EURORDIS
Rare Diseases Europe

P O S I T I O N P A P E R

Patients' Priorities and Needs for Rare Disease Research

2014-2020

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"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease"

William Harvey, English physician (1578-1657)

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EXECUTIVE SUMMARY

The following paper outlines the priorities for rare disease research (RDR) that EURORDIS, the European Organisation for Rare Diseases, has identified for the decade ahead. On behalf of patients affected by rare diseases in Europe, EURORDIS urges public decision-makers to take stance in advancing rare disease research on the eve of the adoption of the 8th EU Research Framework Programme 2014–2020 and the National Plans or Strategies on Rare Diseases, which European governments are engaged to adopt prior to 2013. This document presents an overall strategy based on WHAT are the research priorities by area and HOW to achieve them.

WHAT priorities for rare disease research in 2014-2020. Rare disease research covers a broad range of scientific investigations and its needs are so extensive that no area can be neglected. EURORDIS has identified strategic areas that deserve the attention of policy-makers for funding as a matter of priority:

- Supporting **registries and other infrastructures** is a precondition for the advancement of all fields of rare disease research. In particular, support should be provided to:
  - harmonising procedures and developing a common data set for registries and biobanks;
  - optimising resources, e.g. designing multipurpose registries, registries gathering clusters of diseases or epidemiological platforms;
  - collecting data and high-quality biological samples for biobanks; linking biological samples to data in patient registries by e.g. generating unique identifiers for each rare disease patient;
  - developing harmonised quality requirements for registries and biorepositories;
  - self-registration and association of patients with data collection to complement data entries by clinicians;
  - linking registries and databases to Centres of Expertise;
  - sharing pre-competitive[1] resources to overcome the recurring dilemma of infrastructure sustainability.
- **Understanding the underlying mechanisms of rare diseases** is essential for developing novel therapies. This concerns equally the genetic basis, molecular and pathophysiological mechanisms and the natural history of thousands of RD. Specific actions to be taken include:
  - mapping and cloning genes responsible for RDs, identifying mutations and anomalies, and developing tools to understand how genetic anomalies translate into pathological phenotypes;
  - supporting and reinforcing multidisciplinary networks of experts relying on Centres of Expertise and ensuring funds for performing their role as incubators of discovery research;
  - information to and training for researchers at all career stages.
- **Translating research into therapies for patients** is the most urgent priority for the coming years. The actions to be envisaged pertain to unblocking bottlenecks, such as:
  - identification of appropriate biomarkers and surrogate endpoints;
  - pre-clinical research and proof of concept studies relevant to orphan drugs and RD;
  - developing therapeutics by searching for potentially interesting molecules; developing advanced therapy medicinal products, but also research into combining therapeutic agents, given the complex pathophysiological mechanisms of RD;
  - clinical development of designated orphan drugs, notably those with both EU and US designations;
  - repurposing drugs marketed in a non-orphan indications for a rare disease where potential therapeutic benefits have been demonstrated;
  - training developers of therapies in the drug development path, in particular regulatory aspects;
  - support to national and international networks organising clinical trials, such as European Clinical Research Infrastructure Network (ECRIN);
  - finally, the creation of a body that develops, conducts and coordinates translational and clinical research in Europe, along the line of the European Organisation for Research and Treatment of

[1] It refers to the early stages of the development of a commercial product, during which competitors collaborate.

Cancer (EORTC) should be considered.

- Designing **broad strategy trials**, covering all aspects of patient care beyond, and in addition to, drug treatment is a relatively unexplored area that deserves immediate and urgent action. The therapeutic and care arsenal for rare disease patients may be vast and heterogeneous, and most adopted strategies are not supported by evidence-based research. We therefore encourage support to:
  - evidence-based studies aimed to design strategy trials to comprehensively address patient care;
  - pilot trials to define certain aspects of the care strategy for RD for which scarce data are available;
  - in particular, scientific research on the role of surgery and/or complementary treatments within a broader strategy of care for rare diseases.
- **Research in social sciences** is equally essential in order to provide the most suitable services for addressing the needs of the daily lives of patients as well as contributing to their empowerment. This multidisciplinary aspect encompasses research into quality of life, living and working conditions, social needs, public health needs etc.; descriptive and analytic research on society and rare diseases; studies on research to develop parameters to measures the progress of RD research in Europe; validation of tools to support patient-reported outcomes; etc.

HOW to conduct rare disease research. The second part of the strategy covers the main guiding principles for conducting rare disease research at the national and EU level, as well as the main financial avenues to be explored:

Guiding principles:

- **Empowering patients in research** means recognising that patients are full and equal partners, developers, funders of research in RD. In practice this should translate into fostering:
  - participation of patient groups to EC-funded research projects via simplified procedures;
  - capacity-building of patient organisations via training of their representatives;
  - inclusion of patients in research infrastructures and increased patient-driven governance;
  - patient involvement in each step of clinical trial development, e.g. in evaluation and ethic committees.

  However, real empowerment is only accomplished through appropriate provision of financial support for these activities.
- **Integrated action** is vital to rare disease research, as fragmentation and scarcity are the rule in this field. Networking and cooperation among experts in encouraged in particular by:
  - creating and reinforcing European Reference Networks (ERNs) sharing data and expertise;
  - exploring and supporting other “collaborative models”, such as those involving non-public/non-industry partners and patient groups, as partners for industry, performing research for therapeutics;
  - joining international platforms (i.e. ERA-net for research programmes on rare diseases (E-RARE) and the International Consortium on Rare Disease Research (IRDiRC)) and creating new ones like the abovementioned body to develop, conduct and coordinate translational and clinical research in Europe.
- **Sustainability of infrastructure and projects** is the necessary precondition for rare disease research and long-term engagement from public funders is required to fill the gaps left by private investors. Creative solutions should be found, such as:
  - mechanisms to ensure the continuation of successful projects;
  - development of outcome indicators to assess the performance of projects and demonstrate their return of investment
  - alternative funding mechanisms, e.g. public-private partnerships;
  - rewarding ‘adoption’ mechanisms for successful projects with sound exit strategies;
  - tapping at EU Structural Funds where possible (e.g. upgrading medical infrastructures);
  - setting up bodies at national level which steers and advises on RD research;
  - setting up national/EU centralised database on research projects and research teams.

Financial instruments:

Funding rare disease research should occur through two main channels: specific RD budget lines and participation of RD projects in competitive allocation of funds under general health research budgets.

At the EU level, the upcoming 8th Framework Programme for Research should increase the budget commitment of the past to meet the challenges ahead, including engagement within the IRDiRC Consortium. National budgets should pair this effort and make a clear commitment to dedicated RD research programmes in their national plans or strategies for RD, which are due in 2013. Comprehensive research actions in rare disease research with clear objectives would help to optimise resources and avoid uncoordinated actions.

Finally, the last section of the document describes the **Background** documents used to develop the paper and acknowledges the state of the art of rare disease research in 2011 by tracing back the milestones in RD policy that had an impact in the field of RD research.

1) INTRODUCTION

On the eve of the adoption of the 8th EU Framework Programme 2014–2020 and the National Plans, or Strategies on Rare Diseases, which European governments engaged to adopt before 2013 and that should include measures in the field of rare disease research (RDR), European rare disease patients take stock of actions taken to date in order to outline the priorities for the decade ahead. This is the objective of this EURORDIS position paper, which is addressed to national and EU authorities who will have to make political and financial decisions that will impact on the care and quality of life of rare disease patients in Europe and ultimately world-wide.

Fostering research on Rare Diseases in Europe is an effort that is carried out jointly at the national and EU level. Indeed, in recent years, research on rare diseases has been boosted thanks to the European Commission Framework Programme for Research and Technological Development and a number of different national initiatives adopted across European countries.

Naturally, the role of private funders in rare disease research (whether industry or not-for-profit organisations) is essential and fully acknowledged. However, the objective of this paper is to urge public decision-makers, as we believe that public policy plays a crucial role in advancing rare disease research in a manner that private interest would not naturally do. This is extensively argued in the complementing Position Paper "Why Research on Rare Diseases"[2] adopted by EURORDIS in 2010.

Through this Position Paper the entire European rare disease patient community represented by EURORDIS wants to emphasise its fundamental role as fully legitimate stakeholder in order to progress research.

2) APPROACH

This Paper, while building upon the findings and reflections carried out over recent years, provides a robust analysis of the state of the art of rare disease research and makes an overall strategic proposal outlining specific priorities for the medium and long term (up to 10 years). It refers to research across all rare diseases and specific therapeutic fields, and creates explicit links to other relevant policy actions in the field of rare diseases, integrating national, European and international initiatives.

In this document, the Overall Strategy (section 3) is divided into two parts: WHAT are the priority areas of research (3.1) and HOW these can be achieved, with a description of the guiding principles and of the financial aspects (3.2). Finally, section 4 describes the background (sources, studies and events), which contributed to the content of this paper and to the state of the art of research on rare diseases.

[2] EURORDIS Position Paper "Why Research on Rare Disease?" http://www.eurordis.org/publication/why-invest-research-rare-diseases

3) OVERALL STRATEGY – PRIORITIES AND GUIDING PRINCIPLES

3.1. WHAT priorities for research for rare diseases?

The greatest barrier to the prevention, diagnosis and treatment of rare diseases is insufficient knowledge. Insufficient RDR has delayed the establishment of fundamental scientific knowledge needed to understand the causes and mechanisms for the majority of RD. This has resulted in under-diagnosis, misdiagnosis, delays in diagnosis and inappropriate treatment, whether drug therapy or other medical attention. The key to developing this knowledge is supporting and encouraging all elements of RDR. The utility of RDR for more common diseases has been shown on many occasions and it is widely recognised that basic research with a rare disease focus inevitably sheds light on important biological mechanisms that help in the understanding of more common diseases The complexity of RDR in all research fields is a stamp of excellence for RDR, which is paving the way and making significant contributions to scientific, medical, regulatory and methodological domains3.

Rare disease research (RDR) comprises a broad range of scientific investigations, from basic to clinical. **Basic research** involves the study of underlying pathophysiological mechanisms and their genetic and molecular characterisation. **Translational research** accelerates the transfer of knowledge from basic "bench-side" research into clinical "bedside" applications. **Clinical research** focuses on the development of diagnostic tools and therapeutic solutions. Equally as important in this multidisciplinary field of research, are **quality of life studies, especially on how to manage and cope with a RD, and studies on the social consequences of the disease**, health economy, communication and culture, as well as epidemiological studies and research into the natural history of the disease. These studies also help light the path towards better standards of care and treatment and higher quality of life for RD patients.

As acknowledged in the survey recently carried out by EURORDIS (see above), for rare disease patient organisations research is a long-term process and **all research areas need to be nurtured**.

Nevertheless, although the needs of RDR are so extensive that no area can be neglected, we do recognise that it is necessary to provide priority orientations to help policy-makers to take their policy and budget decisions for the years to come. EURORDIS, based on strategic orientations for RDR that emerged over the last years, has identified the following **strategic areas that deserve the attention of policy-makers for funding as a matter of priority**.

Depending on the RD or group of RD in question and maturity of the specific field, RD priorities in allocation of resources should include:

3.1.1. First things first: registries and other research infrastructures

As a precondition for advancing all fields of RDR, there is an absolute need for developing research infrastructures such as databases, information systems, biobanks and networks of experts. These tools are of fundamental importance for bridging the gap between basic and clinical research.

Registries and databases can be regarded as a hub of information for all stages of research and management of rare diseases, including:

- Natural history of the disease
- Epidemiological research

[3] See also the EURORDIS Position Paper "Why Research on Rare Diseases?", as above.

- Clinical research (patient recruitment for clinical trials)
- Disease surveillance
- Disease follow-up
- Treatment evaluation (efficacy)
- Treatment monitoring (safety)
- Mutation database
- Genotype-phenotype correlation
- Benchmarking for improvement of quality of care and development of clinical care guidelines
- Social planning
- Health planning

In this perspective, the experience of the "TREAT-NMD" project[4], funded by the Research Framework Programme, could be considered one of the "gold standard" experiences, as it has been successful in setting the infrastructures necessary to advance towards clinical development of research, including an international registry for neuromuscular disorders.

In addition, the cystic fibrosis programme EuroCareCF[5] is an excellent example of a successful combination of registries[6] (35 countries participating in a European, uniform registry) and clinical trials. As a result, a first potentially corrective therapy, which successfully completed phase 3 of clinical trials, now exists for patients who carry the cystic fibrosis G551D mutation. Similarly, other examples of advanced registries are the European Huntington Disease Network (http://www.euro-hd.net/html/network), the International Rett Syndrome database (https://interrett.ichr.uwa.edu.au//), as well as the European registry for Wilson disease (http://www.eurowilson.org/en/home/index.phtml).

The ORPHANET study on the state of the art of RDR (see section 4 for more details), clearly indicated that patient registries are one of the three determinants of RDRs: when a solid patient registry is in place, greater chances exist that therapeutic solutions will be found for the disease(s) in question.

From the 15 EUROPLAN National Conferences held in 2010, it was consistently emphasised that the creation of patient registries should be a primary objective and a basic requirement for the development of RDR. Registries for rare diagnoses are needed, with high quality standards and clear definition of rules concerning the storage and use of data to ensure their trustworthiness.

In addition, as rare diseases represent an issue that can only benefit from a globalised effort, scientists and other stakeholders building the International Consortium cooperation have called for greater alignments, better access and improved interoperability of registries as a key prerequisite for fostering research in Europe and at the international level.

The sustainability of these infrastructures is a recurring issue, as it is frequently compromised by the halt of funding sources. Long-term funding of such important infrastructures needs to be clarified.

Actions to be taken:

- Supporting the process of **harmonisation of procedures and technical tools**, or the **mutual recognition of data** in registries and databases, as well as the **development of**

[4] http://www.treat-nmd.eu/

[5] http://www.eurocarecf.eu/

[6] http://www.ecfs.eu/projects/ecfs-patient-registry/intro

common data set for both registries and biorepositories. The International Rare Disease Research Consortium (IRDiRC) engaged to promote the use of commonly accepted "Standard Operating Procedures" (SOP) and "informed consent forms" to facilitate sharing of data/samples. Such activities should be fully endorsed and supported by the European partners involved.

- Fostering the creation of patient registries by trying to **optimise the use of resources**. For example, gathering together clusters of diseases or designing registries suitable both for measuring research progress and fulfilling regulatory requirements. In addition, epidemiological platforms could be supported at the national level, as they are useful tools for describing the content of existing databases on health and cohorts, whether private or public (type of data, coordinators contact details, condition of access, etc.) and therefore to optimise existing resources.

> By way of example, a “Banque Nationale de Données Maladies Rares” (BNDMR) is being set up in France, which aims to collect of a minimum data set of all patients affected by rare diseases.

- Registries linked to **Centres of Expertise** should be supported and funded. This is not only an assurance of greater sustainability of the registry, but it also brings the collection of data closer to the level of care and to patients.

- The **collection of data and high-quality biological samples**, as well as their storage and dissemination, are of fundamental importance at the EU level, in particular concerning rare diseases. Developing and consolidating biobanks specifically for rare diseases should be supported and sustainable financial means should be ensured. Collections of high-quality biological material corresponding to families and/or cohorts of patients with clear phenotypic characteristics should be assembled and linked to meaningful data. Whenever possible, a link between patient biological samples stored in a biobank and his/her data in a registry should be made. In this respect, it would be of fundamental importance to develop or acquire informatics procedures to generate a unique identifier for each rare disease patient.

> An excellent example of this is demonstrated by the Global Unique IDentifier (GUID) developed by the National Database for Autism Research in the US (NDAR, http://ndar.nih.gov).

- **Supporting patient self-registration and associating patients to the collection of data**. Significant progress has been made in recent years in this area, with evidence and publications proving the robustness of such an approach (see the international Rett syndrome database or, in France, the leukodystrophy database). Patient self-registration is complementary to clinician data entry and is functions in particular in the area of post-marketing authorisation surveillance, off-label use of drugs, etc. The development of self-registration good practices, preferably at the international level, should be encouraged and funded. Economic and training support for patient organisations should be also provided, to organise courses on registries and the role of patients (management, self-registration, patient inputs, data protection laws, etc.). Support should be also ensured for some expert-led data moderation, in order to further the use of the gathered data.

- Continuing to sustain **international cooperation initiatives** such as the comprehensive EC-funded infrastructure Biomolecular Resources Research Infrastructure (BBMRI), working to establish a functional pan-European biobank, where a dedicated section for rare disease biobanks should be finally created, or the EPIRARE project, which –with the support of the European Commission- aims to create a platform for European cooperation among RD registries.

In particular the Commission and the Member States should ensure that both the above initiatives will effectively translate into the development of **harmonised quality requirements** (e.g. national quality standards, monitoring bodies and process, etc.) applicable to all registries and biorepositories. The respect of such requirements should be linked to a clear engagement of funding agencies to sustain such infrastructures over the long term.

- Promoting initiatives that make best use of resources for research and of the data generated by the research. Given the small number of patients available to participate in research on rare diseases, as well as the limitations in funding, it is important to support infrastructures whereby industry, academia, and patient organisations **share pre-competitive resources**.

3.1.2. Understanding the underlying mechanisms of rare diseases: basic research

Basic research is the **prerequisite of any therapeutic advance and of any new public health decision**. It is key in identifying the causes and molecular mechanisms of rare diseases, in developing diagnostic tools and methods, and in pinpointing therapeutic targets.

The ORPHANET study, described in section 4, confirmed that if there is no understanding of the genetic and molecular mechanism underlying a RD, then translational research is unlikely. It is important to understand the genetic basis and molecular mechanisms of RDs, and to decipher the clinical heterogeneity of each RD in order to maximise the chances of developing effective interventions.

At present, it is recognised that, while the **genetic and molecular basis** of some hundreds of rare diseases has been resolved, this is not yet the case for thousands of rare diseases. Moreover, access to genetic and molecular diagnoses for known RDs is patchy in Europe.

Similarly, **pathophysiological mechanisms** involved in rare diseases are largely unknown. The identification of genetic mutations must be followed by appropriate physiological studies to enable the development of novel therapeutic strategies. RDR on pathophysiology mechanisms greatly contributes to the understanding of other, more common diseases and, consequently, can help to identify therapeutic options well beyond RD. Monogenic diseases, with unique physiological pathways, such as lysosomal storage diseases, for instance, can help understand other diseases with similar characteristics.

Study of the **natural history** of the disease, its risk factors, its severity and associated complications is also a necessity, both for the development of the best suitable care for affected people and for preparing the basis of an effective treatment development even from the regulatory point of view (e.g. identification and validation of the best endpoints for clinical development).

<u>Actions to be taken:</u>

- Continuing the efforts for mapping and cloning of genes responsible for rare diseases, identification of mutations or other anomalies of gene dosage. In particular for those diseases that already have a model system, studies and establishment of collaboration between different groups should be potentiated in order to characterise animal models as soon as possible.

- Developing tools to understand how genetic anomalies translate into pathological phenotypes (e.g. transgenic animal, animal models other than mice, in vitro models, imaging facilities, etc.).

- The development of multidisciplinary networks associating clinicians, geneticists, epidemiologists, and patients including the Centres of Expertise in EU Member States, while encouraging research focusing on rare diseases performed in institutions not specialised in rare diseases.

- While Centres of Expertise will need to be established in many EU countries, it is important that they are set-up taking on board their role as an incubator of discovery research. Funds for this purpose should be guaranteed, as the scientific activities in Centres of Expertise are resource- and cost-intensive, and cannot be supported by the budget dedicated to the healthcare of patients. The main goal is to develop a comprehensive system of shared resources for discovery research on rare diseases and to facilitate communication and cooperation for such research, by filling the gap between patients, medical doctors, clinical research and basic research.

- Informing and training researchers at all career stages: fellowship programmes directed to graduate students, PhD, Post doctoral researchers and group leaders in the rare disease field. Funding should also be available for scientific and medical awareness and communication activities, such as courses and workshops, conferences, practical courses, symposia and lectures, as well as other types of training media i.e. e-learning.

3.1.3. Translational research towards innovative therapeutics for rare disease patients

The development of therapeutics for patients living with a rare disease is a primary objective the most urgent priority to be addressed in the coming years. This message was echoed from all EUROPLAN National Conferences where it was consistently recognised that, while all areas of research are necessary, **most urgent action is needed on translational research that leads to therapeutics for rare disease patients**. In fact, numerous in vivo/in vitro proofs of concept already exist, which could be transformed into translational research, should motivation and funding become available.

Patient organisations, as shown in the 'EURORDIS survey on patient organisations and research', have limited means for sustaining research on their diseases and call on public authorities to invest more in therapeutic research, notably clinical trials and research on management of care.

Nevertheless, a number of bottlenecks exist for the development of therapies for rare disease patients (see in particular the recent findings of the ORPHANET study mentioned above):

- the diversity of the pathological situations, associated with the lack of knowledge of the pathophysiology of a great number of rare diseases;
- the difficulty to stratify by stage and severity because of the clinical heterogeneity within a single RD;
- the lack of validated biomarkers and surrogate end-points, for generally small, dispersed patient populations;
- the lack of predictive and validated pre-clinical *in vitro* and animal models;
- the scarcity of clinical experts and reference centres;
- regulatory procedures if they are not adapted to the evolution of science and shared at an international level;
- methodological bottlenecks and difficulty in designing studies that are clinically significant and functional to respond to regulatory requirements.

Due to the low individual prevalence of rare diseases and patients, and to the complexity of the diseases, the field of RDR is one that would greatly benefit from specific and targeted coordination and collaboration. The EUROPLAN Recommendations call explicitly for multi-

centre national and trans-national studies in order to reach a critical mass of patients for clinical trials and to exploit international expertise.

Actions to be taken:

- Support for the identification of appropriate markers, biological, functional etc., and surrogate endpoints to be used for diagnosis and evaluation of disease progression and, thus, of treatment efficacy.

- Support for projects of **pre-clinical therapeutic research** and **proof of concept studies**, which are specifically relevant to orphan drugs and rare diseases.

- As for the **development of therapeutics for patients**, supporting projects aimed at:

  - searching for molecules with potential use in the treatment of rare diseases, using two approaches: i) high throughput molecular screening or ii) research of therapeutic molecules based on pathophysiological knowledge of the diseases;
  - developing advanced therapy medicinal products, notably: gene therapy, cell therapy and tissue engineered products;
  - developing innovative devices to alleviate or compensate disabilities linked with the disease.

- Increasing the support to the **clinical development of designated orphan medicines**, as in the last calls of the 7th EC Framework Programme for Research or in the US FDA's Office of Orphan Products Development trial grant program. In particular, products with a designation both in EU and US have a greater chance, as they have a skeleton of development and first feasibility checks have been performed.

- Encouraging **repurposing of existing drugs** that are marketed but not in orphan indications in which they seem to have a potential therapeutic benefit. This research avenue is highly promising and more easily accessible than others. A first effort for identifying the marketed drugs to be repurposed for RD should be performed by analysing off-label use in each market authorisation. This is even more relevant insofar as off-label use of drugs and the related reimbursement seems bound to become more and more restricted in the years to come. An interesting model to support such an endeavour is the US FDA programme on repurposing, which also offers training programmes for investigators on how to apply for OD designation.

- Supporting research into (new) **combinations of therapeutic agents**, in view of the complexity of the pathophysiological mechanisms in RDs.

- **Training developers of therapies** in the drug development path with the provision of information and advice channels by regulators, in order to reduce the risk of failure due to lack of knowledge of the regulatory framework. Researchers should be also trained to perform experimental studies in full compliance with quality, non-clinical and clinical regulatory requirements.

- Training and providing financial and career incentives to new experts, notably in clinical experimental medicine, facilitating the development of expert centres and centres of reference.

- Supporting **national or international networks organising clinical trials**. This is essential to address the limited number of patients and the scarcity of expertise, as well as to promote clinical and preclinical testing in cooperation with the pharmaceutical

industry. The European Clinical Research Infrastructures Network (ECRIN, http://www.ecrin.org), supporting multinational clinical trials in Europe by providing services and instruments to facilitate clinical research to international teams, should continue to be supported and access to its services should be promoted and facilitated, in particular for teams involved in clinical research on RD. In addition, the establishment of an informatics platform(s) with information related to therapeutic research in a non-specialised language (thus directed to society) should be encouraged.

- **Regulatory procedures** need to be adapted to the fast pace of development of science for early assessment of innovative therapies for rare diseases; common criteria should be developed for a "joint assessment" between the regulatory agencies applied to the innovative therapies for rare diseases.

- Finally, the **possibility of creating a body aimed at developing, conducting, coordinating, and stimulating translational and clinical research in Europe should be carefully studied**. To be designed along the lines of the EORTC (European Organisation for Research and Treatment of Cancer, www.eortc.be), it would test more effective therapeutic strategies and, through translational and clinical research, offer an integrated approach to drug development, drug evaluation programmes and medical practices.

3.1.4. Research on best clinical practice of care

A greater deal of attention should be paid in Europe to designing broad “strategy trials”, covering all aspects of patients’ care, beyond and in addition to drug treatment. With only a small portion of rare disease patients having an orphan drug available (almost 6% according to the ENSERio study[7] performed by the Spanish Rare Disease Federation, FEDER), most patients undergo different treatments to improve their quality of life. Drug treatment is only part of it. The therapeutic and care arsenal for rare disease patients may be vast and heterogeneous, “**Strategies of care**” necessary for patients with rare diseases are broad, comprehensive and would include **paramedical treatments**, use of **medical devices**, physiotherapy, nutrition, as well as **surgery** and **complementary treatments**.

For instance, natural, alternative, traditional and complimentary (NATC) products may play an important role in disease primary or secondary prevention and/or treatment. However, scientific evaluation on such products is lacking in most cases and information to patients is often left to market forces. Nevertheless, the existing scientific literature on the role of e.g. vitamins, trace minerals, nutraceuticals, food supplements in the treatment of rare diseases shows that there are experienced teams out there ready to start scientific assessments in order to rationalise the use of these products and better inform patients on what they can expect from them, in a scientifically-sound way.

Today, patients affected by the same rare disease may receive different care protocols depending on the country or region where they live. These different approaches often explain the different quality of life of patients and the different life expectancies within the same rare disease. Evidence-based studies on the best care strategies are largely lacking for most diseases. It is urgent to perform this type of research as these results are needed by specialists to **generate new data for innovative practices of care** and to agree on what optimal treatment strategy should be applied for a specific rare disease. This is typically the work that European Reference Networks of centres of expertise should perform.

[7] Estudio sobre situación de Necesidades Sociosanitarias de las personas con Enfermedades Raras en España, ENSERio: http://www.feder.org.es/panelc/publicaciones/archivos/ZRKCBGYYOEQLTTPATQNAFRCMYRMCOR.pdf. According to the study, 5,96% of patients take orphan drugs, 13,15% patients get drugs from abroad, 6,73% of patients receive "compassionate use" drugs.

Actions to be taken:

- Promoting evidence-based studies aimed at designing strategy trials of comprehensive patient care. Scientific research should rely on patient data collected in registries at Centres of Expertise level, as well as on collaboration (shared data, resources and expertise) within networks of experts. Their results must contribute to the definition of protocols of care for the specific diseases targeted.

- Promoting pilot trials to define certain aspects of the care strategy for rare diseases for which scarce data are available (due to the small number of patients, for instance), in order to develop scientifically viable approaches for the definition of a strategy of care under those circumstances.

- Supporting scientific research on the role of surgery as a part of the strategy of care of rare diseases.

- Supporting scientific research on the role of complementary treatments within a broader strategy of care of rare diseases.

3.1.5. Research in human and social sciences

Research into **quality of life, living conditions, working conditions, social needs, integration at school, multidisciplinary education of social service providers**, etc., are extremely important not only for public health planning, but also for provision of those services most suited to answering the needs of patients in their daily life and that would contribute to empower them. Many EUROPLAN National Conferences highlighted the importance of public health and socio-economic research to be carried out in a multidisciplinary perspective. This type of research should be ultimately aimed at enabling patients to think and implement a "personalised plan" ("project de vie", in French). It should be documented by patients with patient data, and should be developed following a patient-centred approach.

It is equally important to develop **parameters related to the progress of EU research on rare diseases**, such as the attractiveness of research on rare diseases for scientists and research laboratories, the interest of the pharmaceutical industry in the development of projects on orphan drugs, availability of diagnosis, care and treatments for patients, impact of research and health policies on quality of life and life expectancy, etc. The results obtained from these studies would offer important clues for evaluating the middle and long-term efficacy of the research strategies chosen by the EU.

Actions to be taken:

- Developing and validating tools to support patient reported outcomes.

- Supporting the development of more research projects centred on patient quality of life and on a patient-centred approach, including how patients manage and cope with RDs.

- Supporting research projects in the fields of sociology, economy, history of sciences, psychology, law, in particular:

    - descriptive and analytic research on society and rare diseases, e.g. social perception (psycho-sociology, health-economy and ethnology approaches), psychological impact of rare diseases on the patient and his/her environment, accessibility to care, role and best practices of patient associations, etc.;
    - behavioural studies: health behaviour changes, change of practices, therapeutic education;

- public/private scientific co-operation for research and innovation;
- care practices, daily experience of the diseases, self care, health education;
- public research and health policies across the EU.

- Fostering activities (mainly at the level of Centres of Expertise) whereby clinical and basic science could be connected with social and political sciences in order to optimise the provision of both patient care and services that go beyond healthcare.

3.2. HOW to conduct rare diseases research?

In this second part of the paper, we illustrate HOW research on rare diseases should be performed, i.e. the overall strategies that in our opinion would greatly boost and sustain research on rare diseases. To do this, we firstly introduce the main principles that should guide national and EU action in the field of RDR[8]. Secondly, we introduce the main financial avenues to be pursued for funding RDR.

3.2.a. Guiding principles

3.2.a.1. Patients empowered actors of research on rare diseases

Patient associations should have a more proactive role as research partners. In particular, patients should be partners in research not only as subjects, but also as advocates for fundraising and key stakeholders in the drafting of guidelines and policies, and should always be consulted in the drafting and evaluation of national research policy in the context of RD plans.

For optimal support by patient organisations, qualifying training of patient representatives and financial support to patient representatives should be ensured.

The concept of patients and patient groups as real partners in research has been supported in various EUROPLAN National Conferences. Patients and their associations are essential for fostering knowledge sharing; identifying research topics; promoting and helping to maintain patient registries and cohorts and involving patients in clinical trials. Patients also fund research. The EURORDIS Survey on the role of patient groups in research confirmed that patient organisations already have a robust experience of collaboration with researchers as well as with public and private research institution. The quality of this dialogue increases with the age and size of the patient organisations.

Actions to be taken:

- Fostering the **participation of patient groups to EC-funded research projects**, by simplifying the procedure for obtaining support during the application preparatory phase. Patient organisations collaborating with research groups by writing proposals to be included in the main project, should be supported.

- **Reinforcing and supporting capacity-building of patient organisations**. This includes :

  - **Training patient representatives** on specific research topics, such as: patient registries and databases, clinical trials, basic research, etc. In particular, patient

[8] In addition to this, the EURORDIS Position Paper "Why Research on Rare Disease" illustrates the core principles for RDR more extensively.

organisations should be provided with the appropriate tools to create greater awareness on research and drug development among patients; in particular capacity-building should be enhanced in those areas where patient groups fund research, so that they can make the best possible use of their resources.

- Promoting capacity building for patient organisations to define research priorities at the European and national levels. Notably, patient representatives should be trained and provided with the financial support to contribute as fully-fledged partners in the definition of research priorities in the fields of their concern.

- Supporting the development of **research tools and infrastructures that include patient-driven governance** and the sharing of results with patients.

- Involving patients' representatives at each step of the **clinical trial protocol development** to ensure literacy of patient information notices, informed consent forms, case record forms or self-administered questionnaires, report summary for patients, etc.

- Involve patients' representatives in **steering and evaluation committees on research, HTA committees, ethics committees, research on clinical ethics**. A sustainability plan should exist in order to support the participation of the patient.

- Communication amongst involved scientists and patient organisations by setting up special sessions to report and discuss recently obtained scientific results in a non-specialised language should be promoted. Projects related to science communication (scientific reports in a non-specialised language, information booklets, sheets, etc.) would be welcome in order to establish closer links between researchers, policy and decision-makers, media, private sector, NGOs, citizens, etc.

3.2.a.2. Integrated action/collaboration

Expertise on rare diseases is overall scarce and when it exists, it is fragmented and scattered throughout the national or the EU territory. In order to improve scientific and medical knowledge on rare conditions, it is essential to gather together the scattered specialists with complementary expertise so to implement the necessary multidisciplinary approach. To achieve such a coordinated approach, the creation of European structures of excellence via networking and cooperation between expert centres is crucial.
Research on rare diseases cannot be developed in isolation within single laboratories scattered throughout the EU. In most cases, coordination of the very few national experts is not enough for the advancement of research on a specific rare disease and the number of patients available for a study at the national level in any single country is insufficient to generate conclusive results. Therefore supranational action is required. Moreover, pooling and organising the scarce resources of the rare disease field is an efficient way to avoid duplication of efforts and accelerate progress thereby optimising the use of these limited resources.

In conclusion, the specificities of research on rare diseases justify a **concerted action between different national and European financing and management policies, in order to optimise the use of funding, infrastructures and technological platforms.** Facilitating research cooperation, exchange of information and sharing of expertise is essential, especially in smaller Member States where resources to create networks at the national level are scarce. A number of cooperative/collaborative actions are proposed throughout this paper; however in particular the following could added:

<u>Actions to be taken:</u>

- Supporting **European Reference Networks (ERNs)** sharing data through systematic collection of patient data (registries), sharing repositories of biological samples and sharing expertise for research purposes. The establishment of such Networks is a long and costly process and funding is required over a long period. ERNs through collaboration act as a de-risking factor for research on RD[9].

- Other "collaborative models" in research on RD should be explored and supported: in order to ensure that all steps of the research path are properly taken, different players should be involved and these include national public bodies, charities, patient associations and the pharmaceutical industry. In particular, experience has shown that **collaboration between charities or patient groups carrying out research and industry** - at some points of the research path – may help in the accomplishment of research goals, notably the clinical development of a new therapy and its delivery to rare disease patients. Charities (notably non-public, non-industry agencies) and patient groups carrying out research often do not have the means to transform the results of the excellent research they fund in viable therapies available to all patients. Such 'alliances' may provide alternative, concrete possibilities to take all the steps towards making a potential therapy available to patients. In addition, charities provide a valuable model of how excellent research can be selected and managed through an independent mechanism that ensures quality and merit that ultimately leads to the scientific results. Therefore, the role of non public, non industry players in RDR should be acknowledged and encouraged, as it may add value and comprehensiveness to the research process.

- Participating in international platforms, such as ERA-net for research programmes on rare diseases (**E-RARE)** (see below, section 4), to better coordinate research and research policy at the country level.

- Supporting the forthcoming **International Consortium on Rare Disease Research (IRDiRC**). This action is clearly addressed to national research funding agencies, which are invited to express their interest and become funding partners of the Consortium.

As mentioned above, a **European body could be established with an aim to developing, conducting, coordinating and stimulating translational and clinical research in Europe**, with a similar structure and organisation to EORTC, the European Organisation of Research and Treatment of Cancer. It would test more effective therapeutic strategies and, through translational and clinical research, "offer an integrated approach to drug development, drug evaluation programmes and medical practices" (www.eortc.be). This body would be a European clinical research infrastructure from where multinational and multidisciplinary activities are coordinated and run.

3.2.a.3. Long term sustainability

The traditionally short duration of contracts for funding research on rare diseases, both for infrastructures and research projects, puts the existence of RDR itself in danger. Funding RDR through short-term contract hampers the development of shared common infrastructures, long-lasting projects and a sustained approach. At the same time, when the allocation of funds is discontinued, important investments are lost, as these structures have to stop their activities because of the lack of new investors.

[9] For the latest conclusions on CoEs/ERNs, please see the EU CERD Workshop Report Centres of Expertise and European Reference Networks http://www.eucerd.eu/EUCERD/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf

Because of the rarity of the diseases and thus their limited commercial interest, private sponsors do not naturally and spontaneously take over the long-term funding of rare disease research projects or infrastructures created using public financial support.

A strong commitment is necessary from public funders, both at the EU and the national level, to engage in longer-term RDR activities and to ensure their continuity. This is particularly relevant for research infrastructures, such as biobanks, databases, registries and networks of researchers, which require adequate time to establish themselves and to consolidate for proper functioning.

As far as the management of RD research is concerned and its sustainability, creative solutions have been proposed and/or are being experimented that could be sustained.

Actions to be taken:

- Establishing mechanisms to ensure the **continuation of successful research projects** on rare diseases that have not reached maturity or are intrinsically unlikely to receive private support, yet provide scientific and clinical added value.

- Establishing **funding mechanisms that guarantee long-term sustainability of common EU research infrastructures**, such as biobanks, databases and registries. As an example, Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), the comprehensive European biobanking infrastructure, funded by the EC over at least years, moving in the right direction.

- Designing explicit solutions in the **National Plans or Strategies for Rare Diseases** addressing the issue of financial sustainability for initiatives in the field of research on rare diseases.

- Developing **outcome indicators** to assess the success of the funded initiatives and demonstrate the return for investment of RDR funding.

- Supporting and setting up **"adoption" mechanisms** encouraging sound exit strategies whereby EU projects or infrastructures proven to be comparatively more successful are then adopted for further funding by e.g. non-profit agencies, foundations or public institutions. Supporting alternative funding mechanisms, such as **public-private partnerships**, to establish networks between different stakeholders. Alternatively, tapping at **EU Structural Funds** where and when possible e.g. to upgrade their medical research infrastructures (especially in new EU Member States).

- Establishing a **body at the national level that steers and advises on RD research** and develops public private partnerships with industry and associations, creates close links with centres of expertise, and basically acts as a **one-stop shop for all information on RD research** and/or **potential incubator for enterprises** (see, as possible examples, the "Foundation for scientific cooperation", supported in France by the Second NP, or the proposed extended role of the Spanish CIBERER, Centre for Biomedical Network Research on RD).

- Setting up a national/EU **centralised database on research projects and research teams**. Such a system of central coordination would also stop duplication of funding and optimise resource allocation, thus favouring the establishment of a continuous funding scheme (and not only based on call for proposals).

3.2.b. Financial instruments

Funding rare disease research should occur through two main channels:

- **Specific RD budget lines** for funding networks (national and EU level) and infrastructures such as biobanks and registries;

- Participation of RD projects in competitive allocation of funds **under general health research budget lines**, where projects are not selected on the basis of rarity, but according to the criteria of excellence, innovative ideas, concepts and technologies. Naturally, funds must be allocated on the basis of competence and merit.

This is equally important at the EU level and at the national level.

In this regard, the EC Framework Programme for Research and Innovation, as anticipated in the Introduction, is the essential funding source at the EU level. It is of paramount importance that the budget allocations made for rare disease research in the past are confirmed and increased to meet the priorities and the challenges ahead, not last the international engagement taken under the International Consortium on Rare Disease Research (IRDiRC). Therefore, a subsequent budget commitment should be made for the period 2014-2020 in view of the next Financial Perspectives and the 8th Framework Programme.

The EU commitment must be paired by national budgetary support. Under the National Plans that EU Member States agreed to adopt before 2013, national initiatives must be taken possibly in the form of dedicated programmes for RDR. From the Final Report of the National Conferences of the EUROPLAN project it emerges that: "Appropriate funding is crucial in support of dedicated programmes to ensure the longevity of the research projects and their sustainability. Dedicated RD research programmes would also help optimise scattered resources, by improving knowledge on existing research efforts and better coordinating them. Although the majority of Conferences clearly called for public funding, proposals were made to consider private-public partnerships."

Interestingly, also the Institute of Medicine (IOM) Report of October 2010 Report called for a dedicated comprehensive action on RDR in the US: "As one opportunity for improvement, the NIH should develop a comprehensive action plan for rare disease research that covers all institutes and centres and that defines and integrates goals and strategies. This plan should cover programme planning, grant review, training, and coordination of all phases of research"[10]

Multinational platforms such as E-RARE and IRDiRC are strongly supported, as explained above, whereas alternative funding mechanisms could be envisaged, including public-private partnerships.
The role of not-for profit entities as research funders should be also acknowledged and taken into account when designing EU and national programmes.

4) BACKGROUND AND STATE OF THE ART

EURORDIS adopted its last position paper on rare disease research[i] in 2005 and revised it in 2008 in order to contribute to the consultation launched by the European Commission for the preparation of the Commission Communication on Rare Diseases. Since then, significant developments in the field of rare disease in general, and specifically in the area of research, occurred. This Paper takes stock of these developments.

[10] http://www.iom.edu/rarediseaseresearch

In May 2007, EURORDIS organised a European Workshop on "Gaining Access to Rare Disease Research Resources" in Paris[ii]; on 14 June 2007, a Workshop on Rare Diseases and Research was organised by the European Commission and in September 2007 the European Conference entitled "Rare Diseases Research: Building on Success"[iii] took place in Brussels, also organised under the aegis of the European Commission, DG Research.

In 2008, the **Commission Communication on Rare Diseases**[iv] proposed that Member States put in place strategies to foster RD research, including cross-border cooperation and collaboration to maximise scientific resources across the EU.

In 2009, the Council of the EU adopted a **Council Recommendation**[v] inviting Member States to establish and implement plans or strategies to ensure provisions aimed at fostering research in the field of RD. The Recommendation demands a mapping exercise of existing resources to establish the state of the art and to "***identify needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them***".

Both the Commission Communication and the Council Recommendations, milestones in the rare disease policy, call for a RDR policy that is both comprehensive (covering a large scope from basic to clinical research) and integrated (EU and national levels).

In 2010, on the occasion of the Rare Disease Day[vi], EURORDIS and E-RARE (*see a few paragraph below*) jointly organised, in partnership with the European Commission, ORPHANET and EUROPLAN, a **European Workshop** in Brussels entitled "**Bridging patients and researchers to build the future agenda for rare disease research in Europe**". Different stakeholders met to identify the future priorities in RDR and define concrete steps to ensure better collaboration of all interested parties. At the Workshop, three important pieces of investigation on RDR were presented:

- the study performed by ORPHANET describing trends and determinants of RDR in Europe[vii];
- the EURORDIS survey on the role of rare disease patient organisations in research[viii];
- the survey performed by the E-RARE network presenting the priorities and bottlenecks in RDR as identified by mainly rare disease researchers.

These important parallel surveys are a source of fresh, essential information on the recent trends in RDR. The **ORPHANET study**, for instance, revealed that while RDR is growing (approximately 5000 ongoing research projects covering 2000 different rare diseases; 650 clinical trials for more than 300 diseases), research activities such as research project, registries, clinical trials and orphan drug development, are strikingly focused on relatively few rare diseases (e.g. cystic fibrosis or Duchenne muscular dystrophy). For the majority of rare diseases affecting less than 1 person in 10 000, therapeutic research is absent or very limited. From the ORPHANET survey also emerged that the ***three main determinants*** for reaching a significant research activity level in a given rare disease are the ***1) existence of patient organisations***; ***2) patient registries***; ***3) a European network*** (of centres of expertise or of research) where all actors are already involved. Generally speaking, the quality of rare disease research projects is very high and they successfully compete with projects in other health research areas. Rare disease research is an area of excellence and innovation.

The **EURORDIS survey** confirmed that patient organisations are real catalysts of research, not only by raising awareness on their disease but also by stimulating the development of research on that disease. This support includes involvement in shaping the research agenda for their own disease, facilitating the conduction of clinical trials (designing, recruitment and

information to patients) and also financial support to fill gaps and seed money to start up research, especially in basic research, epidemiology and research in social/human sciences. However, patient organisations have limited resources and require public investments specifically on therapeutic research (clinical trials and research on management of care).

The **E-RARE survey** emphasised the importance of increasing funds for RDR, supporting in particular proof of concept studies and gaps in translational research; promoting EU funded research networks; facilitating mobility for clinicians; and promoting rare diseases as model for common diseases in research.

The survey was carried out in the context of the **E-RARE project**[ix], an ERA-net gathering public partners funding rare disease research in their own countries. This document is also the result of the experience gained through the participation of EURORDIS as an Observer in E-RARE, which provides an important forum for Member States to exchange about their respective RDR policy.

Also in 2010, the **EUROPLAN Recommendations** were adopted to complement the Council Recommendation on rare diseases and further specify guidelines and recommendations to elaborate national action for RDR in the context of a national plan. Moreover, throughout the year, **15 National Conferences**, gathering more than 2200 persons and a multitude of national stakeholders in the field of rare diseases, were organised in 15 European countries in the framework of the EUROPLAN project and assessed the transferability of the EU policy documents in six main areas including research on rare diseases. From this Europe-wide experience, coordinated by EURORDIS, it emerged that RDR should become a priority in medical research at national level and ***ad hoc national research measures and programmes*** should be dedicated to rare diseases and supported by dedicated funds. National programmes should especially encourage an approach to RD research that ***covers all research areas, but in particular translational research***. However, basic research needs to be reinforced for many groups of diseases for which it is scarce and there is an urgent need to fund social research**.** The Conferences also outlined the role of qualified patients as fully-fledged research partners; the importance of Centres of Expertise in closing the gap between research and care; the necessity of quality patient registries to develop RDR; and the absolute need for multi-centred national and international investigations, in particular for clinical trials.

The debates around the creation of the **International Consortium on Rare Disease Research (IRDiRC)**, in which EURORDIS is actively involved have also fed the present position paper. Two preparatory workshops were held in October 2010 and April 2011 in Reykjavik, Iceland, and Washington DC, respectively organised by the European Commission, Health Directorate, DG Research and Innovation, and the US National Institutes of Health. Top scientists, funding and regulatory bodies, industry and patient representatives from Europe, US and Canada met to identify areas that would most benefit from trans-Atlantic and international cooperation and to reflect on potential strategies and contributors for implementation.

Finally, this Position Paper also builds on the previous position papers and contributions that EURORDIS adopted in the past years always following extensive internal consultations, not only on research priorities, but also on biobanks, registries, clinical research, orphan drugs, paediatric drugs and advanced therapies (see EURORDIS website, Library section for a selection of those).

Last but not least, this document was finalised through consultation with the patient organisation representatives involved in the EURORDIS European Public Affairs Committee, representing a broad range of rare diseases and EU Member States, EURORDIS Board of Directors and members attending the workshop on research held at the EURORDIS

Membership Meeting 2011 in Amsterdam. Moreover, external experts from industry, academia, charities and health professions contributed to this paper, by providing comments and case studies.

5) TABLE OF ACRONYMS

ACRONYM	Expanded meaning
BBMRI	Biomolecular Resources Research Infrastructure
ECRIN	European Clinical Research Infrastructures Network
ENSERio	Estudio sobre situación de Necesidades Sociosanitarias de las personas con Enfermedades Raras en España
EORTC	European Organisation for Research and Treatment of Cancer
E-RARE	ERA-net for research programmes on rare diseases
ERN	European Reference Networks
EU	European Union
EUROPLAN	European Project for Rare Diseases National Plans Development
FDA	Food and Drug Administration
IOM	Institute of Medicine
IRDiRC	International Consortium on Rare Disease Research
NGO	Non-governmental organisation
NP	National Plan
OD	Orphan Drug
RD	Rare disease(s)
RDR	Rare disease research

[i] EURORDIS. Position Paper on Research Priorities for Rare Diseases, http://www.eurordis.org/publication/research-priorities-rare-diseases

[ii] EURORDIS. European Workshop "Gaining Access to Rare Disease Research Resources". Paris, 4-5 May, 2007. http://www.eurordis.org/IMG/pdf/ECRD2007-Bignami.pdf

[iii] European Commission. Research Directorate General. European Conference "Rare Disease Research: Building on Success" 13 September 2007, ftp://ftp.cordis.europa.eu/pub/fp7/docs/final_programme_130907_en.pdf

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

[v] Council Recommendation of 8 June 2009 on an action in the field of rare disease.

[vi] EURORDIS. Rare Disease Day 2010 "Researchers and Patients, Partners for Life!" http://www.eurordis.org/content/survey-patient-groups-research http://www.eurordis.org/content/international-rare-disease-day

[vii] IOM, Institute of Medicine, Report "Rare Diseases and Orphan Products: Accelerating Research and Development", 4 October 2010, http://www.iom.edu/Activities/Research/OrphanProductResearch.aspx.

[viii] EURORDIS. Survey on "Rare Disease Patient Organisations in Research: their role and priorities for the future", http://www.eurordis.org/sites/default/files/publications/3_FBignami_RDD2010.pdf

[ix] E-RARE: ERA-Net for research programs on rare diseases, www.e-rare.eu