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Rare Diseases Europe

**The Voice of Rare
Disease Patients
in Europe**

EURORDIS'

POSITION ON RARE DISEASE RESEARCH



POSITION PAPERS

“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)

POSITION PAPER
October 2010

WHY
RESEARCH ON RARE DISEASES?

POSITION PAPER
October 2011

PATIENTS' PRIORITIES
AND NEEDS FOR RARE DISEASE RESEARCH
2014-2020





EURORDIS
Rare Diseases Europe

RESEARCH ON RARE DISEASES? **WHY**

October 2010

EXECUTIVE SUMMARY

This paper aims to spell out the ethical, social, economic and scientific grounds that research on rare diseases rests upon. It calls for public policy intervention to address the shortcomings still to be overcome in this field: short-term investments, the large majority of RDs lacking a research project or a research 'community', scattered resources and expertise, scarce research on health economics and socio-psychological areas.

RD research should not happen in isolation from health research in general, as by feeding innovation it contributes to EU competitiveness in a knowledge-based society. Nonetheless, this paper argues that RDs should become a health research priority and consequently, more substantial budgetary support for RD research should be provided in response to three main imperatives:

The ethical and social justice imperative: “extra” vulnerability demands “extra” ordinary measures

The thousands of different pathologies defined as “rare” have in common specific features that enhance patient vulnerability: their low prevalence - thus the isolation and marginalisation of patients affected by them; the heterogeneity of diseases with different research needs and therapeutic responses, as well as the complexity of diseases often affecting different organs - thus requiring multidisciplinary responses; research is actually conducted only on a small number of inventoried diseases; fragmented knowledge or no knowledge at all on the pathogenesis/pathophysiological mechanisms and epidemiology of many RDs, which make diagnosis difficult to make and therapy slow to develop. Frequently incorrect diagnosis, reduced life expectancy and critical transition from paediatric to adult healthcare are additional features making RD patient especially vulnerable individuals.

The **principle of equality** enshrined in the legislative systems of all European countries and in essential legislative and political EU texts, needs to be implemented for RD patients with a positive action, a more favourable treatment of persons who are at a disadvantage. It is the sense of **social justice** and **solidarity** that calls for accrued action in favour of a more vulnerable group.

This action means specific research initiatives, notably:

- Member States should support an EU-wide structure of excellence through networking and cooperation programmes involving Centres of Expertise, coordinating different disciplines and expertise in various countries.
- A thorough rethinking of health and social care is necessary to respond to the complex challenges of RDs, involving continuous training and information provision, as well as participation of patients and carers in co-production of scientific knowledge.
- A supranational response to develop research by minimising isolation and duplication of efforts. Resources -from databases and registries to pharmacovigilance systems- need to be pooled together for their optimal use. Governments must engage in long-lasting investments, able to sustain complex and multinational infrastructures. A pivotal role is to be played by Centres of Expertise at the national level and European Reference Networks at the EU level.

The economic argument: public intervention to overcome a perceived lack of attractiveness

While RDs may be considered to a certain extent an interesting topic for basic research, this does not equally apply to clinical and translational research. Drug development, a complex and expensive process in itself, is especially cumbersome and unattractive when it comes to RDs. Poor knowledge of the causes and the natural history of the diseases, animal models rarely available, scarcity of well-defined markers and surrogates, add to the paucity of patients, hence the need for small population clinical studies, often to be carried out in different countries.

Moreover, the estimated low return on investment discourages the development of orphan products, thus leaving a huge unmet medical need. Yet, the Orphan Drug Regulation produced interesting effects – SMEs show a greater interest in early stage development of ODs, while big pharmaceutical companies tend to take products to a later development stage. The perceived economic unattractiveness of research in RDs is also a deterrent for young researchers who often do not find a research climate favourable to productive long-term collaboration. A more comprehensive medical and scientific training is needed, along with better funding opportunities to build a cooperative research environment able to attract scientists. More generally, the serious gap existing in Europe between basic research and the industry sector needs to be addressed in order to avoid clinical trials “migration” elsewhere and thus a shortage of European translational research. Hence, research on RDs does not happen spontaneously because of the inherent characteristics of RDs and their scarce

commercial interest for private sponsors. This creates a strong case for public support, as only public research funds can bridge the critical gap in RD research. The need for public support is founded on the accomplishment of the universally recognised right to health, a public good that national authorities must pursue, assuming the role of investors in research when private funders do not. “The federal government may be the only institution that can take the financial risks needed to jumpstart the development of treatments for these diseases”, remarked the Acting Director of the US NIH, on the launch of the NIH Therapeutics for Rare and Neglected Diseases Program in 2009.

Altogether, it is critical that the budget for research on RDs be substantially increased over the next years. The efforts of the public sector should be complemented by the private sector (industry, patient organisation, foundations and other stakeholders) and public-private partnership encouraged as decisive element of success for RD research.

RD research is also an area where appropriate policy and legislative decisions may be crucial for the economic environment. Both in the US and the EU, orphan drugs legislation stimulated the blossoming of biotech companies, sustainable jobs and investment in innovation. More than 50% of the world’s leading biotech companies were established in the aftermath of the 1983 US legislation. Data unmistakably follow this trend in the EU since the entry into force of the OD Regulation in 2000. Research on RDs therefore is able to stimulate a high-end technology industrial sector, thus contributing to the EU path towards greater innovation and eventually to the achievement of a more competitive knowledge-based economy, along the lines of the Lisbon Strategy. At the end of the day, these data offset the perception of RD as an unattractive area of research.

Last but not least, the cost of non-research is in all probability higher than the cost of any research aimed to overcome the knowledge gap on so many rare diseases. While regrettably the costs of non research has not been yet quantified, it is indisputably true that misdiagnosis/delayed diagnosis translate into an increase of expenses and a waste of resources for the healthcare and social systems, as well as into increased financial burden - and consequent pauperisation - for families. On the other hand, a patient that is properly treated, stops being a consumer of ineffective treatment or superfluous hospital admissions.

Scientific trends: research on rare diseases brings wider benefits

Research on RDs has proven to be very useful to better understand the mechanism of common conditions, as they often represent a model of dysfunction of a single biological pathway or because they provide insights in pathophysiology of more prevalent diseases. Similarly, treatments developed for rare diseases may be used to develop treatments for other more prevalent ones. Again, pioneering multidisciplinary approaches and new methods or treatments experimented in RD research often proved to benefit a much wider public affected by common diseases, such as clinical trials on small patient series.

Moreover, RDs are at the forefront of personalised medicine which applies genetic information about each patient to tailor treatments and medical care to individual needs. Drugs are increasingly being targeted specifically to the best responder patient subgroups, to improve patient outcomes, minimise side-effects and reduce costs: a practice that regularly apply to many (very) rare diseases.

RDs are also a laboratory for new health care policies. Because of their very nature and characteristics, specific and innovative solutions need to be devised to address the challenges they pose. Centres of Expertise, for instance, provide a rating scheme that helps to identify the most appropriate centers for a particular case and help managers to understand where to target funding. Centres of Expertise are also expected to coordinate their activities at the European level by setting up European Reference Networks for specific (groups of) diseases. A public health model is thus being delineated as a potential prototype for innovative solutions applicable also to more prevalent diseases, as it optimizes resources to the benefit of all citizens.

Lastly, RDs may open innovative avenues in the field of social care for the benefit of society at large. Developing social care responses targeted to the specific needs of patients, the resulting improvements in the patient conditions end up reducing costs of unnecessary hospitalisation or of not adapted treatments. Social care is essential for all those patients who will never be in a position to benefit from a therapy. Quality of life and social research are therefore necessary in general to patients affected by all rare diseases, but also more specifically to HTA agencies assessing the added value of treatments for RDs.

In conclusion the RD community with this paper calls upon public authorities to take the appropriate steps to improve research efforts in the field of RDs. Three areas should be prioritised: (1) RD research in national and EU Research programmes; (2) budgets for research infrastructures should be increased and guaranteed in the long-term; (3) suitable funding should be allocated within the calls for proposals in the field of therapeutics.



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WHY RESEARCH ON RARE DISEASES?

This paper aims to review ethical, social, economic and scientific needs for research into Rare Diseases (RDs). It highlights where the most urgent attention is needed and makes specific recommendations to EU Member States. EURORDIS feels urged to take this initiative following the call of the rare diseases community, supported by the analysis carried out in recent years, on the need for enhanced efforts in the fields of fundamental, translational, epidemiological, clinical and health/social services research; the respective responsibilities of the public and the private sectors; and the impact on patients affected by RDs, their families and the rest of society.

The Orphan Drugs Regulation has stimulated research and development for Orphan Drugs and has enabled approximately 60¹ new treatments for RDs to be authorised across the EU. Market exclusivity and other incentives have been crucial to close the loop between information and interest in RDs, to research commitment and funding, through bringing research outcomes from the bench to the bedside. Such initiatives demonstrate the impact that policy decisions can have in driving forward innovative research.

EU initiatives have also been important elements in stimulating research into RDs and they show the successful outcomes that public policy intervention can achieve. However, much more attention is needed by governments in addressing the perceived lack of attractiveness in researching RDs. RDs patients deserve greater emphasis in both national and European research programmes. A number of important shortcomings are still to be overcome, in particular:

- There are currently 4770 ongoing research projects, excluding clinical trials, covering 2121 diseases². However, some 30 million Europeans and their families are affected by one of the 6000 to 7000 RDs identified so far³. Further investment and support for research is urgently needed for patients who currently have no treatment on the market.
- Research projects on RD run for a short duration and often suffer from neglect at the end of the provision of public funds. Governments must be committed to implement sustainable policies that incentivise the actual development of therapies.
- Due to the perceived lack of commercial interest related to research in RDs, scientists may be reluctant to pursue a career in this field. They may also be less aware of the opportunities offered by research into RDs.
- Despite the urgent need for research, it can be particularly difficult to increase research on RDs because researchers are often scattered within a country, across the EU or even internationally; diseases may require a multidisciplinary research approach in order to find innovative solutions; many diseases lack a "research community" altogether, which is needed in order to gather the expertise into centres of expertise.
- Resources needed to conduct research may be similarly scat-

tered or altogether lacking, e.g., databases, biological resource centres, registries, diagnostic testing and international epidemiological and pharmacovigilance systems.

- Conducting research into RDs may be more costly and time-consuming than in other areas as researchers may need to build ex novo their links with researchers in other disciplines, gather scarce data and deal with the uncertainty of unsustainable funding.
- Trying to keep a realistic stance, it is probable that hundreds, or even thousands, of rare diseases will never benefit from a specific therapy. Therefore, there is a need for alternative research lines to be pursued, at both national and European levels, in the fields of socio-psychological and health economical research for the rare diseases patients that will remain outside the traditional medico-therapeutic sphere. Unfortunately, these fields of research are often not recognised as "hard" science and are often neglected, especially by funders, both private and public.

Because of all of the above, RD patients need greater emphasis in policy-making on research and greater attention in supporting specific research into their conditions. Member States should place higher priority into incentivising and supporting research policy on RDs, including robust policies and programmes, substantial budget investments and incentives for the research community.

This call fits in the broader request for higher prioritisation and more significant budget allocations to health research in general, which will enhance both EU competitiveness in a knowledge-based society and improve social justice. Research into RDs should not be seen in isolation: innovative research into RDs has led to advancements in more frequent diseases and new research avenues being opened up. The paper sets out a number of issues demonstrating why support for research in RDs is needed and suggests some ways forward for generating more research in this field.

1. THE ETHICAL AND SOCIAL JUSTICE IMPERATIVE: "EXTRA" VULNERABILITY DEMANDS "EXTRA" ORDINARY MEASURES

1.1 INTRODUCTION: SPECIFIC FEATURES OF RARE DISEASES

RDs comprise thousands of different pathologies sharing specific characteristics that increase patient vulnerability and demand >

¹ Until May 2010.

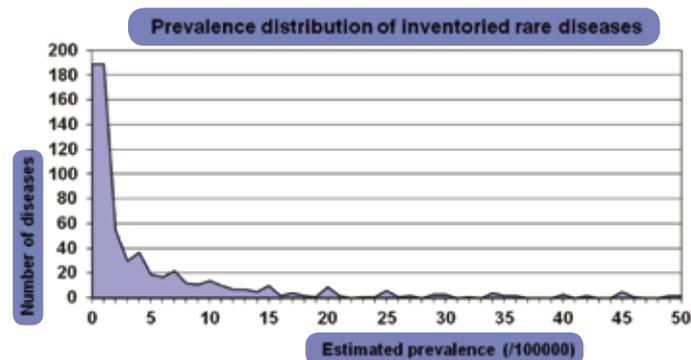
² Ségolène Aymé's presentation at the European Workshop "Bridging Patients and Researchers to Build the Future Agenda for Rare Disease Research in Europe", Brussels 1st March 2010.

³ From ORPHANET website: http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN There are thousands of rare diseases. To date, six to seven thousand rare diseases have been found and approximately five new diseases are described every week in the medical literature. This number also depends upon the accuracy of the definition. Whether a single pattern is considered unique depends on the state of our knowledge, on the accuracy of clinical and investigative analysis and on the way we choose to classify diseases in general. Certain related diseases can be considered as a unique entity (they are lumped together) or subdivided and classified as separate disorders (they are split). This complexity is reflected in the 7 various classifications of rare diseases which are provided by Orphanet.

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► concerted actions. These **common features** are the following ones:

- **Their very rarity:** RDs are defined in the EU as affecting no more than 5 per 10 000 people⁴. This low prevalence results into small or very small numbers of patients who therefore feel particularly isolated. The isolation felt by RDs patients is not only geographical but also means marginalisation within society at large and within healthcare systems designed for common diseases.



The above chart from ORPHANET (www.orpha.net) illustrates that most of the inventoried RDs have a very low prevalence (a few patients/100 000 people).

- **Rare Diseases are a complex mix of heterogeneous diseases**, currently numbering 5000 to 7000 in total. Up to 2009, one or more responsible genes were identified for only 2105 of the over 6000 rare diseases listed on the Orphanet website. For the vast majority of these diseases, no research is being conducted. There are only 395 patient registries across Europe and less than 150 rare diseases do have a marketed drug. Their heterogeneity means that research and therapeutic responses should be diverse and elaborated in each disease or group of RDs. In addition, for the same disease, symptoms can affect different organs or systems. This complicates the diagnosis significantly and requires specialists from different medical areas.

- **Expertise on Rare Diseases is limited.** Because of their rarity and complexity, scientific knowledge on RDs is scarce overall; when it does exist, it is fragmented and scattered across national or EU territory. For most RDs the causes, pathogenesis/pathophysiological mechanisms and epidemiology are still unknown, which makes diagnostic methodologies and therapies difficult to develop. These features result in aggravated patients' vulnerability and disadvantage them relative to the rest of society and to other patients affected by more common diseases.

- Other characteristics aggravating the vulnerability of RDs patients can be named: there is often substantial delay, sometimes for many years, in reaching the correct **diagnosis**; RDs often result in a reduced **life expectancy**; they are usually life-long conditions, testing the resources of health services and challenging models of care (eg. **patients' transition from paediatric to adult healthcare services**); RDs are frequently diagnosed and managed in childhood, thus representing a real challenge for clinical trials, since trial approval for research in children, especially in some countries, can prove problematic and/or very slow.

1.2 THE RATIONALE OF A SPECIFIC EU RESPONSE TO RESEARCH ON RARE DISEASES

The **principle of equality** is reaffirmed by several EU declarations and documents:

- In **Regulation 141/2000/EC on Orphan Medicinal Products**: "Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients". "Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients". In order to achieve this goal, the Regulation provides for specific enhancing measures, notably incentives to sustain development and market approval of orphan drugs: free protocol assistance, fee reductions and ten-year market exclusivity. This policy is a model of how to encourage innovation in disadvantaged areas, thus promoting equality for all citizens.
- In the constitutions of all European countries, as a fundamental principle in structuring the functioning of public authorities and relations between persons⁵.
- In **the Council Conclusions on common values and principles in European Union Health Systems**, Member States share a common commitment to ensure universal access to high quality healthcare on the basis of equity and solidarity⁶.
- In **the Council Recommendation on RDs**⁷: "the principles and overarching values of universality, access to good quality care, equity and solidarity, as endorsed in the Council Conclusions on common values and principles in EU health systems of 2 June 2006, are of paramount importance for patients with RDs".
- In **the Communication on RDs**⁸: "Member States share a common commitment to ensuring universal access to high quality healthcare on the basis of equity and solidarity".

This sense of **social justice** and **solidarity** expressed by any responsive society does call for accrued action in favour of more vulnerable groups, like patients with RDs who need particular measures to be undertaken by their governments and healthcare system in order to experience the same level of treatment as other patients. To help improving the implementation of equality, a more favourable treatment of persons who are at a disadvantage, is necessary. In other words, RDs patients do need "positive action".

4 Council Recommendation of 8 June 2009 on "An action in the field of Rare Diseases".
5 This principle is also laid down in the Lisbon Treaty of the EU, which added to the previous Treaty of the EU the positive obligation to observe equality and equal treatment in all European Union action. In all its activities, the Union shall observe the principle of equality of its citizens, who shall receive equal attention from its institutions, bodies, offices and agencies.
6 Council Conclusions on Common values and principles in European Union Health Systems, OJ 2006/C, 146/01.
7 See footnote n°1.
8 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 RDs: Europe's challenges.

1.3 THE SPECIFIC FEATURES OF RDS DEMAND SPECIFIC RESEARCH INITIATIVES

Because of their rarity and diversity, RDs particularly require the following elements to ensure success:

- A multi-disciplinary and coordinated approach. The only way to improve scientific and medical knowledge on any RD is to combine the complementary expertise of various specialists within and between countries, including alternative avenues in the fields of health economics and psycho-social research need to be further investigated. In order to achieve this coordinated approach, Member States must urgently create European structures of excellence through programmes supporting networking and cooperation between centres of expertise.

Coping with the specific features of RDs involves a global rethinking of health and social care within a wider complex system. This would therefore require a new deal of training and information, from the university stage to the daily care. This innovative participatory approach and continuous training would improve dissemination of scientific advanced knowledge but also co-production of knowledge from patients and carers themselves.

- A supranational response, across Europe and beyond. Research on RDs cannot be developed in isolation: centres of excellence, whether actual or virtual, should serve to make the best use of both experts and patient panels, and minimise duplication and isolation within single laboratories. A true European and international approach is needed.
- Optimised resources, such as databases, BRCs (biological resources centres), registries, international epidemiological surveillance, and pharmacovigilance systems. Governments should pool together scarce resources in order to optimise their use. Only through tight cooperation, efficiency can be improved and duplication of efforts avoided. Disease-specific projects, based on excellence, can be used as models for more rare or common diseases. Supranational common infrastructures, long-lasting investments and a sustained approach are necessary to develop and maintain complex and often multi-national infrastructures needed to advance research on RDs.

In this context, the role of the Centres of Expertise at national level, and their networking activities at EU level, through European Reference Networks, are instrumental to provide excellence of care, as well as to perform and link high level research on RDs with a better use of resources.

Also, the European Commission - and DG Research in particular - have a strong role to play to push forward research into RDs, especially through the upcoming new EU research programme HORIZON 2020. It is also worth noticing that there are good examples of European Research Networks, initiated by Patient Organisations, which coordinate research activities into rare diseases and would certainly benefit from a wider coordination beyond European boundaries, in order to pool together sufficient resources and a critical mass of patients to enter into clinical trials.

2. THE ECONOMIC ARGUMENT: PUBLIC INTERVENTION TO OVERCOME A PERCEIVED LACK OF ATTRACTIVENESS

2.1 INHERENT LACK OF ECONOMIC AND CAREER ATTRACTIVENESS

The perceived lack of attractiveness of researching into RDs does have a negative impact on clinical research and translational research aimed at developing industrial products. This lack of attractiveness is not equally perceived in the area of basic, fundamental research where RDs are being investigated in order to answer questions about mechanisms in biology and they do serve as models of dysfunctioning to advance scientific knowledge.

Even though RDs can be considered as attractive topics for basic research, the situation is much more difficult concerning the development of new therapies. Drug development is already complex, long-term and expensive for common diseases and much worse for RDs. For most of them, it is premature to suggest new treatment options because so little is known about the causes, pathogenesis/ pathophysiology and natural history of the disease. Since animal models are rarely available, preclinical studies are difficult to perform. In addition, there are often no well-defined and validated markers/ surrogates for monitoring disease progression and treatment responses. This overall lack of understanding - due to the scarcity of funds invested and of human resources devoted to investigating RDs - partially explains the difficulty faced by pharmaceutical companies to invest in this area as often they would have to start research from the very fundamental stages⁹. Furthermore, clinical trials need to be multinational because of the limited existing experience at national level as well as the small number of patients affected by the same rare disease. Additional difficulties come from the fact that national clinical trial registration authorities are not familiar with clinical trials in small populations¹⁰. All these hurdles, combined with the estimated low return on investment due to very small markets, can prove discouraging for the pharmaceutical industry and prevent it from developing drugs for RDs, despite the huge unmet medical need. Nevertheless, the Orphan Drug Regulation has shown that mainly SMEs are interested in the early stage of orphan drugs development based on knowledge that has been obtained via academic, publicly funded, research, while big pharmaceutical companies become interested in taking orphan drugs at a later development stage.

This perceived economic unattractiveness also deters scientists from pursuing careers in research on RDs. They may either be ▶

⁹ See WHO Report Priority Medicines for Europe and the World «A Public Health Approach to Innovation», Background Paper "Orphan Diseases", by S. van Weely, Ph.D. and Prof. H.G.M. Leufkens, page 21
¹⁰ A Right to Health is stated in the Universal Declaration of Human Rights (1948), Article 25.

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- ▶ unaware of most RDs or inhibited by the short-term limited funding available. In fact, when PhD students are interested in RDs research, they often do not get funding opportunities to pursue their research or build their own research group after their thesis. To overcome this serious short-fall in young RD researchers, improved medical and scientific training is needed as well as a research climate favourable to collaborate productively in the long-term. Furthermore, one specificity of the basic research field in Europe is that many fundamental advances are being made, but then the gap between the research world and the industry sector is so wide in Europe, that most clinical trials "emigrate" elsewhere. This serious shortage in translational research has to be rebalanced if Europe wants to keep up with the rest of the world.

All these factors explain why the development of therapies for RDs has been hampered until today and why the RD patients' community calls for urgent targeted measures.

2.2 THE CASE FOR PUBLIC SUPPORT

Given the inherent characteristics of RDs which lead to scarce commercial interest for private sponsors, research on RDs does not happen spontaneously. Also, there is not enough competition between potential private investors, and therefore not enough impetus for innovative research. Some RD patient organisations have made valuable attempts to fill this gap by funding research activities (see survey) but there are still huge needs in research funding. As a result, only public research funds can bridge the critical gap in research on RDs. This is especially important for some new Member States and developing countries, where the necessary resources to research into RDs are missing. Public financial intervention is needed for social justice and equal treatment for all patients. The accomplishment of the universally accepted "right to health" is a public good that must be pursued by national authorities, assuming the role of investors in research when private funders do not do it.

The call for public support

The need for public funding had already been identified in the 2004 WHO Report "Priority Medicines for Europe and the World, A Public Health Approach to Innovation", Background Paper "Orphan Diseases"¹²: **"To fill the gaps in our knowledge of RDs more public funding is needed, both at national and at international level. For many RDs, the first gap for pharmacological interventions that has to be filled is performing fundamental research to find the therapeutic targets. Due to the rarity of the patients with a specific disease it is recommended to fund research with public money."**

The recently adopted **Council Recommendation on RDs**¹³ states that **"the development of research and healthcare infrastructures in the field of RDs requires long-lasting projects and therefore an appropriate financial effort to ensure their sustainability in the long term."** It invites Member States to **"include in their plans or strategies pro-**

visions aimed at fostering research in the field of RDs".

This requires a strong commitment by the EU and the Member States to ensure long-term sustainable projects and common infrastructures, such as biobanks, databases and registries. The EU R&D Framework Programmes have been very good instruments for funding this research. Nevertheless, important shortcomings persist, notably the short duration of research projects.

One important advance is the **"Therapeutics for Rare and Neglected Diseases Program" or TRND**, in May 2009 adopted by the NIH (National Institute of Health). As NIH Acting Director Raynard S. Kington explained that "the federal government may be the only institution that can take the financial risks needed to jumpstart the development of treatments for these diseases". The Director of the NIH Office for RDs Research (ORDR), Stephen Groft, added «this is the first time NIH is providing support for specific, preclinical research and product development known to be major barriers preventing potential therapies from entering into clinical trials for rare or neglected disorders."

Clearly, it is critical that **the budget for research on RDs be substantially increased over the next years.** Complementary contributions from the private and public sectors are especially crucial in the field of RDs. In particular, public private partnerships should be encouraged, "private" referring to funds not only from industry but also patient organisations or other interested parties. This spirit of partnership between public sector, private sector and patient organisations is a decisive element of success. The European Commissioner for Research, Innovation and Science, Máire Geoghegan-Quinn¹⁴, stated that "the targeted participation of SMEs (in the EU Research Framework Programmes) remains an issue of concern requiring determined efforts into the future. For our vital Public Private Partnerships, this means more innovation friendly operating rules and conditions". She also pointed out that cooperation with the private sector is important to mobilise investment in innovative markets and international research cooperation.

¹² See footnote n°6 for the full reference.

¹³ See footnote n°3 for the full reference.

¹⁴ Public Hearing before the European Parliament, Committee on Industry, Research and Energy, held on 13 January 2010: <http://www.europarl.europa.eu/hearings/static/commissioners/cre/geoghegan-quinn.pdf>.

Investing for research on RDs

1. EU level: European Commission's Framework Programme for R&D (FP) – estimated budget allocated directly to RDs or for projects potentially useful for them (fundamental research on genetic or cell therapies):

- 6th Framework Programme (FP6) – years from 2002 to 2007 (entire programme duration) = 230 million EUR
- 7th Framework Programme (FP7) – years from 2008 to 2009 – approx. 80 million EUR (FP7 is still ongoing, it will end in 2013)

Hence, in both EC Programmes, the average yearly spending for direct or indirect research on RDs is approximately of 40 million EUR.

2. EU Member States: an indication of the national spending on research on RDs could be provided by the two Calls launched under the E-Rare project¹⁵ and contribution of national funding agencies that participated in the two E-Rare Joint Translational Calls of the project (JTC 2007 and JTC 2009). **These figures of course do not intend to cover all national spending on RD research:**

	JTC 2007	JTC 2009
France	2 500130	1 988 273
Germany	3 360000	2 824 680
Italy	2 000000	1 000 000
Spain	1 502973	585 500
Turkey	505 010	316 150
Netherlands		1 661 968
Austria		582 645
Greece		252 000
Portugal		197 280
TOTAL	10 040 743	9 545 796

Furthermore, the figures of the total research funding for RDs are available for three EU Member States:

France: the INSERM/GIS (Institut National de la Santé et de la Recherche Médicale/Groupement d'Intérêt Scientifique) and then, from 2005, the ANR (French National Funding Agency for Research), entrusted as funding body of rare disease research by the 1st National Plan on Rare Diseases (2004-2008), have been instrumental in funding the research on rare diseases by organizing calls for research proposals: for disease-oriented networks (2002-2005) and for multidisciplinary projects (2005-2009). Since 2002, 277 research projects on rare diseases have been funded for more than 66 Mio €.

Germany: the BMBF (Federal Ministry of Education and Research) and PT-DLR (German Project Management Agency) are responsible for the funding and implementation of the national rare disease research programme (2008-2017; ~7.5 Mio € p.a.), which is the expansion of the previous rare disease programme (2003-2009, 31 Mio €). In the programme, currently 16 consortia for rare disease research are funded. Additionally, the BMBF has funded / is funding research on rare diseases in several other funding initiatives with approximately 10 Mio € per year.

Spain: the ISCIII (Instituto de Salud Carlos III) manages the national programme for rare disease research. Rare diseases are one of the research priorities of the new Strategic Action for Health Research within the National Plan of Spain for

Research, Technological Development and Innovation (2008-2011) within the Strategic Action for Health Research. Funding of Research on rare diseases follows several approaches: (1) the general extramural research funding on Biomedical and other Health Sciences Research based on yearly competitive calls for proposals. These calls are not specific for rare diseases, but rare diseases are included as a call priority. (2). A «Network Centre for Research in Biomedicine for Rare Diseases» (CIBERER) with legal personality, attached to ISCIII, and specialized in rare diseases was launched in 2006 with a 4 year grant. The centre encompasses 61 Spanish research groups with an annual budget of 6 to 7 Mio €. (3) Furthermore there is intramural funding for a branch of ISCIII called Institute for Research on Rare Diseases (IIRER).

3. United States:

The Intramural awards (NIH "Bench to Bedside" programme) for the year 2010 were expected to be worth some 1.620.000 \$, i.e. approximately 270.000 \$ for six projects. The "Therapeutics for Rare and Neglected Diseases Programme" (TRND), a NIH initiative aimed at creating a drug development pipeline, was worth \$24 million in 2009, whereas \$26 million are budgeted for the year 2011.

2.3 COUNTERBALANCING THE PERCEIVED UNATTRACTIVENESS OF RESEARCH ON RDs WHILE PROMOTING REAL INNOVATION

In the US, the blossoming of the biotech industry has been directly attributed¹⁶ to the stimulation created by Orphan Drugs legislation in 1983. That resulted in the establishment of more than 50% of the world's leading biotech companies¹⁷, stimulating sustainable jobs and investment in innovation. Similarly, the implementation of the EC Regulation on Orphan Drugs, adopted in 1999, led to a dramatic (30%) increase in the number of new biotech companies and to many existing companies making a new start on RD research. Jobs related to orphan drugs also increased by 43% on average – which is faster than in industry generally¹⁸. These data show that political/legislative decisions can both stimulate the industrial high technology sector and directly benefit patients.

Moreover, it follows that investment in high profile research can have a positive impact on the overall growth in our knowledge-based society. Because of their diversity, RD research offer abundant opportunities for innovation in high-end sectors and thus contributes to the objective of the Lisbon Strategy: "to make the EU the most dynamic and competitive knowledge-based economy in the world".

2.4 THE COST OF NON-RESEARCH

Too many health professionals are still unaware of too many RDs. Consequent delays or errors in diagnosis are stressful for patients and their families, affect their quality of life, can be costly or even ▶

¹⁵ E-Rare (ERA-Net for research programs on RDs) is a network of ten partners - public bodies, ministries and research management organisations - from European countries, responsible for the development and management of national/regional research programs on RDs.

¹⁶ Reaves N.D. "A model of effective health policy: the 1983 Orphan Drug Act". *Journal of Health & Social Policy, Volume 17, Issue 4 February 2004, pages 61 - 71.*

¹⁷ Including Amgen (Forbes listed world's largest biotech company, whose revenue in 2008 was worth 15 billion US\$), Genzyme, Genentech.

¹⁸ SEC(2006) 832. Commission Working Staff Document of 20 June 2006, on the experience acquired as a result of Reg. 1412/2000/EC on orphan medicinal products and account of the public health benefits obtained.

WHY RESEARCH ON RARE DISEASES?

▶ dangerous by delaying access to accurate treatments. Misdiagnosis/delayed diagnosis translate into an increase of expenses and a waste of resources for the healthcare and social systems, as well as into increased financial burden - and consequent pauperisation - for families. This is particularly unacceptable considering that some RDs may be compatible with a normal life if diagnosed on time and properly managed, which keeps patients into an active life and work system.

Any research that could improve diagnosis, understanding or treatments of just some of the estimated 6 000 to 7 000 different RDs, would substantially reduce costs for healthcare systems. A RD patient, when properly treated, stops being a consumer of irrelevant tests or ineffective treatments or superfluous hospital admissions. Years of recurring diagnostic failures are very expensive and still much too frequent. Ignorance can be more expensive than the research aimed at improving knowledge.

There is a regrettable scarcity of data to quantify the costs of non-research. This scarcity results more from a lack of political will to expose these costs than from the resources needed to shed light on neglected medical domains. Studies on the costs of non-research, and research in the field of health economics at large, are needed to break this vicious circle.

3. SCIENTIFIC TRENDS: RESEARCH ON RARE DISEASES BRINGS WIDER BENEFITS

3.1 RESEARCH ON RDs ADVANCES MEDICAL RESEARCH IN GENERAL

"Research on RDs has proven to be very useful to better understand the mechanism of common conditions such as obesity and diabetes, as they often represent a model of dysfunction of a single biological pathway"¹⁹. Research on specific RDs has given much insight in pathophysiology of more prevalent diseases, like migraine for example²⁰. Furthermore, when SMEs or other companies develop a technology for the treatment of a RD, this may be used for developing treatments for other rare or more prevalent diseases.

In general, history shows that a substantial part of the universal medical knowledge did start with a model of a RD and helped understanding more common diseases. Genetic mapping of some RDs has identified previously unknown or under-appreciated normal biological processes, e.g. in immunological self-tolerance (AIRE) or in primary cilia [defective in polycystic kidney disease]²¹.

Pioneering multidisciplinary approaches and new methods or treatments in RD research can often benefit the much wider public affected by common diseases. When RDs are very serious or life-threatening and with no available therapies, any unknown risks of new treatments must be outweighed by the potential benefits to patients and/or science. For example, there is much research on gene therapy for RDs such as severe combined immunodeficiencies (SCID and ADA-SCID), Adrenoleucodystrophy, Duchenne Muscular Dystrophy (DMD), Spinal Muscular Atrophy (SMA), Wis-kott Aldrich syndrome and Leber's congenital amaurosis. Moreover, that has prompted researchers to devise new methodologies for clinical trials on small patient series; these could equally be applied in common diseases with consequent savings in patients, materials and costs.

In addition, RDs are at the forefront in personalised medicine, which applies genetic information about each patient to tailor treatments and medical care to individual needs. Today, certain drugs are increasingly being targeted specifically to the best responder patient subgroups, to improve patient outcomes, minimise side-effects and reduce costs. Indeed, some diseases are so rare that their proper diagnosis and groundbreaking treatment has to be personalised, e.g. for extremely rare tumours²².

In the last decade, we have witnessed huge progress in medical research, especially in pharmacology, gene and cell therapies, tissue engineering, high-tech medical devices, gene testing and other sophisticated diagnostic tools, including medical imaging. However, bringing these high-value innovations to patients, to optimise medical solutions (as well as use of economic resources), requires both centres of excellence and increased collaboration across the EU.

3.2 RARE DISEASES AS A LABORATORY FOR NEW HEALTH CARE POLICIES

Because RDs are so overlooked, the EU Commission and some national health systems are developing specific solutions and innovative approaches to the challenges they pose in addressing patients needs. It is important to remember that - in application of the subsidiarity principle²³- Health Policies fall within the competences of the national authorities.

As clearly stated in the Commission Communication and in the Council Recommendation, Centres of Expertise should be identified at national and regional levels and resources allocated for diagnosis, care, clinical trials, epidemiology etc. The added value of Centres of Expertise for the national health care system is that of providing a rating scheme that helps patients to access the

¹⁹ 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 RDs: Europe's challenges.

²⁰ De Vries B. et al. (2009); Molecular genetics of migraine. Hum. Genet. 2009 Jul; 126(1):115-32.

²¹ D. Mathis and C. Benoist 2007; A decade of AIRE. Nat Revs Immunol. 7, 645-50.

²² Examples of this are the findings for chronic myeloid leukaemia (CML), seminoma, gastrointestinal stromal tumour (GIST). From the paper "Importance of Research on RDs and Orphan Drugs", Dr. Patrick Corley, Avril Daly, June 2009.

²³ The principle of subsidiarity is defined in Article 5 of the Treaty establishing the European Community. It is intended to ensure that decisions are taken as closely as possible to the citizen and that constant checks are made as to whether action at Community level is justified in the light of the possibilities available at national, regional or local level. Specifically, it is the principle whereby the Union does not take action (except in the areas which fall within its exclusive competence) unless it is more effective than action taken at national, regional or local level. It is closely bound up with the principles of proportionality and necessity, which require that any action by the Union should not go beyond what is necessary to achieve the objectives of the Treaty.

- ▶ Centres most appropriate to their particular case, and also healthcare managers to identify where to target funding²⁴.

Patient registries are necessary to perform clinical research. Centres of Expertise have an important role to play as they can improve knowledge on where RD patients are located. Centres of Expertise are also expected to coordinate most of their activities at the European level by organising themselves in European Reference Networks for specific diseases or groups of RDs, so to combine multidisciplinary expertise in pursuing new research avenues, develop social care guidelines and improved standards of diagnosis and care.

We believe that such a new public health model could be a prototype for innovative approaches to more common diseases. Today, the national health care systems of EU countries are increasingly criticised and in financial deficit. By encouraging existing voluntary European collaborations to improve all partner centres, the emerging RD healthcare model could pioneer new optimised use of existing healthcare resources to the benefit of all citizens.

3.3 TRENDS IN SOCIAL RESEARCH

Many rare diseases will not benefit from a medical treatment for a very long time to come. It is therefore important to invest in the field of social care and social research. The positive outcomes of this type of research are horizontal and will benefit patients affected by all rare diseases. Furthermore, quality of life studies and social research on rare diseases are useful to generate important data needed by HTA Agencies, in view of assessing the added value of treatments for rare diseases and in view of launching clinical trials.

Rare Diseases do represent a “laboratory” with implications in different areas: not only is medical research on RDs valuable for more common diseases; not only the “RDs case study” can be used as a test field to develop new healthcare policies; but it is also expected - and already shown through different initiatives - that RDs may open innovative avenues in the field of social care, which will indeed benefit society at large. In fact, by developing a social response targeted to the specific needs of the concerned patients and their families, the costs are maybe higher in the first place, but the resulting improvement in the conditions of the patients ends up - in the medium term - reducing the hospitalisation costs and potential non-adapted therapies and treatments. Costs of social care are mainly manpower costs, which are proportionate to the national GDP and to the actual level of salaries in the different countries, contrary to the costs of orphan drugs and other medicinal products at large which vary much less from poor to rich countries.

4. IN CONCLUSION

The above arguments should help to overcome the shortcomings in research policy-making. The EU Regulation on Orphan Drugs and its ongoing implementation have partially addressed the perceived unattractiveness of developing therapeutics for RDs. It has also highlighted institutional and political attitudes to this socio-medical problem, especially the lack of political will for the fundamental and translational research demanded by patients' organisations. Time is ripe for scientists to open new research avenues using RDs as “models”, as emphasised throughout this paper. To pursue these opportunities optimally, it is essential that the EU Member States apply the principles of equity and solidarity on which their health and social care systems are founded.

The RDs community at large, comprising of patients, researchers, health professionals, and industry, expects that public authorities take appropriate political steps in order to improve research efforts in the field of rare diseases. In this context, EURORDIS believes that priority actions should be taken alongside three main axes:

1. Within Research programmes, RDs should be given a higher priority at both national and European (or even beyond) levels;
2. Budgets to fund the creation, functioning and maintaining of research infrastructures should be increased and ensured in the long-term, in a sustainable manner;
3. Within the calls for proposals in the field of therapeutics, favourable political decisions should be taken and followed by suitable funding, in order to boost research projects in this area.

POSITION PAPER

“The Council of the European Union...hereby recommends that Member States...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.”

(COUNCIL RECOMMENDATION of 8 June 2009 on an Action in the field of Rare Diseases)





EURORDIS
Rare Diseases Europe

PATIENTS' PRIORITIES
AND NEEDS FOR RARE DISEASE RESEARCH
2014-2020

October 2011

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 new EU research programme HORIZON 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-competitive¹ 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 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 measure 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 is 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 research programme HORIZON 2020 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.



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INTRODUCTION

On the eve of the adoption of the new EU research programme 'HORIZON 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.

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 is divided into two parts: WHAT are the priority areas of research and HOW these can be achieved, with a description of the guiding principles and of the financial aspects. Finally, the last section 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.

OVERALL STRATEGY - PRIORITIES AND GUIDING PRINCIPLES

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**. ➤

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

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

PATIENTS' PRIORITIES AND NEEDS FOR RARE DISEASE RESEARCH 2014-2020

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

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
- › 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" project⁴, 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 EuroCareCF⁵ is an excellent example of a successful combination of registries⁶ (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 2011 ORPHANET/RDPlatform Report on the state of the art of RDR (see section 4 for more details or http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf), 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 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

4 - <http://www.treat-nmd.eu/>

5 - <http://www.eurocarecf.eu/>

6 - <http://www.ecfs.eu/projects/ecfs-patient-registry/intro>

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 its 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**.

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/RDPlatform Report, 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).

Actions to be taken:

- 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.



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- 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.

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 Final Report of the abovementioned ORPHANET/RDPlatform project⁷):

- > 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

⁷ - http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf or for more information on the overall project: <http://www.rdplatform.org/>.

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.ecri.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.

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 study⁸ 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 complementary (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.

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.

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. ➤

⁸ - Estudio sobre situación de Necesidades Sociosanitarias de las personas con Enfermedades Raras en España, ENSERio: <http://www.feder.org.es/panelc/publicaciones/archivos/ZRKCBGYOEQLTTPATQNAFRCLMYRMCOR.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.

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► 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.

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 RDR⁹. Secondly, we introduce the main financial avenues to be pursued for funding RDR.

2.1 Guiding principles

→ 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 fun-

draising 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 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.

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

- 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.

→ 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 be added:

Actions to be taken:

- 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 RD¹⁰.
- 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.

→ 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.

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. ➤

¹⁰ - 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/EUCERD-WorkshopReportCECERN.pdf>

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► **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).

- 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 forthcoming research programme HORIZON 2020.

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 Report¹¹ 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”.

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.

2.2 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;

11 - 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>.

3. BACKGROUND AND STATE OF THE ART

EURORDIS adopted its last position paper on rare disease researchⁱ 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.

In May 2007, EURORDIS organised a European Workshop on "Gaining Access to Rare Disease Research Resources" in Parisⁱⁱ; 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 Report performed by ORPHANET ("RDPlatform project" supported by the European Commission) 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/RDPlatform** Report, 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/RDPlatform Report 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** >

ⁱ EURORDIS. Position Paper on Research Priorities for Rare Diseases, www.eurordis.org/sites/default/files/publications/position-paper-EURORDISresearch-prioritiesFeb08.pdf

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, http://ftp.cordis.europa.eu/pub/ftp7/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. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ.C.2009.151:0007:0010:EN:PDF>

^{vi} EURORDIS. Rare Disease Day 2010 "Researchers and Patients, Partners for Life!" <http://www.rarediseaseday.org/article/rare-disease-day-2010-focus>

^{vii} S. Aymé, V. Hivert (eds.), "Report on rare disease research, its determinants in Europe and the way forward", May 2011, available at: http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf or, for more information on the overall project: <http://www.rdplatform.org/>

^{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

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➤ 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 internal consultations held in EURORDIS (membership, Board of Directors, European Public Affairs Committee, Workshop on Research held in May 2011 during the annual membership meeting) and on contri-

butions of external experts. It also relies on the position papers that EURORDIS adopted in the past years, always following extensive internal consultations, on research priorities, biobanks, registries, clinical research, orphan drugs, paediatric drugs and advanced therapies (see EURORDIS website, www.eurordis.org, Library section, for a selection of those).

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
FP	Framework Programme for Research and Technological Development
IOM	Institute of Medicine
IRDiRC	International Consortium on Rare Disease Research
NGO	Non-governmental organisation
NIH	National Health Institute (United States)
NP	National Plan
OD	Orphan Drug
RD	Rare disease(s)
RDR	Rare disease research
R&D	Research and Development
SMEs	Small and Medium Enterprises

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