INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the 15th Consortium Assembly Meeting

May 22-24, 2019

IRDiRC

EXECUTIVE SUMMARY

The Consortium Assembly (CA), the Constituent Committees (CC) and the Scientific Committees (SC) of the International Rare Diseases Research Consortium (IRDiRC) met on May 22-24, 2019, in Leiden, the Netherlands. It was personally attended by 35 CA members, 15 SC members, and the Scientific Secretariat (SciSec).

1. **Composition of IRDiRC member organisations**
   - Page 4 - This section provides information on the CA representation, including new and past members, and the major actions taken by the members to advance towards IRDiRC goals.

2. **Update on Committee activities**
   - Page 5 to 7 - The Constituent and Scientific Committees provided an update on:
     - Their ongoing activities (period Q1 and Q2 – 2019)
     - The activities foreseen in 2019 but not yet started
     - The membership turnover

3. **List of activities for the Roadmap 2020**
   - Page 7 to 10 - The Constituent and Scientific Committees identified a total of 17 activities. Their level of prioritization was divided into three categories:
     - Continuing activities: activities started in 2018/2019 and finishing in 2020
       - *Database for Funders*
       - *Data Sharing Policies*
       - *Patient Engagement in Research*
       - *Gene counter and Drug counter*
       - *Indigenous Populations*
       - *Clinical Research Networks for Rare Diseases*
       - *Natural History Studies*
       - *Orphan Drug Development Guidebook-Phase 2*
       - *Working Group on Goal 3*
     - New activities with high prioritization level that will be started in 2020
       - *Chrysalis Project*
       - *New Technologies and Integrative OMICS*
       - *Molecular Etiology of Rare Diseases*
       - *Drug Repurposing Guidebook*
       - *Access to Drugs for ALL*
     - New activities with medium prioritization level that might be started in 2020
       - *Access to Diagnosis and Primary Care*
       - *Machine Readable and Computable Consent Models*
       - *Alternative Business Models*
       - *Very Low Prevalence Rare Diseases*

4. Cross-Committee interactions

- Page 10 - The actions to make IRDiRC work more expeditely and effectively within and across Committees were reviewed and included:
  - Stimulating all members to participate in IRDiRC activities. Task Forces should be led by a person and not a Committee.
  - Increasing the representation of IRDiRC at international meeting/congress
  - Expanding IRDiRC membership to organisations/companies/groups/members whose expertise will complement the ones already present within IRDiRC

5. Visibility and impact of IRDiRC activities

- Page 10 to 11 - The solutions and actions required to increase IRDiRC influence on the RD community and to benefit the patients were addressed and included:
  - A better understanding of the funding distribution in the area of RD
  - The development of collaborations with other major RD players (e.g. EJP RD)
  - The development of a specific communication strategy

6. Endorsement policy

- Page 11 - The mechanisms by which a statement is endorsed by IRDiRC were reviewed:
  - Statements are circulated among IRDiRC members for approval or objection
  - A statement expresses the outlook of the IRDiRC community and does not necessarily represent the official endorsement by individual IRDiRC member organisations
  - Participation in IRDiRC should not be construed as an endorsement of all IRDiRC's activities or products

7. Travel and reimbursement policy

- Page 11 - The rules governing travel and accommodation booking, and the reimbursement policy were exposed to IRDiRC members.

8. Next IRDiRC CA meetings

- Page 12 - The agenda of IRDiRC meetings was provided for the period 2019-2020

REPORT

1. Composition of IRDiRC member organisations

Currently, IRDiRC consists of 56 members representing funders, companies and patient advocacy groups from 22 countries in Europe, North America, Asia, Africa, and Australia. Member organizations are represented in the Consortium Assembly and Constituent Committees.

1.1 Membership changes (Dec 2018-May 2019)

- Membership termination because of inactive membership:
  - National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Japan
  - Ionis Pharmaceuticals, USA
  - NKT Therapeutics, USA
  - PTC Therapeutics, USA

- Membership termination because of change in the company focus
  - WuXi NextCODE, USA

- New member:
  - National Rare Diseases Registry System of China (NRDRS)

- Change of representation:
  - E-Rare – from Daria Julkowska to Florence Guillot
  - ISS – from Walter Ricciardi to Domenica Taruscio
  - NCATS, NIH – from Christopher Austin to Anne Parisier
  - NGRI, NIH – from Teri Manolio to Lisa Chadwick
  - WA Health – from Hugh Dawkins to Kristen Nowak

1.2 New Member Presentation

- NRDRS, by Mengchun Gong
  - Initiated in December 2016 as the first nation-wide patient registry system for rare diseases in China and currently involves over 60 medical institutes and hospitals in China.
  - It aims to collect 50 000 rare diseases cases in 5 years and 10 000 genomic sequences, and to build a multi-omics database and also biobank.
  - Currently provides the platform for the registry of over 150 diseases and a database of over 32 000 registered clinical cases and over 2 000 related bio-samples.
  - It incorporates information standards to support interoperability among different platforms and international collaboration, and integrates the data from variable sources including phenotypic, genomic, clinical follow-up, bio-samples, and imaging.
  - Since December 2016, NRDRS invested USD 6,000,000 in research projects relevant to IRDiRC goals.

1.3 Round Table

Representatives of each member organization were invited to present the key actions/events developed in the past six months to advance towards IRDiRC goals 2017-2027. Please see Annex 1 for the detailed information.

2. Committee updates

Funders Constituent Committee FCC

- Representation: FCC is currently composed of 33 members, representing public and nonprofit research funders from North America, Europe, Asia, and Australia; they include different types of funding organizations, including agencies, institutes, ministries, and groups of funders (consortia)
- Membership termination
  - National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Japan
- New members:
  - National Rare Diseases Registry System of China (NRDRS) – representative: Zhang Shuyang
- Activity A – Establish process to coordinate and prioritize research funding efforts: aim is to deliver a tool that allows in-depth analysis of funded projects and the rare diseases research funding landscape at international level.
  - The database of funded projects and analysis tool is being developed in association with MyScienceWork and Orphanet, on the basis of the outcome of the funders survey intended to identify the methods of data collection and analysis. The beta version of the tool has already been tested, and is expected to be operational in 2019-Q3-4. Currently testing the curation process (the next step will test the analytics tool using FCC data)
- Working group on ELSI in rare diseases: activity within FCC with some external experts
  - Manuscript submitted to EJHG (under review). Currently planning the E-Rare/IRDiRC workshop on Social Sciences & Humanities (Sep 20, 2019 in Gdansk, Poland)

Companies Constituent Committee CCC

- Representation: CCC is currently composed of 10 members, representing biotech and pharmaceutical companies from North America, Europe, and Asia.
- Membership termination:
  - Ionis Pharmaceuticals, USA
  - NKT Therapeutics, USA
  - PTC Therapeutics, USA
  - WuXi NextCODE, USA
- Currently, there are no activities undertaken by the Committee

Patient Advocacy Constituent Committee

- Representation: PACC is currently composed of 13 members, representing umbrella organizations from North America, Europe, Asia, and Australia; they include 4 international and 9 national organizations advocating for rare disease patients.

- Activity B – Identification of barriers to patient participation in rare diseases research and recommendations to remove them: aim is to determine how best to empower and enable patient participation in RD research.
  - Current steps (until the end of 2019): Doing a benchmarking exercise of available data around barriers to patient participation in RD research to identify what is known/not known and where the gaps are.
  - It will be followed in 2020 by a more in-depth investigation of patients and families using the Rare Barometer survey and selective focus groups.

Diagnostics Scientific Committee DSC

- Representation: DSC is currently composed of 15 members from North America, South America, Europe, Africa, Asia, and Australia.
- Membership termination:
  - Kym Boycott: Children's Hospital Eastern Ontario, Canada
  - Xavier Estivill: Sidra Medical and Research Center, Qatar
  - Gert Matthijs: University Hospital Leuven, Belgium
- New members:
  - Sergi Beltran Agulló: Centro Nacional de Análisis Genómico - Centre de Regulació Genòmica (CNAG-CRG), Barcelona, Spain
  - Ruty Shai: Sheba Medical Center, Israel
  - Clara D.M. van Karnebeek: Emma Chilldren's Hospital, Amsterdam, The Netherlands
- Solving the Unsolved Task Force (STU): Currently disseminating results via commentary article in Cell (published March 2019)
  - Follow-up article in Annual Review in Genomics and Genetics should be submitted in Sept
  - Related: Special American Journal of Medical Genetics issue on unsolved recognizable patterns of human malformation
- Clinical Data Sharing (CDS) task force and Rare Diseases Counting: the former was on hold pending first report of the Global Commission to End the Diagnostic Odyssey for Children Living with Rare Genetic Diseases. The latter was an activity commenced under Chris Austin, former Chair of IRDiRC, including members of the operating committee.
  - Consideration of combing these two activities and focusing it on data sharing between identities/ identifying and triaging people with potential rare diseases in primary, private and public health care
- Indigenous Population Task Force: approved by the CA in Brussels in Dec 2018; nominations received in May 2019
  - Currently assembling Task Force
  - Related: paper submitted to Nature Genetics, Special Issue on African Genetics for Human Society

Interdisciplinary Scientific Committee

- Representation: The ISC is currently composed of 13 members
- Membership termination: Three members ended their mandate

- Angel Carracedo: University of Santiago de Compostella, Spain
- Hanns Lochmüller: University of Ottowa, Canada
- Domenica Taruscio: Istituto Superiore di Sanità, Italy

- New members: Five new members were appointed in the ISC by the CA.
  - Takeya Adachi: International Human Frontier Science Program Organisation, France
  - Kate Baker: University of Cambridge, UK
  - Marc Dooms: University of Leuven, Belgium
  - Yllka Kodra: Istituto Superiore di Sanità, Italy
  - Mahsa Shabani: University of Leuven, Belgium
- Task force on Clinical Research Networks for Rare Diseases: The call for nominations was open until May 20, 2019. The group will be formed in July 2019 and the activity agenda will be determined with the TF members.
- Task Force on Natural History Studies Related to Rare Diseases: This activity will start after the group formation on Q3, 2019.

Therapies Scientific Committee

- Representation: The TSC is currently composed of 12 members
- Membership termination: Two members ended their mandate
  - Josep Torrent I Farnell: University of Barcelona, Spain
  - Karin Rademaker: University Medical Center, Utrecht, The Netherlands
- New members:
  - Sangeeta Jethwa (Roche, Switzerland) was appointed in the TSC by the CA.
- Task Force on The Orphan Drug Development Guidebook: The current step includes the final review of the Building Blocks classification (geography/section) and checklist. The next step is the dissemination of the results.
- "New" Drug Counter: This work is developed jointly with Orphanet and requires the validation of new methodologies for the identification of orphan medicinal products on the market.
- Articles: The TSC is planning to develop 3 articles
  - Article 1: Drug counter, what is the current orphan medical product situation, collection of data from 2010-2018 in US and Europe
  - Article 2: Trends and gaps in drug development, and how to solve them (models, methodologies developed in the GG)
  - Article 3: Orphan drug development, tools and recommendations

3. List of activities for the Roadmap 2020

The different activities proposed by the Committees and their level of prioritization were divided in three categories:

(1) Continuing activities: Activities started in 2018/2019 and finishing in 2020.
(2) New activities with high prioritization level that will be started in 2020.
(3) New activities with medium prioritization level that might be started in 2020.

It is important to underline that the final Roadmap of IRDiRC activities for 2020 will be validated in

November 2019 during the CA meeting in Paris.

- **(1) Continuing activities: Started in 2018/2019 and finishing in 2020**
  - ***Database for Funders (Task Force, presented by FCC):*** This database is under development and will map the distribution of funding in rare disease research, thus allowing to identify trends, advancement of research on specific diseases and type of research, and ultimately providing recommendations for funders. This tool will also support EJP RD Pillar 1 WP6 in the identification of topics to implement the next joint transnational co-funded calls. The funders tool is expected to be operational in 2019-Q4, and data will be collected automatically from 2020.
  - ***Data Sharing Policies (Working Group, presented by FCC):*** The objective of this activity is to formulate and disseminate standards and guidelines for data and bio specimen sharing, data integration and consent processes. The current steps involve the collection and analysis of exiting requirements for data sharing policies. A working group will be formed in 2019-Q4/2020-Q1 to analyse the existing repositories, discuss the costs to financially support the preparation and sharing of data, and propose recommendations that could be implemented at national and international levels.
  - ***Patient Engagement in Research (Task Force, presented by PACC):*** This activity aims to set up a scan of barriers to and recommendations for patient participation in rare disease research, by leveraging IRDiRC's stakeholder and geographical representation. This activity will use a two-phase approach. The Phase 1 started with a mapping and benchmark exercise. The Phase 2 will include a more in-depth investigation by using surveys and focus groups, and will be completed in 2020-Q4.
  - ***Gene Counter and Drug Counter:*** The Gene Counter provides an annual count of the cumulative number of genes involved in rare diseases (total and year-by-year number). This activity is very relevant to understand the progress made toward the Goal 1 of IRDiRC. The Drug Counter provides an annual count of the cumulative number of new orphan drugs approved by the FDA and EMA (total and year-by-year number). This activity is very relevant to understand the progress made toward the Goal 2 of IRDiRC. Both counters are managed in collaboration with Orphanet and updated on the IRDiRC website.
  - ***Indigenous Populations (Task Force, presented by DSC):*** The objectives of this activity are to identify the priorities and means, both existing and in need for development, to deliver equity in scale and in delivery against Goal 1; specifically, by focusing on underrepresented, including indigenous, populations. The Task Force group will be formed in 2019-Q2 and the activity will by concluded in 2020-Q1/Q2.
  - ***Clinical Research Networks for Rare Diseases (Task Force, presented by ISC):*** The objectives of this activity are to map and analyse the existing ecosystem of national/supranational clinical research networks, develop policy recommendations on

guiding principles for an international framework of collaboration, and provide relevant recommendations for funders based on gaps identified through the mapping exercise. The Task Force group will be formed in 2019-Q2 and the activity will by concluded in 2020-Q1.

- ***Natural History Studies (Task Force, presented by ISC):*** This Task Force aims at mapping of existing ecosystem of resources, guidelines, and standards that impede real-world evidence data collection and the conduct of natural history studies; and to develop recommendations for funders in order to address these challenges and accelerate natural history research. The Task Force group will be formed in 2019-Q3 and the activity will by concluded in 2020-Q2.

- ***Orphan Drug Development Guidebook – Phase 2 (Task Force, presented by TSC):*** The phase 1 was initiated in 2018 and focused on the creation of a guidebook for academic and industrial drug developers describing the available building blocks and initiatives specific for rare disease therapy development and how to best use them. The phase 2 will focus on the development of an interactive representation of this guidebook, and the maintenance of the information provided by this tool. The phase 2 start is expected for 2019 Q3-Q4, and will be achieved in 2020.

- ***Working Group on Goal 3:*** The goal of this Working Group is to identify methodologies to assess the impact of diagnostics and therapies on rare disease patients. The group is composed of 14 members with expertise in health technology assessment, health economics, public health, rare diseases policy, global pricing, patient rights, genetics, and will be led by David Pearce, Vice Chair of the IRDiRC Consortium Assembly. The first teleconference will be held on June 26, 2019, and this activity should be concluded by 2020-Q1.

- **(2) New activities ranked with high prioritization level**

  - ***Chrysalis Project (Task Force, presented by FCC):*** This project will bring together companies and funders to boost research through the identification of key criteria for the development of therapies for specific rare diseases, and the overall understanding of the progress and state of the art of research on these diseases. This interaction will facilitate the set-up of targeted funding opportunities to fill the gaps in the research "pipeline", and obtain a complete portfolio necessary for the industrial partners. Estimated starting date 2020-Q1.

  - ***New Technologies and Integrative OMICS (Task Force, presented by DSC):*** The objective of this activity will be to describe the learnings and new technologies (e.g. liquid biopsy, multi-omics analysis) used primarily in cancer domain applicable to rare disease diagnosis, and provide relevant information to clinicians. Estimated starting date 2020-Q2.

  - ***Molecular Etiology of Rare Diseases (Task Force, presented by ISC):*** This activity will focus on the classification of rare diseases based on their shared molecular etiology rather than

anatomical and clinical phenotypes. This innovative classification can lead to the design of new clinical trials for monogenic rare diseases sharing common molecular etiology. Estimated starting date 2020-Q2.

- ***The Drug Repurposing Guidebook (Task Force, presented by TSC):*** The "Drug repurposing Guidebook" will create a guidebook for academics and companies describing the suitable business models for repurposing drugs, ultimately providing more therapeutic options for rare disease patients. Estimated starting date 2020-Q2.

- ***Access to Drugs for All (Working Group, presented by ISC):*** This activity will address the issue of orphan drugs availability in medium and low-income countries and will review the nation specific restriction on drug importation, the list of medication that should be made available, the mechanisms of financial support for treatment, and the pathways for reporting products within the regulatory requirements. Estimated starting date 2020-Q1.

- **(3) New activities ranked with medium prioritization level**

  - ***Access to Diagnosis and Primary Care (Task Force, presented by DSC):*** The objective of this activity will be to identify areas of intervention to improve and reduce the patient journey from symptom onset to medical attention and diagnosis. This activity will also map areas to develop and support primary care actions (e.g. diagnosis, triage, care coordination, psychosocial and community support).

  - ***Machine Readable and Computable Consent Models (Task Force, presented by ISC):*** This activity will build upon the work of the Task Force on *Model Consent Clauses for Rare Disease Research*, and develop a series of machine-readable and computable consent models for rare disease researchers, biobanks and registries.

  - ***Alternative Business Models (Task Force, presented by TSC):*** This activity will map the specific orphan drug companies (including patient-driven companies), and understand the characteristics of their alternative model of development through the creation of a survey. This activity should highlight the strengths and the gaps of these alternative models, provide recommendations to funders and companies.

  - ***Very Low Prevalence Rare Diseases (Position Article, presented by TSC):*** This activity will investigate and describe the progress and needs in very low prevalence rare disease research.

4. General structure of IRDiRC: Cross-committee interactions

The goal of this discussion was to identify within the Committees the major hurdles towards achieving IRDiRC objectives, and the actions (within and across Committees) to make IRDiRC work more expeditely and effectively.

- Major hurdles

- Time availability for IRDiRC members to participate in the activities
- Access to monetary resources
- Separation between Constituent and Scientific Committees
- Perception that a Task Force belongs only to a specific Committee

- Solutions provided by the CA and SC:

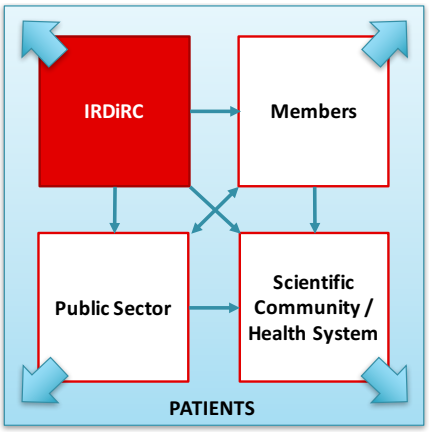
  - The ownership of the activities should be shared within IRDiRC. Task Forces should be led by a person and not a Committee. All the members should feel entitled to participate irrespectively of their Committee.
  - IRDiRC should be represented in more conferences.
  - IRDiRC should expand collaboration with groups that are important for the development of IRDiRC activities (e.g. paediatric groups, regulatory presence, companies)

5. Visibility and impact of IRDiRC activities

The classic IRDiRC channels of influence include IRDiRC members, the scientific community, the health system and the public sector. The contribution of each stakeholders to IRDiRC visibility and impact involve:

- IRDiRC members
  - Funding, investment, portfolio decision
  - Dissemination to researchers, clinicians, patients
- Scientific community/Health system
  - Implementation of recommendations and best practices
  - Access to platforms and use of tools
- Public sector (regulators/politicians)
  - Policy making
  - Agenda setting

The goal of this discussion was to understand how IRDiRC can increase its influence by outreaching to the RD community and having an impact on the patients as described in the following scheme.



- The solutions provided by the CA and SC are listed below:

- Implement an economic evaluation for RD and understand where the funding distribution and gaps are. IRDiRC activities should also impact the funders.
- Use the EJP RD as an implementation tool for IRDiRC to reinforce the channels of influence and outreach the scientific, regulatory and patient communities.
- Develop an effective communication strategy
  → Explore the possibility to reach more the social community/media
  → Develop a communication toolbox to reach patients and countries with few available information
  → Advocate IRDiRC in meetings / Set up IRDiRC sessions
  → Crosslink the website and the newsletter
  → Authorize the translation of the newsletter in other languages

6. Endorsement policy

- The website of IRDiRC and social media are valid means to support and express IRDiRC position on research and other issues relevant to the RD community.
- Statements are circulated among IRDiRC members for approval or objection, and a disclaimer note is added if the statement is published.
  - Statement Disclaimer: This statement expresses the outlook of the IRDiRC community and does not necessarily represent the official endorsement by individual IRDiRC member organisations.
  - IRDiRC Disclaimer: All IRDiRC members or Scientific Committees/Task Force experts participate in IRDiRC's activities as part of an effort to advance the development of diagnosis and treatments for RD or conditions. Participation in IRDiRC should not be construed as an endorsement of all IRDiRC's activities or products.

7. Travel and reimbursement policy

- CA members are responsible for booking their own travel and accommodation.
- Travel and accommodation booking for SC and PACC members should be done by the SciSec. If not, no reimbursement will be granted.
- The budget limit for travel and accommodation is fixed at 15000 euros/Committee (SC and PACC).

8. Next IRDiRC CA meetings

- September 12, 2019: CA conference call
- November 21-22, 2019 - Paris, France: CA face-to-face meeting
- March 11-14, 2020 – Berlin, Germany: 4th IRDiRC Congress organised jointly with RE(ACT)
- March 14-15, 2020 – Berlin, Germany: CA-SC face-to-face meeting
- Fall 2020 (date TBD) – Milan (tentative): CA face-to-face meeting

Actions and deliverables

- The SciSec will contact the Committee Chairs and Vice Chairs to request the full activity proposals and identify the leader(s) for each activity.

- The proposals will be reviewed by the Operating Committee on September 4th and by the CA on September 12. The final validation of the Roadmap 2020 will be done during the CA meeting in Paris, Nov21-22, 2019.
- The structure of IRDiRC will be adapted to improve internal collaboration and allow the members to participate in any activities even if they are not led by their respective Committee. The activity leadership will therefore switch from the Committee to identified IRDiRC member(s).
- The SciSec will identify the relevant international meetings for which IRDiRC representation should be considered.
- The SciSec will develop a communication toolbox to IRDiRC members who will advertise and present the general work of the Consortium during their meeting presentations.