduction

92. Improving the health care of rare disease patients implies allocation of funds for the delivery of improved health and social services over the long term, as well as funding to implement the adaptation of the health system, including the establishment of new structures and/or new tasks, to respond to the unfulfilled needs of rare disease patients. The costs of providing or improving services for rare diseases patients, should be assessed in view of the overarching values of universality, access to good quality care, equity and solidarity as stated on the Council Conclusions on Common Values and Principles in European Union Health Systems (2006/C 146/01) and should be balanced with the subsequent savings in health care and social costs gained from having rare diseases patients in better health.

At national level, the development of infrastructures for rare diseases might be planned in combination with their use for other purposes in the medical fields, so that the balance of costs and returns can be evaluated with reference to a wider strategy.

93. While the decision making process for the organization and funding of the health system is in the national competence, the sustainability of the overall process of care delivery can take much advantage if decisions and responsibilities are agreed among member states in view of establishing transnational collaboration and coordination of services and activities. On the other side, cooperative initiatives, whose success is dependent on wide and long-term participation, like research infrastructures and programs and networks of centres of expertise on rare diseases, should be protected from the discontinuation of the funding of participating local (national) structures, which has been till now based on national decision processes.

#### 7.2. The governance of the cooperative initiatives foreseen in the National Plan or Strategy

94. The European Union currently faces a time of transition and change in the process of European integration, following the entry into force of the Lisbon Treaty. The renewal of the European Parliament and the European Commission, the transition to a new institutional framework, the recast of the EU budget and the direct and indirect effects of the global crisis all illustrate the new shape of the Community agenda for the coming years. Active discussion at EU political level has been on-going for the last years about the

development of a new European governance in relation to the provisions of the Lisbon Treaty, which enshrines the territorial dimension, notably territorial cohesion, as part of the process of European integration and strengthens the mechanisms of multilevel governance<sup>6</sup>. Of special interest may be the debate on the enhanced governance of the European Research Area ERA, the so called “Ljubljana process”, named after the informal Ministerial Meeting (Ljubljana, 14-15 April 2008) where its principles were discussed and the initiatives ensuing from it<sup>7</sup>.

95. Besides the new mechanisms that can be expected from the developments ensuing from this on-going debate, the current EU governance instruments include the open method of coordination, which has been used for a number of years in areas where the European Union is only empowered to coordinate or support. Used on a case-by-case basis, it would offer a way of encouraging cooperation, exchanging good practices and agreeing on common objectives and strategies for the member states, while taking into account the subsidiarity principle. The High level Group on Health Care and Medical Services will be an important seat for debating issues related to the interconnections of health systems and policies. The new EU Committee of Experts on Rare Diseases (EUCERD), may play also an important role in support of the policy developments in rare diseases.

### 7.3. Using European funding for National Plans/Strategies for rare diseases

96. Funding of National Plan or Strategy is a national responsibility under the respective health national budgets. However some European Union budgetary facilities could be used. Certain national actions can be placed under the Joint Actions defined in the EU Second Health Programme (2008-2013). This is the case in 2010 for the two Joint Actions launched by the European Commission to support the Orphanet database and to support the EUROCAT (Surveillance of Congenital Anomalies) network. A Joint Action implicates a shared financial and political responsibility between member states and the European Commission. This is highly efficient in actions which are not feasible with a single national action and need a wide European coordination.

The funding facilities provided by the EU Second Health Programme (2008-2013) can be used to develop the European Reference Networks (ERN) for Rare Diseases. Under the provisions of the Article 13 of the Draft for a Directive of the Council and the European Parliament on Cross-border healthcare, the national participation in ERN could be developed according to national expertise definition and capacity to lead or participate in ERN.

<sup>6</sup> 1) European Commission (2001): European Governance – A white Paper (COM(2001) 428 final). Available on line at: [http://eur-lex.europa.eu/LexUriServ/site/en/com/2001/com2001\\_0428en01.pdf](http://eur-lex.europa.eu/LexUriServ/site/en/com/2001/com2001_0428en01.pdf)

2) Declaration on the occasion of the fiftieth anniversary of the signature of the Treaties of Rome, Berlin, 25 March 2007

3) The Committee Of The Regions' White Paper On Multilevel Governance (CONST-IV-020 ), approved at the 80th plenary session 17 and 18 June 2009. Available on line at: [http://www.cor.europa.eu/cor\\_cms/ui/ViewDocument.aspx?contentid=0b4c7a7b-8bd3-4f04-8556-d3edc75d3fbb](http://www.cor.europa.eu/cor_cms/ui/ViewDocument.aspx?contentid=0b4c7a7b-8bd3-4f04-8556-d3edc75d3fbb)

<sup>7</sup> More information is available at the European Commission web page [http://ec.europa.eu/research/era/specific-era-initiatives\\_en.html](http://ec.europa.eu/research/era/specific-era-initiatives_en.html)

97. Member states can apply for investments in health and social infrastructures and to develop collaboration, capacity and joint use of infrastructures, in particular in sectors such as health using the instruments to pursue the Structural Funds policy objectives for the period 2007-13. The legal bases of these instruments are in a package of 5 regulations adopted by the Council and the European Parliament in July 2006, under the Regulation (EC) No 1080/2006 of the European Parliament and of the Council of 5 July 2006, on the European Regional Development Fund and repealing Regulation (EC) No 1783/1999. For investments to finance infrastructure or other aspects of National Plans of Rare Diseases, the National Strategic Reference Framework (NSRF) should be used which establishes the main priorities for spending the EU Structural Funds that a member state receives between 2007 and 2013. Each member state has its own NSRF. The National Framework is a requirement of the new Structural Funds Regulations for 2007 to 2013 and will establish the high-level strategy for Structural Funds Operational Programmes in the member state for that period. For the period 2007-2013 only six member states have included investments on health in their NSRF: it is the case of Bulgaria, Estonia, Greece, Lithuania, Malta and Slovak Republic, whereas only one has applied specifically for funding their National Plan on Rare Diseases (Greece, see box). Assistance to member states for the use of the Structural Funds is available (see box).

Budget figures will depend in each member state on different variables (e.g. the general health care expenditure of the country and the areas chosen as priority in the National Plan or Strategies). Budgeted actions are currently foreseen in the Bulgarian, Greek, French and Portuguese National Plans and in isolated specific rare diseases actions across some member states, supporting e.g. research (Germany, Italy), centres of expertise, orphan drugs. In other cases, actions are funded within the general health care system budget, from which also rare diseases patients can benefit, such as e.g. expert centres for diseases with particular clinical complexity in the United Kingdom.

The [Greek National Plan on Rare Diseases 2008-2012](#) is the only one having introduced in their financial perspectives an EU funding. From a total budget of 27 703 834 Euros for the period 2008-2012, the Greek authorities intends to obtain a total of 16 335 734 Euro (59.1% of the total budget) declaring their NP on RD as a priority in their NSRF.

**JASPERS** (Joint Assistance to Support Projects in European Regions) is a technical support facility set up in 2006 to help the 12 member states which joined the EU in 2004 and 2007 to identify and prepare projects potentially eligible for assistance under the EU Structural Funds (European Regional Development Fund and Cohesion Fund). JASPERS is managed by the European Investment Bank (EIB) and the other partners are the European Commission, the European Bank for Reconstruction and Development and Kreditanstalt für Wiederaufbau (KfW). JASPERS' main objective is to help these member states make use more rapidly and more effectively of the EUR 347 billion grant finance made available by the European Union for the implementation of EU cohesion policy during the period 2007-2013. The support provided by JASPERS is comprehensive and covers all stages of the project cycle from the initial identification of a project through to the grant application to the Commission

#### 7.4. EUROPLAN recommendations on Area 7 Sustainability

- *The National Plan or Strategy on rare diseases is supported according to the Country health system and decision-making processes.*
- *Possibilities for European funding are exploited for National Plans or Strategies for rare diseases.*
- *The cooperation with other member states is envisaged in order to address the need for sustainability of common European infrastructures, share costs and maximise the efficacy of initiatives.*
- *Participation in the debate on enhanced EU governance is ensured, in order to find agreed and improved mechanisms for the governance of the healthcare, information and research initiatives requiring transnational collaboration.*
- *Agreements for coordinated projects, including long-term sustainability of common infrastructures, are pursued within the framework of the open method of coordination among member states.*

## REFERENCES

Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force. A technical and scientific report from an expert group of the Rare Diseases Task Force To The High Level Group on Health Services and Medical Care. *December 2006.*

[http://www.orpha.net/testor/doc/RDTF\\_anna/WG/StandardsOfCare/reports/RDTFContributiontoEC06FINALVERSION.pdf](http://www.orpha.net/testor/doc/RDTF_anna/WG/StandardsOfCare/reports/RDTFContributiontoEC06FINALVERSION.pdf)

Commission Staff Working Document. Summary of the Impact Assessment Accompanying the Communication from the Commission to the Council, the European parliament, the European Economic and social Committee and the Committee of the Regions On Rare Diseases: Europe's challenges {COM(2008)679} {SEC(2008)2712}

Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. Brussels, 11.11.2008. COM (2008) 679 final.

[http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/rare\\_com\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf)

Council Conclusions on Common Values and Principles in European Union Health Systems (2006/C 146/01). <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:146:0001:0003:EN:PDF>

Council Recommendation of 8 June 2009 on an action in the field of rare diseases OJ (2009/C 151/02) 3.07.2009 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

De Bruin, Picavet HS, Nossikov A. Health interview surveys. Towards international harmonization of methods and instruments. [WHO Reg Publ Eur Ser.](#) 1996;58:i-xiii, 1-161.

DG Enterprise and Industry, European Commission. Inventory of Community and member states' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005. 07/09/2006. Available from:

[http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory\\_2006\\_08.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006_08.pdf)

Direcção-Geral da Saúde [www.dgs.pt](http://www.dgs.pt). Programa nacional para doenças raras (PNDR)

European Society for Medical Oncology. Improving rare cancer care in Europe. Recommendations on Stakeholder Actions and Public Policies.

[http://www.rarecancers.eu/IMG/pdf/ESMO\\_Rare\\_Cancers\\_RECOMMENDATIONS\\_FINAL.pdf](http://www.rarecancers.eu/IMG/pdf/ESMO_Rare_Cancers_RECOMMENDATIONS_FINAL.pdf)

EUROPLAN <http://www.europlanproject.eu/>

Evaluation of population newborn screening practices for rare disorders in member states of the European Union. [http://ec.europa.eu/eahc/health/tenders\\_H09C2.html](http://ec.europa.eu/eahc/health/tenders_H09C2.html)

Federaal Kenniscentrum voor de Gezondheidszorg/Centre Federal d'Expertise des Soins de Santé/Belgian Health care Knowledge Centre (KCE). Policies form Orphan Diseases and Orphan Drugs. KCE reports 112c, 2009.

Folino Gallo P. Orphan Drugs in Italy. Accommodating orphan drugs: balancing innovation and financial stability. In: Accommodating orphan drugs: balancing innovation and financial stability. London; 25 February 2008

Garau M, Chauhan D. Decision-making processes in the orphan drugs arena. The UK perspective. In: Office of Health Economics, editor. Accommodating orphan drugs: balancing innovation and financial stability. London; 25 February 2008.

Meyer F. Orphan Drugs: How Are They Assessed / Appraised in France? In: HAS, editor. 25 February 2008.

Ministère de la Santé et des Sports, Haut Conseil de la santé publique. Évaluation du Plan national maladies rares 2005-2008. Avril 2009

National Institute for Clinical Excellence. Appraising Orphan Drugs. 12/7/2005. Available from: <http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf>

National Plan for Rare Diseases 2009-2013 (Genetic, congenital malformations and non-hereditary disease) Bulgaria

Orphanet (<http://www.orpha.net/consor/cgi-bin/index.php>)

Orphan drugs and the NHS: should we value rarity?, BMJ volume 331, 29 October 2005

P. Serrano-Aguilar et al; Patient involvement in Health research: a contribution to a systematic review on the effectiveness of treatment for degenerative ataxias . Social Science & Medicine 69, 2009

[Plan National Maladies Rares \(2005-2008\)](#). French National Plan. #

Prague Declaration on e-Health (<http://www.ehealth2009.cz/Pages/108-Prague-Declaration.html>).

Proposal for a Directive of the European Parliament and the Council on the application of patients' rights in cross-border health care. COM (2008)41

[http://ec.europa.eu/health/ph\\_overview/co\\_operation/healthcare/docs/COM\\_en.pdf](http://ec.europa.eu/health/ph_overview/co_operation/healthcare/docs/COM_en.pdf)

Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products. OJL 18, 22.1.2000, p.1.

Working Group Pricing and Reimbursement. Improving access to orphan medicines for all affected EU citizens. In: The Pharmaceutical Forum, Editor.; 2008.

The Voice of 12,000 Patients: Experiences & Expectations of Rare Disease Patients on Diagnosis & Care in Europe. [http://www.eurordis.org/article.php3?id\\_article=1960](http://www.eurordis.org/article.php3?id_article=1960)

## ANNEXES

## A.1. EUROPLAN partners and consulted experts (alphabetical Country order)

## Associated partners

Name		Country	Institution
Rumen	Stefanov	Bulgaria	Bulgarian Association for Promotion of Education and Science (BAPES) - Information Centre for Rare Diseases and Orphan Drugs
Vallo	Tillmann	Estonia	University of Tartu (UT) – Department of Paediatrics
Valentina	Bottarelli	France	European Organisation for Rare Diseases (EURORDIS), Paris
Yann	Le Cam	France	European Organisation for Rare Diseases (Eurordis) – Health Policy (Leader WP8 - Promoting the recommendations for rare diseases national plan)
Fabio	Candura	Italy	Istituto Superiore di Sanità (ISS), National Centre for Rare Diseases (CNMR). Europlan Coordinator
Erica	Daina	Italy	Istituto di Ricerche Farmacologiche Mario Negri (IRFMN) – Clinical Research Center for Rare Diseases
Tania	Lopez	Italy	Istituto Superiore di Sanità (ISS), National Centre for Rare Diseases (CNMR). Europlan Coordinator
Pierpaolo	Mincarone	Italy	I.R.I.D.I.A. SRL
Arrigo	Schieppati	Italy	Istituto di Ricerche Farmacologiche Mario Negri (IRFMN) – Clinical Research Center for Rare Diseases
Domenica	Taruscio	Italy	National Centre for Rare Diseases - Istituto Superiore di Sanità (Europlan Coordinator)
Luciano	Vittozzi	Italy	National Centre for Rare Diseases (CNMR) - Istituto Superiore di Sanità (ISS). (Leader WP4 - Describing EU Member States initiatives on rare diseases)
Edvard	Beem	Netherlands	The Netherlands Organisation for Health Research and Development (ZonMw) – Steering Committee on Orphan Drugs
Laura	Fregonese	Netherlands	University Hospital, Leiden
Jolanda	Huizer	Netherlands	The Netherlands Organisation for Health Research and Development (ZonMw) – Steering Committee on Orphan Drugs ((Leader WP7 - Preparing recommendations for rare diseases national plan development)
Sonja	van Weely	Netherlands	Steering Committee OD, The Hague
Manuel	Hens	Spain	Istituto de Salud Carlos III (ISCIII) – Research Institute for Rare Diseases (IIER)
Manuel	Posada	Spain	Istituto de Salud Carlos III (ISCIII) – Research Institute for Rare Diseases (IIER) (Leader WP5 - Selecting indicators to evaluate the achievements of rare diseases initiatives)
Lilisbeth	Perestelo	Spain	Fundacion Canaria de Investigacion y Salud (FUNCIS) – Servicio de Evaluacion y Planificacion
Jan-Inge	Henter	Sweden	Karolinska Institutet (KI) – Department of Woman and Child Health (Leader WP6 - Evaluating selected activities and identifying best practices)
Desiree	Gavhed	Sweden	Karolinska Institutet (KI) – Department of Woman and Child Health
Annika	Larsson	Sweden	Karolinska Institutet (KI) – Department of Woman and Child Health
Edmund	Jessop	UK	London Strategic Health Authority (NCG) – National

## Collaborating Partners

Name		Country	Institution
Olaf	Bodamer	Austria	Institute for Inherited Metabolic Diseases - Paracelsus Medical University and University Children's Hospital
Jean-Jacque	Cassiman	Belgium	Human genetics Center
Maurica	Maher	Canada	Office of legislative and regulatory modernisation Policy, planning and international affairs directorate Health products and Flood Branch
Ingeborg	Barisic	Croatia	Children s University Hospital Zagreb
Violetta	Anastasiadou	Cyprus	The Cyprus Institute of Neurology & Genetics - Clinical Genetics Department
Katerina	Kubachova	Czech Republic	University Hospital of Motol
Milan	Macek	Czech Republic	Institute of Biology and Medical Genetics – University Hospital Motol
Iva	Truellova	Czech Republic	Ministry of Health
Marianne	Jespersen	Denmark	The National Board of Health
Riitta	Salonen	Finland	The Family Federation of Finland - Department of Medical Genetics
Alexandra	Fourcade	France	Ministry of Health – Organisation Department
Véronique	Héon-Klin	Germany	Federal Ministry of Health – Division Molecular Medicine, Bioethics
Birgit	Schnieders	Germany	Federal Ministry of Health – Division Molecular Medicine, Bioethics
Marianna	Lambrou	Greece	The Greek Alliance Of Rare Disease
Miranda	Siouti	Greece	National Organisation for Medicines - Division Pharmaceutical Studies and Research
Janos	Sandor	Hungary	University Pécs, Faculty of Health Sciences, Institute of Applied Health Sciences
Alvaro	Ramirez	Ireland	Hope, Autism Unit; The St. Joseph, Ballinabearna Ballinhassig, Co. Cork
Karolien	Verheyen	Ireland	Blue Beat' - Reenard South Cahirciveen Co. Kerry
Fabrizio	Bianchi	Italy	Institute of Clinical Physiology - National Council of Research - UOSVD Epidemiology UNIT-"Gabriele Monasterio" Tuscany Foundation
Carlo	Francescutti	Italy	Agenzia Regionale della Sanità - Regione Friuli Venezia Giulia
Gemma	Gatta	Italy	Epidemiology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori
Filippo	Palumbo	Italy	Ministero della Salute Direzione generale della programmazione sanitaria, dei livelli essenziali di assistenza e dei principi etici di sistema
Dario	Roccatello	Italy	Ospedale S. Giovanni Bosco, centro Multidisciplinare di ricerche di immunopatologia e documentazione su malattie rare
Monta	Forstmane	Latvia	Ministry of Health, Department of Health Care
Martynas	Pukas	Lithuania	Ministry of Health of the Republic of Lithuania - EU Affairs and International Relations Division
Odetta	Vitkuniene	Lithuania	Ministry of Health of the Republic of Lithuania

Bettina	Vogel	Luxembourg	Personal Health Department - Specialised Medical Care Division Ministry of Health and the rare disease task force of the Grand Duchy of Luxembourg
Isabella	Borg	Malta	Mater Dei Hospital, Department of Pathology Genetics Unit
Jakub	Adamski	Poland	Drug Policy And Pharmacy Department - Ministry of Health
Mirosław	Zielinski	Poland	Polish National Forum on the Treatment of Orphan Diseases – ORPHAN
Luis	Nunes	Portugal	Hospital Dona Estafania – Servicio Genetica medica
Dorica	Dan	Romania	Romanian Prader Willi Association
Jana	Behunova	Slovak Republic	University Children's Hospital, Kosice
Mircha	Poldrugovac	Slovenia	Ministry of Health of the Republic of Slovenia
Virginia	Corrochano	Spain	The Biomedical Network Research Centre for Rare Diseases (CIBERER)
Joan	Lluis Vives Corrons	Spain	European Network for Rare and Congenital Anaemias (ENERCA)
Francesc	Palau	Spain	Scientific Director of the Biomedical Network Research Centre for Rare Diseases (CIBERER);
Pablo	Rivero	Spain	Quality Agency of the Spanish National Health System, Ministry for Health and Consumer Affairs
Josep	Torrent-Farnell	Spain	Autonomous University of Barcelona.
Kerstin	Westermarck	Sweden	Medical Products Agency
Meral	Ozguc	Turkey	Department of Medical Biology, Hacettepe University, Faculty of Medicine, Ihsan Dogramaci Children's Hospital, Sihhiye
Stephen	Groft	USA	Office for Rare Diseases, National Institute of Health

### **Additional experts consulted at the EUROPLAN workshop on EUROPLAN Recommendations - Amsterdam , 17 September 2009**

Andersen, Terkel	Danish Alliance of Rare Disorders
Aymé, Segolene	Orphanet, Paris
Breukelen van, Silvia	VSOP, Soest, NL. National workshop in WP8
Heon-Klin, Veronique	Ministry of Health, Rare diseases and HTA, Bonn
Jessop, Edmund	London strategic health authority, London
Kremp-Roussey, Odile	Ministry of Health, Rare diseases Paris
Leiner, Guenther	International Forum Gastein
Mann, Mirjam	Allianz Chronischer seltener Erkrankungen (ACHSE) e.V., Berlin
Antoni Montserrat	Health and Consumers General-Directorate (SANCO), Luxembourg
Nourissier, Christel	European Organisation for Rare Diseases (EURORDIS), Parijs
Karnström, Jonas	National Board of Health and Welfare (Healthcare Medical Services Department)
Oosterwijk, Cor	VSOP, Soest (Workshop in WP 8)
Europlan Coordinator	
Tambuyzer, Erik	EuropaBio, Brussels
Schuppe, Matthias	International Forum Gastein
Vejvalkova, Sarka	Institute of Biology and Medical Genetics
Zeijden van der, Albert	Dutch Steering Committee OD, The Hague (Chairman Europlan Meeting)

A.2. National conferences comments

(to be added when available)