



**INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM**

POLICIES & GUIDELINES

April 2013



IRDIRC

International Rare Diseases Research Consortium

Policies & Guidelines

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A. INTRODUCTION

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 2500¹. 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 study²). 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 drugs³. 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

¹ 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.

² <http://archive.eurordis.org/IMG/pdf/eurordiscare1-part1.pdf>;
http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf

³ 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 dissect 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

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 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

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:

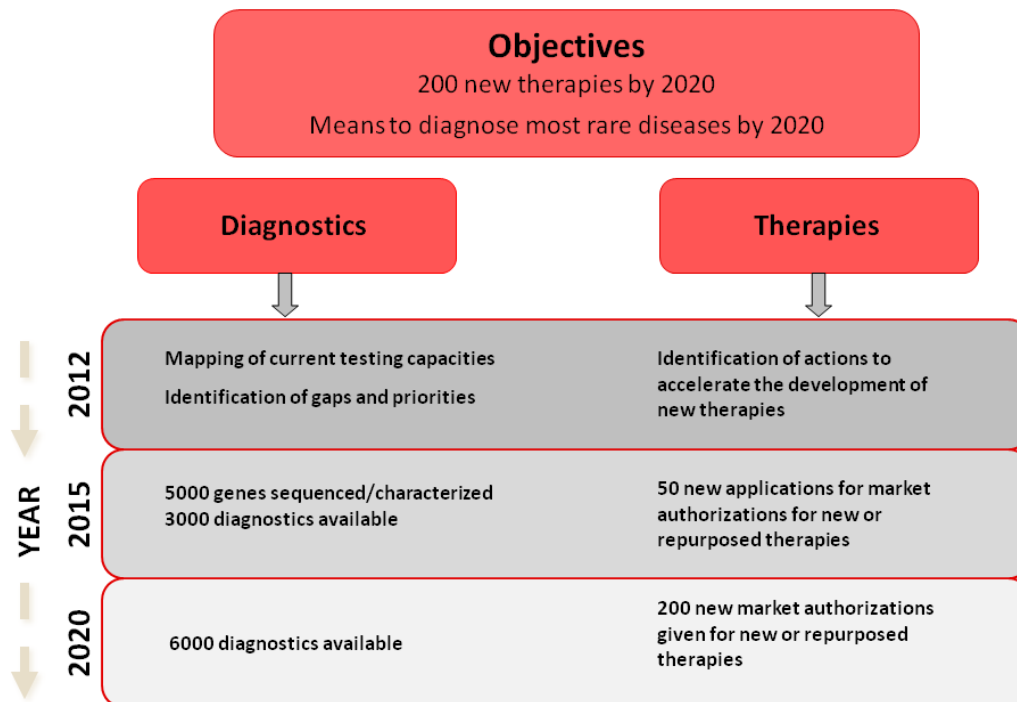
- ▶ coordinate and network patient registries: common standard operating procedures; harmonized ethical approaches, access to patient data and samples.
- ▶ enhance clinical trials: identify and validate biomarkers and surrogate end-points, repurposing drugs, novel compounds.
- ▶ improve the regulatory 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 centers.
- 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

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.

Policy and guidelines for researchers

Researchers involved in IRDiRC associated projects are expected to comply with the following policies and guidelines:

Sharing and collaborative work in RD research

Policies:

- ▶ 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.
- ▶ Data producers acknowledge their responsibilities to release data rapidly and to publish initial analyses in a timely manner.
- ▶ RD patient registries and RD biobanks should aim to be global in geographic scope and practice. Interoperability and harmonization between RD patient registries and RD biobanks should be consistently pursued. Linking and data transfer into existing platforms should be considered “best practice” for RD registries and RD biobanks.
- ▶ Sharing and distributing of biomaterials among RD biobanks is highly encouraged.

Guidelines:

- ▶ Data generated from research projects, including source data, should be deposited in appropriate open or controlled access public databases.
- ▶ Research projects should cooperate with efforts to produce a well-curated and interoperable inventory of RD.
- ▶ Adequate scientific and regulatory information about clinical research should be exchanged by researchers.
- ▶ IP issues and confidentiality agreements need to be balanced with the need to share information for the benefit of research and the patient community.
- ▶ Information about IRDiRC and associated research projects should be disseminated and made available to the RD communities and the public.

Scientific standards, requirements and regulations in RD research

Policies:

- ▶ International, national, regional and local legislation/regulations need to be adhered to with respect to data protection and ethical approvals.
- ▶ Research projects should adhere to standards endorsed by IRDiRC.
- ▶ Research projects should contribute to the development and evolution of standards for RD diagnostic testing and reporting.
- ▶ Research projects should establish criteria and standards for evaluation, qualification and validation of biomarkers.
- ▶ Registries should be broad and not focused exclusively around a single therapeutic intervention or product.
- ▶ 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.
- ▶ Research projects should publish their results in a timely manner in peer-reviewed scientific journals, preferably with open access.

Guidelines:

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

- ▶ 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.
- ▶ Prior to proceeding to clinical trials, experimentation providing multiple lines of evidence should be robust, reproducible and sufficiently powered.
- ▶ Clinical investigations supported by IRDiRC funders should meet requirements set by regulatory agencies.
- ▶ RD research should be published even where its outcomes are negative or do not show convincing results, including clinical trials⁴.
- ▶ Research publications should appropriately acknowledge research funding and the use of infrastructures such as biobanks and registries.

Participation by patients and/or their representatives in research

Policies:

- ▶ RD research should involve patients and/or their representatives in all relevant aspects of the research.

Guidelines:

- ▶ 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.
- ▶ Patients and/or their representatives should be involved in the governance of RD registries and biobanks.
- ▶ 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.
- ▶ Research projects should appropriately acknowledge the contribution of patients and their representatives.

Policy and guidelines for funding bodies, Members of IRDiRC

Policies:

- ▶ IRDiRC members should promote the discovery of all the genes that underlie RD and facilitate the development of diagnostic testing for most RD.
- ▶ 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

⁴ 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.

drugs, or funding preclinical orphan development intended to substantiate proof-of-concept).

- ▶ IRDiRC members will encourage and facilitate rapid data release.
- ▶ IRDiRC members will promote the harmonization, interoperability and open access of ontologies to be applied to databases, registries, and biobanks.
- ▶ IRDiRC members should promote coordination between human and model systems research in RD.
- ▶ IRDiRC members will disseminate relevant information on their research project portfolio through adequate and timely measures, in particular the IRDiRC website.

Guidelines:

- ▶ IRDiRC members should promote collaborative multinational studies, with common study procedures and harmonized policies for regulatory and ethical requirements.
- ▶ IRDiRC shall publish its mission statement, list of member organizations and list of associated projects. IRDiRC shall publish non-confidential proceedings, as well as the minutes and approved documents of its Executive Committee, the Scientific Committees and the Working Groups.
- ▶ IRDiRC associated projects and IRDiRC member organizations should make reference to IRDiRC, where appropriate, on organizational websites, information material and presentations.
- ▶ IRDiRC will promote active exchanges, events and activities between stakeholders, including patient organizations.
- ▶ Education, training and awareness of stakeholders should be encouraged by IRDiRC.



IRDiRC

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