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PROJECT FINAL REPORT

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4.1 Final publishable summary report

1 Executive summary

Rare diseases are life threatening or chronically debilitating conditions from which not more than five affected persons per 10,000 citizens in the European Union (EU) suffer. It is estimated that 6000-8000 different rare diseases exist, affecting between 6% and 8% of the population in the course of their lives. This means that the total number of people affected by rare diseases in the EU is between 26 and 30 million. Most rare diseases are genetic diseases, the others being rare cancers, autoimmune diseases, congenital malformations, toxic and infectious diseases. Research on rare diseases is not only scarce, but also scattered in different laboratories throughout the EU. This scarcity of the expertise translates into delayed diagnosis, few medicinal products and difficult access to care. That is why rare diseases are a prime example of a research area that strongly profits from coordination on a European and international scale. This is also recognized in the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). In this Recommendation, rare disease research is specifically emphasized and it is suggested that the coordination of Community, national and regional programmes for rare disease research should be improved. Furthermore, the needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them should be identified, and interdisciplinary cooperative approaches to be complementarily addressed through national and Community programmes should be promoted. In addition, the Council Recommendation asks for the establishment of national plans/strategies on rare diseases that should cover health care and research.

At present only few European countries fund research on rare diseases through specific dedicated programmes. Therefore, the funding of transnational collaborative research is the most effective joint activity to enhance the cooperation between scientists working on rare diseases in Europe and beyond and thus reducing fragmentation of research in this field. The E-Rare consortium was built to link responsible funding organizations and ministries that combine the scarce resources for rare disease research and thus enable the participation of many researchers to transnational projects via Joint Transnational Calls (JTCs). The calls performed in the E-Rare-1 (2006-2010) and E-Rare-2 (2010-2014) programmes have shown that funding of projects on rare disease research in a coordinated way is clearly possible and needed as there is a significant interest for collaboration between rare disease researchers in Europe. Since 2007 the E-Rare Consortium implemented **6** Joint Transnational Calls for collaborative multidisciplinary research projects open for any rare disease (except rare cancers, rare infectious diseases and adverse reactions to drugs), with wide range of possible topics and approaches. In seven years **56.4 Mio€** were invested to fund **79** research projects involving **347** research teams.

The highly competitive nature of the Joint Transnational Calls resulted in funding of very high quality projects. A large proportion of submitting researchers have outstanding track records with publications in the best-ranking journals. The assessment of the E-Rare funding programme achievements based on the analysis of the final project reports of JTC2007 and JTC2009 confirmed also that E-Rare funded projects largely contribute to reducing fragmentation of resources and achieving critical mass of data and samples for research projects. All funded consortia initiated new infrastructures (databases, registries and biobanks) with which they achieved the critical mass of samples/data necessary for the development of the project. E-Rare funding facilitated the academic training of a substantial number of young researchers: 58 MSc and 76 PhD students were trained in

the context of the 29 analyzed funded projects. Finally, E-Rare was recognized as a catalyst for new collaborations but also for cooperation sustainability. 77 % of consortia established new collaborations thanks to the E-Rare funding and more than half of them succeeded in obtaining subsequent funding for their project. The importance of E-Rare as a collaboration "stimulator" was also confirmed by an inquiry in Spring 2013 among researchers that applied to E-Rare calls JTC2007 up to JTC2012 but did not succeed to obtain funds. The response rate to this survey was more than 20%. Despite the fact that these applicants were not funded by E-Rare, 50% of the responders confirmed that applying to the E-Rare calls triggered the establishment of new collaborations and most of them pursued this collaboration even without E-Rare funding.

Next to performing Joint Transnational Calls and assessment of the funding mechanisms and results of the funded research projects the E-Rare-1 and E-Rare-2 programmes paid attention to deepening the cooperation and coordination among the E-Rare partners by systematic exchange of information on the national programmes and by strategic activities aimed at a sustainable development and extension of the network of rare disease research funders. The E-Rare-2 consortium started with 16 partners from 13 countries in the consortium. Within the period of the E-Rare-2 programme new funding bodies from Belgium, Canada, Hungary, Latvia, Poland and Romania joined (some of) the E-Rare calls and funding bodies of Romania and Latvia joined the E-Rare 2 consortium as full partner and observer, respectively.

In September 2012 the « E-Rare Group of Funders » joined the International Rare Diseases Research Consortium (IRDiRC) with the aim of contributing to its grand challenges and objectives and to continue and expand E-Rare activities in accelerating the development of new diagnostics and therapeutics for patients suffering from rare diseases. The goal of IRDiRC is to team up researchers and funding organizations across the world that are strongly involved in rare diseases research in order to achieve two main and ambitious objectives: deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020. This Consortium was launched by the European Commission and the US National Institute of Health in September 2010 and was immediately joined by Spain, followed by France, The Netherlands, Germany and Italy. As a member of IRDiRC E-Rare strongly promotes transnational funding activities and facilitates participation of a wide range of funding organizations, thus giving them the opportunity to participate in the shaping of the rare diseases research landscape and policies.

2 Project context and objectives

E-Rare-2 is an **ERA-NET for research programmes on rare diseases** funded under the **European Commission's 7th Framework Programme** from October 2010 to November 2014, comprising 17 partners from 14 countries. The ERA-NET serves as a platform for funding agencies and ministries to coordinate transnational collaborative research in the field of rare diseases through yearly joint transnational calls (JTC), which is one of the most important and effective E-Rare-2 activities. **Rare diseases** represent an important public-health issue, affecting 26-30 million persons across Europe, and a major challenge for research. The fragmentation of resources and knowledge for the 6 000-8 000 rare diseases, the delayed diagnosis and the lack of treatment for the majority of them necessitate a coordinated European approach to fight fragmentation of knowledge and resources. E-Rare-2 has been built on the basis of the accomplishments of the first phase of the E-Rare project (E-Rare-1), which launched two successful JTCs (JTC 2007 & JTC 2009). The increasing response of the research community to these joint calls (123 and 137 proposals

submitted to the first and second calls respectively, involving 495 and 566 research teams) and the increasing number of funding agencies participating in these calls have attested the need of, and the acknowledgment from, the research community for transnational funding of collaborative, multidisciplinary and ambitious projects on rare diseases.

Therefore, the **main objective** of this second phase of the E-Rare project (E-Rare-2) was to deepen and extend the existing E-Rare-1 cooperation and to go further in supporting transnational research projects, through the **launch of yearly joint calls for proposals on rare diseases** (except rare cancers and rare infectious diseases). The integration of five new countries in E-Rare-2 (Austria, Greece, Hungary, Portugal and Romania) broadened the basis of experience and the impact of joint actions. **Two "general" joint calls** with broad and open topics were foreseen to allow researchers to choose their projects based on state of the art and research demand for the specific disease. This bottom-up approach is seen as the most suited to cluster the most competitive national research groups in common projects (**WP3**), and effectively opens the national programmes for more international collaboration. Introducing **two "focused" joint calls** enabled E-Rare-2 to address themes of research on rare diseases that need special attention and a focused approach (**WP4**). These calls allowed E-Rare-2 partner countries (and new comers that may join our calls) to support transnational collaborative and multidisciplinary research projects in rare diseases progressing towards a translational research approach, thus serving the patients suffering from rare diseases.

In addition, E-Rare-2 aimed to extend the cooperation among its partners and had **other important objectives**:

1) Updating and extending the **information exchange** on research funding activities taken in the field of rare disease research by different countries both within the consortium (and thus including associated states like Turkey and Israel) as well outside the consortium (e.g. Canada, Scandinavian countries, etc.) (**WP2**). The analysis of this information allowed to reveal opportunities and needs for the set-up of new research programmes and helped to elaborate recommendations accordingly. Particular attention was be given to communication with new EU member states where there is a growing awareness for rare diseases that could generate specific research programmes and/or actions for funding research projects on rare diseases;

2) Monitoring of funded projects (**WP5**) to provide feedback to the planning activities in the network so that strategies for future funding programmes within E-Rare-2 and beyond can be adjusted and optimized;

3) Transforming E-Rare into a **sustainable network** (**WP6**). This included the development of a **common strategic framework programme for rare disease research** which aims at increasing and diversifying the current activities through the increase of funding commitment as well as exploring the inclusion of new funding agencies (e.g. charities, agencies from additional EU, ERA and non-ERA countries etc.) and new research topics.

4) Ensuring that the relevant **stakeholders** (scientists, patient organisations, industry, RTD and health policy makers etc.) are actively engaged in, and informed on, the activities of E-Rare. This goal was reached by gathering the input of the External Advisory Board (EAB), organizing specific workshops and collaborating with other relevant initiatives like EUROPLAN, Orphanet, RDPlatform, ERA-Instruments, ECRIN, BBMRI, EU-OpenScreen etc. The **knowledge** generated in the different work packages was widely disseminated (**WP7**).

7) Enlarging the consortium to include a **critical mass of European, Associated and non-European research-funding agencies**.

Through the joint funding of translational research projects in rare diseases and other activities planned in this ERA-NET, E-Rare-2 contributed to reducing the fragmentation of resources and expertise in this field, thereby shaping the European Research Area in rare diseases.

3 Results

Funding transnational collaborative research on rare diseases

Why public funding for rare diseases research is needed?

Rare diseases are life threatening or chronically debilitating conditions from which not more than five affected persons per 10,000 citizens in the European Union suffer. In the last decades, the notion has evolved that patients suffering from rare conditions should be entitled to the same quality of treatment as other patients with more frequently occurring disorders. It is estimated that 6000-8000 different rare diseases exist which, for 80% of them, are of genetic origin. Patients with a rare disease may suffer significantly from many complaints over a long period of time, partly due to the fact that about 30-50% of the patients have the first symptoms already in childhood, and often have a low quality of life. Factors like lack of information, lack of knowledge on natural history, lack of (early) diagnosis, lack of appropriate medical care, absence of pharmacological interventions or under-use of medication have an important impact on the burden of many rare diseases. In 60% of the rare disease cases, some decrease of symptoms is possible by giving a symptomatic treatment like orthopaedic surgery, removal of spleen, etc. Symptomatic pharmacological intervention may include analgesics and muscle relaxation drugs. However, these treatments do not influence the cause of the disease and may have serious side effects. The European legislation on Orphan Drugs (2000) has accelerated the development of specific therapeutics for rare diseases. However, thousands of rare diseases still remain without any adequate treatment. Thus, drug development for rare diseases needs to be accelerated. Not unexpectedly, recent research has shown that development of orphan medicinal products is clearly increased when more biomedical research on the specific diseases has been performed. Thus, biomedical research is definitely needed to understand rare diseases and to discover new treatments.

A different, but also very important aspect of rare disease research is the fact that a major part of the universal medical knowledge society gained over centuries has started with rare disease research and gave more insight in pathways that are involved in more common diseases. Due to the results of the genomic and proteomic techniques knowledge of new pathways will increase partly due to rare disease research. Another phenomenon due to the increase of knowledge is the concept of personalised medicine: the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition. The treatment of some of the rare cancers can be seen as an example of personalised medicine.

Biomedical research is mainly performed at university laboratories and university hospitals in developed countries. These investigations are mostly financed by public funds from national funding organisations or governments, as the number of private funds for rare disorders is relatively poor. Due to the high risks in development and rather low profits involved, pharmaceutical companies mostly only get involved at a late stage of the development process of orphan drugs, e.g. phase 2 clinical studies. This means that **public funding of biomedical research on rare diseases is still very much needed**.

E-Rare Joint Transnational Calls

Funding transnational collaborative research projects through the organization of **yearly Joint Transnational Calls** is one of the most important activities of E-Rare. Since 2007 E-Rare Consortium implemented **6** Joint Transnational Calls (JTC 2007, JTC 2009, JTC 2011, JTC 2012, JTC 2013 and JTC 2014) for collaborative multidisciplinary research projects open for any rare disease (except rare cancers, rare infectious diseases and adverse reactions to drugs), with wide range of possible topics and approaches. In seven years **56.4 Mio€** were invested to fund **79** research projects involving **347** research teams.

Between 2010 and 2014 E-Rare-2 launched four joint transnational calls with an overwhelming response of rare diseases research community attesting the demand and potential to engage in transnational collaborations with complementary expertise. Indeed 2292 research teams in 527 applications responded to the calls.

Given the large number of proposals submitted to E-Rare calls a two-step submission/evaluation procedure has been implemented in all calls. The proposals were reviewed by external experts, followed by an international peer review panel meeting, which established a ranking list of proposals recommended for funding based on five evaluation criteria (including the scientific quality, impact and feasibility of the proposed work). Through these four JTCs, the **50 projects funded for a total amount of 38.34 Mio€ and involving 227 research teams** cover a wide range of rare diseases while addressing potential therapeutic options using state-of-the-art techniques like pluripotent stem cells, gene therapy vectors and customized animal models.

- **General calls (JTC 2011 & 2013)**

Two "general" joint calls with broad and open topics were implemented to allow researchers to choose their projects based on state of the art and research demand for the specific disease. This bottom-up approach is seen as the most suited to **cluster** the most competitive national research groups in common projects, and effectively opens the national programmes for more international collaboration. The calls are designed to promote the **multidisciplinarity** necessary for progressing towards a translational research approach, thus serving the patients suffering from rare diseases. The resulting synergies ensure a higher **cost-effectiveness** of the limited funding.

National research funding agencies from ten (JTC 2011) and 14 (JTC 2013) countries participated in these general calls. In 2013 funding agencies from **Canada, Hungary, Romania and Switzerland** joined E-Rare call for the first time. The demand of research community was shown by the level of participation: a total of **304 proposals** were submitted to the two calls, which engaged 1354 research groups from 16 countries. E-Rare-2 funded **13** (JTC 2011) and **12** projects (JTC 2013) respectively for a total budget of **18 Mio €**.

- **Focused calls (JTC 2012 & 2014)**

The goal of the two "focused calls" was to address themes of research on rare diseases, which need special attention and focused approach. The selection of suitable topics was done through a multistep procedure starting with the analysis of the results of the previous calls, strategic workshops and consultation of the research community carried out in E-Rare-1. A set of topics including:

- Improving the access to technology research platforms such as high throughput sequencing and drug screening
- Facilitating the harmonization/merging of existing national biobanks and registry databases
- Enabling a start-up for research cooperation on ultra-rare diseases for which there is currently little, if any, on-going research
- Supporting the cooperation of young investigators to facilitate early career development and training in rare disease research
- Supporting projects on social and economic issues related to rare diseases,

was proposed for discussion. The objective was to agree on a topic most pertinent for rare diseases research community and with a high funding potential (high added value for funding agencies). The final decision was taken after thorough consultation with E-Rare-2 External Advisory Board composed of scientific experts, patients' organizations, regulatory authorities and pharmaceutical industry representatives.
Based on this consultation in 2012 the first focused call was dedicated to "European Research Projects on Rare Diseases driven by independent Young Investigators". The aim was to facilitate early career development and training and to provide to young, independent investigators the opportunity of building transnational collaborations in the field of rare disease research. A total of 82 proposals involving 327 research groups from 11 countries were submitted, and **11 projects were funded for a total of around 9 Mio€**.

A first appraisal of the E-Rare funded projects and calls showed that proposed research and approaches often cover the whole spectrum of research on a rare disease, going from clinical research (registries, biobanks) up to pre-therapeutic research. In order to further contribute to the progresses in research and opening routes for new treatments the E-Rare-2 consortium decided to dedicate its 2nd focused call to the pre-clinical development of therapeutic approaches in suitable existing animal or cell model for rare diseases. A total of 141 proposals involving 611 research groups from 22 countries were submitted, and **14 projects were funded for a total of 10.7 Mio€**. The projects cover cell-based, gene and pharmacological therapeutic approaches for 11 rare diseases including one ultra rare condition.

Monitoring of call procedures - Lessons learnt

Launching of a joint transnational call is not solely limited to a common agreement on the topic of the call and funding commitment. The implication of numerous funding agencies with varied background and experience in national calls requires a collective agreement on procedures of call implementation and evaluation of research projects. In order to improve the procedures, at the end of each transnational call, the practicability of administrative and operational mechanisms is evaluated and lessons learnt are drawn. Based on the experience of six joint calls E-Rare consortium was able to adapt and ameliorate call implementation. New mechanisms targeting higher transparency and fairness towards researchers were introduced. The two-step evaluation procedure with pre-proposal and full proposal application was judged the most adapted for the volume of the call. The recruitment of independent experts for the scientific evaluation committee was adjusted every year based on the preliminary analysis of submitted pre-proposals and according to the needs per medical domain. All pre-proposals and full proposals were evaluated by at least two and four scientific experts respectively. The researchers were given a right to respond in so called "rebuttal" step allowing them to comment the evaluation reports of reviewers. This step

was particularly appreciated by the research community and contributed to more appropriate final evaluation of projects. Finally, the comments of researchers, evaluators and funding agencies were regularly collected and helped in adaptation of call documents, guidelines and application forms. In general this monitoring exercise allowed building of a robust, agreed and flexible model of joint calls and evaluation procedures whose efficacy is acknowledged by both recurrent and new call partners.

Added value of transnational research cooperation

The achievements of the E-Rare-1 funding programme (Joint Transnational Calls 2007 & 2009) were assessed after the 3-year funding period for each of the two joint transnational calls. To this end, the follow-up and final reports of the research projects that received funding through the joint calls of E-Rare-1 were thoroughly analyzed, and the findings compiled into an assessment report.
The analysis confirmed that **E-Rare funded projects largely contribute to reducing fragmentation of resources and achieving critical mass of data and samples for research projects**. All 29 funded consortia initiated new infrastructures (databases, registries and biobanks) with which they achieved the critical mass of samples/data necessary for the development of the project. 100 % of registries and 70 - 80 % of databases and biobanks were confirmed sustainable.
E-Rare funding also **facilitated the academic training of a substantial number of young researchers**: 76 PhD students were trained, 45 post-doctoral fellows were hired and more than 40 researchers participated in mobility or professional exchange.
The highly competitive nature of the Joint Transnational Calls resulted in funding of very high quality projects. A large proportion of submitting researchers have outstanding track records with publications in the best-ranking journals. As an example, the J**TC2007 projects resulted in 39 publications** with an **average impact factor of 9.5**. Since 2008, the number of citations follows a steep increase and the average citation rate is now 9.8 citations/paper.
Finally E-Rare was recognized as a **catalyst for new collaborations** but also for **cooperation sustainability**. 77% of consortia established new collaborations thanks to the E-Rare funding and more than half of them succeeded in obtaining subsequent funding for their project. The importance of **E-Rare as a collaboration "stimulator"** was also confirmed by the inquiry, in Spring 2013, among more than 1400 researchers that applied to E-Rare calls (JTC 2007 up to JTC 2012) but did not succeed to obtain funds. The response rate to this survey was more than 20%. Despite the fact that these applicants were not funded by E-Rare, 50% of candidates confirmed that applying to the E-Rare calls triggered the establishment of new collaborations and most of them pursued this collaboration even without E-Rare funding.

Further fostering of transnational collaboration
In order to further enhance the collaboration of rare diseases researchers funded by E-Rare the consortium employed different means of communication tailored to the needs of the community. For this purpose two specific tools were elaborated on E-Rare website. The contact between rare diseases researchers and other stakeholders is of particular importance and no dedicated virtual platform existed until recently. Based on the previous inquiry among RD researchers, E-Rare undertook the development of "Looking for collaboration" module. A partnering tool specifically adapted to the needs of scientists looking for partners in view of setting up a transnational collaboration in response to the E-Rare calls. Secondly, in order to better respond to inquiries of researchers related to the joint calls an interactive FAQ was created. The module allows consulting the FAQ or asking questions related to the joint calls. The questions are transmitted immediately to the coordination that responds on 24h delay. Each new question is integrated and enriches the FAQ. Both tools are used successfully and the community expressed the need for their further

adaptation and expansion.

E-Rare funded researchers had also the opportunity of networking at a dedicated scientific meeting organized by the consortium in January 2014 in Athens. The event gathered representatives of all JTC 2009, 2011 and 2012 funded projects together with important stakeholders: E-Rare Scientific Evaluation Committee members, E-Rare External Advisory Board representatives, delegates of European Commission, IRDiRC, European Research Infrastructures, patients - EURORDIS and Greek officials involved in health, research and rare diseases domains. A specific session was dedicated to project reporting and networking, where researchers had the occasion to present their work, discuss with E-Rare funding agencies but also discover European Research Infrastructures. A poster session was organized for the young coordinators of JTC 2012 projects. A jury composed of the members of Scientific Evaluation Committee assessed the posters and attributed the Best Poster prize. All participants evaluated the meeting ex post via an on-line survey. They had also a possibility to indicate specific needs for training sessions or dedicated workshops. All comments and ideas gathered will serve E-Rare to ameliorate forthcoming scientific events.

Finally, E-Rare organized a Scientific Symposium in October 2014 with a specific focus on collaboration in rare diseases research. The acquired knowledge on national research programmes and conclusions for the future, and the overall achievements and lessons learnt of the E-Rare-2 programme were exposed at this occasion. The event presented a perfect opportunity to gather rare diseases stakeholders and to invite the representatives of funding agencies not yet involved in E-Rare. The coordinators of several projects funded by E-Rare were invited to present their success stories. The representatives of IMI, EMA, Innorare and EURORDIS introduced the on-going or future collaboration initiatives planned with E-Rare. A broad public (more than 100 participants coming from 21 countries) composed of researchers, national and international stakeholders in the field of rare diseases, including clinicians, policy makers, programme owners (legal entities) and patients associations attended the meeting. The symposium has given an overview on how cooperation among funders, scientists and other relevant stakeholders helps in advancing rare diseases research with benefit to patients.

State of the art of existing rare diseases research funding in Europe and beyond

Further achievements of E-Rare concern the systematic exchange of information and best practices through the mutual knowledge of the partners' national programmes and beyond.

In 2009, the European Council recommended to identify the on-going research and the research resources in the national and Community frameworks in order to map and improve the coordination of rare diseases research. In response to this recommendation, each of the 27 member states has been committed to elaborate and adopt a national plan/strategy for rare diseases at the end of 2013, including their plans and earmarked budgets for rare diseases research. In order to obtain a broad and enlarged picture of rare diseases research funding E-Rare-2 launched a dedicated survey addressed first to E-Rare partner countries and, in its second phase, to selected countries outside the E-Rare consortium in order to gather information on non-European research programmes. These included countries with a comparable cultural and socio-economic context (e.g. Canada, Australia, USA) to European countries. The survey allowed a cross-sectional analysis of current research programmes and research funding within and outside Europe pointing out substantial gaps at different levels of national funding systems. First of all, many research-funding agencies lack the organized databases permitting the extraction of rare diseases research projects.

This is further complicated by the missing common terminology (key words) that could serve for identification. These important aspects make the fine analysis laborious and demanding. However, based on the obtained results it was possible to conclude that very few funding agencies have a specific rare diseases research programme and even among those, the programme is not embedded into a national strategy for rare diseases. The majority of questioned agencies do not have any particular RD program and therefore **E-Rare represents for them a unique mode of rare diseases research funding**. The level of budget dedicated to rare diseases is extremely variable: from 2 to 20% of total committed biomedical funds. Finally, there is no specific trend indicating any increase of RD funding between 2009 and 2012, years where rare diseases were designated as one of the major preoccupations for European health and research strategies. In conclusion, the results of the survey clearly indicate that participation in E-Rare calls often delineates a single solution for rare diseases research funding in many countries. That is why E-Rare efforts should be further reinforced, expanded to new countries and the national and EU commitments strengthened.

Harmonization of common policies

In view of development of common research policies at European level, E-Rare-2 engaged the discussion on the ethical and legal implication of large-scale exome/genome sequencing (WES/WGS) in the context of research on rare diseases by organizing a workshop on "Ethical aspects of exome and whole genome sequencing studies in rare diseases".
The main objectives of the workshop were to:

- Review the nature and content of informed consent for patients with rare diseases in the era of WES and WGS studies;
- Capture the European initiatives for harmonizing policies and legal frames for informed consent.

The workshop was organized on the 14th of January 2013 in Tel Aviv, Israel by the Chief Scientist Office of the Health Ministry of Israel, a member of the E-Rare Consortium, gathered top-level specialists in ethics, law and genome/exome sequencing applied to rare diseases. The programme, biographies and videos of all lectures of the workshop were published on the E-Rare website www.e-rare.eu and contributed to the collective reflection on this important topic.

Developing international collaboration

Next to performing Joint Transnational Calls and assessment of the funding mechanisms and results of the funded research projects the E-Rare consortium paid attention to deepening the cooperation and coordination among the E-Rare partners by systematic exchange of information on the national programmes and by strategic activities aimed at a sustainable development and extension of the network of rare disease research funders. In September 2012 the « E-Rare Group of Funders » (FWF, Austria; FNRS, Belgium; FWO, Belgium; ANR, France; BMBF, Germany; GSRT, Greece; ISS, Italy; CSO/MOH, Israel; FCT, Portugal; ISCIII, Spain; ZonMw, The Netherlands and TUBITAK, Turkey) joined International Rare Diseases Research Consortium (IRDiRC) with the aim of contributing to its grand challenges and objectives and to continue and expand E-Rare activities in accelerating the development of new diagnostics and therapeutics for patients suffering from rare diseases. The goal of IRDiRC is to team up researchers and funding organizations across the world that are strongly involved in rare diseases research in order to achieve two main and ambitious objectives: deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020. This Consortium was launched by the European Commission and the

US National Institute of Health in September 2010 and was immediately joined by Spain, followed by France, The Netherlands, Germany and Italy.
The joining of the "E-Rare group of funders" in IRDiRC is of double importance. On one hand it allowed some research funding organisations to participate in IRDiRC both on national and on transnational level by dedicating *separate budget lines* to rare diseases research: a budget line for their national funding programme and a budget line for the E-Rare rare diseases research funding programmes. On the other hand the membership in "E-Rare group of funders" offered the opportunity to participate in IRDiRC activities to "smaller funders", that would not be able to commit a high budget individually. As a member of IRDiRC E-Rare not only strongly promotes transnational funding activities and facilitates participation of a wide range of funding organizations, but also gives them the opportunity to participate in the shaping of the rare diseases research landscape and policies.

Towards sustainable joint programme on RD research

The initiative of the E-Rare consortium relies on long-term interactions initiated more than ten years ago by several highly committed partners' countries (France, Spain, Germany). These countries were also among the first ones to join IRDiRC. The systematic exchange of information and active collaboration between these three partner countries facilitated the first phase of E-Rare (2006 – 2010) together with additional EU and EU-associated countries: Belgium, Israel, Italy, The Netherlands, and Turkey. This successful collaboration has further allowed the inclusion of new member countries into the E-Rare-2 project (2010 – 2014). Austria, Greece, Hungary, Portugal and Romania joined as full partners and Latvia and Poland as observers. Furthermore, E-Rare calls opened the initiative to new members like Switzerland and Canada enlarging the participation from six (2007) to sixteen (2014) countries in eight years.

The satisfaction from E-Rare activities and outcomes was confirmed by all participating organizations in a monitoring exercise executed at the beginning and at the end of E-Rare-2 four-year period (2010 – 2014). The ambitions and expectations of consortium members like: (i) promotion of transnational research in rare diseases; (ii) achieving of critical mass in terms of expertise and resources for funded projects; (iii) promotion of knowledge and training; (iv) sharing of expertise and building common funding programme, towards E-Rare were fulfilled in all respects.

All organizations participating in E-Rare confirmed through their commitment to funding research on rare diseases and awareness that collaboration is the key for transnational integrated programmes and for the mutual opening of national programmes as a mean to encourage researchers to cooperate internationally. The consortium members are leading organizations that fund, manage and implement strategically planned focused research programmes in the field of health. All implement and fund international collaborative research programmes, (e.g. bi-lateral, multi-lateral), and all participate into numerous international and European initiatives that match their national strategic issues on research. The combination of their expertise in one consortium is a major strength of E-Rare, which is necessary to build a sustainable programme with the ambition to maintain the launch of yearly joint transnational calls for collaborative research projects on rare diseases. As a result of this aspiration E-Rare consortium decided to pursue its activities and respond to the Horizon 2020 call for "ERA-NET on rare disease research implementing IRDiRC objectives". The project will allow extending the activities of E-Rare for five more years (2014 – 2019). In this new phase E-Rare settles its recent international dimension and its position in IRDiRC by integrating three funding agencies from Canada. Moreover, three new funding bodies from

Austria (FFG), Germany (DFG) and Italy (Emilia Romagna Region) bring to the consortium additional capacities in terms of funding and specific and diverse knowledge like funding of clinical trials, collaboration with patients organizations in research funding and promotion of public-private partnerships. Altogether this international collaboration of 25 funding agencies (E-Rare-3) will further pave the way to a common transnational research programme on rare diseases.

4 Impact & exploitation of results

E-Rare as an international platform for implementing Joint Transnational Calls for rare diseases

E-Rare is a solid, competent and internationally recognized consortium. It has established and agreed on a flexible model of joint calls and evaluation procedures whose efficacy is acknowledged by both recurrent and new call partners. This inestimable experience is of high added value for the European and International community, which benefits strongly from a continued commitment of the EC and E-Rare partner countries. Finally, E-Rare has become an entry portal for countries that wish to participate in transnational research funding activities on well-established and proficient basis.

With **17 partners from 14 countries and regions,** E-Rare is a major contributor to transnational research on rare diseases. Since 2007 almost 56.4 Mio€ were invested to fund 79 research projects involving 347 research teams. This represents a leverage factor of **more than 28-fold** for the EC investment in the coordination of research funding through E-Rare, largely above the mean for ERA-NETs under FP6 & FP7 (ERA-LEARN NEWSLETTER VOL 7 NOVEMBER 2014). The overwhelming response to the E-Rare-2 four joint calls (2292 research teams in 527 applications) attests the demand and potential of the rare disease research community to engage in transnational collaborations with complementary expertise.

The number of countries and funding organizations participating in E-Rare has increased since its commencement: from 6 countries in 2006 (E-Rare-1) to 14 countries in 2014 (E-Rare-2) and 25 partners in 17 countries in E-Rare-3. A survey carried out by E-Rare-2 (WP2) showed that only 6 European funding agencies (out of 31 inquired) declared having specific programmes for funding research on rare diseases. Therefore, the participation of national funding agencies in E-Rare joint transnational calls is considered as **the most effective way to fund research in this field**. Moreover, it was recognized that the cooperation of funding organizations in E-Rare, especially for the implementation of JTCs, influenced **the alignment of processes, funding procedures and timeline of JTCs in addition to the gained common knowledge among national agencies**. E-Rare will further advocate and work on harmonization and interoperability of national programmes and their implementation in the international landscape.

Contribution to strategic impact on rare diseases research and development of new therapies for rare diseases

The high quality of the submitted research proposals and the responsible researchers in joint transnational calls demonstrates the European potential for excellent rare disease research. The projects tackle complex research issues in multidisciplinary settings. The highly competitive nature of the E-Rare joint calls and the implementation of thorough evaluation procedures further ensure the high quality of the funded research. The assessment of E-Rare funding program achievements based on the analysis of final project reports (JTC 2007 & 2009) confirmed that E-Rare funded projects largely contribute to reducing fragmentation of resources and achieving critical mass of

data and samples for research projects. As member of **IRDiRC**, the E-Rare consortium fully supports its goals, namely to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by 2020: i) research performed by the 27 consortia funded within JTC2007 and JTC2009 resulted in identification of 18 new genes responsible for rare diseases, creation of 13 new diagnostic tools and development of 9 new biomarkers. In addition, 18 animal and 15 cell models have been created contributing to better understanding of rare diseases; ii) E-Rare funded researchers are and will be requested to follow IRDiRC policies and guidelines. In addition, the topic chosen for E-Rare JTC 2014, i.e. Innovative therapeutic approaches for rare diseases, is another example of the alignment of E-Rare activities with IRDiRC goals in delivering 200 new therapies by 2020. By 2018 these preclinical research projects are expected to produce results towards the development of new therapies for rare diseases and some of them may need further support for continuing their work.

Contribution to the development of European Research Area

Rare diseases are a perfect example of a field that profits from cooperation. Although collaboration is essential it can be accomplished only by associating all relevant stakeholders and dimensions. The activities of E-Rare are not limited to funding of rare diseases research. Therefore by:

- Largely contributing to European and international efforts
- Monitoring of inputs and outputs of its activities
- Analyzing European rare diseases funding landscape
- Communicating and responding to the needs of rare diseases researchers
- Identifying the bottlenecks raised by different stakeholders.

E-Rare largely contributes to the challenges raised by rare diseases community by using and strengthening the ERA. To that point, based on the recent analysis of E-Rare funded projects and in response to the common demand of funders and researchers, E-Rare engaged in close collaboration and mutual support with the European infrastructures (EATRIS, BBMRI, ECRIN) and other relevant EU initiatives (e.g. EU-OPENSCREEN, INFRAFRONTIER) determined to dedicate part of their expertise and services to facilitate and support the discovery of novel therapeutics for RD with high patient impact. This cooperation will be strengthened by the mutual exchange of information and best practices in E-Rare-3. A working group comprising representatives of relevant infrastructures and interested E-Rare members will develop an adapted model of implication of the infrastructures in E-Rare calls but also the customization of their services to the demand of rare diseases researchers. The information pages, webinars and FAQ will be available from the E-Rare website to disseminate and assist scientists looking for services appropriate for their projects. By involving funders, scientists and relevant European research platforms. E-Rare reduces redundancies and creates synergistic approaches that profit ERA.

Involvement of patients' associations in research funding

One of the unifying elements among rare disease patient organizations and national funding agencies is the desire to drive research and its translation for better prevention, diagnosis and treatment - and ultimately a cure. Rare disease patient organizations show a high interest in and a strong commitment to research and a strong willingness to collaborate with researchers, including logistical and financial support. The E-Rare consortium involved patients' associations in its activities from the start. The representatives of EURORDIS were invited as members of External Advisory Board of E-Rare. They took part in the discussions on topics for E-Rare call and any

strategic decision of the consortium. They participated actively in all public events organized by the consortium and reciprocally promoted E-Rare activities at different occasions. To further strengthen this important collaboration E-Rare opened the discussions on common research funding. A survey of EURORDIS showed that patient organizations in Europe devoted a total minimum of 13 million euros to research in 2009 and funded mostly basic research, but are also interested in and concerned by all areas of research (basic, clinical, genetics, therapeutics, social science, etc.) (http://www.eurordis.org/content/survey-patient-groups-research). In March 2014, EURORDIS launched a survey in which 60 patient organizations expressed their interest to participate in E-Rare (out of those 60, 44 patient organizations have funding capabilities). Some E-Rare funding organizations have or are gaining experience in collaborating with patient organizations/associations or charities in co-funding (rare disease) research. For example Canadian Institutes for Health Research has been able to successfully collaborate with Canadian patient organizations to jointly fund research projects through E-Rare-2 JTCs. In the most recent E-Rare-2 call (2014), four Canadian voluntary health organizations made up to $1.2M CND (about 0.8 Mio euro) available in support of Canadian research components within their respective mandates. Moreover, Muscular Dystrophy Canada foundation provided funding of 210 K€ for a French research team involved in one of the projects. This latter collaboration is a first example of successful cross-border funding implicating Canadian voluntary health organization and French National Research Agency (ANR) in E-Rare. Building upon this encouraging experience, E-Rare partners together with EURORDIS will work in concert to develop a funding model for collaboration with patient organizations that is expanded and adapted to the European context to be used for E-Rare JTCs. Furthermore, EURORDIS will act as a resource that will enable/facilitate connections between researchers who want to involve patient groups in their research effort as well as integrating patient organizations into E-Rare strategic activities/workshops.

The address of the project public website, if applicable as well as relevant contact details.

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