INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the Consortium Assembly Meeting

06-07 March 2024
Online

IRDiRC

ACRONYMS

CA	Consortium Assembly
CCC	Companies Constituent Committee
CORD	Chinese Organization for Rare Disorders
DSC	Diagnostics Scientific Committee
EFPIA	European Federation of Pharmaceutical Industries and Associations
EJMG	European Journal of Medical Genetics
EJP RD	The European Joint Programme on Rare Diseases
EMA	European Medicines Agency
ERDERA	European Rare Diseases Research Alliance
ERN	European Reference Network
FCC	Funders Constituent Committee
FDA	US Food and Drug Administration
HTA	Health Technology Assessment
INSERM	Institut National de la Santé et de la Recherche Médicale
IRDiRC	International Rare Diseases Research Consortium
ISC	Interdisciplinary Scientific Committee
KOL	Key Opinion Leader
KPIs	Key Performance Indicators
LMICs	Low- and Middle-Income Countries
NBS	Newborn Screening
NIH	US National Institutes of Health
ODDG	Orphan Drug Development Guidebook
OpComm	Operating Committee
PACC	Patient Advocacy Constituent Committee
PPP	Public-Private Partnership
RD	Rare Disease
RDI	Rare Diseases International
RSC	Regulatory Scientific Committee
TBC	To Be Confirmed
TSC	Therapies Scientific Committee
WODC	World Orphan Drug Congress

MEETING REPORT CONTENTS

THE REPORT

The International Rare Diseases Research Consortium (IRDiRC) held a two-days online meeting of the Consortium Assembly (CA) on 06-07 March 2024, via teleconference. It was attended by 52 online participants representing 43 member organizations, Chairs and Vice Chairs of the Scientific Committees, and members of the Scientific Secretariat.

1. Introduction and Welcoming

a) New IRDiRC members

- **Federación Peruana Enfermedades Raras (FEPER), Peru**
  Represented by Pilar Estremadoyro, Vice President.
  Member of the Patient Advocates Constituent Committee.

- **Congressionally Directed Medical Research Programs (CDMRP), USA**
  Represented by Kristy Lidie, Deputy Director for Program Management.
  Member of the Funders Constituent Committee.

- **Alexion AstraZeneca Rare Diseases, USA**
  Represented by Wendy Erler, Vice President of Patient Experiences, STAR and Advocacy.
  Member of the Companies Constituent Committee.

- **ITALFARMACO SpA, Italy**
  Represented by Samantha Parker, Patient Advocacy and Communication Lead Rare Disease Europe.
  Member of the Companies Constituent Committee.

b) Change of representation

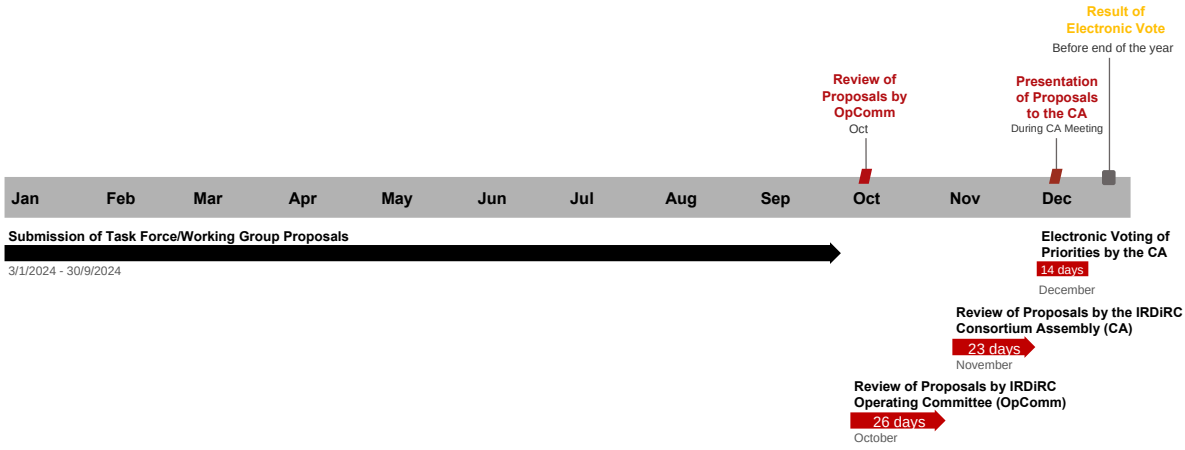
- Takeda – Laura Rosen, Head Neuroscience Translational Medicine, replaced former Takeda representative, Ceri Davies

- Pfizer – Denis Keohane, VP Global Medical Affairs, replaced former Pfizer representative, Katherine Beaverson

c) Task Force submission timeline in 2024

Task Force proposals can be submitted until October 2024, afterwards the proposals will be sent to the Operating Committee (OpComm) for review (for a period of 26 days). After the OpComm review, the recommended proposals will be transmitted for voting and validation to

the Consortium Assembly. The results of the electronic vote will be announced before the end of 2024.



2. Updates from the IRDiRC Constituent Committees

- **Funders Constituent Committee (FCC)**

  The FCC is brainstorming on a new Task Force focusing on moving RD medicines to first in human trials. The FCC is exchanging ideas with members of the RSC and the CCC. The traditional regulatory approval process does not seem to be practical for RDs with limited patient populations. It was suggested that the regulatory sciences and processes need to be adapted to the unique challenges of RD drugs. This discussion highlights the need for changes in the regulatory framework to better serve RD patients and encourages alignment between regulatory agencies to address these issues on a global scale. A joint Task Force is foreseen which acknowledges that current HTA approval regulations may not be suitable for RD therapies and aims to explore reciprocity in RD medicine approval between HTAs. Additionally, it addresses manufacturing approvals for essentially N-of-1 (or N-of-many) medicines, collaborating with Regulatory Scientific Committees, and potentially with the Companies Constituent Committee.

- **Companies Constituent Committee (CCC)**

  In the first quarter of 2024, the Companies Constituent Committee welcomed two new members:
  - Alexion AstraZeneca Rare Disease
  - ITALFARMACO SpA

  In addition, there were two changes of the official representation in IRDiRC for Takeda and Pfizer.

  In terms of operational activities, the committee planned the group meetings for 2024 (the first committee meeting already took place on 31st of January) and will further work towards advancing its priorities set up for 2024, one of them being the development of the Public-Private Partnership (PPP) project, together with

EFPIA and the RD Moonshot group. First output of the project is planned to be delivered in October 2024, at the CA Meeting in Milan (Italy).

- **Patient Advocates Constituent Committee (PACC)**

  The mission of the PACC is to articulate points in the diagnostic and therapeutic development process where patient involvement is crucial. The mission of the PACC includes three main points: understand what is important to patients and bring it to IRDiRC to inform our research, translate research findings into real benefits for the patients, and develop a life cycle approach from diagnosis to therapies and care follow-up.

  The PACC mission is currently translated into three ongoing priorities:

  - A Task Force whose objective is to develop a framework of holistic, multidimensional, and evolving life-long experiences of patients and families living with a rare disease.
  - A Working Group to identify the barriers in accessing drugs in low-and-middle income populations.
  - Understand patient involvement in IRDiRC activities addressing diagnostic and therapeutic development.

- **Diagnostic Scientific Committee (DSC)**

  The DSC is developing a joint task force proposal with the TSC on linking diagnosis to therapy. Quarterly online meetings are planned for 2024. A DSC recruitment campaign will be launched in summer 2024 and five DSC members will terminate their mandate by the end of 2024.

- **Interdisciplinary Scientific Committee (ISC)**

  Four members will end their mandate in April 2024. A membership recruitment campaign was launched in March. The ISC is looking for candidates from Middle East and Africa with expertise in (1) Phenotyping, ontology or digital health, (2) Patient Advocates with research experience, (3) Policy and/or legal expertise, and a (4) Mental health expert.

  The ISC is developing a proposal addressing stigma and mental health as an integral aspect of the overall life experience of individuals with RD. The ISC is also working jointly with the TSC to explore drug-eluting devices for patients with rare diseases Furthermore, the ISC is setting up a collaboration with ERN-EuroBloodNet for the development of a project focused on basket trials for haematological disorders.

- **Therapies Scientific Committee (TSC)**

  The TSC is collaborating with the DSC to prepare a Task Force proposal on how to translate diagnosis into the right therapeutic. The TSC is also preparing a proposal aiming to develop consolidated guidance for small population research, potentially building on the SPIRIT items. Additionally, the TSC plan to set up a working group focusing on paediatric patient engagement in therapeutic development. A TSC sub-group is also working on the development of guidelines for digital biomarkers, with a paper to be drafted on the current landscape and emerging perspectives in the application of digital endpoints in rare diseases.

- **Regulatory Scientific Committee (RSC)**

  The RSC is conducting a landscape analysis of orphan drug approvals in multiple jurisdictions (FDA, EMA, PMDA, Canada, Australia, Saudi Arabia) trying to highlight variations where things are different and where things are the same. The RSC is drafting a paper addressing issues such as regulatory approval reciprocity and the global nature of these trials, leading to discussions on streamlining processes. Looking ahead in 2024, the RSC plans to engage in discussions with FCC about manufacturing and regulatory flexibility.

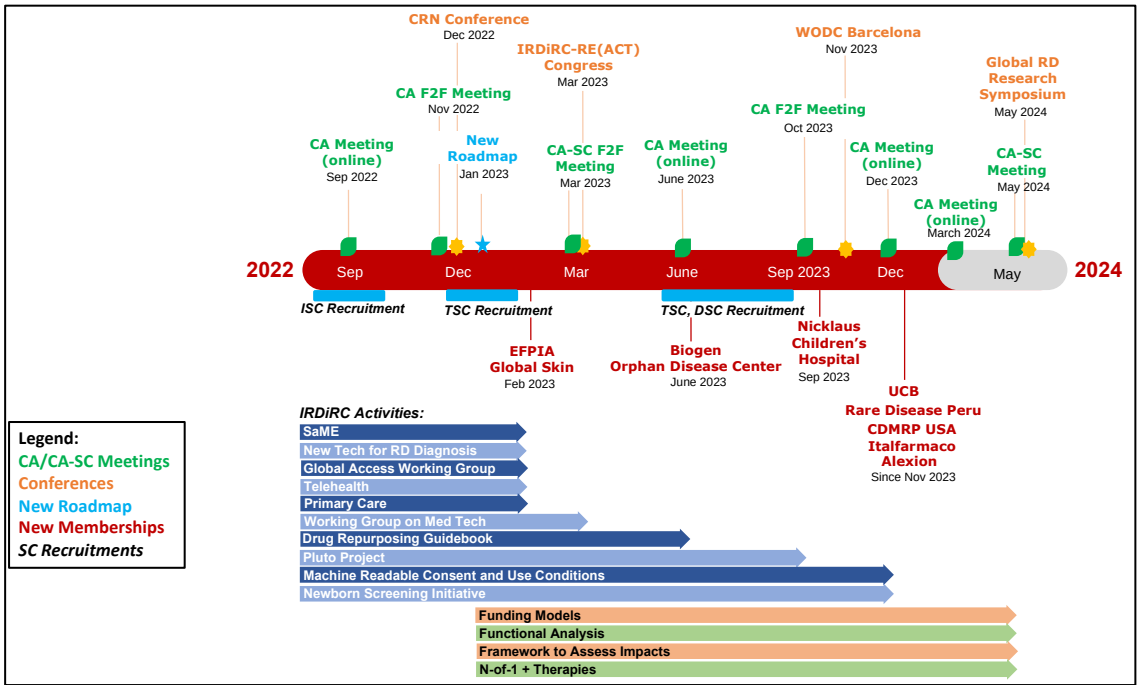
3. Communication Sub-Committee Updates

- The objective of this group is to improve the visibility of IRDiRC for internal and external stakeholders to have a credible and trusted communication approach, at the same time highlighting the impactful changes that IRDiRC produces.

- **Outputs:**
  - Creation of communication slide deck for external events.
  - Review of the current website and create a list of suggested changes for improvement.
  - Creation of a LinkedIn account.
  - Rare Disease Day campaign.

- **Next Steps:**
  - Complete the IRDiRC slide deck with the Task Forces information and restructuring of the available tools in a comprehensive way.
  - Ongoing review of the website structure and content – *planned for Q2 2024.*

4. Annual Overview of IRDiRC Activities and Publications in 2023



In 2023, IRDiRC received a consistent number of applications during the openings for different scientific membership positions or during the recruitment of members for the Task Forces.

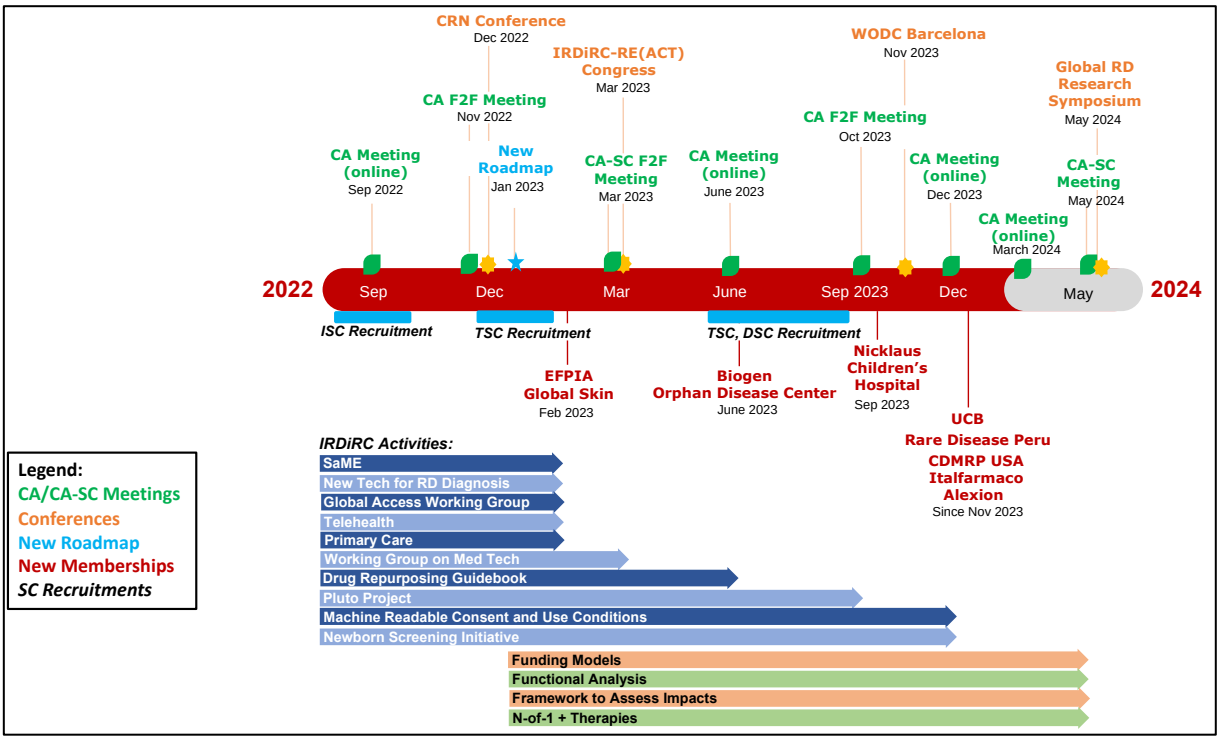
Scientific Committees

- 2 open positions in DSC: 21 applicants
- 1 open position in ISC: 8 applicants
- 3 open positions in TSC: 6 applicants

Task Forces

- Framework to assess impacts: 30 applicants
- Functional Analysis: 20 applicants
- Funding Models: 32 applicants
- N-of-1: 46 applicants

In terms of **Events and Conference** participation, at RE(ACT) congress (15-18 March 2023, Berlin, Germany), 30 speakers from IRDiRC participated in 25 sessions. In addition, 22 speakers from IRDiRC participated at the World Orphan Drug Congress Europe (30 October – 2 November 2023, Barcelona, Spain) in 31 sessions. The booth received a lot of interest from the congress participants, accounting for 56 sign-ups for further follow up on membership application and social media subscription.



Highlighting the **publications** in 2023, 7 papers were published by different IRDiRC Task Forces and one from the Therapies Scientific Committee. A collaboration with the EJMG Journal on a special edition following the RE(ACT) congress in Berlin produced 9 papers, currently under Journal review.

- **Task Forces and Working Groups**

  - **Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations**

    Objectives: To connect different N-of-1 efforts to reduce duplication, achieve global consensus, and create a roadmap towards development and implementation of N-of-1 treatment; to raise awareness of the N-of-1 concept and challenges with all stakeholders, and identify major challenges hampering N-of-1 therapy development and timely patient access, which can potentially lead to development of proposed solutions and create better opportunities for strategic planning and delivery.

    Progress Update:

    - **State-of-the-Art of N-of-1 therapies paper –** submitted to Nature Reviews Drug Discovery on March 6th
    - Last meeting with the group planned for mid-April

    Outputs:

    - List of current literature resources on N-of-1
    - Review of education resources
    - Second publication on "Future perspectives" planned for Q2-Q3 2024

- **Operationalizing a Comprehensive Framework to Assess the Impacts of Diagnoses and Therapies in RD Patients**

  Objectives: To develop, operationalize, and test a comprehensive framework of holistic, multidimensional, and evolving life-long experiences of patients and families living with a RD, (derived from or leading to a natural history study); to develop, operationalize, and validate multidimensional indicators and measures (qualitative and quantitative) of impacts associated with diagnosis, treatment, support, and community integration that can be used to capture changes along the patient "journey"; and to investigate qualitative case studies to represent a number of parameters that could inform on impacts.

  Expected Output: Framework to assess impacts; White Paper**.**

  Progress Update: The group started a literature review search to identify the elements of the framework. Four clusters have been identified and are currently investigated by the Task Force members: clinical impacts, care impacts, socio-economic impacts, and RD ecosystem impacts.

  - Clinical Impacts: Diagnostic, Disease knowledge, treatment
  - Care Impacts: Mental health, Care coordination, Socio-cultural determinants
  - Socio-economic Impacts: Economic determinants, Socio-economic determinants, Informed burden of disease.
  - RD Ecosystem impacts: Patient group support, RD ecosystem & landscape, Patient and family roles and expectations

The group is currently investigating the literature for each cluster to identify measures of impacts, gaps, and map them on the patient pathway. One of the objectives is to map quantitative indices and qualitative measures to step on Patient Pathway and identify the gaps in data.

- **Functional Analysis**

  Objectives: To further development, standardization, and quality improvement of the experimental and computational methods of functional assays ; to foster ecosystem building, infrastructure development and partnerships for the effective chain from fundamental research to clinical applications of functional assays; and to foster equity in RD diagnostics and treatment through the application of indiscriminative multiplexed assays of variant effect and variant effect maps to the fundamental research and clinical practice in RDs.

  Planned Output: Framework for the robust and effective ecosystem of functional analysis in RDs; White Paper.

Progress Update: The group has established a framework that will serve as the foundation of their future white paper, including step-by-step diagram of functional analysis that involves education, policy, and sustainability. The group has established different sub-groups focused on specific themes. An in-person Task Force workshop took place on 11-12 March 2024 in Paris, France.

- ***Working Group 1***
  - Diagnostic, therapeutic and scientific drivers to improve generation and coordination of knowledge base, tools and platforms;
  - Education and awareness of functional analysis in primary and specialist care, from prevention to diagnosis, treatment, and research;
  - Basic research.

- ***Working Group 2***
  - Compilation and accessibility of current (and evolving) functional analysis knowledge – a. Retrospective; b. Prospective -> Mandate as requirement for publication; c. what exists/what needs to be built or added;
  - Matching gene and variant to functional analysis (main means to match gene and variant to functional analysis) - a. funded; b. not funded.

- ***Working Group 3***
  - Standardization/Quality Control/Regulation;
  - How to best analyze and integrate multi-omics?
  - How to overcome challenging molecular mechanisms?
  - Criteria for clinical use/cut-offs, need or not for orthogonal methods for confirmation.

- ***Working Group 4***
  - Cost, access, sustainability;
  - Perspective of PLWRD and equity;
  - Increasing throughput and disease/multiplexing/gene agnostic methods.

- **Funding Models to Support the Spectrum of RD Research and Development**
  Objectives: To identify key motivating factors for different types of funders of RD research and how different types of funders decide at which point in a

research study's lifecycle they will provide support; identify the key influencing factors for effective public-private partnerships at different stages of a treatment's life cycle and models of public-private partnerships, including means of sharing information (with attention to tech transfer issues and regulatory requirements).

Planned Output: First manuscript will be submitted to a scientific journal, and it will include a literature review and the KOL interview results. The second manuscript will include the Orphan Drug Database Analysis results based on US-FDA and EMA, and it is planned to be developed as a business article.

Progress Update: The group has successfully completed a literature review and conducted online interviews with 21 selected key opinion leaders which help obtain insights into research funding strategies and decision-making processes. Analysis of collected data and review of interview summaries are currently being performed. Simultaneously, an in-depth analysis of a database containing orphan drug designations from EMA and FDA is also ongoing. The first manuscript outline has been defined, focused on 11 blocks (mission-oriented investments: (1) public funders and foundations, (2) patient groups and foundations, (3) private investors and companies, (4) cautionary comment regarding IP; (5) health economics, (6) market timing, (7) partnerships: public-private, industry partnerships with foundations; roles and opportunities for Patient Advocacy Group investments, Venture Philanthropy; (8) Funding Mechanisms; (9) Downstream requirements; (10) Human resources; (11) Scientific Quality.

Orphan Drug Designation Database

The scope of the Orphan Drug Designation Database is to provide a quantitative clinical and regulatory insight into the status of FDA and EMA Orphan Drug Designations awarded in 2017, including the description of the preclinical and clinical discontinuations that have taken place.

- **Newborn Screening Initiative**

  Two special editions in the Rare Disease and Orphan Drugs Journal.

  Theme 1 - **Real World Applications and Technologies** (associate editor: Virginie Bros-Facer):

1) A systematic review of real-world applications of genome sequencing for newborn screening (systematic review) – *published.*
2) Federated databases: An approach to enhance secure data sharing in newborn genomic screening (opinion paper) – *published.*

3) Next-Generation Sequencing-Based Newborn Screening Initiatives in Europe: An Overview (original research) – *published.*
4) Enhancing the Efficiency and Efficacy of Newborn Screening by using Real-World Data and relevant technologies – *under revision by authors following Journal's peer-review.*
5) Towards genomics in Newborn Screening for Inherited Metabolic Disorders: Expert opinion from IRDiRC-Newborn Screening Initiative – *re-submitted to Journal on March 8th*.
6) Incorporating a new disease in the Newborn Screening programmes in Europe: The Spinal Muscular Atrophy case study (opinion paper) – *under review by Journal.*
7) Newborn Screening in Mexico and Latin America: Present and Future (perspective paper) – *under revision by authors following Journal's peer-review.*

Theme 2 - **Policy, Ethics and Patient Perspectives** (associate editors: Helen Malherbe & Mary Wang):

1) Introductory Editorial – *to be drafted during review process.*
2) Development of newborn screening policies in Spain 2003-2022: what do we actually need to reach an agreement? – *published.*
3) The Australian landscape of newborn screening in the genomics era – *published*.
4) Patient advocacy in action for Newborn Screening: role of patient organizations in the timely diagnosis of RDs and quality of life – *under revision by authors following Journal's peer-review*.
5) Overcoming challenges in sustaining newborn screening in low-middle-income countries: the Philippine newborn screening system – *published.*
6) Newborn screening in South Africa the past, present, and plans for the future – *published.*
7) NBS in the rural community – *withdrawn*

- **IRDiRC Timeline 2024**

The annual IRDiRC strategic meeting with the Scientific Secretariat took place on the 12th of January in Paris (France), and among the topics for discussion were the roadmap for 2024 and the transition from INSERM to the Foundation for Rare Diseases (France). IRDIRC chairs and some of IRDiRC members announced their participation at the following events:

- Genomics of Rare Disease, UK
- Orphan Drugs & Rare Diseases Global Congress, UK
- WODC USA, Boston, USA
- ECRD Conference, Brussels, Belgium
- Global Rare Diseases Research Symposium, Shanghai, China
- BIO International Convention, USA
- DIA Global Annual Meeting, USA
- ICORD Conference, Buenos Aires, Argentina
- UDNI Conference, Seoul, South Korea
- WODC Europe, Barcelona, Spain

- **IRDiRC Publications**

Recently published in **January-March 2024**:

- **Advancing Diagnosis and Research for Rare Genetic Diseases in Indigenous Population** *(output of the Indigenous Populations Task Force)*. Gareth Baynam, Daria Julkowska, Sarah Bowdin, et al. *Nature Genetics,* 2024. Access the paper here.

- **Newborn screening in South Africa: the past, present, and plans for the future** *(output of the Newborn Screening - "Policy, ethics and patient perspectives" special edition).* Helen Malherbe, Jim Bonham, Michelle Carrihill, et al. *RDODJ,* 2024. Access the paper here.

In Preparation or Under Review:

- **Primary Care: "**Global Health for Rare Diseases through Primary Care" – *Manuscript under review by journal.*

- **Integrating New Technologies for RD Diagnosis**: "Leaving no patient behind! Expert recommendations for the use of innovative technologies in the diagnosis of rare diseases" – *Manuscript under review by journal*.

- **Enabling and Enhancing Telehealth for RDs Across the Globe: "**Telehealth for rare disease care, research and education across the globe: a review of the literature by the Telehealth Task Force" – *Manuscript under internal review.*

- **Machine readable consent and use conditions:** "Getting Your DUCs in a Row – Standardising the Representation of Digital Use Conditions": using Digital Use Conditions as a framework that facilitates advancing scientific discovery and sharing of research data, healthcare records, biosamples, and biomedical resources – *Manuscript under review by journal*.

- **Machine readable consent and use conditions:** "Common Conditions of Use Elements. Atomic Concepts for Consistent and Effective Information Governance": standardized digital representation of diverse use conditions – *Manuscript under review by journal.*

- **Medical Technologies for RD in Orphanet Journal:** "Developing orphan medical devices for use in rare diseases: a landscape overview" - *Manuscript under internal review.*

- **Pluto Project on Under-Researched RD -** *Manuscript under preparation.*

- **Interoperability of Clinical Research Networks -** *Manuscript under preparation.*

- **N-of-1 Future Perspectives -** *Manuscript under preparation.*

- **Parallels of COVID-19 and RDs** – *Manuscript under preparation.*

Special Issue Collaboration with the European Journal of Medical Genetics "Globally Trending Topics in Rare Disease"**:** Special bundle issue, nine articles were submitted in October 2023. The manuscripts under review by journal.

1) The history of the International Rare Diseases Research Consortium (IRDiRC) and its conferences;
2) Addressing Diagnostic Gaps and Priorities of the Global Rare Diseases Community: Recommendations from the IRDiRC Diagnostics Scientific Committee;
3) Catalogue of inherited autosomal recessive disorders found amongst the Roma population of Europe;
4) Defining the Next Frontier: Insights & Reflections on Galvanizing Global Action in Rare Disease Research;
5) Demystifying Gene(tic) Therapies;
6) Lessons learned from the RE(ACT) Conference on Medical Devices for Rare Diseases;
7) Living with a Rare Dermatological Disease: A Global Perspective on Impact and Action;
8) Rare Care – Cross-sector care coordination;
9) Telehealth for Rare Disease Care, Research, and Education across the Globe: A Review of the Literature by the IRDiRC Telehealth Task Force.

5. Scientific Secretariat Updates

2024 Priorities

- **The transition of Scientific Secretariat to Foundation for Rare Diseases**
  Starting September 2024, and for a period of 7 years, the Scientific Secretariat will be supported by the European Commission through the European Rare Diseases Research Alliance (ERDERA). The Scientific Secretariat will be hosted by the Foundation for Rare Diseases (France) and will be coordinated by Prof. Daniel Scherman.
- **Task Force Timeline in 2024**
  Collection of Task Force proposals is planned for September-October 2024. The Task Forces will be presented at the Consortium Assembly meeting in Milan, followed by step-by-step procedure presented in the IRDiRC Governance. The announcement of the selected Task Forces for the 2025 Roadmap is planned to be delivered before the end of December 2024.
- **The State of Play Report 2022-2024** is planned to be delivered in the first quarter of 2025.
- **RE(ACT) Congress –** The preparations for the 2025 edition of the RE(ACT) congress have started. The congress will be organized jointly by IRDiRC, ERDERA and Black Swan Foundation in March 2025, back-to-back with the IRDiRC Consortium Assembly meeting.
- **CA Chair and Vice Chair Renewal** – The open call will start in September 2024.
- **Membership openings** - Several scientific membership openings are foreseen in 2024: Interdisciplinary Scientific Committee – 4 openings in Q1; Therapies Scientific Committee – 1 opening in Q2; Diagnostics Scientific Committee – 5 openings in Q4.

IRDiRC Consortium Assembly – Scientific Committees Meeting in Shanghai, China (22-23 May, 2024)

The Scientific Secretariat presented the meeting agenda and several important administrative aspects.

IRDiRC KPIs

- **KPIs for IRDiRC and SciSec:**
  - Internal KPIs
    - Project Management and Events
    - Communication (website traffic, social media activity and engagement metrics, newsletter subscribers)
    - IRDiRC Membership (Number of New Members, Meeting Participations, etc.)
    - Budget
  - External KPIs
    - Translation of IRDiRC Goals
    - Brand Awareness (participation to conferences, presentations, external collaborations, etc.)
  - Publications
    - Altmetric Score
    - Number of Citations
    - Twitter Posts (based on Altmetric)

        - Corresponding to IRDiRC Goals
    - IRDiRC activities translated to the IRDiRC Goals
        - Scientific and Societal Impact

- **Sustainability**
    - After ERDERA
    - Support for other activities and task forces
    - VMF