RARE DISEASES
a major unmet medical need

Research & Innovation
Projects for Policy
RARE DISEASES - A major unmet medical need

European Commission
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Printed by OP in Luxembourg.
Manuscript completed in June 2017.
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Rare diseases comprise from 5000 to 8000 life-threatening or chronically debilitating diseases which together affect from 27 and 36 million people in the European Union. A lack of efficient treatment and accurate diagnosis for the majority of rare diseases represents an enormous unmet medical need and a major challenge for public health. The main challenge for policies and related R&I is to improve the lives of patients with rare diseases.

This report demonstrates how the results of recent research and innovation (R&I) projects funded by the EU contribute to five areas of policy challenges related to rare diseases:

> Improving diagnosis, prevention and treatment of rare diseases;
> Facilitating the regulatory pathway for potential treatments;
> Effective and equal provision of healthcare for patients with rare diseases;
> Effective management and pooling of research and medical data to benefit all patients;
> Contributing to and benefiting from global collaboration.

EU Framework Programmes have funded research on rare diseases for more than two decades. In FP7 and Horizon 2020, 164 projects have produced results and a selection of these were analysed in the context of the five policy challenges to develop five key policy recommendations.

**FIVE KEY POLICY RECOMMENDATIONS FOR ADDRESSING RARE DISEASES**

- **Support integration and networking among EU research, patient and healthcare organisations.**
- **Adapt implementation of regulatory requirements, especially for clinical trials in rare diseases.**
- **Support health technology assessment, standards and evidence-base for guiding public health policy.**
- **Develop legally and ethically robust agreements for collecting and exchanging health and genetic data.**
- **Collaborate globally through the International Rare Diseases Research Consortium (IRDiRC) to accelerate research on improving the lives of patients with rare diseases.**
Rare diseases are life-threatening or chronically debilitating diseases which affect fewer than 5 in every 10,000 people in the EU. Rare diseases comprise from 5000 to 8000 diseases, such as cystic fibrosis, Duchenne muscular dystrophy, Huntington’s disease and acute myeloid leukaemia. Although individually rare, together they affect between 27 and 36 million people in the EU, making rare diseases a major public health issue.

This report presents research and innovation (R&I) contributions for five current policy challenges regarding rare diseases. These challenges were selected because they have been the subject of specific targeted activities in collaborative health research across consecutive EU Framework Programmes and encompass the major societal and economic aspects related to rare diseases. They are all clearly linked to the European Commission’s political priorities\(^1\).

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\(^{1}\) https://ec.europa.eu/priorities/index_en
RARE DISEASES  a major unmet medical need

Rare diseases are serious chronically debilitating diseases which place a significant burden not only on the individual affected but on their families, too. Many rare diseases manifest at an early age, result in a shortened lifespan, and lead to a dependency on care throughout the patient’s life. About 80% of rare diseases are genetic diseases. Patients with rare diseases often spend years enduring a ‘diagnostic odyssey’ before receiving the correct diagnosis. Based on the data on the Orphanet portal for rare diseases and orphan drugs, a diagnostic test is available for some 3000 rare diseases, which means the majority of such diseases lack a specific test.

The lack of effective treatments for most life-threatening and chronically debilitating rare diseases represents an enormous unmet medical need. As only small numbers of patients are affected by individual rare diseases, the potential return on investment in the research and development of medicines to treat these diseases is limited. This reduces incentives for businesses to invest in this area.

The EU’s orphan medicinal products Regulation provides incentives for the development of these products, which include a 10-year market exclusivity for designated products, fee waivers, scientific assistance for marketing authorisation requests and the possibility of a Community marketing authorisation. Currently, there are over 1400 orphan designations, i.e. products under development, and some 130 orphan medicines authorised in the EU. Despite the success of the incentives to promote the development of orphan medicines, this remains a very limited number compared to the total number of rare diseases.

1. IMPROVING DIAGNOSIS, PREVENTION AND TREATMENT OF RARE DISEASES

The major challenge is to gain a better understanding of rare-disease mechanisms and ensure that research and innovation is effectively translated into new diagnostics and treatments for rare diseases, with large industry and SMEs playing an active role in taking the solutions further.

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2  www.orpha.net
3  Regulation (EC) No 141/2000
2. FACILITATING THE REGULATORY PATHWAY FOR POTENTIAL TREATMENTS

Orphan drugs, like any medicinal product, must be clinically tested before attaining marketing authorisation. Clinical trials for rare diseases face many challenges, including the difficulty of recruiting sufficient numbers of patients, and the very different natural histories and characteristics of rare diseases. These factors make traditional randomised clinical trials difficult to conduct in rare diseases.

The major challenge is to develop novel approaches to clinical trial methodologies for small patient populations to facilitate demonstration of the safety and efficacy of orphan drug candidates in order to attain marketing authorisation and enter clinical practice.

3. EFFECTIVE AND EQUAL PROVISION OF HEALTHCARE FOR PATIENTS WITH RARE DISEASES

Health systems in the EU seek to provide high-quality, cost-effective care. This is particularly challenging for conditions requiring concerted resources or expertise, and even more so for rare diseases where the knowledge on individual diseases is scarce and scattered across the different EU Member States.

Member States are responsible for their health policies and for organising the delivery of healthcare in their country – indeed, access to healthcare varies widely across the EU. The EU’s healthcare policies have aimed to support and further the cooperation between Member States in this area. A Commission Communication on an overall strategy for effective and efficient recognition, prevention, diagnosis, treatment, care and research of rare diseases in Europe has been adopted, and a Council Recommendation calls on Member States to put national strategies in place.

Recent Council Conclusion calls for strengthening the balance in the pharmaceutical systems in the EU and its Member States.

European Reference Networks (ERNs) created under the Directive on patients’ rights in cross-border healthcare aim to improve patients’ access to highly specialised, high-quality and safe care, pooling knowledge and improving diagnosis and care in medical fields where expertise is rare. ERNs are expected to have a major structuring effect on research and care by linking thematic expert centres across the EU and providing a sound and sustainable research structure which will gather data and expertise on rare diseases.

4 Commission Communication COM(2008) 679 final
5 Council Recommendation 2009/C 151/02
6 Council press release 350/16 of 17/06/2016
7 Directive 2011/24/EU
New orphan drugs are often very expensive, sometimes costing more than EUR 100,000 per patient per year. This poses a major challenge for health authorities which face growing pressure for cost containment and efficient resource allocation. Therefore, despite EU-level marketing authorisation, none of the EU-approved orphan drugs are currently accessible to patients in every Member State. Health technology assessment (HTA)\textsuperscript{8} brings together information about the medical, social, economic and ethical issues related to the use of a health technology which is useful in making decisions on how to allocate resources. Thus, it is also an important tool for assessing orphan medicines. The special characteristics of rare diseases again pose challenges for the typical approach to HTA.

The major challenge is to absorb rare diseases innovation efficiently into healthcare while improving the equity of healthcare provision across the EU on rare diseases, and to improve HTA methodologies so that they can also be fully applied specifically to interventions addressing rare diseases.

\section{Effective Management and Pooling of Research and Medical Data to Benefit All Patients}

Patient registries and databases are key instruments for improving healthcare planning and delivery, and for clinical research in the field of rare diseases. New ‘-omics’ technologies (genomics, proteomics, epigenomics, interactomics, metabolomics, pharmacogenomics, etc.) generate data which can advance knowledge on the diseases and help to develop new therapies and diagnostic tools. Combining these with data from electronic health records, hospital records, wearable devices, mobile phones and patient-reported outcomes provides new possibilities for research and innovation, including studying the safety and efficacy of interventions.

Pooling data from different countries is the only way to achieve a sufficient sample size for epidemiological and/or clinical research into rare diseases. However, this requires access, interoperability, sustainability and quality control. The health-related data has to be managed, shared and stored in a way that optimises scientific discovery, innovation, trust and societal benefit.

The major challenge is to establish accepted standards to govern the collection, organisation, sharing and reuse of health data, and that rare disease databases and patient registries are highly fragmented.

\textsuperscript{8} https://ec.europa.eu/health/technology_assessment/policy_en
5. CONTRIBUTING TO AND BENEFITING FROM GLOBAL COLLABORATION

Pooling and coordinating resources and research efforts at a global level are key elements for success in addressing the challenges posed by rare diseases. New knowledge and innovations concerning rare diseases developed in one country should benefit rare disease patients around the world. As the largest global rare diseases information portal, the Orphanet portal for rare diseases and orphan drugs plays an important role in knowledge dissemination. The exchange of experiences and practices between countries enables a more efficient use of scarce healthcare resources. The development of national plans and strategies for rare diseases has stimulated similar actions in other EU countries and beyond.

However, the sharing of information, data and medical samples worldwide is currently being hampered by the absence of a comprehensive rare disease classification, standard terms of reference and common ontologies, as well as harmonised regulatory requirements.

To address this challenge, in 2011 the European Commission and the US National Institutes for Health initiated the International Rare Diseases Research Consortium (IRDiRC)\(^9\) to foster international collaboration and accelerate research efforts on rare diseases around the world. IRDiRC teams up researchers and organisations investing in rare disease research in order to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by the year 2020. Since its founding IRDiRC has grown to encompass more than 40 partners from four continents.

\[^9\] https://www.irdirc.org

The current challenge is to ensure the active and broad participation of European and international research stakeholders in IRDiRC activities and the wide uptake of collaborative results.
PORTFOLIO OF RECENT EU-FUNDED R&I PROJECTS
A selection of 120 projects funded under the Seventh Framework Programme for Research and Technological Development (FP7) Health theme and 44 projects funded in the Horizon 2020 Health, Demographic Change and Wellbeing challenge were included in this portfolio analysis based on the relevance of the projects to rare disease research. In addition to the projects included in this portfolio, there are potentially more contributing to rare disease objectives under other FP7 and Horizon 2020 work programme areas, such as Future and Emerging Technologies (FET-Open), Marie Skłodowska-Curie Actions, the Research Infrastructures programme and European Research Council grants.

**KEY FACTS IN THE PROJECT PORTFOLIO**

- Research into rare diseases has been supported by 164 FP7 and H2020 EU-funded projects with EU funding of over EUR 874 million for 1861 participants.

- EU support in this area shows a growing trend peaking in 2012-2013 when several specific topics were issued marking the launch of IRDiRC.

- Funded projects cover several rare disease areas, including neurology, cancer, neuromuscular diseases, immunology, pneumology, dermatology and metabolic diseases.

- Substantial financial contribution, close to EUR 180 million, is being devoted to private research organisations, including SMEs, representing 20% of the total EU contribution in this field.

Projects with results most relevant to the five major policy challenges have been used as the basis for the policy recommendations in this report.
1. **FP7 AND H2020 WORK PROGRAMMES ADDRESSING RARE DISEASES**

Rare disease research has been a priority area for EU Research Framework Programmes for more than two decades and has impacted policy development in several fields. In FP7, EU contributions in excess of EUR 660 million were invested in over 120 collaborative research projects relevant to rare diseases. With five more years of project selection still to come, during the first two years of Horizon 2020 (2014-2015), more than EUR 214 million had already been committed to projects in the field. These projects span across several disease areas, such as neurology, neuromuscular diseases, immunology, cancer, pneumology, dermatology and metabolic diseases. Annual EU support in this area indicates a growing trend over the funding period analysed from 2007 until 2015.

**FIGURE 1 EU financial contributions from project start (EUR million)**

Yearly EU contributions to new rare disease research projects show a growing trend since the start of FP7. Work programmes 2012-2013 included several specific topics for rare disease research, marking the launch of IRDiRC in 2011.

The EU-funding strategy for rare disease research focuses on understanding the underlying causes of these diseases and on diagnosis, prevention and treatment, thereby combining advances in scientific knowledge in the field with benefits for rare disease patients. In addition, projects are being funded to coordinate and support the research area.

More than 90% of the projects in the analysed portfolio were funded under the FP7 Collaborative Projects (CP) scheme, most of which are Focused Integrating Projects (CP-FP). In H2020 Research and Innovation Actions, several small projects were launched by individual SMEs using the SME phase-1 instrument for feasibility studies of breakthrough technologies.
2. PORTFOLIO OF BENEFICIARIES

Most of the participants involved in rare-disease-related projects in the analysed portfolio are higher education establishments (HES) and public research organisations (PRC). A substantial financial contribution is being devoted to private research organisations, including SMEs, for which the estimated EU contribution is close to EUR 180 million, which is 20% of the total EU contribution in this area. Twenty-six patient organisations are participating in the projects as beneficiaries.

The most active countries in rare-disease-related projects are Germany (EUR 156 million), United Kingdom (EUR 152 m), France (EUR 109 m), Italy (EUR 90 m), and the Netherlands (EUR 87 m), in terms of EU contributions to project beneficiaries per country. The location of FP7 and H2020 participants by region/city shows a concentration of resources in Paris, London, Milan, Rome, Stockholm, Leiden, Munich, Berlin, Vienna, Amsterdam, Madrid, Heidelberg, Lyon and Rotterdam.
**FIGURE 4A** Level of EU contribution per country to the beneficiaries in the analysed project portfolio

EU Financial Contribution
- 78,386,725 and more
- 15,000,000 - 78,386,725
- 10,424,785 - 15,000,000
- 25,000 - 10,424,785

**FIGURE 4B** Geographical distribution of beneficiaries

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The rare disease research project portfolio also includes an important international dimension with 71 beneficiaries from third countries outside the EU and Associated Countries. The United States is by far the most active third country with 37 beneficiaries, and the estimated EU contribution of EUR 20 million reflecting the eligibility of US entities to receive funding from the FP7 Health theme and the Horizon 2020 Health, Demographic Change and Wellbeing challenge. The second and third most active ‘overseas’ countries are Australia and Canada, for which the estimated EU contribution is EUR 2 million each to 12 and 7 beneficiaries, respectively.

3. PORTFOLIO OF RESEARCH TOPICS COVERED

Different work programmes throughout the FP7 Health theme and the Horizon 2020 Health Demographic Change and Wellbeing challenge have enabled the funding to be focused on specific research challenges related to rare diseases, such as natural history studies, the development of new therapies and diagnostic tools, as well as promoting the participation of SMEs and patient organisations.

Since 55% of rare-disease-related projects are funded on topics which are not specific to rare diseases but are open to research related to all types of diseases, proposals related to rare diseases strive well in open competition. Among the rare-disease-related projects funded under Horizon 2020, the most represented disease areas are infectious diseases, cancer, respiratory diseases, immunological disorders, neurodegenerative diseases, neuromuscular diseases, gastroenterology, haematology, neonatology, and obstetrics and gynecology.

As far as the relevance to the policy challenges described in section 1 of this report are concerned, 90% of the projects address the challenges of improving diagnosis, prevention and treatment of rare diseases and effective and equal provision of healthcare for patients with rare diseases. This has clearly been the focus for FP7- and Horizon 2020-funded projects. As a secondary objective, many of these also address the challenge of effective management and pooling of research and medical data on rare diseases to benefit all patients. Currently, 25% of the projects are building links with IRDiRC, thereby addressing the challenge of contributing to and benefiting from global collaboration on rare diseases. Other projects address the challenge of facilitating the regulatory pathway for potential treatments.
IMPACT AND RESULTS OF EU FUNDING
1. ADDED VALUE OF EU-LEVEL R&I INVESTMENT

Small and dispersed patient populations, fragmented expertise and the limited availability of research resources have made rare diseases a high-need area for European-level research collaborations. Funding from EU Framework Programmes has had a strong integrating effect in the field by bringing together multi-disciplinary teams from universities, research organisations, hospitals, SMEs, industry and patient organisations across Europe and beyond in a critical mass of expertise that no individual EU Member State can provide.

EU-level activities provide high added value, for example in pooling resources, knowledge and expertise, fostering research and cooperation, and granting authorisation of the best-possible medicines – ‘orphan drugs’ – for the whole EU. ERA-NETs have been a driving force in coordinating research on rare diseases at both European and international levels. In E-Rare-3, joint transnational calls have involved funding agencies from 13 EU Member States as well as Canada, Israel, Switzerland and Turkey, and are paving...

RESULTS OF EU-LEVEL R&I INVESTMENT

EU-level collaborations, including the ERA-NET E-Rare-3, pooled a critical mass of resources, multi-disciplinary knowledge and expertise, which is a crucial prerequisite for advancing research in the field of rare diseases.

Results of EU-funded projects have achieved concrete benefits for EU citizens in terms of better and optimised treatment options and faster and more accurate diagnostic tools for rare diseases, as exemplified by the ALPHA-MAN, BESTCILIA and TAIN projects (see below page 22).

EU projects employed more than 4000 people and have had a major impact on the mobility, training and skills development of researchers.

29 clinical trials were launched to test the safety and efficacy of drug candidates for rare diseases, enabling SMEs in particular to introduce new innovations in the development pipeline.

Results provided insights into new methodologies for clinical trials in small populations and health technology assessment strengthening the evidence base for future policy making.

EU-level activities provide high added value, for example in pooling resources, knowledge and expertise, fostering research and cooperation, and granting authorisation of the best-possible medicines – ‘orphan drugs’ – for the whole EU. ERA-NETs have been a driving force in coordinating research on rare diseases at both European and international levels. In E-Rare-3, joint transnational calls have involved funding agencies from 13 EU Member States as well as Canada, Israel, Switzerland and Turkey, and are paving...
European R&I funding is also important for supporting the participation of European research organisations in international collaborations on rare diseases, and enabling the European participants to make use of the international joint resources and knowledge. With the help of the SUPPORT-IRDiRC project, the International Rare Diseases Research Consortium has created the ‘IRDiRC Recognised Resources’ quality label which is a peer-reviewed quality indicator to identify resources (i.e. standards, guidelines, tools and platforms) designed to accelerate the pace of discoveries and their translation into clinical applications for rare disease research. Currently, 13 labels have been awarded for resources dedicated to data sharing, knowledge organisation and ontologies, the networking of patient registries, and therapeutic development.

2. R&I ACHIEVEMENTS

EU-funded projects have brought together isolated cases of rare diseases into a critical mass of patients in databases, registries and biobanks, thereby enabling researchers to reach the statistical power required for addressing ambitious research questions. For example, the DESSCIPHER project could carry out the largest-ever multinational observational trial on systemic sclerosis, involving 4600 patients, while the NEUROSIS project enabled a multi-centre, randomised and controlled blind study of the efficacy and safety of inhaled budesonide in more than 800 pre-term infants. The IMPACTT project succeeded in recruiting more than 160 cystic fibrosis patients for a clinical trial through a network involving nine EU countries.

The results of EU-funded projects bring new knowledge on the epidemiology and pathophysiology of rare diseases, elucidate the natural history of diseases, define relevant clinical outcome measures and biomarkers needed to evaluate therapy response and carry out clinical trials to test new diagnostic and therapeutic approaches, and compare existing treatments for the optimised management of diseases. A total of 29 clinical trials were launched during the projects.

Numerous animal and cellular models were generated in several projects, such as EURENOMICS and NEUROMICS, while the application of ‘-omics’ technologies has enabled disease mechanisms to be explained at both the cellular and molecular level. It has also opened up avenues for the development of new diagnostic tools and therapies, including small molecules, gene and cell therapies, immunotherapies and re-purposed drugs for rare diseases. In addition, a better understanding of the mechanisms of rare diseases has the potential to inform future research on common diseases such as hypertension, diabetes and cancer.

Project results have been published in scientific peer-reviewed journals, including those with high-impact. Together, 61 finished projects report a total of 2138 publications which means an average of 35 publications per project. Open access has been granted to most publications, and 44 patent applications have been reported by these 61 finished projects.

10 Building on two preceding ERA-NETs, the EU-funded ERA-NET project E-RARE-3 aims to further develop and strengthen the coordination of national and regional research programmes. Together with its predecessors, E-RARE-3 has funded close to 100 research projects with the total budget of over EUR 90 million coming mainly from national resources.
3. IMPACTS FOR SOCIETY, HEALTHCARE AND INDUSTRY

Results of EU-funded projects bring concrete benefits for EU citizens in terms of better and optimised treatment options and faster and more accurate diagnostic tools for rare diseases. For example, the FP7-funded ALPHA-MAN project demonstrated the safety and clinical efficacy of an enzyme-replacement therapy for alpha-mannosidosis, which has been submitted to the European Medicines Agency for EU-wide marketing authorisation. The TAIN project developed a new hydrocortisone formulation that can be safely administered to children under six years suffering from adrenal insufficiency. The BESTCILIA project has developed a standardised diagnostic test for primary ciliary dyskinesia which has increased the number of newly diagnosed cases in Cyprus, Greece and Poland by 21.4%, thereby significantly improving the diagnostic rate for this disease.

Many projects have resulted in the release of evidence-based guidelines for the diagnosis and management of rare diseases. For example, CHILD-EU generated a ‘best practice checklist’ for the diagnostics of childhood interstitial lung diseases (chILD) and compiled ‘standard operating procedures’. The EURADRENAL project developed and validated AddiQoL, a quality-of-life instrument for clinical trials. In turn, the RARE-BESTPRACTICES project promotes communication on the clinical management of rare diseases by disseminating trustworthy best practice guidelines. The PatientPartner project emphasised the importance of using patients and patient organisations as a paradigm for improving the quality, quantity and effectiveness of clinical research. Involving patient organisations has the potential to increase the rate of enrolment of trial participants and to have a positive effect on clinical trial performance.

EU-funded projects also result in concrete benefits for healthcare practice. For example, the FP7-funded TECHGENE project developed and implemented high-throughput sequencing techniques for clinical genetic testing of several rare diseases, whilst also addressing the ethical and economic aspects related to testing. The FP7-funded EUROGENTEST2 project focused on harmonising genetic testing and improving the quality of genetic services in Europe. Clinical utility gene cards published by the project provide guidelines for the application of genetic tests in clinical practice for several rare diseases. The project published general guidance documents regarding genetic prenatal diagnostic tests, diagnostic next-generation sequencing and genetic counselling, and contributed to the revision of the international standard (ISO 15189) for quality and competence requirements in medical laboratories and assisted diagnostic laboratories with its implementation. These results help healthcare providers by improving the quality of genetic-testing services and harmonising practices throughout Europe.

Projects funded by FP7 have supported the competitiveness of the healthcare industry by enabling research and innovation-oriented companies to link up with complementary expertise and research resources in academia, hospitals and patient organisations. Through this support, SMEs have been able to bring new potential drugs and diagnostic tools closer to the market (e.g. in the ALPHA-MAN project).

Rare-disease-related EU projects employ more than 4000 people and provide stakeholders with financial support of over EUR 800 million for their R&I activities. This has a major impact on researcher mobility and on training and skills development for rare disease stakeholders. Since 57% of those employed by the projects are women, job opportunities are being created for female researchers and gender equality is being promoted in R&I.
4. IMPACTS FOR POLICIES

Both the above-mentioned Commission Communication and Council Recommendation call on Member States and the Commission to strengthen research into rare diseases, including the development of medicines, and to improve the coordination of community, national and regional programmes for rare disease research. Thus, the support of over EUR 800 million in collaborative research on rare diseases has made a major direct contribution towards the overall EU strategy on these diseases.

EU activities in the field of rare disease research have led to a major concerted effort in the Union and beyond, and have created a momentum to be maintained and integrated to a greater extent within healthcare structures. Research collaborations have provided a seedbed for developing ERNs linking thematic expert centres across the EU and which are set up under the cross-border healthcare Directive (2011/24).

EU-funded research can also bring useful results for regulators. Small, scattered and heterogeneous patient populations constitute a major challenge for clinical trials on rare diseases. It is often not possible to recruit sufficient numbers of rare-disease patients for traditional randomised controlled trials. The FP7-funded projects IDeAI, ASTERIX and InSPiRe on statistical design methodologies for clinical trials for small population groups have provided important input to regulatory science. In addition, in close cooperation with the EUnetHTA Joint Action, the Advance-HTA project’s findings offered policymakers at the EU and Member State level insights into how health technology assessment of medicines (including orphan drugs) and medical devices can be improved.

As explained above, funded projects also include beneficiaries from third countries. EU projects can address specific research challenges of third countries and enable direct dissemination of results and impact beyond the EU/EEA. For example, participation in the key FP7-funded data-sharing project RD-Connect has helped the Western Australian Department of Health to efficiently translate new genomics knowledge into the delivery of clinical services related to genetic testing. This not only shows policy impact in another continent but also indicates the importance of involving policymakers in research projects.
POLICY RECOMMENDATIONS
This section proposes recommendations for addressing the selected current policy challenges based on the results from recent R&I projects funded under European Framework Programmes. Taken together, these recommendations aim to improve the lives of patients suffering from rare diseases. More information on the evidence and concrete results underlying these recommendations can be found on the project websites listed in Annex II of this report.

**FIVE KEY POLICY RECOMMENDATIONS FOR ADDRESSING RARE DISEASES**

- Support integration and networking among EU research, patient and healthcare organisations.

- Adapt implementation of regulatory requirements, especially for clinical trials in rare diseases.

- Support health technology assessment, standards and evidence-base for guiding public health policy.

- Develop legally and ethically robust agreements for collecting and exchanging health and genetic data.

- Collaborate globally to accelerate research on improving the lives of patients with rare diseases through IRDiRC.
1. SUPPORT INTEGRATION AND NETWORKING AMONG EU RESEARCH, PATIENT AND HEALTHCARE ORGANISATIONS

Huge challenges remain in terms of unmet medical needs as most rare diseases lack the means for effective treatments and accurate diagnostics. Therefore, research into rare diseases must remain at the top of the R&I agenda at both European and national levels. EU-funded projects show the value of multi-disciplinary and multinational approaches in bringing together the critical mass required for tackling ambitious R&I challenges.

Following the experience gained from the PatientPartner project and from EU-funded projects that worked to develop new therapies for rare diseases, other research-funding agencies should actively promote the participation of patient representatives in the research projects they fund. Patient participation helps to ensure that research addresses the right questions and incorporates outcomes that are most relevant for patients.

Feedback loops should be created between research and healthcare organisations to ensure optimal use of scarce research and healthcare resources in line with the most important societal needs. It is important to build on established resources such as the EU-funded research networks, ESFRI research infrastructures and the future European Platform for Rare Disease Registration developed by DG JRC in collaboration with DG SANTE, as well as the European Reference Networks established under the cross-border healthcare Directive.

2. ADAPT IMPLEMENTATION OF REGULATORY REQUIREMENTS, ESPECIALLY FOR CLINICAL TRIALS IN RARE DISEASES

Regulatory pathways towards marketing authorisation for orphan medicines should be streamlined, taking into account the specific characteristics of rare diseases and the limitations regarding conducting clinical trials. The European Commission, the EMA and other regulators and stakeholders, including patient organisations, should engage in discussions on the research results and conclusions regarding new statistical designs for clinical trials in small populations. Further research should be considered on strengthening the evidence-base for improving the methodology for clinical trials in rare diseases. Policymakers at EU and Member State level should encourage processes towards harmonising the requirements for clinical trials in EU/EEA Member States and with overseas partners to facilitate international multi-centre clinical trials.

Use of scientific advice and protocol assistance by the EMA should be encouraged to make sure that appropriate tests and studies are performed in the development of orphan drugs as regards the evaluation of marketing-authorisation application. The EMA’s PRIME scheme offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine’s benefits and risks and enable accelerated assessment of medicines applications. FP7-funded FIGHT-HLH project is supporting the clinical development of a drug candidate for the treatment of hemophagocytic lymphohistiocytosis which was granted PRIME designation.

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11 COM(2014) 548 final
12 FP7-funded projects IDeAI, ASTERIX and InSPiRe
3. SUPPORT HEALTH TECHNOLOGY ASSESSMENT, STANDARDS AND EVIDENCE-BASE FOR GUIDING PUBLIC HEALTH POLICY

The use of research evidence to develop public health policy should be promoted by making it easier to access research results and other information on rare diseases. A greater effort should be made to support the development of evidence-based clinical guidelines and measures for overcoming barriers to the uptake of research results, including through demonstration activities and training. Orphanet, the rare diseases information portal, is an excellent platform for the dissemination of rare disease information and research results.

It is also important to support progress towards agreed common standards and standard operating procedures. In addition, support should be provided for their implementation, since these are key to boosting innovation and improving healthcare.

The Advance-HTA project highlighted substantial differences among Member States regarding the HTA process and methodologies, which also affect the way in which orphan drugs are assessed. The project underlined that the EU Orphan Drug Regulation provides for an EU-wide marketing authorisation for medicines, and strengthened EU cooperation on HTA could contribute to improving EU patients’ access to newly authorised orphan drugs.

The process for this is already in place, with the HTA network and EUnetHTA Joint Actions ensuring the strategic and technical aspects of this voluntary cooperation. Finally, the Commission launched a public consultation in October 2016 and is working on an initiative to strengthen EU cooperation on HTA beyond 2020. In this context, it is paramount to create feedback loops between drug development, the regulatory framework, HTA systems, payment and reimbursement schemes and healthcare decision-making, in which patients and patient organisations should play a key role.

4. DEVELOP LEGALLY AND ETHICALLY ROBUST AGREEMENTS FOR COLLECTING AND EXCHANGING HEALTH AND GENETIC DATA

Research data on rare diseases should be collected in standardised formats so that the results obtained from different projects and countries are comparable. Orphanet Rare Disease Ontology (ORDO) and Human Phenotype Ontology (HPO), promoted by several EU-funded projects, provide standards for describing diseases and their related phenotypic characteristics. Research, innovation and health policies should promote the wider use of these standards in both the research and clinical contexts.

Policymakers in charge of research, innovation and health policies also need to collaborate by establishing links with international platforms to improve data sharing and the reuse of big data and research data using the principles of responsible data sharing and governance. These principles include the use of standardised consent forms.

Support should be given to integrated approaches and tools bridging databases in research and healthcare. EU-funded projects provide models for linking data from genomics and other ‘omics’ platforms, patient registries, biobanks, clinical trials and natural history studies – breaking down existing data silos. Pan-European research infrastructures, such as BBMRI,

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14 The success of EUROGENTEST2 indicates that agreed standards and ways of working are a key ingredient and boost for innovation. IRDiRC is another good example of developing standards that promote innovation.
16 RD-Connect project established a platform which is available internationally for linking ‘omics’ data, clinical data, patient registries and research data contributions, following the principles for responsible sharing and governance of research data.
ELIXIR, ECRIN and EATRIS, as well as the future European Platform for Rare Disease Registries, should play key roles in these processes. New data sources, such as patient-reported outcomes, should also be considered.

In the context of the General Data Protection Regulation\textsuperscript{17}, support should be given to developing legally and ethically robust agreements, including codes of conduct for exchanging health and genetic data.

5. **COLLABORATE GLOBALLY THROUGH IRDiRC TO ACCELERATE RESEARCH ON IMPROVING THE LIVES OF PATIENTS WITH RARE DISEASES**

The international ‘overseas’ dimension of research networks should be actively promoted at the EU and Member State level. IRDiRC\textsuperscript{18} provides a suitable channel and has indisputably helped to accelerate research, as indicated by the increased rate of new marketing authorisations for orphan medicines granted by US and EU regulators since 2011. Researchers should be encouraged to adopt internationally recognised standards, guidelines, tools and platforms (IRDiRC-recognised resources) and to introduce them in discussions with funding organisations for potentially wider dissemination.

The European Commission should continue its active involvement in IRDiRC and raise the level of organisational commitment to demonstrate leadership at a level in line with the level of investment in rare diseases. National and regional funding agencies, as well as private foundations and organisations investing in rare diseases, should be encouraged to join IRDiRC.

Research-funding agencies should promote IRDiRC policies and guidelines regarding data sharing, disease and phenotype ontologies, interoperability and the involvement of patient organisations in research.

Further support should be given to global information databases on rare diseases, such as Orphanet, as well as to the development and implementation of common disease and phenotype ontologies and codification, and to exchanging best practice and experiences on the organisation of research and healthcare.

\textsuperscript{17} Regulation (EU) 2016/679
\textsuperscript{18} SUPPORT-IRDiRC: www.irdirc.org
ANNEXES
ANNEX I  RECOMMENDATIONS FOR FUTURE R&I PROGRAMMING

This annex provides recommendations for addressing the policy challenges concerning rare diseases through future R&I programme funding activities. The recommendations are targeted at those developing the work programmes for Horizon 2020 and the follow-up EU Framework Programme.

To respond to the challenges identified in this report, the results of rare disease research and innovation should be delivered more efficiently to patients in terms of new and optimised treatments, diagnostic tools and integrated care, making sure they receive the maximum benefit from the research and investments carried out at the EU and Member State levels. This should be supported when developing the work programme by highlighting the expectations for effective dissemination and exploitation of research results as key tasks for the funded projects.

The EU Framework Programmes for Research and Innovation should provide the tools to support further integration and networking of the various actors in the field. The European Commission and Member States should explore the possibility of launching a joint initiative on rare disease research designed to bring together a wide range of stakeholders in the field to ensure the rapid translation of research results into clinical applications and uptake in healthcare.

A broad range of research questions should continue to be addressed, including: further explanation of pathomechanisms and molecular pathways in rare diseases; development of new diagnostic means; natural history studies; preclinical research for new therapies; clinical trials for new and/or repurposed therapies, including advanced therapies; discovery and validation of biomarkers; socio-economic- and healthcare-oriented studies, including burden of illness studies; and health services research to improve patient outcomes and healthcare systems, and to develop evidence-based clinical, public health and healthcare system guidelines. Research should harness developments across all relevant domains, including ‘-omics’, information technology, machine learning and artificial intelligence, etc.

Research on regulatory science should continue to provide evidence, for example, for new methodologies for clinical trials in small populations.

Measures that enhance uptake of research results should be promoted, including supporting the implementation of new technologies in healthcare (e.g. next-generation sequencing in diagnostics) and promoting the involvement of health policymakers in strategically steering the programme. An efficient technology-transfer facility should be included to ensure that industry, including SMEs, can introduce exploitable results into R&I pipelines.

The proposed joint initiative should foster the development and implementation of common standards and mechanisms for collecting and sharing health data on rare diseases. This could be achieved by supporting a virtual platform for rare disease information, research data, samples, tools and standards building on the existing resources, including pan-European research infrastructures and linking to the European Open Science Cloud.

Capacity-building activities should include training and support activities focusing on research data management, product development, HTA, translational research, and defining and sharing best practice guidelines involving large groups of stakeholders, including patient organisations, to ensure that innovation is accessible equally across the EU.
ANNEX II  LIST OF PROJECTS MENTIONED

Information on projects, and links to their websites can be obtained by entering the project number in the CORDIS project search at: http://cordis.europa.eu/projects/home_en.html

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Full list of projects included in the selected project portfolio analysed in this report can be downloaded at: http://ec.europa.eu/research/p4p
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Research and innovation results generated by EU Framework Programmes play a key role in addressing societal challenges, strengthening sustainable growth and creating new jobs. They can also provide solid evidence and the latest knowledge to inform and improve policymaking. ‘Research and Innovation Projects for Policy’ is a series of reports exploring this opportunity and putting it into practice. Each report focuses on selected issues and challenges in a topical policy area, highlighting the corresponding pertinent results from Framework Programmes and concluding with concrete recommendations for policy actions in Europe and internationally.

*Research and Innovation policy*