Strategic Research Agenda of E-Rare in relation to other initiatives on rare diseases

E-Rare-3 Work Package 8
Task 8.1.2/MS 10
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<th>Abbreviation</th>
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<tr>
<td>BBMRI</td>
<td>Biobanking and BioMolecular resources Research Infrastructure</td>
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<td>EATRIS</td>
<td>European Infrastructure for Translational medicine</td>
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<td>EC</td>
<td>European Commission</td>
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<td>ECRIN</td>
<td>European Clinical Research Infrastructure Network</td>
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<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
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<td>EJP Cofund</td>
<td>European Joint Programming Cofund action</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>ERA-NET</td>
<td>European Research Area Network</td>
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<td>E-Rare</td>
<td>ERA-NET for research programmes on rare diseases</td>
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<td>ERN</td>
<td>European network of reference</td>
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<td>ESF</td>
<td>European Social Fund</td>
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<td>ESFRI</td>
<td>European Strategy Forum on Research Infrastructures</td>
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<td>ESIF</td>
<td>European Structural and Investment Funds</td>
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<td>EU</td>
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<td>EU-OpenScreen</td>
<td>European infrastructure for Chemical Biology</td>
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<td>FP7</td>
<td>Framework Programme 7</td>
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<td>GA4GH</td>
<td>Global Alliance for Genomics and Health</td>
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<td>H2020</td>
<td>Horizon 2020</td>
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<td>ICHPT</td>
<td>International Consortium of Human Phenotype Terminologies</td>
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<td>IC PerMed</td>
<td>International Consortium for Personalised Medicine</td>
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<td>IMI</td>
<td>Innovative Medicines Initiative</td>
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<td>IRDIRC</td>
<td>International Rare Diseases Research Consortium</td>
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<td>JPI</td>
<td>Joint Programming Initiative</td>
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<td>JPND</td>
<td>Joint Programme - Neurodegenerative Disease research</td>
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<td>JTC</td>
<td>Joint Transnational Call</td>
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<td>MIUF</td>
<td>Medical Infrastructure/Users Forum of project CORBEL</td>
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<td>MS</td>
<td>Member States</td>
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<td>PPP</td>
<td>Public Private Partnership</td>
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<td>RD</td>
<td>Rare Diseases</td>
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<td>SME</td>
<td>Small and Medium Enterprise</td>
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<td>SRA</td>
<td>Strategic Research Agenda</td>
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<td>WP</td>
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Executive Summary

The E-Rare Strategic Workshop was organised on March 7, 2016 in Barcelona (Spain) to give input on themes of the coming Joint Transnational Calls JTC 2017 and JTC 2018, and to give input for the Strategic Research Agenda of E-Rare-3 (ERA-NET for Research Programmes on Rare Diseases) in relation to other initiatives on rare diseases in near and further future.

A preconference paper was sent to the participants before the Workshop (see Annex C). The invited participants were members of the E-Rare External Advisory Board, chairs of the IRDiRC scientific committees, members of the Scientific Evaluation Committee of E-Rare Calls, leaders of relevant European projects on rare diseases, other experts and stakeholders and members of the Network Steering Committee of E-Rare. The E-Rare Strategic Workshop was part of a week of activities on rare disease research organised by E-Rare, the Blackswan Foundation (Swiss Foundation for Research on Orphan Diseases) and the European Medicines Agency in Barcelona.

At the Workshop an overview of E-Rare and its activities in the past 10 years was presented by Daria Julkowska, E-Rare coordinator. Subsequently, several research agendas of ongoing and future initiatives for rare diseases were discussed (session 2) to get a broader scope of the rare disease research domain. In session 3 several stakeholders, each from their own perspective, indicated what is needed in rare disease research and where E-Rare can contribute significantly. This could imply a specific focus for funding in future Joint Transnational Calls (JTCs) of E-Rare but also suggestions for future activities of E-Rare in general. The focus of session 4 was how a future framework can be built for sustainable rare diseases research and the role of the E-Rare consortium in this framework: which scenarios for sustainable activities beyond E-Rare-3 are feasible.

Main Conclusions

- Better coordination and collaboration in programming rare disease research is key to move forward in rare disease research. Therefore, E-Rare should continuously monitor activities of programmes of the European Commission and other ERA-NETs and Joint Programming Initiatives to avoid duplication of rare disease research and to create synergies.
- E-Rare should encourage collaboration between projects and initiatives on rare diseases, including sharing of samples and data and facilitating access to services. Everyone should make good use of all tools and resources for rare disease research that are present today.
- E-Rare JTCs should give applicants a fair chance of success. If the available budget is low the call should be more focused.
- E-Rare JTCs should meet unmet medical needs, in particular in diagnostics and in therapies. E-Rare should follow the recommendations of the International Rare Diseases Research Consortium (IRDiRC). The participants of the Workshop have indicated many specific topics within the domains of diagnostics and therapies for which more research is needed. These suggestions will be used when choosing the topics for E-Rare JTC 2017 and JTC 2018.
- E-Rare will use the recommendations from the participants of this Workshop to reflect on its future role in sustainable collaboration in rare disease research and which instrument(s) would be best for fulfilling this role.
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Rare diseases landscape in Europe

Rare diseases are life threatening or chronically debilitating conditions from which fewer than five affected persons per 10,000 citizens in the European Union (EU) suffer. It is estimated that 6,000-8,000 different rare diseases exist, affecting between 6% and 8% of the population in the course of their lives and that about 30 million people are affected by a rare disease in Europe. Today, research on rare diseases remains scarce and 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 was also recognised in the Council Recommendation of June 8, 2009 on an action in the field of rare diseases (2009/C 151/02). In this Recommendation, rare disease research is specifically emphasised and it is suggested that the coordination of Community, national and regional programs 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 programs should be promoted. In addition, the Council Recommendation asked for the establishment of national plans/strategies on rare diseases that should cover health care and research. In the last years a national plan or national strategy on rare diseases was developed in 22 EU countries.

Over the years the EU has supported key actions to produce data necessary to improve identification and knowledge on rare diseases, and has provided recommendations on specific areas to support and guide Member States policies on rare diseases. Part of the EU’s comprehensive approach to tackle the rare diseases burden in Europe is to co-finance projects and actions. An example is the Rare Disease Joint Action (RD Action).

An additional important initiative for research on and healthcare for rare diseases is the development of European networks of reference (ERNs) in which specialists in various disciplines in different countries in Europe may join their efforts to treat rare diseases that require highly specialised healthcare and a concentration of knowledge and resources. The ERNs criteria and capacities are knowledge and expertise to diagnose, follow up and manage patients, evidence of good outcomes, multi-disciplinary approach, capacity to produce good practice guidelines and to implement outcome measures and quality control, and research, teaching and training. In the context of the development of the European networks of reference several countries may look for possibilities to apply for the European Structural and Investment Funds (ESIFs)/European Social Funds (ESF).

The EU invested about € 620 million in research on rare diseases in the Framework programme FP7 (2007-2013). The EU support includes not only large multinational scientific projects but also strategic and coordination initiatives, e.g. the International Rare Disease Research Consortium (IRDiRC), a consortium of researchers and organisations from Europe, USA, Australia and Asia investing in rare diseases research to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases. A number of grand challenges are being addressed through collaborative actions to reach these 2020 goals such as establishing and providing access to harmonised data and samples, performing the molecular and clinical characterisation of rare
diseases, boosting translational, preclinical and clinical research, and streamlining ethical and regulatory procedures. To attain these goals EU supports several associated projects like RD-Connect, a global infrastructure project that links up databases, registries, biobanks and clinical bioinformatics data used in rare disease research into a central resource for researchers worldwide and RARE-Bestpractices, a platform to improve the management of rare disease patients by promoting communication on the management of rare diseases by disseminating trustworthy guidelines globally, identify and prioritise rare diseases research needs and facilitate timely, effective and efficient translation of research results into patient oriented strategy on the clinical as well as the public health level.

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. E-Rare, the ERA-NET for Research Programmes on Rare Diseases (www.e-rare.eu) was established in 2006 and since then its activities are co-funded by the European Commission (EC). The E-Rare consortium was built to bring responsible funding organisations and ministries together to combine the scarce resources for rare disease research and thus enable the participation of many researchers to transnational projects via Joint Transnational Calls (JTCs). E-Rare-1 (2006-2010) was renewed in 2010 (E-Rare-2: 2010-2014) and is now funded under Horizon 2020 ERA-NET Cofund (E-Rare-3: 2014-2019). Today, E-Rare-3 is a network of twenty-five partners – public bodies, ministries and research funding organisations – from seventeen countries: Member States (Austria, Belgium, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Spain, The Netherlands), three Associated States (Switzerland, Israel and Turkey) and Canada.

The calls performed in the E-Rare-1 (2006-2010), E-Rare-2 (2010-2014) and E-Rare-3 (2014-2019) programmes have shown/are showing 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. E-Rare-3 launched a co-funded call (JTC 2015 cofunded call) with a general topic in order to allow researchers to apply with projects based on the state of the art and research demand for the specific disease. Next to this E-Rare-3 launched/will launch three additional Joint Transnational Calls (JTC 2016, JTC 2017 and JTC 2018).

For the focus of JTC 2016, input was already gathered from the outcomes of previous strategic workshops and the priorities identified by the IRDiRC scientific committees.

**Aim of the Workshop**

This Strategic Workshop is organised to get input for the focus of E-Rare transnational calls JTC 2017 and JTC 2018. Furthermore, E-Rare would like to discuss with the participants the scientific policy agenda and future activities of E-Rare in relation to other European initiatives on rare diseases research.
Session 1  10 years of E-Rare: overview and outcomes

Daria Julkowska (coordinator of E-Rare, ANR, France) welcomed the participants and thanked everyone for coming to the meeting, also on behalf of Ralph Schuster (PT-DLR, Germany) and Sonja van Weely (ZonMw, The Netherlands) (chair and vice-chair, respectively, of the Network Steering Committee).

Ralph Schuster introduced the outline of the Workshop. In session 1 an overview of E-Rare and its activities in the past 10 years was presented by Daria Julkowska. Subsequently, several research agendas of ongoing and future initiatives for rare diseases were discussed (session 2) to get a broader scope of the domain. In session 3 several stakeholders, each from their own perspective, indicated what is needed in rare disease research and where E-Rare can contribute significantly. This could imply a specific focus for funding in Joint Transnational Calls of E-Rare but also suggestions for future activities of E-Rare in general. The focus of session 4 was how a future framework can be built for sustainable rare diseases research and the role of the E-Rare consortium in this framework: which scenarios for sustainable activities beyond E-Rare-3 (in terms of timeline and instrument) are feasible and what is currently needed?

About E-Rare

In session 1 Daria Julkowska introduced E-Rare, the ERA-NET (European Research Area Network) for Research Programmes on Rare Diseases.

E-Rare-3 (www.e-rare.eu) consists of 25 partners (funding bodies and ministries) from 17 European, Associated and non-European countries. The average annual national budget for rare disease research of the agencies within the E-Rare consortium is about 100 million euro; in addition, they spent about 36 million euro in the Joint Transnational Calls of E-Rare-2 (2010-2014). New partners are welcome to join E-Rare.

A short analysis within the E-Rare consortium showed that the participating countries can be divided into two major groups:

- Countries with a well-defined, strong community with academic and clinical coverage; supported at national level either through national plans or specific funding programmes; existence of spin offs or start-ups and clinical trials funding available; access to tools like genetic identification, bioinformatics, omics, etc. (AT, BE, CA, DE, FR, ES, IT, IL, NL, CH);
- Countries with fragmented or no specific approach to rare diseases at national level or national plan in development; lack of national registries or longitudinal studies; lack or low access to specific tools (GR, HU, RO, LT, PL, TR).

This analysis underlines the importance of E-Rare as a funding programme but also as an international initiative, gathering partners with different “background”.

The objectives of E-Rare are: (1) To harmonise and develop synergies between research programmes on rare diseases in Europe; (2) To set up sustained and long-lasting
cooperation between partners; (3) To maintain and expand the competitiveness of European research on the international scale; (4) To coordinate national actions in order to overcome the fragmentation of research on rare diseases and to promote interdisciplinary approaches; (5) To develop a common policy for research funding on rare diseases.

E-Rare is member of IRDiRC and implements the objectives of IRDiRC by funding transnational research in its Joint Transnational Calls (JTCs).

**Joint Transnational Calls**

The E-Rare consortium organised five open calls and two focused calls until now; in addition, the focused call JTC 2016 is currently running.

In the seven JTCs performed by E-Rare between 2007 and 2015 1021 projects were submitted of which 98 projects were funded with a total budget of € 78 million and with 449 research groups involved. Projects funded through E-Rare calls cover a wide range of medical areas. Rare cancers, rare infectious diseases and rare adverse drug events were excluded from the scope of JTCs.

In the open calls clinical studies, physiopathology, pre-clinical therapeutic research, epidemiology and natural history studies, animal models and biomarkers may be funded. In JTC 2012 the focus was on young researchers and clinicians proposing projects on rare diseases; in JTC 2014 the focus was on innovative therapeutic approaches. In the currently running JTC 2016 the clinical research for new therapeutic uses of already existing molecules (repurposing) in rare diseases is in the spotlight. The outcomes of all funded E-Rare projects have clear impact on patients’ life. New causative disease genes were discovered that have a major impact on diagnosis and potential treatment of patients with a rare disease. The better understanding of the natural history of disease through registries and the harmonisation through guidelines will improve treatment of patients. Creating animal and cellular models forms the basis for future research into diseases mechanisms and therapeutic options.

Daria Julkowska gave more detailed information on the results of the JTCs, e.g. on the medical domains of submitted and funded projects in E-Rare JTC 2009-2015. Neurology and nephrology/urology are the domains in which most projects were funded (almost 25% and 15% of all funded E-Rare projects, respectively). E-Rare is encouraging the participation of research groups from Eastern European Countries using a so-called widening concept. Besides the JTC 2015 (cofunded by the EC) and the currently running JTC 2016 two other JTCs (JTC 2017 and 2018) are planned in the timeframe of E-Rare-3.

**Focus on collaborations: partnerships**

One of the activities in E-Rare-3 is to improve its collaboration with several organisations and infrastructures. Next to the presence of EURORDIS in the External Advisory Board of E-Rare a funding model for collaborations with patient organisations for E-Rare JTCs is being developed building upon Canadian experience and with EURORDIS as broker. To enhance its contribution to excellent and sustainable rare disease research results, E-Rare-3 established collaboration with a number of European Research Infrastructures (BBMRI, EATRIS, ECRIN, Elixir, EU-Open Screen, Infracorefrontier) with the aim to customise
their services to the demand of rare disease researchers. In order to inform about provided services and to link scientists and infrastructures, E-Rare-3 developed a dedicated portal (www.erare.eu/infrastructures).

The collaboration of E-Rare with the European Medicines Agency (EMA) has the aim to assist rare disease researchers especially by communication and learning via dedicated pages on the E-Rare website and promoting scientific advice for development of orphan medicines. E-Rare has also collaborated with the Blackswan Foundation to organise the RE(ACT) congress from 9-12 March, 2016 in Barcelona.

Next steps
In addition to abovementioned activities E-Rare is preparing its future, e.g. by organising this Workshop to get input on its role.
Session 2  Strategic research agendas of ongoing and future initiatives in rare diseases

Several research agendas of ongoing and future initiatives for rare diseases were discussed in session 2.

IRDiRC: priorities and perspectives for near future
Hans Lochmuller, professor at Newcastle University (UK) and chair of the IRDiRC Interdisciplinary Scientific Committee, gave an update on the International Rare Diseases Research Consortium (IRDiRC). The objectives of this international consortium is to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by 2020. The basic principles of IRDiRC are:

- Co-operation at international level to stimulate, better coordinate and maximise output of rare disease research efforts around the world;
- Teams up public and private organisations investing in rare diseases research;
- Research funders with relevant programmes spending more than 10 million American dollars over a 5-year period can join and work together;
- Each organisation funds research in its own way;
- Funded projects adhere to a common framework.

IRDiRC monitors the progress towards its goals on a monthly basis and can be followed on the website www.irdirc.org. At the end of 2015 183 new orphan drugs, counted in the US (FDA) and EU (EMA) databases, were developed and about 500 new rare diseases were discovered since January 2010. Although the goal of delivering 200 new therapies may be reached at the end of 2016 there is still no therapy available for most rare diseases.

IRDiRC was set up by the European Commission and the National Institutes of Health (NIH), USA in 2010. The current chair is Christopher Austin, director of the National Center for Advancing Translational Sciences/NIH. Three Scientific Committees (on diagnostics, on therapies and on interdisciplinary issues) have been put in place; the Scientific Secretariat is located in Paris (France). The Executive Committee members of IRDiRC (currently from Europe, North America, Asia, Australia and Middle East) finance projects that contribute to the objectives and targets of IRDiRC. These are high leverage projects with strong translational potential and international scope, not covered by national initiatives.

IRDiRC had several working groups in the past, e.g. on registries and bioinformatics. Since 2015 ad hoc taskforces have started and will work for 1-1.5 year on a specific topic.

The current topics for action are:

- International Consortium of Human Phenotype Terminologies (ICHPT). The objective of ICHPT is to provide the community with standards to be used to achieve interoperability between databases, in particular to allow the linking of phenotype and genotype databases for rare diseases. These tools are critical to facilitate interpretation of genomic variants as well as high-throughput sequence data. A core set of 2370 terms has been selected, common to all terminologies (www.irdirc.org/ICHPT).
- Matchmaker exchange. The joint IRDiRC-Global Alliance for Genomics and Health (GA4GH) Matchmaker Exchange project aims at providing data sharing tools between clinical geneticists to match unsolved genome/exome sequence cases.
- Automatable discovery and access. In order to make the most of clinical data sources worldwide, accessing the level of patient consent towards data sharing and research participation becomes crucial. Therefore, clinical data are being associated with the scope
of consent given; standardised and computer-readable data use types are being
developed in consent forms to be able to align a user’s permission against permitted
data use type. This action of IRDiRC is coordinated with GA4GH and other initiatives like
the European FP7 project RD-Connect. An IT tool is developed and is ready for being
implemented.

- Patient-Centered Outcome Measures. The development and adoption of patient-centered
  outcome measures are instrumental in accelerating research and development in rare
diseases. A post-workshop report and recommendations are available
  (www.irdirc.org/activities/current-activities/tf-pcom/).
- Small Population Clinical Trials. Collaborative effort on adaptive design, statistical
  methods and acceptability of new methods in small population clinical trials. Several
  agencies and FP7 funded projects are involved in this taskforce.
- Data mining/repurposing. This new taskforce leverages on developments in computa-
tional linguistics and graph theory to build a representation of knowledge which is auto-
matically analysed to discover hidden relations between any drug and disease and in this
way may identify new therapeutic targets and repurposing of drugs. This is an oppor-
tunity to increase the speed of new drugs available for rare disease patients.

Next to these topics two other actions of IRDiRC were mentioned by Hanns Lochmuller. The
Participant Unique Identifier is a joint IRDiRC-GA4GH taskforce that will produce guidelines
on technical and ethical-legal requirements of patient identifiers in rare disease research
and will produce recommendations for the most practical, streamlined and minimalistic
approach that maximises uptake whilst complying with relevant legal regulations.
Furthermore, the “IRDiRC recommended” label is developed to highlight tools, standards,
platforms and guidelines which contribute directly to IRDiRC objectives and to identify key
resources for research communities to accelerate translation into clinical services. Examples
of “IRDiRC Recommended” sources are e.g. ICHPT and Orphanet.
In the discussion the project GeneMatcher (https://genematcher.org/about) was mentioned, a freely accessible website designed to enable connections between clinicians and researchers from around the world who share an interest in the same gene or genes. The principal goal for making GeneMatcher available is to help solve “unsolved” exomes. This may be done with cases from research or clinical sources. It is possible to query MatchmakerExchange.org to see if they contain matches. Hanns Lochmuller suggested that funding agencies should stimulate data sharing and may give some financial incentives and education for researchers to encourage data sharing. A remark was made that matchmaking is one piece of the puzzle but that it is also important to know the effect of the mutation(s) in (groups of) gene(s) using model systems.

**Summary of Strategic Research Agendas of ongoing programmes of the EC with respect to rare diseases**

After the review on the current state of the international collaboration on rare disease research the European Strategic Research Agendas of Horizon 2020 (work programmes 2016-2017 and beyond) and of Innovative Medicines Initiatives in relation to rare diseases were introduced by Anders Colver and Bernd Stowasser, respectively.

**Rare diseases - how Europe is meeting the challenges: Horizon 2020 Work programmes 2016-2017 and beyond**

Anders Colver, project officer at the Innovative and Personalised Medicine Unit of DG Research and Innovation of the European Commission, indicated that the EU invested over € 620 million in 120 rare disease research projects in the Framework Programme FP7 and continued strong investment in its subsequent research programme Horizon 2020 with about € 220 million in 2014-2015.

In Horizon 2020 three multi-annual work programmes have been/are being developed (2014/2015; 2016/2017 and 2018/2019/2020) with topics that are broad, challenge-driven, with less prescriptive topic texts and with stronger focus on end users in comparison to earlier programmes. In many instruments of Horizon 2020 health research is involved, e.g. in collaborative health research (SC1), in public-public partnerships, in public-private partnerships, health research infrastructures but also in loans for de-risking Research and Innovation, etc.

One of the topics in a Call from 2015 was ‘new therapies for rare diseases’. There was very much interest in this topic as in the first stage 421 proposals were applied of which 120 were invited for stage 2 and finally 10 projects could be funded. These 10 projects started in 2016 with an EU contribution close to € 60 million. In 5 of these 10 projects preclinical research will be performed and the other 5 will focus on clinical research. The involved rare diseases are 3 neurodegenerative diseases, 2 cancers, 1 immunological, 1 respiratory, 1 gastroenterological and 1 metabolic disease. Concerning the drug class: 5 out of the 10 projects will investigate small molecules and the others involve advanced therapies/cell-based therapy/gene therapies.
In other calls in the Work Programme 2014-2015, that were not specific for rare diseases, 36 rare disease research projects are being funded besides E-Rare-3 itself.

The main priorities in the work programme 2016-2017 with a budget of € 935 million are personalised medicine, promoting healthy ageing, maternal and child health, human biomonitoring, infectious diseases and health ICT. For rare diseases research two calls are of great interest. In the focus of understanding health, wellbeing & diseases there will come the Call Topic “Diagnostic characterisation of rare diseases” (SC1-PM-03-2017) with a scope on application of genomics and/or other -omics and/or other high-throughput approaches for molecular characterisation of rare diseases in view of developing molecular diagnoses for a large number of undiagnosed rare diseases. The project budget may be about € 15 million; the indicative deadline for (full) proposals is April 11, 2017. In the focus of treating and managing diseases there will be the Call Topic “New therapies for rare diseases” (SC1-PM-08-2017). The scope of these projects is clinical trials on substances where orphan designation has been approved by the EC, where the proposed clinical trial design takes into account recommendation of protocol assistance given by the European Medicines Agency, and where a clear patient recruitment strategy is presented. The project budget may vary from € 4-6 million. This call has a deadline on October 4, 2016 for Stage 1 and April 11, 2017 (indicative) for Stage 2.

Anders Colver also gave a list of other Call Topics in the Work programme 2016-2017 that could be of relevance for rare diseases like clinical research on regenerative medicine, PCP-eHealth innovation in empowering the patient, in silico trials for developing and accessing biomedical products, standardisation for pre-analytical and analytical procedures for in vitro diagnostics in personalised medicine and supporting innovative SMEs in the healthcare biotechnology sector.

At the end of his presentation Anders Colver announced the personalized medicine conference on June 1-2, 2016 in Brussels where the International Consortium for Personalised Medicine (IC PerMed) will be launched.

Innovative Medicines Initiatives (IMI) 2
Bernd Stowasser, associate vice-president and head of European Public Private Partnerships Office of Sanofi, introduced the Innovative Medicines Initiative 2 (IMI 2). He summarised the rationale and benefits of public-private partnerships (PPP) in biomedical research, when this research is performed in a non-competitive space: linking all stakeholders in R&D to form a neutral platform that can have access to data, samples and compounds on global level and share risk, resource and knowledge in order to translate science into drugs, allow diversity of approaches, allow significant and sustained investment on risky projects and address complex and urgent issues.
IMI is a platform for collaboration between several big pharma companies (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations), academic institutions, small and medium enterprises (SMEs), regulators and patient organisations. The budget is provided by EFPIA companies (in kind by personnel, samples, data) and the EU (in cash to academic/public partners). The budget for IMI 1 (2008-2013) was € 2.0 billion and for IMI 2 (2014-2023) is € 3.2 billion (in both periods split between EFPIA and EC).

Topics/calls are defined by EFPIA companies, but also input from public institutions has been taken into consideration. The topics address bottlenecks that require intensive collaboration between all stakeholders and are competitive for public applicant consortia, using independent panels reviews. Specific rules ensure a balance between creation of value (intellectual property) and publications. Until so far, 61 public-private IMI consortia have been launched under IMI 1/IMI 2 including 764 academic teams, 433 EFPIA teams, 146 SMEs, 25 patient organisations and 17 regulatory institutions.

The first Strategic Research Agenda of IMI 1 (2007 SRA) had a primary focus on idea generation, basic research up to non-clinical testing and first in man testing. In the next SRAs the focus shifted closer to the patient: in the 2011 SRA challenges in society and healthcare were addressed and in 2013 SRA for IMI 2 real life medical practice was included with rare/orphan diseases as one of the therapeutic areas.

Four major axis of research were defined: target and biomarker identification, innovative clinical trial paradigms, patient tailored adherence programmes and innovative medicines. IMI projects are mainly in the non-competitive space as Bernd Stowasser showed with some examples of IMI projects. An example on relative effectiveness research is the project GetReal (www.imi-getreal.eu/) that has the objective to show how real world evidence can be adopted in medicine development and healthcare decision-making, and provide tools required to achieve this. Another non-competitive example is the project Precisesads (www.precisesads.eu/imi/) that aims to develop a new molecular taxonomy of systemic autoimmune diseases based on meaningful clinical biomarkers. Bernd Stowasser also
introduced some of the latest topics in the area of rare diseases. In the 7th Call of IMI 2 with a deadline on March 17, 2016 one of the topics was ‘A comprehensive ‘paediatric preclinical proof of concept platform’ to enable clinical molecule development for children with cancer’. One of the 6th Call topics to enable innovative clinical trial design/outcome research was ‘Development of an outcomes-focused platform to empower policy makers and clinicians to optimise care for patients with hematologic malignancies’. The project Adaptsmart (http://adaptsmart.eu/) is an example of supporting new regulatory pathways: this project explores strategies for adapting clinical trials to allow fast availability of new medicines to patients and incorporate effectiveness parameters. Bernd Stowasser concluded his presentation with the recommendation for potential applicants that it is important to use their networks.

**Summary of current rare disease research projects in Europe**
Specifically for this Workshop Natalia Martin and Ana Rath have performed an analysis on rare disease research projects in current Joint Programming Initiatives and ERA-NETs, and in the Orphanet database, respectively. The reason for asking the two presenters to perform these analyses was to avoid overlap in funding by E-Rare and other national or European initiatives.

**Rare disease research in current Joint Programming Initiatives (JPIs) and ERA-NETs**
Natalia Martin (ANR, France) analysed the rare disease research projects that were funded in the JPI JPND (neurodegenerative diseases), ERA-NET Neuron (diseases of the brain and the nervous system), two ERA-NETs that are not disease-focused - i.e. EuroNanoMed (nanomedicine) and EraCoSysMed (systemics medicine), the ERA-NETs TransCan (cancers) and Infect-Era (infectious diseases) and the Strategic Research and Innovation Agenda of the International Consortium for Personalised Medicine (IC PerMed).

**JPND** is a Joint Programming Initiative of 30 countries gathered with the goal to improve impact and effectiveness of national research programmes on neurodegenerative diseases (www.neurodegenerationresearch.eu/). JPND organises at least one Joint Transnational Call (JTC) once a year since 2011. The diseases covered in these JTCs are Alzheimer’s disease and other dementias, Parkinson’s disease and related disorders, motor neuron diseases, Huntington’s disease, Spinocerebellar ataxia (SCA) and spinal muscular atrophy (SMA). The diseases included in these groups are for the most part rare diseases. Natalia Martin analysed that in the JPco-fuND 2015 two funded projects were focused on the rare diseases Amyotrophic Lateral Sclerosis (ALS) and SCA 3. In JTC 2013/2014 topic ‘cross-disease analysis of pathways’ three funded projects focused on rare diseases and at least four funded projects dealt with rare diseases or rare forms of common diseases. Daria Julkowska showed in her presentation in session 1 that almost 25% of the funded projects in the E-Rare JTCs 2009-2015 were in the neurological domain. Natalia Martin confirmed in her presentation that for example in E-Rare JTC 2014 with the topic ‘Innovative therapeutic approaches’ two out of 14 projects were focused on three rare neurodegenerative diseases. Therefore, E-Rare decided to exclude projects in its JTC 2015 cofund on those neurodegenerative diseases that could be submitted in the JTC 2015 cofund of JPND that was launched at the same time.
Furthermore, Natalia Martin suggested that some other activities of JPND, such as e.g. the JPND report on longitudinal cohort studies in neurodegenerative research and the JPND report on patient and public involvement in JPND research could be of use for E-Rare. This would strengthen the synergy between E-Rare and other EU-funded projects.

*Neuron*, the ERA-NET on diseases of the brain and nervous system consists of 24 partners and 2 associated partners and launches annual JTCs since 2008 ([www.neuron-eranet.org](http://www.neuron-eranet.org)). Rare diseases or rare forms of more common diseases that are covered by Neuron are neurodevelopmental disorders (including autism and intellectual disability syndromes), mental disorders (including schizophrenia) and epilepsy. The analysis of Natalia Martin showed that in most JTCs of Neuron one or no projects dealt with rare (forms of) diseases, but in its JTC 2015 at least 4 out of 10 projects dealt with rare forms of neurodevelopmental disorders - as the focus of the JTC 2015 Neuron call was neurodevelopmental disorders. In the JTC 2015 cofunded Call of E-Rare there were no funded projects covering the topic of neurodevelopmental disorders. Natalia Martin noticed that the diseases and types of studies funded by Neuron did not overlap with funded E-Rare projects in the neurological domain.

In the Strategic Research Agenda 2015 of Neuron options for future joint Neuron activities are indicated and the diseases of the peripheral, central and autonomic nervous system and diseases of the neuromuscular junction are included in this Agenda ([www.neuron-eranet.eu/en/390.php](http://www.neuron-eranet.eu/en/390.php)). E-Rare will take in consideration this Agenda and the topics covered by future NEURON calls to avoid funding similar projects.

*EuroNanoMed* is an ERA-NET of 20 partners from 17 countries/regions that organises annual JTCs since 2009. The research projects are technology-driven covering the following three topics: regenerative medicine, diagnostics and targeted delivery systems ([www.euronanomed.net](http://www.euronanomed.net)). EuroNanoMed has funded three out of 51 projects that deal with rare diseases of which two for ALS. At least three of the funded projects on regenerative medicine may have impact on rare diseases. Although E-Rare received an increasing number of nanomedicine-related proposals none of them has been funded as yet.

In the JTC 2015 cofunded call of *EraCoSysMed*, an ERA-NET on systems medicine, two out of 9 funded projects deal with rare diseases of which one is a rare cancer. This is the only call that EraCoSysMed has organised thus far.

E-Rare has excluded rare cancers and rare infectious diseases in its calls in the past because of the presumed activities of the ERA-NETs TransCan and Infect-Era as well as existence of other funding sources for these medical domains. Therefore, the question arose whether indeed these two types of rare diseases are tackled by these two ERA-NETs. Natalia Martin confirmed that in *TransCan* 6 out of 30 funded projects between 2011-2013 were dealing with rare cancers. In *Infect-Era* at least 3 projects out of 25 funded projects between 2013-2015 were dealing with rare infectious diseases.

Finally, the E-Rare Coordination unit and some other E-Rare partners participate in the International Consortium Personalised Medicine (IC PerMed) that developed a Strategic Research and Innovation Agenda ([www.permed2020.eu/_media/PerMed_SRIA.pdf](http://www.permed2020.eu/_media/PerMed_SRIA.pdf)). In this document several recommendations, including the need to develop technologies to study more rapidly and efficiently the phenotypic impact of variants, avoiding duplication of efforts and creating synergies, are similar to recommendations of the IRDiRC scientific committees.
Natalia Martin finished her presentation with several questions for discussion:
- Should E-Rare in future JTCs exclude topics that are covered by other initiatives?
- Should other initiatives exclude rare diseases in their JTCs?
- Would it be of added value to envisage common calls with some of the other initiatives?
- Would it be of added value to analyse whether the different initiatives are funding the same teams?
- Would it be of added value to organise more activities together to create synergies: e.g. should E-Rare use JPND report on longitudinal cohorts or should E-Rare organise joint actions with other initiatives for training for researchers (i.e. translation of funded projects’ results...).

Orphanet database of research activities: analysis of rare disease research in Europe and beyond
Ana Rath (INSERM, France) introduced the activities of Orphanet, the European database for rare diseases, active in almost 40 countries (www.orpha.net). For this presentation she performed an analysis on research activities (research projects and clinical trials) and on orphan designations/orphan drugs.

Research projects
The definition of a research project in Orphanet is an ongoing and unpublished research project explicitly focusing on a rare disease/group of rare diseases AND funded by a funding body with a scientific committee (after competitive evaluation) or the regular funding of a research institute.

In the database 4181 research projects are registered from 2010 to December 2015 and cover 1739 rare diseases or groups of rare diseases. Most of these projects (91%) are funded at national level; 9% at EU level. Of these projects 71% involve basic research (e.g. animal
model creation/study, gene search, biomarker development), 14% observational/-epidemiological studies and 15% preclinical research (e.g. diagnostic tool/protocol development, preclinical drug development, medical device).

When the kind of research is analysed further it appears that the registered basic research projects are especially in the medical domains neurology (27%), dysmorphology (10%), oncology (10%), metabolic diseases 6%; other medical domains have 5% or less basic research projects. The distribution of the preclinical research projects is as follows: neurology 29%, oncology 13%, metabolic diseases 11%, ophthalmology 11%, infectiology 7% and other medical domains 5% or less. Upon a question Ana Rath indicated that the number of diseases differs per domain; e.g. there are many neurological diseases.

For 764 among all rare diseases there is just 1 basic research project registered in the Orphanet database whereas for some diseases several basic research projects for a specific disease are registered (e.g. 86 for cystic fibrosis and 59 for retinitis pigmentosa). 220 diseases are tagged with only 1 preclinical project whereas for some rare diseases there are much more (e.g. 36 for retinitis pigmentosa and 20 for cystic fibrosis). Ana Rath concluded in this part of her presentation that rarity of the disease (measured as number of projects/disease by prevalence range) does not seem to influence research projects, but does seem to influence clinical trial research (measured as number of clinical trials/disease by prevalence range) as she would show later.

**Clinical trials**

The definition of a clinical trial in Orphanet is an interventional study aiming to evaluate a drug (or combination of drugs, or a biological product, etc.) to treat (or prevent) a rare disease or group of rare diseases. A clinical trial is defined nationally as it must be registered in each country involved according to the regulations. Registering clinical trials provides visibility on therapeutic development in the field of rare diseases.

In the Orphanet database 2712 clinical trials are registered for 806 rare diseases at the 31th December 2015. Of these trials 43% are national, 40% are global and 16% are European. 1764 clinical trials are ongoing of which at least 51% are recruiting patients. Most of the ongoing clinical trials are in phase II or III. In 76% of these ongoing trials drugs are investigated, in 3% cell therapy, 2% medical devices and 1% gene therapy. In 18% the category is unknown. For many diseases there is just one clinical trial ongoing, but the top 5 of ongoing clinical trials registered (83-215) are for rare cancers.

When the clinical trials are distributed over the medical domains it appears that most of them are for oncology (56%), neurology (8%), pneumonology (6%), internal medicine (6%), haematology (6%), metabolic diseases (4%); the other medical domains have 2% or less.

**Orphan drugs - products in development**

There are 1328 products in development for 460 diseases at the end of 2015. These products are distributed over the medical domains as follows: oncology 31%, neurology 13 %, pneumology 8%, metabolic diseases 7%, haematology 6%, ophthalmology 5%, immunology 5% and the other medical domains 4% or less.

In 26 rare diseases more than 10 products are in development. The number of European orphan drugs with marketing authorisation has increased from almost 40 in 2010 to almost
90 in 2015 for treatment of 213 rare diseases. Of these orphan drugs 44% are for rare cancers.

**General observations**
Dependent on the medical domain the number of basic research, preclinical or clinical research projects differs. For some domains emphasis is on clinical research (e.g. oncology), for other domains it is basic research (e.g. dysmorphology), preclinical research (e.g. metabolic diseases) or basic research and preclinical research (e.g. neurology).

Ana Rath concluded that the Orphanet database allows both landscape and targeted analysis in order to identify trends and gaps in research and identify gaps and opportunities for R&D including clinical trials. The database also allows to estimate the size of affected population for a given disease/group of diseases and to identify facilitators (registries, patient organisations, ongoing research). E.g. in Orphanet 718 patient registries are annotated. Ana Rath informed the participants that Orphadata is a freely-accessible dataset from Orphanet that can be used for own analyses ([www.orphadata.org](http://www.orphadata.org)). Some datasets however need a Data Transfer Agreement.

In the discussion the possibility of repurposing of drugs in rare disease research was discussed: a drug may fail in disease A but may work in disease B. It was mentioned that there is no database as yet in which all drugs investigated for which disease a summary is made with the reason why the research has stopped. One of the solutions to get more information on this is to publish negative results.

**RARE-Bestpractices project: introduction and RAREGAP - a RARE-Bestpractices database of rare disease research needs**

Domenica Taruscio (National Centre for Rare Diseases – Italian National Institute of Health (ISS)), project leader of the RARE-Bestpractices project, introduced the platform for sharing best practices for management of rare diseases ([www.rarebestpractices.eu](http://www.rarebestpractices.eu)). This 4-year project started in January 2013 and is funded by the European Commission (FP7). The consortium consists of 15 partners from 9 European countries and it is supported by an advisory board of 15 international experts representing European and extra-European organisations/agencies all with strong commitment in basic and clinical research on rare diseases. RARE-Bestpractices has also established collaboration with organisations/ projects, including E-Rare.

The RARE-Bestpractices platform has been conceived to promote the development of trustworthy health care guidelines and to identify and collect research recommendations on rare diseases. To this end RARE-Bestpractices consortium: 1) has been working with the experts of the Grading of Recommendations Assessment, Development and Evaluation system (GRADE) in identifying approaches to methodological issues in developing guidelines on rare diseases; 2) has organised training courses and tools for health care guideline developers and users; 3) has defined to what extent conclusions from cost-effectiveness analyses for pharmaceuticals are accounted for and implemented in health care guidelines
across a range of countries; and 4) has created two databases: RAREGUIDELINE (www.rbpguidelines.eu/), a collection of health care guidelines appraised for quality using a validated tool (AGREE II), and RAREGAP (http://rbpresearch.eu/), a collection of research recommendations for the management of rare diseases. Additionally, the consortium conceived a new journal aimed at providing a forum in the area of public health: Rare Diseases and Orphan Drugs, an international Journal of Public Health.

Cristina Morciano from ISS introduced the RAREGAP database in more detail. The role of research recommendations is to highlight uncertainty in existing knowledge and translating this uncertainty into proposals for future research. RAREGAP is an on-line open access resource which can be used to support healthcare professionals, patients and carers for an informed decision-making and researchers and research funders to plan new research. The Rare-Bestpractices consortium defines uncertainty as any aspect of rare disease management where no up-to-date reliable systematic review of the evidence has been carried out or where up-to-date reliable systematic review of the evidence has identified inadequate or conflicting information to direct effective care.

Research recommendations are identified from the ‘Implications for research’ section of Cochrane systematic reviews (www.cochranelibrary.com/) published from 2012, since Cochrane reviews are recognised as a gold standard of systematic reviews and as such they include genuine evidence gaps where investing further research resources would be useful. Added value of RAREGAP is the standardization of the reporting of research recommendations. Thus the ‘Implications for research’ section of Cochrane reviews are organized in records following the PICO format (Population/Subpopulation, Intervention [exposure: e.g. drugs/test/risk factor], Comparators, Outcomes). This would ensure that recommendations are more effectively used. Additionally, RAREGAP provides information on ongoing studies which replicate the inclusion criteria of studies in each Cochrane review (from ClinicalTrials.gov registry and the World Health Organization International Clinical Trial Registry Platform).

Cristina Morciano described the content of RAREGAP in order to provide examples of gaps in secondary research (systematic reviews) and on-going research (trials). She grouped systematic reviews by three areas of intervention: no 1 - drugs, vaccines, biologicals; no 2 - radiotherapy, surgery, perioperative interventions, devices, and diagnostic interventions; and no 3 - education and training, health service delivery, psychological interventions, complementary interventions, diet, physical interventions, exercise, mix and others.

It emerged that until so far systematic reviews were identified only for 26 diseases that consist of diverse medical domains like rare cancers (e.g. neuroblastoma, thymoma), blood diseases (paroxysmal N haemoglobinuria) and inborn errors of metabolism. In total 43 systematic reviews of 209 trials and 65 related ongoing trials were retrieved.

It should be noted that of the 43 systematic reviews only 10% are dedicated to area no 2 (diagnostic interventions, radiotherapy, surgery, devices) with just one related on-going trial. More than half of the systematic reviews (63%) and the majority of the on-going trials (83%) are dedicated to area no 1 (drugs, vaccines or biologicals). The remainder of systematic reviews (23%) are related to area no 3 (education, training, health service delivery and other kinds of intervention (e.g. psychological, diet, physical)) with 10 related on-going trials.
Cristina Morciano elaborated the case study of Behçet’s disease as an example of gaps in applied research for a specific rare disease by using a systematic review of trials (Taylor J et al, Interventions for the management of oral ulcers in Behçet’s disease. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD011018). The research question was to assess the effectiveness and safety of 13 drugs/biologicals on pain, episode frequency of oral ulcers and on quality of life in patients with Behçet’s disease. Although 15 randomised trials were conducted with the involvement of 888 rare disease patients no clear and conclusive evidence was produced and further research was required to answer the study question. In summary, the research gaps identified in these trials were due to the content and the methodology (validity of findings). For example one of the main content problem was the heterogeneity of the outcome measurements (nine different oral outcome measurements used) which made difficult to compare results and to carry out a meta-analysis. With respect to methodology, the included trials were judged at high risk of bias mainly due to poor study execution and reporting. This could be an example of research gaps as well as of avoidable waste in research production that underlines the need of actions to focus on mechanisms for ensuring the production of reliable and usable evidence.

Cristina Morciano concluded that investments in additional research should be preceded by systematic evaluation of existing evidence. A research gap may be further developed in prioritisation into research needs of the end-users of research (patients, clinicians, policymakers). Ways to identify research gaps can be diverse starting from existing secondary research (systematic reviews, health care guidelines) or starting from proposals of end-users of research. However this last approach needs to be explicitly structured in terms of people and process involved, including evaluation of existing evidence and ethical issues such as conflict of interest.
Session 3  Scope of future activities of E-Rare
(including future topics for Joint Transnational Calls where E-Rare can contribute significantly to the unmet needs in rare diseases)

Several stakeholders were asked to indicate, each from their own perspective, what is needed in rare disease research in (near) future and where E-Rare may contribute significantly. This could imply a specific focus for funding in Joint Transnational Calls of E-Rare but also suggestions for future activities of E-Rare in general.

Statements from different stakeholders: patient representative, clinician, basic researcher and a representative of a philanthropic alliance

Mathieu Boudes from patient alliance EURORDIS (Rare Diseases Europe) in France indicated that EURORDIS recognises the value of E-Rare with its network of researchers, the implementation of IRDiRC goals and policies and the collaboration with Research Infrastructures, but that it is also key to scale up the activities after 10 years of existence. There is still a lack of funding for researchers and no real common pot that may impair one day the selection of proposals solely on scientific criteria. Moreover, EURORDIS deplores that few European countries are not partners in E-Rare-3 but acknowledges and supports any activities to "recruit" such countries.

According to EURORDIS the key items for next E-Rare JTCs are data collection (in collaboration with existing structures like the Joint Research Centre of the EC, RD-Connect and RD Action), research on patient relevant outcomes, research on the efficiency of care with multiple harm studies, and research on best clinical practices to define the best standards of care. In addition to these four key items EURORDIS would like to see that in next E-Rare Joint Calls social research could be funded to study the impact on patient, family and carers. Finally, EURORDIS would also strongly support training of researchers in regulatory processes and on benefit, methods, tools and good practices on engagement with patients at the earliest stage of research. This could even become one mandatory aspect of the E-Rare-3 calls.

Carla Hollak working as clinician in rare inborn errors of metabolism at the Academic Medical Centre in The Netherlands, sees that her every day practice has improved, but she also sees less positive aspects. Positive aspects are the increasing number of centres of expertise and multidisciplinary clinics, more treatment and better collaboration, like exchange of protocols and (inter)national websites/databases/registries. However, she also experiences lack of time and resources (e.g. registries are not sustainable), rivalry, influence of pharmaceutical industry, a gap between central regulatory evaluation of an orphan drug and local judgment of the value of cost effectiveness of the drug, high costs of the orphan
drugs and diagnostic issues e.g. benign variants are picked up of uncertain clinical significance.

Carla Hollak clarified herself with an example of new treatment and screening of lysosomal acid lipase (LAL) activity that may result in Wolman disease or cholesteryl ester storage disease, dependent on the level of residual enzyme activity. An enzyme therapy product (sebelipase alfa) is authorised on short term efficacy for all patients in 2015. This authorisation is based on outcomes of surrogate markers. The costs for this product are 100,000-500,000 euro per patient per year. In practice this therapy is not available in The Netherlands as the local decision on reimbursement is pending. The Marketing Authorisation Holder (a pharmaceutical firm) sponsors retrospective natural history studies, has a LAL deficiency registry (demanded by the European Medicines Agency) and sponsors screening initiatives for LAL deficiency.

Carla Hollak sees the European Reference Networks as an excellent opportunity to collaborate independently on databases for natural history studies, to improve availability of diagnostic facilities and to develop guidelines and protocols for screening, diagnosis, treatment and post-marketing evaluation of (orphan) drugs. She referred to a position statement on the role of healthcare professionals, patient organisations and industry in European Reference networks (Orphanet J Rare Dis 2016 Jan 25 11(1):7).

She would like to recommend E-Rare that:
- initiatives should build on developing or maintaining existing independent registries;
- investing in independent natural course studies;
- new technologies for diagnosis should be used according to strict protocols and invest in deep phenotyping through sustainable collaborative high quality databases to avoid misdiagnosis;
- when companies are involved include requests to keep medication affordable to improve access to therapy;
- Fund translational research from bench to bed and from bed to society.

Olaf Riess, from the Institute of Medical Genetics and Applied Genomics, Rare Disease Center at University of Tübingen in Germany, summarised the main problems that has to be addressed in rare diseases from his personal view as a basic researcher, working across countries. One of the problems is the unsolved issues on defining the “genetic” cause of the symptoms. These unsolved issues may be divided into two groups: (A) Inconclusive DNA variants: variants may fit to phenotype but there is no clinical certainty that the variant causes the disease symptoms and (B) Suspicious Whole Genome Sequencing (WGS) results: variants do not relate to the phenotype found. Solutions for these unsolved issues can be (a) Curation of clinical useful databases and necessity of international expert teams (as 27% of all mutations in databases are wrongly annotated or are polymorphisms); (b) Improvement of in silico prediction of pathogeneity scores; (c) Research on structural variants of the genome; (d) System biology approaches such as (1) Combination of epigenomics, RNA sequence analysis, WGS data and proteomics in iPSC cell lines with functional screening assays, (2) Disease gene expert groups as core service providers and (3)Pathway prediction.

Olaf Riess mentioned four other problems in rare diseases that also need further research. Molecular and/or functional characterisation of disease genes and pathways. In this topic research is needed on new disease genes (ultra-rare e.g. in consanguineous families or late
onset "sporadic" manifestation), disease modifiers (genetic, epigenetic), system biology approaches (core facilities, service providers – not big but network of many experts), bioinformatics of systems and models (network modelling), complexity of gene regulation (promoter variants, miRNA, transcription factor complexes) in health and disease, role of gene isoforms in normal function and disease and interplay of environment/metagenome with the genome in human diseases.

Also research on models for rare diseases is needed as a mild phenotype in man may result in a severe phenotype in a mouse model, e.g. Investigations are needed for making truly humanised models, investigations in yeast, fly, nematode, zebra fish and mouse/rat; investigations of multiple disease gene modifications, of modification of functional domains of proteins and of specific amino acids and investigations in structure of wild type and mutant proteins using e.g. crystallography and Nuclear Magnetic Resonance.

More research is needed for interrupting disease pathways and preclinical screening. To tackle this Olaf Riess mentioned several ways: define large scale protein-protein interaction networks, define large scale protein modification (posttranslational modification) and how it influences this interaction network, define how genetic variants in genomic core regulation regions influence pathways, genetic interference screening, compound screening (including development of readouts).

Furthermore, research is needed in relation to clinical trials for rare diseases, like biomarker development, "Genetic" drug development, therapy resistance or side effects, and biobanking (fibroblasts, filter cards).

In the opinion of Olaf Riess collaboration of expert groups in functional geneOmic expert networks could be of great help for rare disease research. In such a network, experts in specific diseases, work together with expert groups in modelling and with technology platform groups (e.g. on genomics, RNA sequencing, proteomics, systemic screens, etc.).
Erik Tambuyzer focused on the research that is needed to be able to bridge the gap between basic research and therapies, being chairman of the Board of BioPontis Alliance for Rare diseases, a philanthropic alliance that focuses on turning basic science into medicines with a focus on rare neurological diseases for now.

Lessons from the past has shown that pharma and biotech industry are only interested in therapy development if certain results are already available like e.g. know-how that is patented and proof of concept. However, academic researchers often do not understand the industry language, the product development or regulatory rules and rare disease patient organisations that invest in research often have no ownership of the results.

Many aspects have to be dealt with before research is therapy-development-research: The underlying biology of the disease should be known, a confirmed diagnosis with full genome sequencing is a must for genetic diseases, knowledge on disease progression with and without treatment including natural history data and registries and indicators for disease predictability and disease progression. Although animal models and screening assays for lead generation and drug discovery are necessary, these techniques do not guarantee success. Input from rare disease patients are needed in the several therapy development stages: to help defining which critical aspects of disease should be addressed by the therapy, with developing biomarkers and clinical endpoints and preparing themselves to take part in clinical trials and to help advocate at regulatory agencies. BioPontis will organise Patient Integration Workshops in 2016 in US and EU to integrate patients into the preclinical development phase and is also building bridges with academia, philanthropy and industry.

Erik Tambuyzer concluded his presentation with the following recommendations for E-Rare:

- Evaluate how to involve patients’ organisation experts in set up of projects and review of results;
- Evaluate to expand the number of projects on therapy development and involve volunteer industry development experts and regulatory experts;
- Reflect whether philanthropic entities like BioPontis can be involved and funded.
Session 4  Future framework for sustainable collaboration in rare diseases

As indicated in the preconference paper there are several possible scenarios for sustainable collaboration in rare disease research and the future role for E-Rare. Potential solutions will depend on the available instruments to finance activities and matching actions of Member States and European Commission.

The most elementary scenario would be that E-Rare is continuing its activities as in the past years by performing Joint Transnational Calls and extending its network of research funding agencies and ministries within and outside the European Union. The contribution of countries is based on a variable participation model where in every year each funding agency/Ministry decides whether it will join the JTC with a specific budget. The corresponding EC instrument would be an ERA-NET Cofund as it is for E-Rare-3 now. This instrument is designed to support public-public partnerships in their preparation, establishment of networking structures, design, implementation and coordination of joint activities as well as to give topping up of single joint calls and of actions of a transnational nature. The format of ERA-NET does not encourage a common pot funding mechanism, which is necessary to maximise funding of transnational projects. Co-funding by the European Commission is a good solution to complement efforts of Member States but it is limited to one joint call within the five years’ framework of the instrument. Thus, to fully exploit the funding and strategic experience of E-Rare and potential for further development of initiated actions a more elaborated instrument could be considered.

A more ambitious scenario would be to extend strategic and funding activities into concerted, joint planning on rare disease research to increase the value of relevant national and EU funding. The instrument for this activity is called Joint Programming Initiatives (JPI). JPIs centre on tackling major societal challenges of transnational nature that are too big for one country to address on its own. They imply the definition, development and implementation of common Strategic Research Agendas based on a common vision on how to address those major societal challenges. This entails putting resources together, selecting or developing the most appropriate instrument(s), implementing, and collectively monitoring and reviewing progress. At its most ambitious aim, Joint Programming requires that Member States are prepared to move in the direction of implementation of common research agendas with multi-annual, commonly decided activities (planning, launching, evaluating) and funding mechanisms. (European) Joint Programming could be a solution combining the proficient mechanism of joint transnational calls set up by E-Rare and scientific guidance of IRDiRC as tools for a major aligned initiative.

In Horizon 2020 (H2020) a new instrument has been designed, European Joint Programme Cofund action (EJP Cofund), that supports coordinated national research and innovation programmes and aims at attracting and pooling a critical mass of national resources on objectives and challenges of Horizon 2020 and at achieving significant economies of scales by adding related Horizon 2020 resources to a joint effort. The main activity of an EJP Cofund is the implementation of a joined 5-year programme of activities ranging from research to coordination and networking activities, including training activities, demonstration and dissemination activities, support to third parties, etc. This instrument may have the opportunity to combine E-Rare research funding activities in the same way as in the current ERA-NET with activities of other rare disease initiatives like services on registries performed by the Joint Research Centre and the RD-Connect project, services from the several
European Research Infrastructures, and other activities like funding development and dissemination of standards of care and guidelines for rare diseases with help of European Reference Networks. The scope of such an EJP Cofund on rare diseases should be clearly defined to have concrete results after five years that improve the quality of life of rare disease patients.

The most ambitious (from the legal point of view) scenario would be that Member States involved in E-Rare and EU initiate jointly a durable research programme on rare diseases. This could be achieved through the Article 185 Initiative. Such an instrument represents a degree of integration of Member States’ research activities that goes beyond the programme coordination of the ERA-NETs. Other than participation of funding organisations forming a network and responding to a call, the decision and priorities of an Article 185 Initiative are decided between several Member States and the EU.

Future framework for sustainable collaboration

Irene Norstedt (Head of Innovative and Personalised Medicine Unit, DG Research and Innovation, European Commission) indicated that the EC has a strong track record on funding rare disease research and is committed to the IRDiRC goals. The challenge is now to integrate all efforts “from bench to bedside” in Europe and beyond so that the research will be of benefit for the patients. Therefore, the funding of rare disease research is diverse: basic and pre-clinical research, data and standards, biomarkers and diagnostics, prevention/therapies/cure, evidence base for application and policy.

When E-Rare has the vision to go for sustainable collaboration, the EC has a toolbox consisting on the following instruments among others: Support and Coordination Actions, Research and Innovation Actions, Pre commercial procurements, ERA-NET Co-Fund, European Joint Programme Co-fund Instrument, Public-public partnership (Art. 185). Irene Norstedt would like to advice E-Rare to reflect on issues like:
- Does E-Rare like to keep the idea of joint programming/funding or strive for a common pot;
- How would E-Rare like to act in data sharing, patient registries, etc.;
- Are there thoughts on dissemination and/or training programmes;
- Is there a role for European Reference Networks;
- How to involve the European Research Infrastructures;
- How to support IRDiRC;
- What about the regional dimension (structural funds);
- What will be the overarching objectives;
- Would E-Rare like to be involved in the innovation cycle from bench to bedside or a section of this cycle;
- What will be the level of integration;
- What will be the timeframe in short, medium and long term.

Dependent on the choices of the abovementioned topics E-Rare could think of using one instrument or a combination of instruments.
**RD Action – promoting implementation of recommendations on policy, information and data for rare diseases**

Ana Rath gave a second presentation as coordinator of RD-Action ([www.rd-action.eu](http://www.rd-action.eu)). This Joint Action on rare diseases is funded from June 2015-May 2018 by the European Commission and is a result of European policies on rare diseases: the Commission Communication on rare diseases: Europe’s challenges (COM 2008 679) from November 2008 and the Council Recommendation on an action in the field of rare diseases (2009/C 151/02) from June 2009. This resulted in

- Assembling of experts and representatives of Member States to work on policies for rare diseases: Rare Diseases Task Force (2004-2009); European Union Committee of Experts on rare diseases (EUCERD) (2010-2013) with the EUCERD Joint Action (2013-2015) and Commission Expert Group on Rare Diseases (CEGRD) (from 2014);
- A database for rare diseases that became European and global: Orphanet, that is EU cofunded since 2000
- A dedicated nomenclature for rare diseases (ORPHA nomenclature and preparation of coding of more numbers of rare diseases in the International Classification of Diseases, ICD11).

RD-Action consists of 34 beneficiaries and 29 collaborating partners including some partners outside Europe. The objectives of RD-Action are (1) To continue the implementation of the policy priorities identified in the Council Recommendation and Commission Communication and support the work of the CEGRD by gathering expertise and producing data necessary to its action; (2) To contribute to solutions to ensure an appropriate codification of rare diseases in health information systems, and (3) To support further development and sustainability of the Orphanet database.

RD-Action is made up of six work packages: coordination (WP1), dissemination (WP2) (that consists of e.g. RD-Action website, Orphanews with more than 16,000 subscribers, conferences at national level as a survey for the EUROPLAN network, documents and workshops to produce evidence for sustainable health systems for rare diseases), evaluation (WP3), Orphanet (WP4), adoption of Orphacodes across Member States (WP5) and policy development and integration with other initiatives (WP6). In WP6 a consultative group has been formed that will choose the thematic priorities. European Reference Networks (ERNs) are seen as an opportunity for e.g. eHealth and data-sharing, interoperability, development of best practice guidelines and registries and for links with research infrastructures. A taskforce has started to consolidate and formalise interactions between the rare disease projects and eHealth communities and expects to produce a proposal for a European interoperability roadmap for sharing data in the framework of the operation of ERNs. Ana Rath concluded her presentation with the message that structuring, standardisation and sharing of data in projects is key.

**Structural funds for health and rare diseases, how to?**

Giada Li Calzi (expert in structural funds for health, advisor for the Italian Ministry of Health) answered three questions on the European Structural and Investment Funds (ESIFs): What could be the link and what would be the gap between the help of structural funds and
(infrastructure for) research in rare diseases in future and what should be done related to rare diseases.

A lot of different infrastructures are needed for rare disease research. The ESIF could play a role in e.g. building expertise, establishing/expanding/sharing biobanks, managing data resources and support for advancing biomedical innovations, and work with cohorts. The Commission published a guide on those areas that ESIF 2014-2020 can support in the health sector, like research and innovation in health, support to SMEs, e-Health; health promotion; access to healthcare, health professionals’ education and lifelong training; and cross-border healthcare and cooperation between EU Member States and regions.

The ESIF is managed by the Member States and the European Commission (DG Regio - Regional and Urban policy, and DG Empl - Employment, Social Affairs and Inclusion). DG Santé (Health and Food safety) works closely with the two mentioned DGs on the use of ESIF for health investments. The Commission coordinates the funding modalities and thematic priorities with the Member States. The Member States are responsible for implementation of the investments at national level (http://ec.europa.eu/health/health_structural_funds/used_for_health/index_en.htm) and www.esifforhealth.eu/Health_areas.htm)

E-Rare-3 is a programme funded in the Horizon 2020 that is managed by DG Research that works closely with DG Santé. The question that Giada Li Calzi raises is whether DG Santé, DG Research and DG Regio look at rare diseases in the same direction because of the different authorities, different programmes, different origins and different scopes. Therefore, Giada Li Calzi is in favour of developing a strategic approach in combining funding programmes of the different DGs. She proposed a conceptual map for combining (scopes of) funding programmes using two pillars: the centres of expertise and the European Reference Networks. General criteria in the pillar of centres of expertise (e.g. research and training capacity, exchange of expertise and information systems) could be funded by
Structural Funds. Specific criteria in the pillar of centres of expertise (like disease/disease group specific competence, expertise and outcomes of care) and some of the general criteria in the pillar of European Reference Networks (like highly specialised healthcare for complex rare diseases, multi-disciplinary approach) could be funded by Horizon 2020. Some other general criteria for European Reference Networks (like exchange of knowledge and production of good practice guidelines, contribution to research, national and international collaboration and networking) could be funded by the Public Health programme (DG Santé).

Giada Li Calzi gave suggestions how to get more knowledge on ESIF – which are investment funds (and not financing funds). She called attention to the INTERREG Europe cooperation programme, a policy learning programme for European public authorities promoting exchange of experience and transfer of good practices. She also suggested to look into possibilities of the ESPON 2020 Cooperation programme. One of the activities in this programme is an open invitation to policymakers and practitioners to submit proposals for targeted analyses, meeting their particular policy demands and evidence needs with the objective of directly contributing to information policy decisions and territorial development strategies (www.espon.eu/main/menu_calls/Menu_Invitation-Stakeholders/index.htm).

Involvement of medical research infrastructures

Jacques Demotes (ECRIN, France) is chair of the ESFRI Biological and Medical Science Research Infrastructures (BMS-RI) Strategy Board. A subgroup of these research infrastructures signed some years ago the InnoRare Memorandum of Understanding: EU-OpenScreen (chemical libraries and screening), BBMRI (biobanks), EATRIS (translational medicine), and ECRIN (clinical trials). The main objective of this collaboration is to connect research infrastructures involved in discovery, preclinical and clinical development of innovative diagnostics and therapeutics, in order to create a complete research and development innovation chain for rare diseases.

ECRIN-IA (European Clinical Research Infrastructure Network; 2012-2017) is a FP7 funded project on structuring pan-European investigating capacity. One of the priorities of this project is rare diseases (next to medical devices and nutrition). Examples of the work of ECRIN is development of tools/operational support to facilitate multinational trials, partnerships with e.g. Orphanet (on inventory of expert centres and clinical trial capacity), with project TREAT-NMD (regulatory database), with EURORDIS (patient involvement), funding rare disease trials (ECRIN-IA WP7). In addition, ECRIN-ERIC supports H2020 and E-Rare-3 funding applications for rare diseases trials (ECRIN-on Board), and rare diseases currently represent about 20% of ECRIN multinational trial portfolio – multinational cooperation makes particularly sense when patients and medical expertise are rare. ECRIN has partnerships with medical research communities and medical research infrastructures (CORBEL) and international partnerships (bilateral, e.g. with Australia, Korea and US NIH/NCATS) and multilateral.

The CORBEL project (www.corbel-project.eu/about-corbel.htm), funded by Horizon 2020, is a joint initiative of the BMS-RIs, which together create a platform for harmonised user access to biological and medical technologies, biological samples and data services required
by cutting-edge biomedical research. A WP3 Medical Infrastructure/Users Forum (MIUF) was established, including representatives of the medical research infrastructures and of medical research communities viewed as thematic priorities, represented by JPIs and ERA-NETs, and other strategic initiatives. E-Rare, RD-Connect and EURORDIS represent rare diseases in the MIUF. The role of the MIUF is to capture needs from medical research communities in terms of infrastructure and services, to drive the development of tools and services by the research infrastructures, and to develop a consistent strategy for the pan-European structuring of medical research, avoiding gaps and overlaps and clearly defining the role of infrastructures (developing technology and services) vs. pan-European medical research communities (developing the scientific content).

CORBEL may help in solving challenges for infrastructures in rare diseases, like capturing infrastructure needs, developing a de-fragmented service platform and improving outreach to scientific and medical communities. In addition, coordination and cooperation with other groups (like IRDiRC, European paediatric network EPCTRI, the World Health Organisation, E-Rare) will help in solving these rare diseases challenges. CORBEL performs a survey on user needs of research communities, in order to foster collaboration with research infrastructures across Europe and to develop specific or common services (http://ecrin.limequery.com/index.php/689673/lang-en).
General discussion and conclusions

The discussions based on the scope of future activities of E-Rare and framework for sustainable collaboration on rare diseases (sessions 3 and 4) started with several statements of Jacques Beckmann (Swiss Institute of Bioinformatics) concerning his focus on future. In his opinion the following topics in rare disease research are needed and should be stimulated:

- Interoperable, standardised ontologies and databases (like Human Phenotype Ontology, Orphanet), data sharing and harmonisation (applied in all projects);
- Robust, secure, clinically approved mHealth (mobile health, used for the practice of medicine and public health supported by mobile widespread connected tools), tailored for specific diseases to collect long term phenotypic data;
- mHealth should be part of the arsenal for longitudinal deep phenotypes, natural disease history, gene-environment interaction, early (pre-symptomatic) detection, follow-up on therapeutic trials including adverse drug reactions, as humans are the best model system;
- mHealth should enable to increase sample size, reach large number of patients and countries; allow the construction of better, defragmented registries (even in poorly covered countries), epidemiological studies, etc.;
- And is also related to Best Practice;
- Focus on comorbidities, now that several of these paediatric patients may have "extended" life expectancies and thus adult diseases, whose specificities may be poorly covered by regular medicine;
- Necessity to emphasise that rare diseases are extremes of common diseases, and can thus teach us a great deal on the latter: hence, can't common disease resources also fund rare disease research?
- Research on microbiome (catalogue of the genes of microbes associated with humans) shows impact on e.g. gender, age of onset, penetrance, severity, and therapy; May provide new avenues for therapeutic interventions.
- Repurposing of failed drugs (from pathway & drug databases to sharing).

Several of these statements emphasised the importance of ontologies, databases and further research on phenotyping that were also mentioned by several speakers in session 3. Research on repurposing of drugs was mentioned several times and is in fact the focus of E-Rare JTC 2016.

In the discussion several other suggestions were given concerning what kind of research E-Rare should fund. It was mentioned that 95% of rare diseases are still without treatment despite orphan drug regulations in USA and EU and that E-Rare should focus on funding non-expensive therapy projects. The example was given of the repurposed drug nitisinone, originally developed as herbicide that received a marketing authorisation from the European Medicines Agency in 2005 for treatment of hereditary tyrosinemia Type 1. For patients it is important to invest in research for both diagnostics and therapies. Although the problem of access of treatment was discussed, E-Rare cannot have influence on access of treatment of patients as this has to be dealt with by Member States and companies.

It was emphasised that there should be synergies between IRDiRC recommendations and its global orientation and E-Rare funding mechanisms for transnational research: keep focusing on topics and themes that comply with IRDiRC recommendations. Furthermore, the restricted budget for rare disease research was mentioned: as the competition between
applicants in E-Rare calls and in Horizon 2020 calls is fierce and an applicant should have a realistic chance of success it was suggested that calls in funding programmes for rare disease research should be more focused.

Coordination and collaboration between projects are very important according to the Workshop participants. E-Rare should avoid that funded projects have an overlap with activities in other projects. Therefore, tools should be installed to have independent evaluation of results and impact of research projects on medium and long term. Coordination is also needed to facilitate access to services and facilitate incorporation in calls, not only in E-Rare calls but also in EC calls. Everyone should make good use of all tools and resources that are present today.

To have a better coordination in programming the content of calls it was recommended to develop indicators for unmet needs, exploit the information that already exists from gap analyses and systemise the pathway to fill working programmes. Processes like partnering and engagement are key for the rare disease community. Resources should be shared: the EC and E-Rare should push the boundaries and aim high. In the opinion of one of the participants EC and E-Rare could be more directive by thinking of incentives e.g. for sharing samples and data.

Daria Julkowska concluded that the participants in this Workshop have given a lot of information on several European research projects and have given valuable input for topics and themes for the next calls of E-Rare.

Several key elements were mentioned for sustainable collaboration in rare disease research in future: (1) Different instruments have to be used to avoid overlap and to push research forward; (2) Unmet medical needs of rare disease patients should be the focus of rare disease research; (3) Coordination of and collaboration between the several initiatives, projects and programmes are key to move forward in rare disease research.

E-Rare will use the input of this Workshop to reflect on its future role in sustainable collaboration in rare disease research and which instrument(s) would be best for fulfilling this role.
Acknowledgements

We thank all participants of the Strategic Workshop for their presentations and/or their input in the discussions and reading the draft report. We also thank Daria Julkowska, Natalia Martin and Juliane Halftermeijer (ANR, France), Ralph Schuster (PT-DLR, Germany), Domenica Taruscio (ISS, Italy), Ignacio Baanante (ISCIII, Spain), Anabela Isidro (FCT, Portugal) and Harald Moonen (ZonMw) for their help in designing the Workshop programme.
Annexes

A. Programme
B. List of participants
C. Preconference paper
E-RARE
STRATEGIC WORKSHOP
Barcelona, Spain
2016

10 E-Rare YEARS
2006 - 2016
PROGRAMME

General comments: Closed session (on invitation only)

12:30 - 13:30 LUNCH

SESSION 1: 10 YEARS OF E-RARE: OVERVIEW AND OUTCOMES

13:30 - 13:35 Welcome
Daria Julkowska (E-Rare coordinator, ANR, France)
Ralph Schuster (E-Rare Network Steering Committee chair, DLR-PT, Germany)
Sonia van Weely (E-Rare Network Steering Committee co chair, ZonMW, The Netherlands)

Ralph Schuster (DLR-PT, Germany)

13:45 - 14:00 10 years of E-Rare: overview and outcomes
Daria Julkowska, E-Rare coordinator, ANR, France
  o Introduction of E-Rare
  o Overview of the topics in the past Calls (JTCs) of E-Rare
  o Outcomes

SESSION 2: STRATEGIC RESEARCH AGENDAS OF ONGOING AND FUTURE INITIATIVES IN RARE DISEASES

Chairs: Orly Elpeleg (Hadassah Medical Center, Israel) and Natalia Martin (ANR, France)

14:00 - 14:20 IRDREC: priorities and perspectives for near future
Hanns Lochmuller, chair of IRDREC Interdisciplinary Scientific Committee, Newcastle University, UK

Summary of Strategic Research Agendas of ongoing programmes of the EC with respect to rare diseases

14:20 - 14:40 Horizon 2020 Work programmes 2016-2017 and beyond
Anders Colver, European Commission, DG Research

14:40 - 15:00 Innovative Medicines Initiatives (IMI) 2 Bernd Stowasser, Head of European Public Private Partnerships, Sanofi, Germany

15:00 - 15:20 Rare disease research in current Joint Programming Initiatives (JPIs) and ERA-Nets
Natalia Martin, ANR, France

15:20 - 15:40 Analysis of rare disease research projects collected in Orphanet
Ana Roth, Orphanet, INSERM, France
E-RARE
STRATEGIC WORKSHOP
MONDAY, MARCH 7
BARCELONA, SPAIN

15:40 - 16:00  RARE-BestPractices project
   - Introduction: Domenica Taruscio, Coordinator RARE-BestPractices, ISS, Italy
   - RAREGap: a RARE-BestPractices database of rare disease research needs
     Cristiana Marciano, ISS, Italy

16:00 - 16:20  COFFEE BREAK

SESSION 3: SCOPE OF FUTURE ACTIVITIES OF E-RARE (including future
   topics for joint Transnational Calls where E-Rare can contribute significantly to the
   unmet needs in rare diseases)

   Chairs: Domenica Taruscio (ISS, Italy) and Frits Lekkerkerker (The Netherlands)

   16:20 - 16:50
   - Statement from patient alliance representative: Mathieu Bouches, Eurordis, France
   - Statement from clinician involved in rare diseases: Carla Holloak, AMC, The Netherlands
   - Statement from basic researcher involved in rare diseases: Olaf Riess, University of Tübingen, Germany
   - Bridging the gap between basic research and therapies: Erik Tambuyzer, BitoPontis, Belgium

16:50 - 17:15  Panel discussion

SESSION 4: FUTURE FRAMEWORK FOR SUSTAINABLE COLLABORATION
   IN RARE DISEASES

   Chairs: Lucia Monaco (Telethon, Italy) and Manuel Posada (Institute of Rare Diseases Research, ISCIII, Spain)

   17:15 - 18:30
   - Irene Norstedt, European Commission, DG Research
   - Ana Rath, coordinator RD Action, INSERM, France
   - Giada Li Calzi, expert in structural funds for health, advisor for Italian Ministry of Health, Italy
   - Jacques Demotes on behalf of Research Infrastructures/Working group on Rare Diseases, ECRIN, France

18:30 - 18:55  Panel discussion

18:55 - 19:00  Concluding remarks: Daria Julkowska (ANR, France) and Ralph Schuster
   (DLR-PT, Germany)
**B. List of participants**

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C. Preconference paper

Preconference paper for the E-Rare Strategic Workshop on March 7, 2016 in Barcelona

Strategic Research agenda of E-Rare in relation to other initiatives on rare diseases

Aim of the E-Rare Strategic Workshop

The main focus of the Strategic Workshop is the scientific policy agenda and discussions on future activities of E-Rare in relation to other initiatives on rare diseases research.

Outline of the Workshop

An overview of E-Rare and its activities in the past 10 years will be presented. Subsequently, several research agendas of ongoing and future initiatives for rare diseases will be discussed (session 2) to get a broader scope of the domain. In session 3 several stakeholders, each from their own perspective, indicate what is needed in rare disease research and where E-Rare can contribute significantly. This may imply a specific focus for funding in Joint Transnational Calls of E-Rare but also suggestions for future activities of E-Rare in general. The focus of session 4 is how a future framework can be built for sustainable rare diseases research and the role of the E-Rare consortium in this framework: which scenarios for sustainable activities beyond E-Rare-3 (in terms of timeline and instrument) are feasible?

Rare diseases landscape in Europe

Rare diseases are life threatening or chronically debilitating conditions from which fewer than five affected persons per 10,000 citizens in the European Union (EU) suffer. It is estimated that 6,000-8,000 different rare diseases exist, affecting between 6% and 8% of the population in the course of their lives. Today, research on rare diseases remains scarce and 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 was also recognized in the Council Recommendation of June 8, 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 asked for the establishment of national plans/strategies on rare diseases that should cover health care and research. In the last years a national plan or national strategy on rare diseases was developed in 22 EU countries.

Over the years the European Union has supported key actions to produce data necessary to improve identification and knowledge on rare diseases, and has provided recommendations on specific areas to support and guide Member States policies on rare diseases. Part of the EU’s comprehensive approach to tackling the rare diseases burden in Europe is to co-finance projects and actions. An
example is the Rare Disease Joint Action (continuation of EUCERD Joint Action initiated in 2011) that has the general objectives to (i) support the further development and sustainability of the Orphanet database on rare diseases (the biggest repository of information about rare diseases globally), (ii) contribute to solutions to ensure an appropriate codification of rare diseases in health information systems; (iii) continue implementation of the priorities identified in the 2009 Council Recommendation and the 2008 Commission Communication on Rare Diseases, and (iv) support the work of the Commission Expert Group on Rare Diseases by gathering expertise and producing data necessary to its action.

An additional important initiative for research on and healthcare for rare diseases is the development of European networks of reference (ERNs) in which specialists in various disciplines in different countries in Europe may join their efforts to treat rare diseases that require highly specialised healthcare and a concentration of knowledge and resources. The ERNs criteria and capacities are knowledge and expertise to diagnose, follow up and manage patients, evidence of good outcomes, multi-disciplinary approach, capacity to produce good practice guidelines and to implement outcome measures and quality control, and research, teaching and training. The opening of the first Call of the European Commission (EC) for ERNs for rare diseases is planned for March 2016. In the context of the development of the European networks of reference several countries may look for possibilities to apply for the European structural and investment funds (ESIFs)/European Social Funds (ESF).

Between 2007 and 2015 the European Union invested about 680 M€ in research on rare diseases. The EU support includes not only large multinational scientific projects but also strategic and coordination initiatives, e.g. the International Rare Disease Research Consortium (iRDiRC), a consortium of researchers and organizations from Europe, USA, Australia and Asia investing in rare diseases research to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases. A number of grand challenges are being addressed through collaborative actions to reach these 2020 goals such as establishing and providing access to harmonized data and samples, performing the molecular and clinical characterization of rare diseases, boosting translational, preclinical and clinical research, and streamlining ethical and regulatory procedures. To attain these goals EU supports several associated projects like RD-Connect, a global infrastructure project that links up databases, registries, biobanks and clinical bioinformatics data used in rare disease research into a central resource for researchers worldwide and RareBestPractices, which is a platform to improve the management of rare disease patients by promoting communication on the management of rare diseases by disseminating trustworthy guidelines globally, identify and prioritize rare diseases research needs and facilitate timely, effective and efficient translation of research results into patient oriented strategy on the clinical as well as the public health level.

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1 www.orpha.net
2 http://ec.europa.eu/health/rare_diseases/expert_group/index_en.htm
5 www.irdircc.org
6 http://rd-connect.eu/
7 www.rarebestpractices.eu
E-Rare

E-Rare, the ERA-Net for Research Programmes on Rare Diseases⁸ was established in 2006 and since then its activities are co-funded by the EC.

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), E-Rare-2 (2010-2014) and E-Rare-3 (2014-2019) programmes have shown/are showing 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.

At the start of E-Rare-1 in 2006 the consortium consisted of eight countries and extended in the following years. Today, E-Rare-3 is a network of twenty-five partners – public bodies, ministries and research funding organizations – from seventeen countries: Member States (Austria, Belgium, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Spain, The Netherlands), three Associate States (Switzerland, Israel and Turkey) and Canada responsible for the funding of national/regional research programs or research projects on rare diseases.

E-Rare is member of IRDiRC and implements the objectives of IRDiRC by funding transnational research in its Joint Transnational Calls (JTCs). In the seven JTCs performed by E-Rare between 2007 and 2015 1021 projects were submitted of which 98 projects were funded with a total budget of 78 M€ and with 449 research groups involved. Projects funded through E-Rare calls cover a wide range of medical areas. The outcomes of these funded projects have clear impact on patients’ life. New causative disease genes were discovered that have a major impact on diagnosis and potential treatment of patients with a rare disease. The better understanding of the natural history of disease through registries and the harmonisation through guidelines will improve treatment of patients. The creation of animal and cellular models lay the basis for future research into diseases mechanisms and therapeutic options. Besides the JTC 2015 (cofunded by the EC) and the currently running JTC 2016 two other JTCs (JTC 2017 and 2018) are planned in the timeframe of E-Rare-3.

In addition to funding and monitoring the transnational research projects with measurable indicators, E-Rare also identifies rare disease research needs to implement in the focus of Joint Transnational Calls. Until now, three focused calls were organised: in JTC 2012 the call was dedicated to young researchers and clinicians proposing projects on rare diseases, in JTC 2014 the focus was on innovative therapeutic approaches and in the currently running JTC 2016 the clinical research for new therapeutic uses of already existing molecules (repurposing) in rare diseases is in the spotlight.

Recently, rare disease research may also benefit from several of the European Research Infrastructures and other initiatives, which were developed in the past years. These infrastructures

⁸ www.e-rare.eu
aim at facilitating rare disease researchers to gain access to resources and knowledge and to contribute to sharing of data and avoiding duplication of efforts.

To enhance its contribution to excellent and sustainable research results, E-Rare-3 established collaboration with a number of these infrastructures (BBMRI-ERIC, EATRIS, ECRIN, Elixir, EU-Open Screen, Infrafrontier) and also with the European Medicine Agency (EMA), with the aim to customize their services to the demand of rare disease researchers. In order to inform about provided services and to link scientists and infrastructures, E-Rare-3 developed a dedicated portal\(^9\). Furthermore, the E-Rare consortium promotes the use of European infrastructures within its calls for projects.

In the last 10 years E-Rare has created a sustainable network of rare disease research funders. E-Rare-3 has the intention to let this sustainable network grow with new funding agencies and other actors, including patient organisations. Eurodis\(^10\) – Rare Diseases Patients Europe – accompanied E-Rare for many years but since 2014 the organization became a full partner of the consortium and contributes actively to development of new models of funding and implication of patient organizations in research.

Although E-Rare is not principally dedicated to support patients care systems it aims at contribution to strengthening of collaboration between research and health services. The currently running JTC 2016 is a precise example of collaboration between ministries of research and health to foster use of repurposed drugs as new therapies for rare diseases with clear benefit to patients. Furthermore, E-Rare is aware of and participates through its different member agencies and involved ministries in other relevant initiatives like International Consortium on Personalized Medicine (IC PerMed) to ensure the close collaboration and alignment of common actions for both initiatives.

**Possible scenarios for sustainable collaboration in rare disease research in future**

There are several possible scenarios for sustainable collaboration in rare disease research and the future role for E-Rare. Potential solutions will dependent on the available instruments to finance activities and matching actions of Member States and European Commission.

The most elementary scenario would be that E-Rare is continuing its activities as in the past years by performing Joint Transnational Calls and extending its network of research funding agencies and ministries within and outside the European Union. The contribution of countries is based on a variable participation model where in every year each funding agency/Ministry decides whether it will join the JTC with a specific budget. The corresponding EC instrument would be an ERA-Net Cofund\(^11\) as it is for E-Rare-3 now. This instrument is designed to support public-public partnerships in their preparation, establishment of networking structures, design, implementation and coordination of joint activities as well as give topping up of single joint calls and of actions of a transnational nature. However, at the current level of maturity of E-Rare this instrument might be limiting because it often restrains in depth involvement of relevant ministries due to the fact that an ERA-NET is mainly considered as a funding instrument. In addition, the format of ERA-NET does not encourage a common pot funding mechanism, which is necessary to maximize funding of transnational projects. Co-funding by the European Commission is a good solution to complement efforts of Member States but it is limited to one joint

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\(^9\) [www.erare.eu/infrastructures](http://www.erare.eu/infrastructures)

\(^10\) [www.eurodis.org](http://www.eurodis.org)

call within the five years framework of the instrument. Thus, to fully exploit the funding and strategic experience of E-Rare and potential for further development of initiated actions a more elaborated instrument could be considered.

A more ambitious scenario would be to extend strategic and funding activities into concerted, joint planning on rare disease research to increase the value of relevant national and EU funding. The instrument for this activity is called Joint Programming Initiatives (JPI)\(^\text{12}\). JPIs centre on tackling major societal challenges of transnational nature that are too big for one country to address in its own. They imply the definition, development and implementation of common Strategic Research Agendas based on a common vision on how to address those major societal challenges. This entails putting resources together, selecting or developing the most appropriate instrument(s), implementing, and collectively monitoring and reviewing progress. At its most ambitious aim, Joint Programming requires that Member States be prepared to move in the direction of implementation of common research agendas with multi-annual, commonly decided activities (planning, launching, evaluating) and funding mechanisms.

As shown by the success of E-Rare calls and respective funding activities of the EC there is a clear need for researchers to collaborate transnationally in projects and the outcomes of these projects are improving the situation for patients with the rare disease investigated. In addition, the efforts of IRD IRC in establishing recommendations and shaping an international rare diseases research agenda start showing measureable impact on national policies. At present, due to their scarcity, geographical scattering and difficulties of treatment, rare diseases are recognized as an important challenge at European and international level. Therefore (European) Joint Programming could be a solution combining the proficient mechanism of joint transnational calls set up by E-Rare and scientific guidance of IRD IRC as tools for a major aligned initiative. On the other hand, latest evaluation of the existing JPIs showed that, due to the complexity of alignment of national strategies, joint effort often requires (financial) assistance of European Commission, in order to be productive. Thus, it is not sure that a JPI for rare diseases would be sufficient to bring an added value above the current configuration.

In Horizon 2020 (H2020) a new instrument has been designed, European Joint Programme Cofund action (EJP Cofund)\(^\text{13}\), that supports coordinated national research and innovation programmes and aims at attracting and pooling a critical mass of national resources on objectives and challenges of H2020 resources to a joint effort. The main activity of an EJP Cofund is the implementation of a joined 5-year programme of activities ranging from research to coordination and networking activities, including training activities, demonstration and dissemination activities, support to third parties, etc. A minimum number of five legally independent national ministries and/or funding agencies of Member States or associated countries are needed to apply for this action. This instrument may have the opportunity to combine E-Rare research funding activities in the same way as in the current ERA-NET with activities of other rare disease initiatives like services on registries performed by the Joint Research Centre and the RD-Connect project, services from the several European Research Infrastructures, and other activities like funding development and dissemination of standards of care and guidelines for rare diseases with help of European Reference Networks. The scope of such an EJP Cofund on rare diseases should be clearly defined to have concrete results after five years that improve

\(^{12}\) https://ec.europa.eu/research/bioeconomy/index.cfm?pg=policy&lib=jpi

the quality of life of rare disease patients.

The most ambitious (from the legal point of view) scenario would be that Member States involved in E-Rare and EU initiate jointly a durable research programme on rare diseases. This could be achieved through the Article 185 initiative\(^\text{14}\). Such instrument represents a degree of integration of Member States’ research activities that goes beyond the programme coordination of the ERA-NETs. Rather than participation of funding organizations forming a network and responding to a call, the decision and priorities of an Article 185 Initiative are decided between several Member States and the EU. Article 185 Initiatives are also required to have dedicated structures (such as a non for profit association or secretariat) for their implementation.

As presented above, countries involved in E-Rare already demonstrated their steady commitment to rare diseases research funding and willingness to align their strategic agendas with the recommendations provided by IRDIRC. Thus, an Article 185 Initiative could not only combine the scarce resources and reduce fragmentation of rare diseases research funding but would also put a legal framework around already existing structures by strengthening national commitments. In addition, application of the unique rules for participation in the EU Framework Programme could benefit the alignment and management of funding procedures. Finally, activities initiated by E-Rare like collaboration with European Research Infrastructures (also funded at national level) could equally profit from a well-established framework offered by an Article 185 Initiative.

\(^{14}\) http://ec.europa.eu/research/era/art-185_en.htm