



**INTERNATIONAL  
RARE DISEASES RESEARCH  
CONSORTIUM**

**POLICIES & GUIDELINES**

Long version

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**IRDIRC**

# International Rare Diseases Research Consortium

## Policies & Guidelines

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## A. INTRODUCTION

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Unlike common diseases, a rare disease **affects a relatively small number of persons**. A disease is considered rare when it does not affect more than one person in 1500 to 2500<sup>1</sup>. This **low prevalence** is the common feature shared by all rare diseases (RD), which altogether affect all biological systems, ranging for instance from nervous system diseases through vascular diseases to muscular, immunologic or metabolic disorders. It is estimated that **there are some 6,000 to 7,000 different RD**, together resulting in millions of patients affected with rare diseases worldwide. Most RD are of **genetic origin**, and are usually **life-threatening or chronically debilitating**. The severity of these diseases generally impacts heavily on the quality of life of affected patients, as well as of their family members.

Patients affected with a particular RD in any one country are scarce, as also are relevant specialized clinicians. The causes and natural history of RD are very often poorly understood. The rarity of patients and the high phenotypic heterogeneity of RD, combined with the lack of knowledge, information and training about these diseases result in frequent delays in correct diagnosis (see for example EurordisCare study<sup>2</sup>). In addition, for a significant number of RD a validated diagnostic test does not exist.

Orphan drugs (intended to treat RD) generally lead to a lower commercial return compared to treatments targeting more common diseases, due to the lower number of patients. Therefore, under normal market conditions, the pharmaceutical industry showed limited interest in developing new orphan drugs. To change these market conditions and to provide a better return on investment, several countries have adopted various pieces of legislation that provide incentives for the development of orphan drugs<sup>3</sup>. Nevertheless, to date, a very limited number of orphan drugs are marketed, **leaving a large majority of rare diseases without any effective treatment**. Even in the absence of a specific orphan drug, identifying best clinical/care practice amongst various existing approaches would highly benefit the patients. Delayed diagnosis and absence of specific treatment and standards of care often place a heavy burden not only on patients and families, but also on health care systems. Appropriate clinical management of rare disease patients would therefore have a positive impact for health care systems.

Increasing the number of therapeutic and care options for RD patients requires a better knowledge of pathophysiology and natural history of the RD, to help identify potential therapeutic targets, validate biomarkers and define appropriate surrogate end-points to adequately evaluate treatments and therapies. In order to translate research results into marketable orphan drugs, it is important that meaningful, validated data are collected and

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<sup>1</sup> In the EU a rare disease is defined as affecting not more than 5 in 10,000 people; in USA less than 200,000 people in the national population; in Japan less than 50,000 people in the national population.

<sup>2</sup> <http://archive.eurordis.org/IMG/pdf/eurordiscare1-part1.pdf>;  
[http://www.eurordis.org/sites/default/files/publications/Fact\\_Sheet\\_Eurordiscare2.pdf](http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf)

<sup>3</sup> Regulation (EC) N° 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products; USA Public Law 97-414 “Orphan Drug Act” (1983)

shared internationally. Furthermore, it is essential to strengthen the links between academia and industry, so that industry better capitalizes on strong academic research results to translate these into new diagnostic tools and therapies. Patients have an important role in this process.

In contrast with more common diseases, which are generally multifactorial in their causes, rare diseases often result from a dysfunction of a single pathway (like a defective gene or protein). Understanding the impact of a single defect can often yield insights into the more complex pathways involved in common diseases. In other words, research on rare diseases will help dissecting the more complex pathways underlying common diseases. Strategies for the treatment of RD, with restricted patient populations, are also relevant to those envisioned for personalized medicine, in that they require personalized and timely diagnostics to identify the specific RD affecting the patient, as well as timely, effective, and safe personalized treatment and care. Investigating the pathophysiology and developing specific therapies for RD require new, innovative approaches, which can subsequently be applied to other diseases.

For rare disease research, coordination of efforts is key to success, in order to maximize the output from investments in research funding. International sharing of information, data and samples is currently hampered by the absence of an exhaustive RD classification, standard terms of reference and common ontologies, as well as by a lack of harmonized regulatory requirements. Better sharing of resources would reduce redundancy in research efforts, and would enable the creation of better links between teams working on similar issues.

The International Rare Diseases Research Consortium will streamline access to relevant information, harmonized data and samples, and affected patients. It will stimulate and coordinate basic and clinical research, by promoting links between existing resources, fostering the molecular and clinical characterization of RD and encouraging translational, preclinical and clinical research. Priorities for such an international endeavor are the elaboration of standard terminologies and common ontologies with a view to an adequate classification of diseases, the development of predictive, validated *in vitro* and *in vivo* animal models, the identification and validation of biomarkers and surrogate end-points, and the development of new diagnostics and therapies.

## B. ESTABLISHING THE CONSORTIUM

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Maximizing scarce resources and coordinating research efforts are key to success in the rare diseases field. Therefore the European Commission's Health Research Directorate and the US National Institutes of Health took the first steps to establish an international consortium to ensure that synergies and complementarities of rare disease research at an international level can be achieved.

Following their first workshop in Reykjavik, Iceland in October 2010 where the initiative was shaped and the goals to deliver, by 2020, **200 new therapies for rare diseases and means to diagnose most rare diseases** were set, the International Rare Diseases Research Consortium has, and continues to gain strength. As of early 2013 there are over 30 members, and new members are joining the consortium at a steady pace. The three IRDiRC Scientific Committees (Diagnostics, Interdisciplinary and Therapies) have been established and 12 working groups were formed.

The latest information concerning the state of play for IRDiRC can be found at the following website: <http://www.irdirc.org/>

## C. CONSORTIUM GOALS

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### *Overarching objectives: developing by 2020*

**1) 200 new therapies for rare diseases (orphan drugs).** The consortium will develop all the necessary measures and policies to facilitate the development of new therapies for rare diseases, such as:

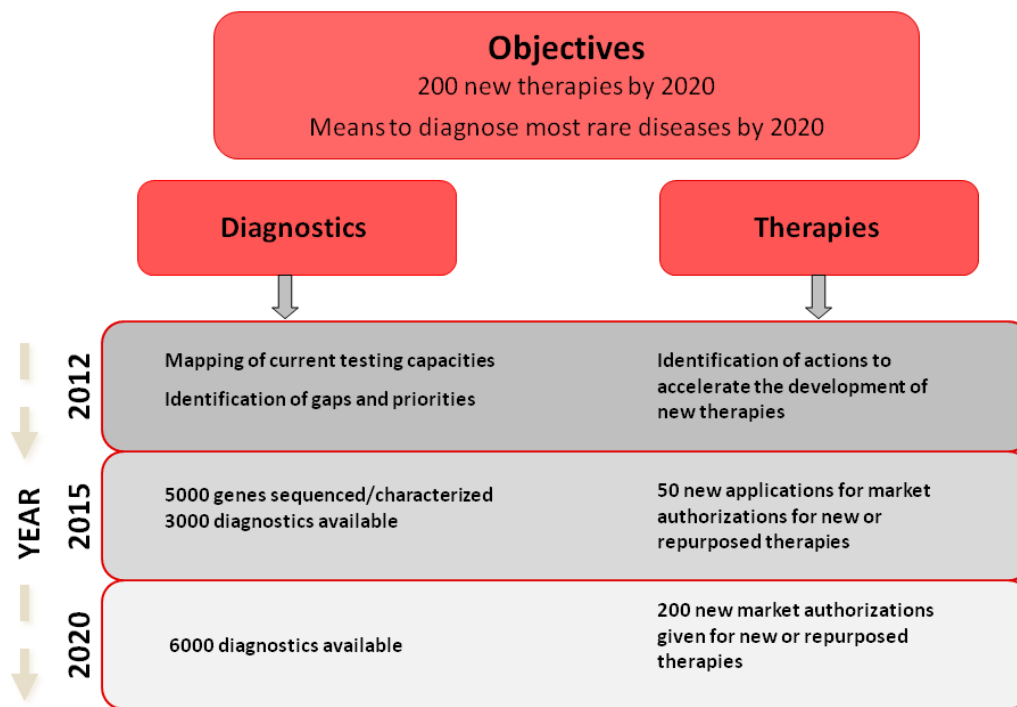
- ▶ coordinate and network patient registries: common standard operating procedures; harmonized ethical approaches, access to patient data and samples.
- ▶ enhance clinical trials: identify and validate biomarkers and surrogate end-points, repurposing drugs, novel compounds.
- ▶ improve the regulatory framework to facilitate the development of novel therapies (involvement of EC, EMA, FDA and patient associations is essential).

**2) Means to diagnose most rare diseases.** Avenues that will be exploited include:

- ▶ the use of "omics" and other approaches to identify biomarkers of rare diseases (e.g. coordination of genome sequencing of patients with rare and non classified syndromes).
- ▶ in conjunction with industry stimulate the development of efficient, multi-purpose diagnostic tests for rare diseases.

To support those goals, and streamline processes beyond 2020, the consortium will also strengthen international cooperation in a number of enabling areas. The consortium will:

- a. support top basic research for better understanding the **pathophysiology** of rare diseases, including the support to the development of **models** and resources to catalyse research in rare diseases.
- b. support the development and use of adequate disease **classification** (adequate definition, codification and inventorying of rare diseases), common **ontologies**, and determination of the **natural history** of diseases.
- c. **make data accessible** to the entire research community as rapidly as possible, and with minimal restrictions. The consortium will work towards establishing **common bioinformatics tools and standards** that will ease networking between data centres.
- d. set up an **efficient structure that will coordinate this international effort** so that the interests and priorities of individual participants, self-organizing consortia, funding agencies and nations are addressed.
- e. The consortium will **encourage the minimization of redundancy** between the different projects around the world.
- f. establish a **strong dissemination and communication plan** to all potential stakeholders and in particular to patients and general medical practitioners.



### Foreseen deliverables by 2020

- ▶ **200 new therapies for rare diseases**
- ▶ **Diagnostic means for most rare diseases**
- ▶ Mapping of rare diseases research and funding
- ▶ Better classification of rare diseases
- ▶ Networking (worldwide) of patient registries
- ▶ Commonly accepted Standard Operating Procedures (SOPs) and ontologies
- ▶ Better follow up and standard of care of patients
- ▶ Common web platform: communication to stakeholders

## D. CONSORTIUM POLICIES AND GUIDELINES

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### Objectives of a consortium policy and guidelines document

A **consortium policy** is a principle which consortium members agree to follow. Although policies will likely be long-lasting, the IRDiRC will periodically review its policies.

**Consortium guidelines** refer to recommendations made by IRDiRC scientific committees/working groups that offer advice as to “best practices” at a given time. Considering the rapid evolution in technologies and new knowledge gained guidelines are likely to evolve in the coming years.

It is also expected that approaches will need to vary based on disease type, local laws, or other factors. In such cases, comparisons and clarifications of different approaches, relative to IRDiRC guidelines should be presented.

The IRDiRC Scientific Committees will be the “guardians” of updating this policy document, and propose changes to the Executive Committee for adoption. The Scientific Committees will work closely with the working groups to ensure that policies and guidelines are relevant and implemented.

The IRDiRC policies and guidelines document should be communicated widely, and contain sufficient information to allow funding bodies and scientists in many countries to make decisions on future participation.

### Generalized Principles

The overarching goals of IRDiRC are to diagnose most RD and to develop 200 new RD treatments by 2020. Much RD research is currently fragmented and compartmentalized. This leads to lack of integration, duplication of efforts, lack of critical mass, thinking in “silos” and waste of resources, hindering progress towards better diagnosis and therapy for RD patients. Current regulatory and ethical systems can also be a barrier to collaboration, further increasing the disadvantage and vulnerability of RD patients. There are particular difficulties in clinical trials for RD, involving small patient numbers and a frequent lack of well defined outcomes. Most RD are inherited and chronic, leading to long-term disabilities. They can be difficult to diagnose, often lack an effective treatment, and usually require specialist care and access to expert centers. However, while RD are seen as very diverse and different from one another, commonalities between different RD exist that can be utilized and exploited, and this is best achieved through collaborative approaches. For example, many RD share common pathogenic pathways, so coordinated research can help better understand their pathogenesis and identify therapeutic targets. Model systems such as animals and cell lines can be used to elucidate mechanisms of disease and test new therapies in a manner common to many RD. Strategies based on molecular biology such as gene therapy or exon-skipping technology are therapeutic



approaches that are generalizable to groups of RD. Thus, there is an urgent need for better integration of RD research, in particular with a view to sharing approaches that will enhance the development of better diagnoses and therapies. Integration and increased collaboration through IRDiRC will accelerate these developments, avoid wasting money and other resources and provide efficiency gains. This integration mandates a quantum change in mindset and the direct involvement of all relevant stakeholders (scientists, doctors, patients, industry, regulators). Therefore, it is essential to recognize and address the needs and concerns of all stakeholders and ensure their commitment. The key outcome is improved health (through better diagnoses and therapies) for people living with RD worldwide.

#### **Policies:**

- ▶ **Policy 1:** RD research should be collaborative. Resources, data and results should be shared among IRDiRC research projects and made publicly available to the broader community, and duplication should be avoided.
- ▶ **Policy 2:** RD research should involve patients and/or their representatives in all relevant aspects of the research.
- ▶ **Policy 3:** International, national, regional and local legislation/regulations need to be adhered to with respect to data protection and ethical approvals.

#### **Guidelines:**

- ▶ **Guideline 1:** The impact of research on people living with a RD should be a key consideration for each project. Best ethical practices for ensuring the interest of the individuals living with RD should be applied.
- ▶ **Guideline 2:** Information about IRDiRC and associated research projects should be disseminated and made available to the RD communities and the public.
- ▶ **Guideline 3:** Education, training and awareness of stakeholders should be encouraged by IRDiRC.

## **Data Sharing and Standards**

To achieve the stated goals of IRDiRC, many types of resources and data will be generated and shared; this will facilitate discovery of genes and treatments while ensuring efficient utilization of resources. Resources may include, but are not limited to, patient and family material (extracted DNA, cell lines, pathological samples), technical protocols, informatics infrastructure, and analysis tools. Datasets may include, but are not limited to, phenotypes, genomic variants, other 'omic' data (including transcriptomic, metabolomic, biomarkers), natural histories, and clinical trial data. Ultimately, it is critical to the overall success of IRDiRC that datasets obtained from one project will be directly comparable to datasets obtained from another project (even if generated using a different approach or technology).

Please note that several Policies and Guidelines under General Principles are directly relevant to Data Sharing and Standards and are therefore not restated here.

### **Policies:**

- ▶ **Policy 4:** Research projects should adhere to standards endorsed by IRDiRC.
- ▶ **Policy 5:** Data producers acknowledge their responsibilities to release data rapidly and to publish initial analyses in a timely manner. IRDiRC members will encourage and facilitate rapid data release.

### **Guidelines:**

- ▶ **Guideline 4:** Data generated from research projects, including source data, should be deposited in appropriate open or controlled access public databases.

## **Ontologies**

Ontologies are structured, automated representations of knowledge and provide computer-readable classifications of the entities within a domain and their relationships to one another. They are increasingly being used to define a standard, controlled vocabulary for different fields in science and medicine and they can be utilized for data integration, organization, searching, and analysis. To be successful, an ontology must be widely used, and an ontology is only as valuable as the data that is annotated to it. Multiple ontologies are required to describe all relevant aspects of the field of RD. Two of the most important kinds of ontologies for RD clinical medicine and research are ontologies of phenotypic features (signs, symptoms, and findings of diseases), and ontologies of diseases and disease groups (nosologies). Additional ontologies and standards are required for other areas in RD research, including standards for mutation nomenclature and reporting of diagnostic results, ontologies and standards to support biobanking, clinical trials, natural history, as well as for RD medications and treatments. It is important that ontologies be interoperable; this is best achieved if there is minimal overlap in the concepts covered by the ontologies (orthogonality) and if the ontologies are semantically compatible with one another. To achieve broad use, the developers and managers of RD ontologies must be responsive to the community, and must strive to reflect community needs and norms.

Many of the key problems in clinical RD medicine and research require structured detailed clinical description, intelligent searching and integrative analysis of data from multiple sources for a definitive diagnosis. The process of information retrieval and analysis could be greatly accelerated if different databases used a single set of standards (ontologies, database schemes, network protocols) for collecting, storing, annotating and communicating data. This would have a multiplier effect on improving research and patient care not only in diagnostics but also in networking and harmonizing patient registries, biobanks, and other RD database initiatives.

### **Policies:**

- ▶ **Policy 6:** IRDiRC members will promote the harmonization, interoperability and open access of ontologies to be applied to databases, registries, and biobanks.

### Guidelines:

- ▶ **Guideline 5:** Ontologies utilized by RD research projects should build upon existing best practice and allow integration and interoperability across different ontologies, including those for model organisms. Ontologies should include a RD classification ontology (nosology), a phenotype ontology with comprehensive coverage of RD manifestations including laboratory values and imaging, as well as ontologies to support biobanking, clinical trials, and research.

## Diagnosics

An accurate molecular diagnosis is essential for informed patient management and family counseling, as well as for RD research including natural history studies, biomarker identification and clinical trials. There are approximately 7000 RD and the relevant gene is known (as of early 2013) for approximately half of these, thus around 3500 are without a defined molecular pathogenesis. In addition, a significant fraction of RD patients that have a defined molecular pathogenesis nonetheless lack a molecular diagnosis due to issues related to accessibility of diagnostic testing.

For diagnostic testing to be available for the majority of rare diseases by the year 2020, IRDiRC must focus on the discovery of the genes for the 3500 phenotypes that are currently without an associated disease gene. To further enable the diagnostic goal of IRDiRC we must revolutionize the ability to interpret genomic variation. A genotype-phenotype database that collects and curates information on all variants causing specific human disease phenotypes is essential to the provision of accurate and reliable diagnostics for RD. International efforts to establish guidelines for the clinical reporting of genomic sequencing in a clinical setting, including the approach to incidental findings, will expedite the delivery of high-throughput and cost-effective testing to the RD patient community as a whole.

Please note that several Policies and Guidelines under General Principles and Data Sharing and Standards are directly relevant to Diagnostics and are therefore not restated here.

### Policies:

- ▶ **Policy 7:** IRDiRC members should promote the discovery of all the genes that underlie RD and facilitate the development of diagnostic testing for most RD.
- ▶ **Policy 8:** Research projects should contribute to the development and evolution of standards for RD diagnostic testing and reporting.

### Guidelines:

- ▶ **Guideline 6:** Research projects should cooperate with efforts to produce a well-curated and interoperable inventory of RD.

## Biomarkers

A biomarker is a measurable biological characteristic that is an indicator of normal biological and pathogenic processes and/or response to therapeutic or other interventions. Biomarkers are central to the future of medicine. They can be used to monitor the effects of medical interventions including therapeutic responses in diagnostic and prognostic tests, and can contribute to better defining the target population most likely to respond to a particular therapy. They are usually linked to changes in particular aspects of a complex biological system. However, it should be emphasized that using biomarkers in biomedical research has several limitations as they may or may not be correlated with clinical outcomes. The work needed to understand the relationship of biomarker changes to either a clinical outcome or other aspects of a biological system is often substantial.

It has been suggested that the use of appropriate biomarkers can reduce the overall cost of developing new innovative treatments including therapies for orphan diseases. Moreover, biomarkers may also enhance the efficacy and safety of new treatments and provide a more rational pathway to facilitate advances in RD preclinical and clinical therapeutic development. Therefore, early dialogue with regulatory authorities is essential and will facilitate successful biomarker qualification and regulation in order to translate exploratory biomarkers in clinical practice into shorter times for product development, clinical trials and regulatory review.

Please note that several Policies and Guidelines under General Principles and Data Sharing and Standards are directly relevant to Biomarkers and are therefore not restated here.

### Policies:

- ▶ **Policy 9:** Research projects should establish criteria and standards for evaluation, qualification and validation of biomarkers.

### Guidelines:

- ▶ **Guideline 7:** The use of biomarkers in RD therapeutic development should be discussed and agreed with regulatory authorities through established procedures.

## Patient Registries

Patient registries are organized databases where patient information, including demographic, medical and family history information are collected, stored and available for retrieval via standardized and secure methods. Patient registries are increasingly recognized as crucial tools for RD research. For most RD, no single institution, and in many cases no single country, has sufficient numbers of patients and resources to conduct clinical and translational research. Identifying patients with specific genotypes and phenotypes is a major constraint to patient recruitment into research and clinical trials. Therefore, international collaboration is absolutely

essential to ascertain pathogenicity of rare genotypes, achieve a unified collection of RD phenotypic data, foster natural history studies, facilitate studies to identify appropriate clinical endpoints or biomarkers, identify participants for research and clinical trials, and support the safety and efficacy evaluation of potential therapies. Patient registries are often used as part of regulatory decisions and post-marketing surveillance requirements. In addition, they may play an important role in providing health care to RD patients in the context of reference and specialist networks.

While patient registries are considered important tools for RD research, there remains a clear need for their standardization, coordination and further development. In particular, patient registries must overcome the following challenges to develop their full potential in RD research: a) lack of harmonization due to the high variability among registries according to RD coding systems, geographical coverage and type of data collected; b) lack of data sharing since only a minority share data with other databases, biobanks or centers of expertise; c) lack of sustainability since RD patient registries often expire due to lack of commitment from data providers, lack of funding, or study termination, leading to loss of data and loss of investment; and, d) lack of utility for research owing to absence of quality control, standardized data elements, and genetic data.

Please note that several Policies and Guidelines under General Principles and Data Sharing and Standards are directly relevant to Patient Registries and are therefore not restated here.

#### **Policies:**

- ▶ **Policy 10:** RD patient registries should aim to be global in geographic scope and practice. Interoperability and harmonization between RD patient registries should be consistently pursued. Linking and data transfer into existing platforms should be considered “best practice”. Registries should be broad and not focused exclusively around a single therapeutic intervention or product.

#### **Guidelines:**

- ▶ **Guideline 8:** RD patient registries should be linked with data and biological specimens in biobanks, natural history studies and clinical trials and should include measures of quality control and updating.
- ▶ **Guideline 9:** Patients and/or their representatives should be involved in the governance of RD registries.

## **Biobanks**

Biobanks are collections of biomaterials with associated data. Biobanking is an essential tool to provide access to high quality human biomaterial and data for fundamental and translational research. RD research benefits from the provision of human biomaterials through biobanks, and each human sample from a person with a RD has a high value as it may hold the key to answering an important research question. The rarity and diversity of RD and their associated

biomaterials present specific challenges and opportunities for biobanking, requiring transnational collaboration and harmonization. Legacy samples, small collections, or even individual samples may be extremely precious for RD research. Such samples include primary cells, tissue, DNA, RNA, serum, urine, CSF, human induced pluripotent stem cell (hiPSC) lines, and others. Collection, storage and dissemination of biomaterials often requires specialist input and appropriate quality standards. RD biobanks rely on the active participation of patients and patient organizations. Providing and managing information and access to valuable biological samples through a simple and reliable process is crucial for RD research. It underpins the development of new diagnostic techniques, biomarker development, identification of potential therapeutic targets and testing therapeutic response.

Biobanks are important tools for RD research. There remains a clear need for policy interoperability, standardization, coordination and further development of RD biobanks. Biobanks need to overcome the following challenges to develop their full potential in RD research: a) lack of policy and IT harmonization; b) lack of biomaterial and data sharing; c) lack of sustainability; and, d) lack of utility for research.

Please note that several Policies and Guidelines under General Principles and Data Sharing and Standards are directly relevant to Biobanks and are therefore not restated here.

#### **Policies:**

- ▶ **Policy 11:** RD biobanks should aim to be global in geographic scope and practice. Interoperability and harmonization between RD biobanks should be consistently pursued. Linking and data transfer into existing platforms should be considered “best practice”. Sharing and distributing of biomaterials among RD biobanks is highly encouraged.

#### **Guidelines:**

- ▶ **Guideline 10:** RD biobanks are essential resources and should be sustainable. RD research studies should utilize biobanks for processing and storage of biomaterials and should include methods of quality control and updating.
- ▶ **Guideline 11:** Patients and/or their representatives should be involved in the governance of RD biobanks.

## **Natural History**

Understanding the natural history and evolution of a disease is an essential step not only in drug development but also in better understanding of patients’ needs and in improving care. The pathogenesis, clinical manifestations, natural evolution and prognosis of many RD are still poorly or incompletely understood. Performing natural history studies will facilitate the identification of disease characteristics that can be used when planning and conducting clinical investigations for RD therapies. Moreover, this knowledge will also serve to define a trial’s target population, develop biomarkers for disease progression and therapeutic response,

determine appropriate surrogate and relevant clinical endpoints and decide on the study duration.

Ideally, natural history studies should be global in scope and can involve patients at any age although it is recommended to include younger patients. The data for a natural history study can be collected in a prospective or retrospective manner. However, prospectively well-designed natural history studies with a proper follow-up period of observation yield more robust data, especially when disease-care measures that can modify the disease course are taken into consideration. These measures include clinical care and treatment recommendations together with screening, genetic counseling, modification of environmental exposure and prognostic factors.

It is well recognized that RD are highly diverse in nature and that there is no one set of data elements that can be recommended for data collection in all natural history RD studies; rather the disease characteristics should reflect the prominent features of the RD.

Please note that several Policies and Guidelines under General Principles and Data Sharing and Standards are directly relevant to Natural History and are therefore not restated here.

#### **Policies:**

- ▶ **Policy 12:** Research projects should contribute to the development and evolution of a set of standards for RD natural history studies. The outcomes of natural history studies should be considered in the design of clinical research.

#### **Guidelines:**

- ▶ **Guideline 12:** Patients and/or their representatives should be involved in defining the objectives, the design, the outreach, and the analysis of clinical research and natural history studies.

## **Therapeutics**

Clinical trials on rare diseases represent a major challenge for the development of rare disease therapies intended to treat, cure, prevent or diagnose patients affected by a RD. It is well known that clinical investigation in this field is associated with several hurdles that may jeopardize the performance of these investigations, when compared with common diseases. Small patient populations, together with geographical dispersion, add additional complexity to the design and performance of trials aimed at providing efficacy and safety information supporting a marketing authorization/approval of these therapies. Delays in obtaining proper genetic and clinical diagnoses still exist for many RD. In addition, there is still a lack of adequate epidemiological and medical knowledge on the natural history of many RD. Combined efforts are required of investigators, industry, patients' representatives, research institutions, and regulatory authorities to overcome all bottlenecks associated with biomedical research in low-prevalence conditions. Orphan designation procedures have brought a large number of investigational products into the development pipeline. Incentives associated with orphan

designation also play a major role in stimulating orphan product research and can be beneficial to industry-sponsored and investigator-driven clinical research. Of the incentives provided by orphan designations, protocol assistance and scientific advice from regulatory bodies plays a key role in guiding the conduct of studies to address the benefit/risk analysis for marketing authorization and approval.

The design and specific methodological aspects of a study need to be carefully discussed with all relevant partners. Centers of expertise specialized in RD should play a major role in fostering clinical research networks and infrastructures and in disseminating and sharing study outcomes. Training of investigators and patients' representatives will ensure a better understanding of regulatory, methodological and ethical requirements. Equally, adequate support should be given to existing infrastructures for clinical research, which take into account the intrinsic characteristics of rarity and may develop common and harmonized practices to submit, monitor and report multicentre and multinational rare disease clinical trials.

Please note that several Policies and Guidelines under Publications and Intellectual Property are directly relevant to Therapeutics and are therefore not restated here.

#### **Policies:**

- ▶ **Policy 13:** IRDiRC members will encourage the development of therapies that could be approved by 2020, while respecting each funding entity's strategic research agenda (including products with an existing orphan designation, the repurposing of already marketed drugs, or funding preclinical orphan development intended to substantiate proof-of-concept).

#### **Guidelines:**

- ▶ **Guideline 13:** Clinical investigations supported by IRDiRC funders should meet requirements set by regulatory agencies.
- ▶ **Guideline 14:** Adequate scientific and regulatory information about clinical research should be exchanged by researchers.
- ▶ **Guideline 15:** IRDiRC members should promote collaborative multinational studies, with common study procedures and harmonized policies for regulatory and ethical requirements.

## **Models**

Cellular models provide insight into the function of genes and the mechanisms underlying rare diseases. Experimental organisms such as yeast, *C. elegans*, fruit flies, zebrafish, and mice have long been critical for uncovering the molecular mechanisms fundamental to life, thereby providing a shortcut to understanding human biology.

Currently, we only understand the biological function of a fraction of human genes. Cellular systems and model organisms can be manipulated experimentally much more readily than humans for both ethical and technical reasons, allowing important questions that cannot be



addressed in patients to be addressed. Model organisms enable experimental interventions that can establish causal mechanisms of gene action, thereby putting disease genes into biological context. The generation of analogous mutations in a model organism or the substitution of a wild-type version of the gene with the human variant can provide a clear indication that the suspected variant is indeed causative for disease. The deep pathological insight that model organisms can yield facilitates the development of targeted therapeutics. Lastly, studies of therapeutic interventions require model systems to demonstrate efficacy and identify potentially harmful effects.

Please note that several Policies and Guidelines under General Principles, Data Sharing and Standards and Ontologies are directly relevant to Models and are therefore not restated here.

#### **Policies:**

- ▶ **Policy 14:** IRDiRC members should promote coordination between human and model systems research in RD.

#### **Guidelines:**

- ▶ **Guideline 16:** Prior to proceeding to clinical trials, experimentation providing multiple lines of evidence should be robust, reproducible and sufficiently powered.

## **Publication and Intellectual Property**

IRDiRC research results should be rapidly shared and made highly visible to the scientific, health care, patient and pharmaceutical communities. Their utility must be clearly demonstrated and potential users must have the opportunity to receive training in the techniques and tools developed. This includes negative results, which can be as important for the RD field as are new scientific breakthroughs (in relation to data sharing policies and guidelines). A high level of visibility in scientific meetings and through scientific publications is mandated. The scientific impact of IRDiRC research projects should be maximized by pursuing opportunities for publication. Online publication of research results after peer review will be pursued in full respect of international copyright law. Where the most suitable journal for the results offers the possibility of paying a publication fee to ensure free access to all, this option will be strongly encouraged. Some IRDiRC members already mandate open-access publication for all projects they fund, and some cover open-access fees where required. In addition, journals might allow the author to post an electronic copy of the publication on their website. Publications in lay journals may be prepared in order to attract maximum attention to rare diseases.

Intellectual Property (IP) is an important factor for the public and the private sector, in particular to cover the significant cost of developing new therapies. Issues related to IP rights need to be assessed and handled in accordance with fundamental ethical rules and principles. Tools to handle IP issues may include exploitation and technological implementation plans, non-exclusive licensing, patenting, knowledge property rights and pre-existing know-how. In many instances, confidentiality agreements may be required between the parties involved.

### **Policies:**

- ▶ **Policy 15:** Research projects should publish their results in a timely manner in peer-reviewed scientific journals, preferably with open access.

### **Guidelines:**

- ▶ **Guideline 17:** Research publications should appropriately acknowledge research funding and the use of infrastructures such as biobanks and registries, as well as the contribution of patients and their representatives.
- ▶ **Guideline 18:** IP issues and confidentiality agreements need to be balanced with the need to share information for the benefit of research and the patient community.
- ▶ **Guideline 19:** RD research should be published even where its outcomes are negative or do not show convincing results, including clinical trials<sup>4</sup>.

## **Communication on IRDiRC**

Through its research projects, IRDiRC will generate new knowledge, tools and resources and stimulate debate. Its outputs require high visibility to a range of stakeholders and a clear strategy to train and educate a next generation of scientists and other users. Target groups include the global scientific community both within and outside the RD field, professionals involved in healthcare including diagnostics and the delivery of new therapies, policymakers involved in health care planning at national and international levels, the pharmaceutical industry, and the RD patient communities. In addition, there is a strong imperative to raise awareness of this area with the general public and increase its profile in the media. The goals of an external dissemination strategy are to promote international academic and industrial cross-fertilization, both within and outside IRDiRC, and to provide information on IRDiRC research to other research projects, the scientific community, industrial groups, government bodies, policymakers and the general public, including patients. IRDiRC communication will be built on the principles of openness, public accessibility, transparency, inclusivity and timeliness. IRDiRC will communicate through various means, in particular through electronic communications and the internet as well as paper-based versions.

### **Policies:**

- ▶ **Policy 16:** IRDiRC members will disseminate relevant information on their research project portfolio through adequate and timely measures, in particular the IRDiRC website.

### **Guidelines:**

- ▶ **Guideline 20:** IRDiRC shall publish its mission statement, list of member organizations and list of associated projects. IRDiRC shall publish non-confidential proceedings, as well

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<sup>4</sup> Journals publishing negative findings : Orphanet Journal of Rare Diseases, PLoS ONE, Journal of Negative Results in Biomedicine, All Results Journal, Negative Observations in Genetic Oncology, etc.

as the minutes and approved documents of its Executive Committee, the Scientific Committees and the Working Groups.

- ▶ **Guideline 21:** IRDiRC associated projects and IRDiRC member organizations should make reference to IRDiRC, where appropriate, on organizational websites, information material and presentations.
- ▶ **Guideline 22:** IRDiRC will promote active exchanges, events and activities between stakeholders, including patient organizations.



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