INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

POLICIES AND GUIDELINES

May 2020

IRDiRC

PREFACE

The current version of the IRDiRC Policies and Guidelines has been updated in its introductory sections (A and B), to reflect the evolution in the Consortium vision, goals and governance.

The main body of the document (section C) presents IRDiRC Policies and Guidelines as originally established.

International Rare Diseases Research Consortium

Policies & Guidelines

Last updated: 15 May 2020

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A. ESTABLISHING AND DEVELOPING THE IRDiRC CONSORTIUM

Unlike common diseases, a rare disease affects a relatively small number of persons (typically fewer than 1 in 2, 000 to 10, 000 individuals).[1] This low prevalence is the common feature shared by all rare diseases (RD), which altogether affect all biological systems. There are an estimated 6,000–8,000 different RDs,[2] of which most are genetic and usually life-threatening or chronically debilitating. Although individually uncommon, RDs affect in aggregate 300 million people worldwide,[3] and the challenges facing people living with RDs are common across diseases and across countries. These challenges include delays in diagnosis (5 years on average to receive an accurate diagnosis),[4] lack of clinical expertise, few treatment options available (< 6% have an approved treatment),[5] and difficulties in accessing high-quality care and support. RD also poses particular challenges for research and clinical development due to the small numbers of patients, lack of natural history data, limited scientific knowledge of the disorders, costly and lengthy research and development process. Additionally, RD research is still often scattered within and across countries resulting in fragmentation and unnecessary duplication of efforts.

Maximizing scarce resources and coordinating research efforts are thus key to success in the RDs field. 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 RD 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 RDs and means to diagnose most RDs were set, the International Rare Diseases Research Consortium (IRDiRC) continues to gain strength. IRDiRC has since developed a number of new initiatives, e.g., the IRDiRC Task

1 In the EU a rare disease affects not more than 1 in 2,000 people; in USA each rare disease affects less than 200,000 people; in Japan less than 50,000 people.

2 EU rare diseases research (Factsheet)

3 Nguengang Wakap, S., Lambert, D.M., Olry, A. *et al*. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020)

4 The Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease (Report)

5 Southall, N., Natarajan, M., Lau, L.P.L. *et al*. The use or generation of biomedical data and existing medicines to discover and establish new treatments for patients with rare diseases – recommendations of the IRDiRC Data Mining and Repurposing Task Force. Orphanet J Rare Dis 14, 225 (2019).

Forces and Working Groups (https://irdirc.org/activities/task-forces/) and the "IRDiRC Recognized Resources," (https://irdirc.org/research/irdirc-recognized-resources/).

In April 2017, IRDiRC updated its governance to reflect the evolution of the Consortium (https://irdirc.org/about-us/governance/). The Consortium counts currently 60+ members from across the globe (https://irdirc.org/about-us/people-organisation/), whose representatives compose the Consortium Assembly. Members are organized into three Constituent Committees (Funders, Companies and Patient Advocates), working in close collaboration with the Diagnostics, Interdisciplinary and Therapies Scientific Committees, made of recognized experts appointed from all over the world.

The latest information concerning the state of play for IRDiRC can be found in the Consortium's website.

B. IRDiRC VISION AND GOALS

With the first objectives being reached ahead of time – three years earlier than expected –, in 2017 IRDiRC updated its vision and goals for the next decade.[6]

IRDiRC vision:

Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention

IRDiRC Goals by 2027:

Goal 1 All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline

Goal 2 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options

Goal 3 Methodologies will be developed to assess the impact of diagnoses and therapies on rare diseases patients

6 For more detailed information on the past progress and future actions, please read these three IRDiRC published papers: Austin, C., Dawkins, H. Next decade's goals for rare diseases. Nature 548, 158 (2017); Dawkins, H.J.S. *et al*. Progress in rare diseases research 2010–2016: an IRDiRC perspective. Clin. Trans. Sci.11(11), 20 (2018); Christopher P Austin, Christine M Cutillo, Lilian PL Lau, *et al*. Future of Rare Diseases Research 2017-2027: An IRDiRC Perspective. *Clinical and Translational Science*, August 2017.

C. IRDiRC 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 Committees will be the "guardians" of updating this policy document, and propose changes to the Consortium Assembly for adoption. The Committees will ensure that policies and guidelines are relevant and implemented through IRDiRC Task Forces, Working Groups, and all initiatives carried out with its partners to facilitate delivery of its goals.

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 research funders

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 and beyond, 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).
- 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.

Participation by patients and patient organizations in RD 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 researchers

Researchers involved in projects supported by IRDiRC members 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 trials.
- Research publications should appropriately acknowledge research funding and the use of infrastructures such as biobanks and registries.

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