



**INTERNATIONAL  
RARE DISEASES RESEARCH  
CONSORTIUM**

**Minutes of the Consortium  
Assembly Meeting**

**03-04 October 2023  
Montréal, Canada**



**IRDIRC**

## ACRONYMS

AI	Artificial Intelligence
ALAPA	Argentina Patient Alliance
ATMP	Advanced therapy medicinal products
BGTC	BESPOKE Gene Therapy Consortium
CA	Consortium Assembly
CCC	Companies Constituent Committee
CORD	Chinese Organization for Rare Disorders
DSC	Diagnostics Scientific Committee
EJP RD	The European Joint Programme on Rare Diseases
EMA	European Medicines Agency
ERDERA	European Rare Diseases Research Alliance
FCC	Funders Constituent Committee
FDA	US Food and Drug Administration
FFRD	Fondation Maladies Rares
Inserm	Institut national de la santé et de la recherche médicale
IRDiRC	International Rare Diseases Research Consortium
ISC	Interdisciplinary Scientific Committee
MAA	Marketing Authorisation Applications
NBS	Newborn Screening
NCATS	National Center for Advancing Translational Sciences
NIH	US National Institutes of Health
PACC	Patient Advocacy Constituent Committee
PPP	Public-Private Partnerships
PROMS	Patient Reported Outcome Measures
RD	Rare Disease
ROI	Return on investment
RSC	Regulatory Scientific Committee
RUGD	Rare Undiagnosed Genetic Disease
RWE	Real World Evidence
SC	Scientific Committee
SciSec	IRDiRC Scientific Secretariat
SMA	Spinal Muscular Atrophy
SoA	State-of-the-Art
TF	Task Force
Together4RD	Together for Rare Diseases
ULAPA	Latin American Union of Patients with Rare Diseases
WG	Working Group
WODC	World Orphan Drug Congress

## EXECUTIVE SUMMARY

The International Rare Diseases Research Consortium (IRDiRC) held a two-days hybrid meeting of the Consortium Assembly (CA) on 3-4 October 2023, via teleconference and Face-to-Face (F2F) in Montréal, Canada. It was attended by 37 in person participants and 20 online participants representing 35 member organizations, Chairs and Vice Chairs of the Scientific Committees, and members of the Scientific Secretariat.

### 1. Introduction and Welcoming of New Members

- FCC membership
  - New FCC member: **Nicklaus Children’s Hospital (USA)** represented by Daria Salyakina, Director of Center for Precision Medicine
- CCC leadership
  - New CCC Chair: **Vinciane Pirard**, Lead Scientific Advocacy and Insights, Global Medical Affairs Rare Diseases, Sanofi
  - New CCC Vice Chair: **Adriana Huertas-Vazquez**, Senior Director, Global Medical Affairs, Illumina

### 2. Updates from the IRDiRC Constituent Committees (Parallel Sessions)

- Funders Constituent Committee (FCC)
- Companies Constituent Committee (CCC)
- Patient Advocates Constituent Committee (PACC)

### 3. Cross-Committee Exchanges

- PACC led session (FCC + CCC + **PACC**)
- FCC led session (**FCC** + CCC + PACC)
- CCC led session (FCC + **CCC** + PACC)

### 4. Featured Session Topics

- Advancing RD Research and Development through Public-Private Partnership
- Revolutionizing RD Research: Harnessing the Power of Artificial Intelligence

### 5. IRDiRC Strategies, Scientific Secretariat Activities, and AOB

- **Upcoming IRDiRC Meeting and Events**
  - Online CA meeting: 6-7 December 2023
  - Online CA meeting: 06-07 March 2024
  - In-person Joint Consortium Assembly and Scientific Committees meeting: 22-23 May 2024, Shanghai, China
  - In person CA meeting: Fall 2024 in Italy
- **World Orphan Drug Congress in Barcelona: 30 October – 02 November 2023**
  - Several presentations and panels by IRDiRC members
  - IRDiRC booth at the congress

- <https://www.terrapinn.com/conference/world-orphan-drug-congress/agenda.stm>

➤ **Communication Sub-Committee Updates**

- The sub-committee was created to identify communication issues, potential solutions and tactics to improve IRDiRC visibility.

➤ **Irdirc Membership Definition**

➤ **Irdirc Scientific Secretariat Operations** (including budget)

**6. Keynote presentation:** “FDA, NIH & Industry: Lessons learned along the way” (Speakers: Anne Pariser & Elizabeth McNeil)

**7. Updates on Task Forces, Working Groups, and Initiatives**

- Working Group on MedTech for Rare Diseases
- Pluto Project – Under-researched RDs
- Drug Repurposing Guidebook
- N-of-1+ Therapies
- Operationalizing a Comprehensive Framework to Assess the Impacts of Diagnoses and Therapies in Rare Disease Patients
- Functional Analysis
- Funding Models to Support the Spectrum of RD Research and Development
- Parallels of COVID-19 and RD
- Newborn Screening Initiative
- Demystifying Gene Therapy
- Updates on Publications from previous Task Forces (from January 2023)
- Special Issue in the **European Journal of Medical Genetics** presenting articles authored by IRDiRC members. Submission of the articles at the end of 2023.

## THE REPORT

### 1. Summary of the last CA meeting

- CA members met in Montréal on 3-4 October 2023. This event was attended by 37 in-person participants and 20 online participants representing 35 member organizations. It allowed the committees to meet individually and hold cross-committee sessions. Updates on IRDiRC activities were provided.
- Two featured sessions were organized and one keynote presentation:
  - Advancing RD Research and Development through Public-Private Partnership
  - Revolutionizing RD Research: Harnessing the Power of Artificial Intelligence
  - FDA, NIH & Industry: Lessons learned along the way (*keynote presentation*)

### 2. New CCC Leadership

- New CCC Chair: **Vinciane Pirard**, Lead Scientific Advocacy and Insights, Global Medical Affairs Rare Diseases, Sanofi, Belgium
- New CCC Vice Chair: **Adriana Huertas-Vazquez**, Senior Director, Global Medical Affairs, Illumina, USA

### 3. IRDiRC Scientific Committee Members changes

#### New Members

- DSC members (2):
  - **Charles Steward**: Head of Patient and Participant Engagement, Genomics England, UK
  - **Florencia Braga Menéndez**: Director, Argentina Patient Alliance (ALAPA); Founding Member, Latin American Union of Patients with Rare Diseases (ULAPA), Argentina
- TSC members (4):
  - **Alaa Hamed**: Global Head of Medical Affairs, Sanofi, USA
  - **Diana Kwast**: Board Member, Dutch Pituitary Foundation, ePAG Endo-ERN, The Netherlands
  - **Martina Kawome**: Department of Ophthalmology, College of Health Sciences, Harare, Zimbabwe
  - **Rajesh Krishna**: Scientist and Global Lead, Rare Diseases Center of Excellence, Certara, USA

#### End of Mandate

- DSC members (2):
  - **Juergen Reichardt**: James Cook University, Australia
  - **Francois van der Westhuizen**: North-West University, South Africa
- TSC members (2):
  - **Maurizio Scarpa**: Udine University Hospital, Metab-ERN, Italy
  - **Prajnya Ranganath**: Nizam's Institute, India

### Constituent Committee Updates

#### Funders Constituent Committee

- Presentation of iHope Genetic Health
  - Ryan Taft, Vice President of Scientific Research at Illumina, presented the iHope philanthropic program, a project initiated by Illumina. The program has two

primary objectives: (1) to provide clinical whole genome sequencing to as many patients as possible each year, and (2) to assess the program's impact across different geographic regions and income levels. He emphasized the importance of democratizing whole genome sequencing globally, not limiting it to only a small percentage of individuals who can afford it.

- Regulatory Science for RD Research and Cross-Border Panels
  - It was raised that there are inadequacies of regulatory systems in the context of rare diseases, and that existing regulatory processes in various countries, including the FDA, EMA, Health Canada, and others, are primarily designed for more common diseases that involve small-molecule drugs manufactured on a large scale. The traditional regulatory approval process, which often requires large-scale double-blind placebo-controlled trials, does not seem to be practical for rare diseases with limited patient populations. Additionally, the cost and administrative burden of keeping a medicine on the registry in Europe are issues that challenge the development and approval of therapies for rare diseases. It was suggested that the regulatory sciences and processes need to be adapted to the unique challenges of rare disease drugs. This discussion highlights the need for changes in the regulatory framework to better serve rare disease patients and encourages alignment between regulatory agencies to address these issues on a global scale.

#### **Companies Constituent Committee**

- Meeting on the next strategic steps for CCC took place on 05 September 2023, announcing also the change in CCC leadership
- **Key points identified:**
  - How to elevate the priorities of companies within IRDiRC, how to ensure better engagement and communication? How to raise the interest of companies for joining IRDiRC and have a more extended scope?
  - What bridges should the companies create with the other groups (patient advocates, funders), identify the overlapping themes and possible benefits from such collaborations?
  - Reflect on the areas of interest of companies (Public-Private Partnership, Tech Transfer, Business Development, Start-up Life, Optimization of Care/Unmet Need) and what are the perspectives missing
- Plan to implement a concrete feasible action in the next 6 months

#### **Comments:**

- Each company representative prepared a presentation on the activities performed and how they would match the vision and goals of IRDiRC, but also specifying their expectations. Some of the topics raised during the discussion included the green rare disease drug development, sustainability of gene therapies, data sharing, and natural history studies;

- The mission of the companies involved in IRDiRC should be made clearer and focused on the power of collaboration no matter the size or type of the companies;
- Areas of interest:
  - Improved medicines access to patients
  - Improved national history of disease
  - Validation of biomarkers and clinical endpoints
  - Private-public partnerships
  - Platform approaches to research & regulatory science
  - Evidence generation projects in RUGD and NBS
  - Medical Education and Societal engagement, including genetic disease testing
  - Improvement of human health

### **Patient Advocacy Constituent Committee**

- Members discussed how PACC can play a better role in engaging patients/patient groups into IRDiRC's activities and facilitate the sharing and the understanding of IRDiRC outcome activities within the patient community.
- The proposed actions include:
  - Invite members of PACC to present their organization and what they do in research;
  - Invite members of Task Forces and other constituencies to present their work;
  - Summarize and comment the outcome of IRDiRC activities to facilitate their uptake and understanding by the global patient community.
- The members have also clarified the mission of the PACC which is to improve value of rare disease research through active participation of patient community. The mission 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;
  - Develop a life cycle approach from diagnosis to therapies and care follow-up.

### **Cross-Committee Exchanges**

- a) FCC + CCC + **PACC** (session led by PACC)

Summary of PACC-led discussions: how can PACC better engage patient and patient groups into IRDiRC, how can PACC facilitate the uptake and the understanding of IRDiRC activities by the global patient community? What are the opportunities for IRDiRC activities to enhance development of PACC and other members of the global patient community?

PACC suggestions include:

- Invite Patient representatives from TF/WG to present the activities and get feedback from PACC;
- PACC mandate could be to translate IRDiRC work to the community and bring feedback;

- PACC should ensure that what IRDiRC does reflects the life cycle approach i.e., from translational, clinical research to collection of Real-World Data/Real-World Evidence.

The funders, the research community don't use enough patients considering that they are the more knowledgeable about the disease. Funders should consider patient compensation, accessibility to grants for patient groups and participation in peer review. It was also suggested that funders should require that patients are included in the governance of the research projects.

b) **FCC + CCC + PACC** (session led by FCC)

### 1) **Chrysalis Task Force Findings & Results**

The background of the Task Force was to analyse the corporate interest and success in rare disease therapeutics, having the objective to identify key financial and non-financial factors that make RD research and development attractive to companies.

**Methodology:** Through a collaborative effort of task force members, representing leaders from companies, patient advocacy groups, and research funders, a survey was designed and distributed to companies of different sizes with varied investment portfolios and interests in the RD research, accompanied by interviews with respondents.

The results of the survey highlighted investment decisions such as return on investment and risk-reward, an estimation of the future cash outflows (investments) and inflows (returns), and risks associated with the cash flows. With rare diseases, there are certainly problems related to the scale and certainty of the cash flow, because rare disease patient populations are small, and in consequence the returns are limited. The barriers to development are potentially large. There are other factors to be considered such as:

- Familiarity with rare disease research is important
- Many rare diseases progress slowly, which affects funding timelines
- Ability to accurately diagnose the disease is critical
- The regulatory landscape is also critical – shifting requirements with rapidly advancing scientific knowledge (both efficacy and adverse effects)
- Need to balance short vs long-term clinical outcomes
- Pricing/reimbursement has a major impact on ROI (consider price vs value)
- Challenges with academic collaborations are real

### 2) **Presentation on Fondazione Telethon's Strimvelis Marketing Authorization**

Fondazione Telethon (Italy) obtained the positive response by the European Medicines Agency (EMA) on the transfer of the marketing authorization from Orchard Therapeutics for the approved ex-vivo gene therapy for ADA-SCID, becoming the first charity in the world holding the manufacturing and distribution rights of an approved ATMP, and providing an example of a sustainable model for market access for advanced therapies for rare and ultra-



rare diseases and becoming an alternative to industry when there is no other way to ensure the availability of drugs to patients.

c) FCC + CCC + PACC (session led by CCC)

Summary of CCC-led discussions:

- The companies should act as a sounding board, facilitating also cross-sector interactions especially with regulators (e.g. for trial design methodology), but in the first place it is essential to understand the viewpoint of the companies involved in IRDiRC;
- **Natural history studies** – questions were raised if they are better performed at community level, but it also leads to the problem of ensuring that the data collected is qualitative, standardized and will allow a flexibility to evolve over time; CCC can contribute to basket trials;
- **Precompetitive space** – clarify the sustainability of gene therapies, green rare disease development, and its optimization depending on the available resources;
- A few questions were raised from the audience such as: for funders, it can be hard to fund natural history studies since it is required to define a sustainable model for it, the distribution of data and the anonymization process can be complicated, while the community-based programmes can be considered as a solution, the companies need to provide a clearer process on the long-term sustainability of this approach; the scope of the clinical study should also be explicit, is it for helping in the design of protocols, is it for clarifying the onset of disease? It can also be used as a control group when setting up the study (with the exception of haemophilia studies), but the question that remains is how the data will be shared afterwards.
- **RWE and PROMS** – for clinical trials on gene therapies ongoing in Canada, the patients are required to go to certain hospitals, how the process can be simplified by ensuring the carriers are sent where they are needed; decentralized trials can offer certain solutions, but expectations on the foreseen results should also be managed in a realistic manner;
- The implementation of smaller scale projects should be considered (the example of Japan);
- Cross-committee talks, in particular with the regulators and patient groups, would offer insights on the possible methodologies for clinical trials design and understand where everyone stands at this moment.

### Featured Session Topics

- 1) **Advancing RD Research and Development through Public-Private Partnership**  
*Panelists: PJ Brooks (FCC member), Daria Julkowska (IRDiRC coordinator), Vinciane Pirard (CCC chair), Franz Schaefer (invitee), Sheela Upadhyahya (invitee); Moderator: Samantha Parker (IRDiRC vice chair)*

The session was led by the panelists PJ Brooks (NCATS/NIH), Daria Julkowska (EJP RD/IRDiRC), Vinciane Pirard (Sanofi), Franz Schaefer (Heidelberg University Hospital), and Sheela Upadhyahya (FIPRA). It was moderated by Samantha Parker (IRDiRC vice chair).

Public-Private Partnerships (PPP) are usually referred to with different definitions, but there are some requirements when thinking about successful PPP: transparency, sharing an understanding of common goals and objectives, a confidence approach and continuous sharing of information between the public sector and industry, in which a clear structure of governance and a sustainable long-term plan play a key role. During the last years, different initiatives and programs have tried to provide a model for PPP: BESPOKE Gene Therapy Consortium (BGTC), IMI Consortia, Together for Rare Diseases (Together4RD), EU-PEARL, RD-Moonshot, IRDiRC Clinical Research Networks for Rare Diseases Task Force, etc., however the question that remains is how to make this tangible by continuous mapping and understanding how these initiatives can be inter-linked, without being restricted to certain geographies. In this sense, IRDiRC can help in mapping all these initiatives and programs and connect them for developing a stronger roadmap since it has the global expertise and the representation to facilitate the discussion and the creation of a structured worldwide available PPP model. Establishing a collaborative between the industry partners and public entities prerequisites sharing of relevant information among the stakeholders, including nonetheless regulatory and legislative regulations in different regions and countries. IRDiRC, through its international dimension, can be an accelerator of the results between countries and can build on knowledge sharing, also providing recommendations on the standardization of processes and procedures and in the development of the global contact pathways.

## 2) Revolutionizing RD Research: Harnessing the Power of Artificial Intelligence

*Presenter: Gareth Baynam (ISC chair)*

### How can AI improve the lives of people and families living with rare diseases

- By reducing diagnostic odyssey – faster response time, cost reduction;
- Finding new treatments – discoverability of the available data based on dataset analysis (biological, chemical information, drug efficacy prediction, safety);
- Empowering patients and families – educational role, database of personalized information, guidance, resources;
- Development of digital therapeutics – apps, games, wearable devices;
- Symptom matching;
- Disease education.

AI can ensure improvements in care coordination: diagnosis and screening, drug discovery and development, public health interventions, and care coordination models. The examples of **IMPROVE**, **UTOPIA** and **CP CoderR** were presented.

The meeting participants were asked to provide their ideal model of care. The implementation of AI for rare disease diagnosis would ensure an accelerated process for the undiagnosed patients, but in the same time one of the functions of AI remains to eliminate low quality data and be flexible enough to integrate different types of data, not just from the medical records. AI should be applied in the monitoring of therapeutic success (or failure) based on RWE and help in the identification of gaps that need to be addressed. Nevertheless, AI should assist in providing the lived experience to patients and ensure a better understanding of the whole process from the patient experience (having a lay summary with a friendly design for patient access, also considering the appropriateness of the language). The advancements of the

clinical development should be one of the key points of AI usage, including in identifying the common pathways of RDs (shared molecular targets), potential screening of molecules and biologicals, capturing and monitoring of patient symptoms and their evolution.

### 3) FDA, NIH & Industry: Lessons learned along the way (*Keynote presentation*)

*Presenters: Anne Pariser (RSC chair) & Dawn Elizabeth McNeil (ISC member)*

In the next decade, it is foreseen that the pharma industry will shift its focus towards the rare diseases research (Source: PharmaVoices – *Why the pharma industry is digging deep in the rare diseases*). While rare diseases affect approximately 300 million people worldwide, currently 90% of diseases have no available treatment. Orphan designations and approvals have marked an upward trajectory in the last years, with funding coming principally from publicly available grants (academia, NIH) or philanthropy. The shared lessons learned from FDA emphasized a strict focus on the safety and efficacy trials. In the assessments performed by FDA, the cost doesn't represent a blocker when it comes to patient safety. A case study was presented.

NIH is the largest public funder in the world, being composed of different thematic institutes with a different funding and management. A great majority of the funds is designated for the public health priorities, and grant scoring normally is shifted towards innovation and based on prior experience. A case study was presented of a clinical research study for a disease with no approved products.

From the industry perspective, the developmental phases are heavily driven by bench science, but most of the times are conditioned by tight financial resources, limited funding, and short-term milestones. A case study of a small population clinical trial was presented with no approved therapy for a poorly understood disease. A strong collaboration with NIH and patient organizations could advance the clinical research.

The SMA example was described, starting from a historical perspective, and explaining the evolution of research in this area along the years.

**Disclaimer:** *This session was a summary of personal impressions shared by the presenters and it does not reflect an official position by the institutions mentioned in the presentation/text.*

#### **IRDiRC Strategies, Scientific Secretariat Activities, and AOB**

- Upcoming IRDiRC meetings and events
- Communication Subcommittee updates
- IRDiRC membership definition
- IRDiRC Scientific Secretariat operations (including budget)

#### **Upcoming IRDiRC meetings and events**

- **World Orphan Drug Congress (WODC) Europe 2023**
  - IRDiRC was participated the WODC from 30 October – 2 November, in Barcelona, Spain, where several IRDiRC members participated as speakers,

panelists or moderators of different sessions: Virginie Hivert, Daniel O'Connor, Marjon Pasmooij, Anneliene Jonker, Violeta Stoyanova-Beninska, Cesar Hernandez, Virginie Bros-Facer, Samantha Parker, David Pearce, Daria Julkowska, Durhane Wong-Rieger, PJ Brooks, Maria Cavaller Bellaubi, Mary Wang

- Full congress agenda: <https://www.terrapinn.com/conference/world-orphan-drug-congress/agenda.stm>
- IRDiRC was showcased and had a booth.

### Next CA/CA-SC Meetings

- 06-07 December 2023: Online Consortium Assembly Meeting at 15:00-17:00 CET
- 22-23 May 2024: In person Consortium Assembly Meeting in Shanghai (China)
  - 1.5-day meeting; Back-to-Back with China RD Research and Translational Medicine Annual Conference
  - Meeting organization supported by Chinese Organization for Rare Disorders (CORD), Hope for Rare Foundation and Fudan University Children's Hospital China

### Communication Sub-committee Updates

- The first group meeting held on the 24 May 2023
  - Introductions and identification of communication issues, potential solutions and tactics to improve IRDiRC visibility;
- The group has worked on the creation of a communication slide deck for IRDiRC to be utilized at different events by its members;
- Website review and restructuring is planned for the next 3 months to ensure a better organization of the available resources, e.g. if a user is interested in diagnosis, to be able to access all related resources on the website (task forces, deliverables, recognized resources, publications, tools).

**Comments:** Some members suggested that IRDiRC should emphasize more the role it has in helping patients by aligning the RD research priorities globally (promotion of therapy development, optimization of care, improvement of funding models, etc).

### IRDiRC Membership Definition

- The presence of an alternative representative at the meetings was validated and will be integrated in the governance; funding of PACC representative(s) by the SciSec will remain restricted only to one member, with the possibility of having another representative joining the meetings through his own organization funding.

### The Scientific Secretariat in ERDERA

In September 2024, there will be a transition of the IRDiRC Scientific Secretariat coordinating entity from Inserm (France) to Fondation Maladies Rares (France). This process will imply that

all ongoing activities need to be finalized by August 2024. Based on the anticipated budget, it is foreseen that two Task Forces per year will benefit to have the costs covered for an in-person meeting/workshop. The Clinical Research Network conference will continue to take place every 2 years.

### **Task Forces, Working Groups and Other Initiatives**

#### ➤ **Updates were provided for the following activities:**

- Working Group on MedTech for Rare Diseases
- Pluto Project – Under-researched RDs
- Drug Repurposing Guidebook
- N-of-1+ Therapies
- Operationalizing a Comprehensive Framework to Assess the Impacts of Diagnoses and Therapies in Rare Disease Patients
- Functional Analysis
- Funding Models to Support the Spectrum of RD Research and Development
- Parallels of COVID-19 and RD
- Newborn Screening Initiative
- Demystifying Gene Therapy
- Updates on Publications from previous Task Forces (from January 2023)

#### ➤ **Working Group on MedTech for Rare Diseases**

- Objectives: To understand and map the current incentives, supportive frameworks, and unmet technical and functional needs for developing medical devices for rare diseases. The group would also like to identify the regulatory landscape in the different regions for medical devices.
- Expected Output: The Working Group intends to publish a comprehensive overview of incentives and frameworks for medical devices worldwide, opportunities for harmonization approaches in the regulatory space, and the involvement of patients in medical device development.
- Progress Update: The Working Group is currently submitted an article that summarizes the state-of-the-art in rare diseases and medical technologies. They have also engaged in discussions on patient involvement in MedTech development and participated in few speaking engagements. A Wikipedia page on medical technologies was created and a survey was sent to the Europeans Reference Networks to understand their needs for medical devices and the problem they encounter.

#### ➤ **Pluto Project on Under-Researched Rare Diseases**

- Objectives: To identify those rare diseases that appear to have attracted virtually no interest from academic researchers and industrial developers; determine the characteristics they have in common; and understand roadblocks in developing effective treatments for such diseases.
- Progress Update: A new working definition of under-researched rare disease has been drafted as a disease that has a “4-Zero Concept”: No clinical trial activity, No scientific publication available, No regulatory authority orphan drug designation,

and no approved medicine/therapy. 4-Zero Concept is now questioned as initial methodological approach has shown that databases are either incomplete with redundant terminology and or duplications. Requirement for further database integration to identify groups of diseases based on variables that can be consistently and robustly measured drawing valid conclusions. Therefore, the TF will develop new methodological approaches to measure the characteristics of under-researched rare diseases.

- Expected Output: The Task Force will aim for a short commentary paper with some of the methodology that is sufficiently robust and to set the scene for further piece of work – outside of the Task Force.

#### ➤ **Drug Repurposing Guidebook**

- Objectives: To create a guidebook focused on repurposing approaches (incentives, regulatory tools, initiatives, development tools, etc.).
- Progress Update: The group agreed on a definition of repurposing and identified four model cases for the guidebook which are on/off patent and with/without Marketing Authorisation Applications (MAA). The group finalized the preparation of the materials including, the building blocks, the activity chart, the START checklist. A manuscript was submitted to Nature Review Drug Discovery.
- Expected Output: The Orphan Drug Development Guidebook has been completed with the materials developed by the Task Force. A commentary article describing the drug repurposing guidebook has been published by Nature Reviews Drug Discovery journal.

#### ➤ **N-of-1+ Therapies**

- 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.
- Progress Update: The group reviewed the literature and drafted the state-of-the-art paper. The therapy roadmap for N-of-1 therapy development is drafted. Currently the first publication is under internal revision based on the comments received from the journal. An in-person workshop was organized on November 2-3 in Barcelona, back-to-back with World Orphan Drug Congress.
- Expected Output: SoA paper, another publication planned to be drafted in 2024.

#### ➤ **Operationalizing a Comprehensive Framework to Assess the Impacts of Diagnoses and Therapies in Rare Disease 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 rare disease.
- 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, rare disease ecosystem impacts. The aim is to identify the role of the patients and the families, identify gaps, and select quantitative indices and qualitative measures that can be mapped on the patient pathway.

- Expected Output: Framework to assess impact. White paper.

➤ **Funding Models to Support the Spectrum of RD Research and Development**

- Objectives: To Identify key motivating factors for different types of funders of rare disease research and how different types of funders decide at which point in a research study’s lifecycle they will provide support. To identify the key influencing factors and models for effective public-private partnerships at different stages of a treatment’s life cycle.
- Progress Update: The group is actively conducting interviews with key opinion leader to gain insights into funding strategies and decision-making processes. Simultaneously, an in-depth analysis of a database containing orphan drug designations from EMA and FDA is currently being performed. This analysis includes an examination of the number of products in the preclinical stage at the time of designation, the progression of these into clinical trials, reasons for product failure, the distribution of public and private grants across different development stages, and the involvement of small or medium-sized companies and academic researchers in partnerships with larger pharma/biotech entities.
- Expected Output: A summary paper of findings and a Funding Model/Good Practices Toolbox.

➤ **Functional Analysis**

- Objectives: To create a framework for the robust and effective ecosystem of functional analyses in rare diseases.
- Progress Update: The group is actively engaged in crafting the framework that will serve as the foundation of their future white paper. Simultaneously, preparations are underway for an in-person workshop in the near future.
- Expected Output: Framework for the robust and effective ecosystem of functional analyses in rare diseases. White paper.

➤ **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 (perspective 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 – *internal review*;
  - 5) Pitfalls and limits of NBS for inborn errors of metabolisms and how NGS could be the next complementary test – *final draft in development*;
  - 6) Success and challenges in European NBS Alliance on SMA – *internal review*;
  - 7) Newborn Screening in Mexico: Present and Future – *first draft in development*.

- Theme 2 - **Policy, Ethics and Patient Perspectives** (associate editors: Helen Malherbe & Mary Wang):
  - 1) Introductory Editorial – *to be drafted during review process*;
  - 2) More evidence is not enough to reconcile equity and efficiency in neonatal screening policies: Analysis of the trend in Spain, 2003-2022 – *accepted for publication*;
  - 3) The Australian landscape of newborn screening in the genomics era – *submitted to journal*;
  - 4) Patient advocacy in action for Newborn Screening: role of patient organizations in the timely diagnosis of rare diseases and quality of life – *submitted to journal*;
  - 5) Overcoming challenges in sustaining NBS: the Philippine model – *final internal review*;
  - 6) Newborn screening in South Africa – *final internal review*;
  - 7) NBS in the rural community – *submitted to journal*.
- **Parallels Between COVID-19 and Rare Diseases (initiative)**
  - The main goal is to publish a position paper drawing parallels between COVID-19 pandemic and “Operation Warp Speed” explaining the urgent and ongoing silent epidemic of Rare Diseases;
  - The activities performed so far: a) a writing committee was formed, and the goals set, b) the first draft of the manuscript was completed, c) revisions and editing are performed currently through videoconferencing and email exchange;
  - Expected outcome: position paper highlighting the ongoing Rare Diseases emergency; Publishing timeline and journal TBC.
- **Demystifying Gene Therapies**
  - The information on gene therapies submitted by the session participants in Berlin (Germany) was collected and collated.
  - A review article will summarize this knowledge and will be submitted to the European Journal of Medical Genetics Special Issue as review article.

## Publications update 2023

### Published

- **IRDIRC Drug Repurposing Guidebook: making better use of existing drugs to tackle rare diseases.** Anneliene Jonker, Simon Day, Michaela Gabaldo, Heather Stone, Martin de Kort, Daniel J. O’Connor & Anna Maria Gerdina Pasmooij. Access the paper [here](#).
- **Defining rare conditions in the era of personalized medicine.** Daniel J. O’Connor, Michela Gabaldo, Annemieke Aartsma-Rus and Anneliene Hechtelt Jonker. Access the paper [here](#).



- **The IRDiRC Chrysalis Task Force: making rare disease research attractive to companies.** Katherine L. Beaverson, Daria Julkowska, Mary Catherine V. Letinturier, Annemieke Aartsma-Rus, Jennifer Austin, Juan Bueren, Simon Frost, Misako Hamamura, Jane Larkindale, Greg LaRosa, Rita Magenheimer, Annamaria Merico, Anna Maria Gerdina Pasmooij, Vinciane Pirard, Nicholas Ekow Thomford, Michihiko Wada, Durhane Wong-Rieger, and Adam L. Hartman. Access the publication [here](#).
- **How to START? Four pillars to optimally begin your orphan drug development.** Anneliene Hechtelt Jonker, Liliana Batista, Michela Gabaldo, Virginie Hivert & Diego Ardigo on behalf of the IRDiRC ODDG TF and IRDiRC TSC. Access the paper [here](#).
- **Targeting shared molecular etiologies to accelerate drug development for rare diseases.** Galliano Zanello, Macarena Garrido-Esteba, Ana Crespo, Daniel O’Connor, Rima Nabbout, Christina Waters, Anthony Hall, Maurizio Tagliatalata, Chun-Hung Chan, David A Pearce, Marc Doms, Philip John Brooks. Access the paper [here](#).
- **Towards the international interoperability of clinical research networks for rare diseases: recommendations from the IRDiRC Task Force.** Rima Nabbout, Galliano Zanello, Dixie Baker, Lora Black, Isabella Brambilla, Orion J. Buske, Laurie S. Conklin, Elin Haf Davies, Daria Julkowska, Yeonju Kim, Thomas Klopstock, Harumasa Nakamura, Kim G. Nielsen, Anne R. Pariser, Jose Carlos Pastor, Maurizio Scarpa, Maureen Smith, Domenica Taruscio, Stephen Groft. *Orphanet Journal of Rare Diseases, 2023*. Access the paper [here](#).
- **Sustainable approaches for drug repurposing in rare diseases: recommendations from the IRDiRC Task Force.** Galliano Zanello, Diego Ardigo, Florence Guillot, Anneliene H. Jonker, Oxana Iliach, Hervé Nabarette, Daniel O’Connor, Virginie Hivert. *Rare Disease and Orphan Drugs Journal, 2023*. Full text available [here](#).

## In preparation

- **Indigenous population** – Advancing rare genetic diseases diagnosis and research for indigenous people – *Manuscript accepted in Nature Genetics*
- **IRDiRC-RDI Global Access Working Group Part II** – Barriers to access essential medicines for rare diseases – case studies – *Manuscript in review*
- **IRDiRC Drug Repurposing Guidebook** – Making better use of existing drugs to tackle rare diseases – *Manuscript in review*
- **Primary care** – Global Health for Rare Diseases through Primary Care – *Manuscript in review*
- **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 in review*

- **Enabling and enhancing telehealth for rare diseases 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 in review*

**Collaboration with the European Journal of Medical Genetics**

- Special bundle issue under preparation, foreseen to be submitted by the end of 2023.