INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the Consortium Assembly Meeting

30 November - 01 December 2022

IRDiRC

ACRONYMS

AI	Artificial Intelligence
CA	Consortium Assembly
CCC	Companies Constituent Committee
CSR	Corporate Social Responsibility
DSC	Diagnostics Scientific Committee
DUC-CCE	Digital Use Conditions-Common Conditions of use Elements
EJP RD	European Joint Programme on Rare Diseases
EPND	European Platform for Neurodegenerative Diseases
FCC	Funders Constituent Committee
GA4GH	Global Alliance for Genomics and Health
HPO	Human Phenotype Ontology
IHI	Innovative Health Initiatives
ISC	Interdisciplinary Scientific Committees
KOL	Key Opinion Leaders
LOI	Letter Of Intent
MAA	Marketing Authorization Application
MHRA	Medicines and Healthcare products Regulatory Agency
NCATS	National Center for Advancing Translational Sciences
NHS	National Health Service
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
OJRD	Orphanet Journal of Rare Diseases
OpComm	Operating Committee
PACC	Patient Advocates Constituent Committee
PAO	Principal Authorizing Official
PPP	Public Private Partnership
RSC	Regulatory Scientific Committee
TF	Task Force
TSC	Therapies Scientific Committee
RD	Rare Disease
RDI	Rare Disease International
ROI	Return-Of-Investment
ULEIC	University of Leicester
UMCG	University Medical Center Groningen
WG	Working Group
WHO	World Health Organization

EXECUTIVE SUMMARY

The International Rare Diseases Research Consortium (IRDiRC) held a two-days hybrid meeting of the Consortium Assembly (CA) on 30 November – 01 December 2022 via web/teleconference and Face-to-Face (F2F) in Paris, France. It was attended on-site by 33 participants representing 21 member organizations (11 Funders, 3 Companies, and 7 Patient Advocates), two members (chair and vice-chair) of the Interdisciplinary Scientific Committee (ISC), one member (vice-chair) of the Diagnostics Scientific Committee (DSC), two members (chair and vice-chair) of the Therapies Scientific Committee (TSC), one member (vice-chair) of the Regulatory Scientific Committee (RSC), and six members of the Scientific Secretariat (SciSec), including 20 online participants on average per day.

30 November 2022

1. Parallel Sessions and Cross-Committee Exchange

- Session 1
  - Patient Advocates Parallel Session
  - Funders and Companies Cross-Committee Exchange
- Session 2
  - Companies Parallel Session
  - Funders and Patient Advocates Cross-Committee Exchange
- Session 3
  - Funders Parallel Session
  - Companies and Patient Advocates Cross-Committee Exchange

2. Summary of Parallel Sessions and Cross-Committee Exchange

- Funders Constituent Committee (FCC): FCC members used this session as a Funders' Forum sharing strategies and experiences with emphasis on the following:
  1. Funding strategies in the region or country
  2. Current or previous funding challenges and difficulties
  3. What is currently working well in the region/country that could be advised to the other funders in the meeting?
  4. How can IRDiRC further add value to the works of the funders?

- Companies Constituent Committee (CCC): CCC members discussed strategy on membership definition and identified expectations for future members and current members. Strategic outreach to potential CCC members aligned with IRDiRC's goals was also discussed, identifying organizations that can have a valuable impact.

- Patient Advocates Constituent Committee (PACC): PACC members used this session to discuss their submitted Task Force proposal for the IRDiRC Roadmap 2023, "Framework to Assess Impacts Associated with Diagnosis, Treatment, Support, and Community Integration that Can Capture Changes Along the Rare Disease Patient and Family History", and assessed the impact and contribution of PACC representatives in different IRDiRC Task Forces.

3. IRDiRC Task Forces (TF) and Working Groups (WG)

- IRDiRC-RDI Global Access Working Group (in collaboration with RDI)
- Machine Readable Consent and Use Conditions (in collaboration with EJP RD)
- Shared Molecular Etiologies Underlying Multiple Rare Diseases (led by the ISC)
- Integrating New Technologies for the Diagnosis of Rare Diseases (led by the DSC)
- Primary Care (led by the DSC)
- Enabling and Enhancing Telehealth for Rare Diseases Across the Globe (led by the FCC)
- Working Group on MedTech for Rare Diseases (led by TSC and ISC, in collaboration with University of Twente)
- Pluto Project (led by the CCC and TSC)
- Drug Repurposing Guidebook (led by the TSC)

01 December 2022

4. Plenary Discussions

- Parallels Between COVID19 and Rare Diseases
  IRDiRC members identified the following parallels between COVID19 and Rare Disease:
  - Low investment in rare disease research due to Return-Of-Investment (ROI) concern; low desire for risk by institutions, industry, and patient population.
  - Limited resources and qualified personnel.
  - Rare diseases field is constrained by stringent procedures and regulations; it should have the same flexibility that was provided for COVID-19.
  - Support the social investment, promote solidarity by creating common platforms for treatments that have no economic business models in patient's benefit.
  - Using Telehealth for health services and support, but also for educational purposes and community mobilization of resources and capabilities.
  - Reducing the fragmentation of the market, by adapting the treatment prices between countries and ensuring pricing negotiations.
  - Government-private partnerships.
  - Ensure public workforce: Evaluate and research for new insights and innovations that can be applied in the development of therapies; checking where the RD use cases could fit in the frameworks that have been used in COVID-19 management.

5. IRDiRC Priorities and Strategies

- IRDiRC Events and Communication Activities
  - Upcoming CA Meetings in the Year 2023
    1. 14-15 March 2023: Joint Meeting with Scientific Committees (semi-hybrid) in Berlin, Germany
    2. 07-08 June 2023: Consortium Assembly Meeting (Online)
    3. 02-03 October 2023: Consortium Assembly Meeting (Hybrid) in Toronto, Canada
    4. 06-07 December 2023: Consortium Assembly Meeting (Online)

- Upcoming IRDiRC Events
    1. 15-18 March 2023: IRDiRC-EJPRD-RE(ACT) Congress (In Person) in Berlin, Germany

- IRDiRC Communication Activities
    1. Statistics of IRDiRC's Communication Platforms
    2. IRDiRC Communication Activities in a Nutshell for Year 2022

➢ IRDiRC Initiatives
- Newborn Screening: Virginie Bros-Facer from CCC presented the two special issues currently being prepared, which are focused on (1) Real World Applications and Technologies; and (2) Policy, Ethics, and Patient Perspectives. Manuscripts will be published in the Rare Disease and Orphan Drugs Journal.

➢ IRDiRC Governance and Procedures
- Revision of IRDiRC Governance: The IRDiRC Governance version 6.0 includes the addition of the new Regulatory Scientific Committee (RSC), changes to the mandate of the Consortium Assembly (CA), Operating Committee (OpComm), Constituent and Scientific Committee, including changes to the nomination and membership procedure for Scientific Committees, and information about Task Forces and Working Groups were added. Comments were received and are under review.

- Task Force Proposal Submission and Validation: The new task force proposal submission and validation process was re-iterated, including the timeline of each process and requirements from future Task Force Chairs. Feedback was collected from the Consortium Assembly.

➢ IRDiRC Roadmap 2023
- Four OpComm-recommended Task Force proposals submitted by the IRDiRC Constituent and Scientific Committees were officially presented to the Consortium Assembly by the Task Force proposers:
    1. Framework to Assess Impacts Associated with Diagnosis, Treatment, Support, and Community Integration that Can Capture Changes Along the Rare Disease Patient and Family History (led by the PACC)
    2. Functional Analysis (led by the DSC)
    3. Funding Models to Support the Spectrum of Rare Disease Research and Development (led by the FCC)
    4. Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations (led by the TSC)

REPORT

1. Summary of Parallel Sessions and Cross-Committee Exchange

- **Funders Constituent Committee (FCC) Parallel Session**
  - FCC members shared their activities, projects, and new funding calls.
  - FCC members also discussed about funding for data management and the continuum of basic research to translational, including data sharing and incentivisation framework.
  - The Vice Chair of the FCC led the funders' forum on funding strategies with an emphasis on the following topics:
    - Funding strategies in the region or country
    - Current or previous funding challenges and difficulties
    - What is currently working well in the region/country that could be advised to the other funders in the meeting?
    - How can IRDiRC further add value to the works of the funders?

- **Companies Constituent Committee (CCC) Parallel Session**
  - CCC members used this session to discuss and evaluate the following items:
    - CCC membership definition and requirements, including the value of being part of IRDiRC
    - Revised Letter of Intent (LOI) for companies interested in becoming IRDiRC members, and maintaining the interest of organizations even after onboarding
    - Strategic outreach to new companies that aligns with IRDiRC goals, including venture capital representatives
    - Inconsistent participation of companies in IRDiRC activities and creating a strategic direction
    - Participation in different industry-related events

- **Patient Advocates Constituent Committee (PACC) Parallel Session**
  - PACC members used this session to review their recently submitted task force proposal for IRDiRC Roadmap 2023 and measure its impact.
  - PACC members also assessed the impact and contribution of PACC representatives in various IRDiRC Task Forces (experience and lessons learned), and identified possible representatives for new Task Forces.
  - Mentorship and skill development of rare disease patient advocates has also been discussed.

- **Funders and Companies Cross-Committee Exchange**
  - FCC and CCC discussed the importance of public-private partnerships and having specifically defined roles and responsibilities for each entity to advance partnerships. The IRDiRC Chair requested the Consortium to share examples of successful public-private partnerships and requested to share their reflections on the actual components of a successful public-private

partnership. The IRDiRC Chair proposed to have a workshop focused on this topic. The following are some of the key takeaways from this exchange:

- Sharing a common objective;
- Specify clearly the goals, the financial and non-financial expectations and contributions;
- Industry to provide not just monetary support, but also scientific input;
- Multiple funding models (adapted also for small size companies and academics);
- Creation of networks between different regions.

- FCC and CCC also discussed related topics on drug repurposing:
  - Evaluate what new clinical trials on drug repurposing can bring and the commercial risks for companies;
  - Regulatory perspective: Commercial boundaries; Development of endpoints and a unified framework;
  - Compassionate use and possible issues related to it;
  - Data sharing and protection for the parties involved;
  - Patient advocacy groups to be more involved in the development of clinical trials for drug repurposing and gene therapies;
  - Public philanthropic partnerships.

➢ **Funders and Patient Advocates Cross-Committee Exchange**

- FCC and PACC discussed about a collaboration between funders and patient advocates through promoting calls for projects focused on patients' real needs and encouraging social responsibility national programs with a focus on advocacy and awareness. Other topics discussed were the following:
  - Third-party entity to have a role in the selection of the best project for a specific disease to ensure transparency of the process;
  - Funding of patient organisations in research projects and international collaborations (e.g. School of Biology in North America, Asia, Middle East, and Africa – European clinicians collaborate with local representatives during a one-week training programme with the cost being supported by pharmaceutical companies);
  - Increase training programmes for clinicians and patients from different regions (including from outside Europe);
  - Review the regions depleted of investments and include local expertise to ensure a global perspective;
  - Train the patient advocacy representatives to have the required skills for participation in research projects, including defining research priorities and funding options.

➢ **Companies and Patient Advocates Cross-Committee Exchange**

- CCC and PACC emphasized the need of having high-quality, standardized data registries. PACC mentioned that patient organisations receive requests from various companies to recruit patients for certain diseases, and that molecular diagnosis is not available in many

countries. CCC and PACC discussed about the use of hospital databases for patient identification.

- CCC and PACC discussed about a need for unified guidelines (e.g. for CSR grant applications) and potentially having a dedicated IRDiRC Task Force to work on this, with considerations of the following:
  - Monetary disparities and accessibility;
  - Continuous education and strong engagement (educate CSR administrators, and work together with representatives from local ministries);
  - Understand the challenges and gaps for patient organizations;
  - Encourage social responsibility by elevating RD awareness and visibility, request suggestions and feedback for improvement;
  - Evaluate the drug access costs (for certain regions such as Africa, where cost is too high and access too difficult);
  - Sustainability issues, especially for low and middle-income countries;
  - Include the latest international developments.

- PACC raised the need for toolkits and resources to access the latest information on drug development for their communities, from basic science to operational aspects. PACC suggested creating diagnostic pathways applicable in real-world and tailoring appropriate therapies based on patients' needs. PACC also mentioned the promotion of programs that stir clinicians' interest in finding rare disease diagnostic solutions and therapies, and raising awareness of clinical trials, especially for ultra-rare diseases.

- CCC and PACC also discussed different diagnosis models such as:
  - With different patient paid options
  - Patient Care Fund (crowd funding schemes)
  - Partnerships with industry (including full cost coverage)

2. IRDiRC Task Forces (TF) and Working Groups (WG)

- Updates on ongoing activities were presented by Task Force/Working Group leaders.
- **Nine Activities are Ongoing for the Year 2022**
  - IRDiRC-RDI Global Access Working Group (in collaboration with RDI)
  - Machine Readable Consent and Use Conditions (in collaboration with EJP RD)
  - Shared Molecular Etiologies Underlying Multiple Rare Diseases (led by the ISC)
  - Integrating New Technologies for the Diagnosis of Rare Diseases (led by the DSC)
  - Primary Care (in collaboration between FCC, ISC, and DSC)
  - Enabling and Enhancing Telehealth for Rare Diseases Across the Globe (led by the FCC)
  - Working Group on MedTech for Rare Diseases (led by the University of Twente)
  - Pluto Project (led by the CCC and TSC)
  - Drug Repurposing Guidebook (led by the TSC)

- **IRDiRC-RDI Global Access Working Group**
  - Presentation: Mary Wang from RDI (PACC representative, on behalf of Durhane Wong-Rieger, PACC Chair) presented the updates and summary of progress. This WG is a collaboration with RDI.
  - Objective: The goal is to improve standards of care for RD patients by promoting access to approved medicines, to initiate research into barriers to accessing RD medicines and to define opportunities to address those barriers. The Phase 1 of this WG was concluded through the publication of a paper in July 2021 entitled "Essential list of medicinal products for rare diseases: Recommendations from the IRDiRC Rare Disease Treatment Access Working Group". Phase 2 is using a bottom-up approach to identify common themes and challenges, and approaches on how the problems were addressed in different countries by gathering real experiences and case studies regarding the accessibility to medicines and by analyzing the approaches taken by different stakeholders to source medicines and promote the changes in a systemic way.
  - Progress Update: This WG is currently developing a case study on cystinosis i.e., identify the barriers encountered by different stakeholders to accessing cystinosis drugs, (Cystagon, Custadrop, Procysbi) in different regions and develop recommendations, and one on cystic fibrosis that includes the standard of care medicines that are both disease-specific and addressing the symptoms (medications and supplements). The process implies collecting information from Israel, Ireland, South Africa, Columbia and Italy and interviewing patient organizations and clinicians. Current findings include the following:
    - Challenges at the diagnosis level means some countries do not have identified cystinosis patients, and thus no conversations were taking place regarding access to treatment.
    - Varied care management: paediatric nephrology vs inborn error of metabolism (IEM)
    - When a medicine is not available, cost is often cited as the main barrier.
    - Medicines may be imported or made available via subsidiary company or partner company.
    - Procysbi is available in Latin America through a managed assistance program through partner Uno Healthcare Inc (according to Horizon's Annual Report 2021).
    - Cystagon is available in Australia via Alphapharm (a Mylan Company).
    - Compounding is seen in several countries (especially for eyedrops).
    - Good access includes a comprehensive care system, awareness, and access to future medicines.
  - Expected Output: Publication based on case study approach to describe the barriers to access stratified by types of therapy, characteristics of rare disease populations, and key country parameters.

- **Machine Readable Consent and Use Conditions**
  - Presentation: Esther van Enckevort from University Medical Center Groningen (UMCG) presented the updates and summary of progress. This Task Force is led by Esther van Enckevort (from ISC) and Anthony Brookes (from the University of Leicester (ULEIC), in

collaboration with the European Joint Programme on Rare Disease (EJP RD). The team comprises of approximately 40 international scientists.

- Objectives: To create machine-readable profiles for consent and use for registries and biobanks by building on Global Alliance for Genomics and Health (GA4GH) + IRDiRC standard data structures and semantics.
- Progress Update: At record level, the creation of an individual level consent template is under development, mapped to the DUC-CCE structure; the needs for the record level consent and use conditions are under evaluation for biobanks. At resource level, different Real-World Pilots are under development:
  - BBMRI-ERIC Directory
  - MOLGENIS component for RD registries
  - Stand-alone software by ULEIC
  - Use/Access Policy in Gates Workbench (IHI EPND project)
  - And under consideration by HDR-UK
- Expected Output: Two manuscripts are ready to be submitted in Q2 2023: (1) DUC, (2) CCEs; Work with ontology developers to define new classes and properties to fill gaps identified in the ontologies; Extend the CCE concepts to provide a basis for consent and use conditions at record level, in DUC format.

➢ **Shared Molecular Etiologies Underlying Multiple Rare Diseases (SaME)**

- Presentation: PJ Brooks from NCATS, NIH (USA) presented the updates and summary of progress. This Task Force is led by the FCC and ISC (PJ Brooks and Marc Dooms).
- Objectives: To assess the global landscape of clinical trials of drugs targeting SaME, including approaches to identify and include patients, and to identify potential clusters of rare diseases that may benefit from the SaME approach. The group would also like to explore the applicability of the tissue-agnostic oncology basket trials framework for basket trials of drugs targeting SaME underlying multiple rare diseases and identify the roadblocks, potential regulatory pathways, and ethical issues for such trials.
- Progress Update: The group is preparing a manuscript describing (1) Definition of SaME as validated by the group (same type of mutations, pathways); (2) Rational for basket trials in RD (Clinical/R&D perspective, patient needs, economic/costs); (3) Landscape analysis - Description of selected basket clinical trials in RD; (4) Key elements/considerations for setting up basket trials in RD (design, methodology, analysis); and (5) Implications for future studies.
- Expected Output: Recommendation paper on the SaME basket clinical trials in RD (Q1 – 2023). An invitation to submit in EMBO Molecular Medicine was received. A session will also be dedicated at the RE(ACT) Congress in March 2023, in Berlin (Germany).

➢ **Integrating New Technologies for Rare Diseases Diagnosis**

- Presentation: Gareth Baynam from Western Australia Department of Health (Australia) presented the Task Force objectives, timeline, updates, and summary of progress. This Task Force is led by the DSC Vice Chair, Clara van Karnebeek, and ISC Chair, Gareth Baynam.
- Objectives: To identify new technologies in development or in experimental use which would likely increase the diagnostic rate of rare diseases patients and to develop a clinical

framework or guideline for implementing a combined diagnostic approach of metabolomics, genomics, and AI.

- Progress Update: The Task Force members are currently writing the manuscript and creating a flowchart guideline indicating which technology are currently in research and clinical application, including sampling considerations, and whether they are applied either for phenotype or molecular diagnostic categories.
- Expected Output: Publication Title "Leaving No Patient Behind! Innovative Technologies to Diagnose Rare Diseases".

- **Primary Care**
  - Presentation: Gareth Baynam from the Western Australia Department of Health presented the updates and summary of progress. This Task Force is led by the DSC (Gareth Baynam), FCC (Adam Hartman), and Stephen Groft (from NCATS/NIH).
  - Objectives: To bring together representatives from different stakeholders to identify the current state of play, priority research areas, and the challenges and opportunities in rare diseases research in primary care.
  - Progress Update: The Task Force members have completed the manuscript and is now being reviewed and polished by the Task Force Chairs. The manuscript covers three main topics: Access and Awareness of Rare Diseases; Training and Education in Rare Diseases; and Empowering the Patient-Clinician Partnership and Referral Optimization.
  - Expected Output: Publication Title "Empowering Rare Disease Patients, Patient Advocates, and Primary Care Providers to Improve and Optimize Patient Care Pathways."

- **Enabling and Enhancing Telehealth for Rare Diseases Across the Globe**
  - Presentation: Melissa Parisi from NICHD/NIH (USA) and Faye Chen from NIAMS/NIH (USA) presented the updates and summary of progress. This Task Force is led by the FCC.
  - Objectives: To conduct a survey and systematic review of existing telehealth models and identify its barriers and opportunities to improve access to rare diseases diagnosis, care, and research, and leverage the output to develop best practices for introducing telehealth services into the rare diseases' community.
  - Progress Update: Telehealth Key Opinion Leader (KOL) interviews are ongoing to complement the data collated from the 356 literature reviewed by the Task Force members. The Task Force has three areas of focus based on the World Health Organization (WHO) definition of Telehealth: (1) Diagnosis, Treatment, and Prevention, (2) Research and Evaluation, (3) Continuing Education of Health Care Providers.
  - Expected Output: Identify barriers, facilitators, and "best practices" for introducing Telehealth services into rare disease communities, culminating in a publication that summarizes the literature search and key stakeholder interviews.

- **Working Group on MedTech for Rare Diseases**
  - Presentation: Anneliene Jonker from the University of Twente (The Netherlands) presented the Working Group's updates and summary of progress, including the current Orphan

MedTech industry landscape and developments globally. This Task Force is initiated by the TSC and ISC and funded by the University of Twente.

- 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.
- Progress Update: The group is preparing a state-of-the-art article summarizing (1) Rare diseases and medical technology; (2) Regulatory landscape & Legislation; (3) Need for further development; (4) Legislation; and (5) Current medical technologies and medical technology development. Since September, the group is working on patient engagement in MedTech development (Members presentations from PAO with discussion on best practices). Other achieved outputs include an article in a MedTech journal, a thematic collection in OJRD, participation in the EC workshop on orphan devices, a submitted IHI call idea and preparation of the RE(ACT) session.
- Expected Output: Publication providing a comprehensive overview of incentives and frameworks for medical devices around the world, opportunities for harmonization approaches in the regulatory space, and patient involvement in medical device development.

- **Pluto Project on Under-Researched Rare Diseases**
  - Presentation: Daniel O'Connor from MHRA (UK) presented the Task Force updates and summary of progress. This Task Force is led by the TSC.
  - 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. A workshop was organized last 28-29 November 2022 in Paris, France.
  - Expected Output: Recommendation paper describing identified commonalities between disregarded RD, roadblocks for therapy development, and opportunities to overcome them and foster research and development.

- **Drug Repurposing Guidebook**
  - Presentation: Anneliene Jonker from the University of Twente (The Netherlands) presented the Task Force updates and summary of progress. This Task Force is led by the TSC.

- 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. The group identified, created, and revised the building blocks. The group identified four model cases for the guidebook which are On patent - off patent and with Marketing Authorisation Applications (MAA) and none. A workshop was organized last 13-14 October 2022 in Paris, France
- Expected Output: Create a guidebook describing the available tools and initiatives for drug repurposing and how to best use them.

3. Plenary Sessions

➢ **Parallels Between COVID19 and Rare Diseases**

- The ISC Chair shared that COVID19 suffered from a lack of investment in long-term basic research and that a need for fundamental research without an immediate objective is essential and is currently missing for rare diseases. Many laboratories involved in fundamental research are not financed to perform long-term basic research. In addition, he also shared the development of novel treatments and vaccines both for COVID19 and rare diseases.
- Some key points raised by the IRDiRC members:
  - Low investment in rare disease research due to Return-Of-Investment (ROI) concern; low desire for risk by institutions, industry, and patient population
  - Limited resources and qualified personnel;
  - Rare diseases field is constrained by stringent procedures, administrative requirements, and regulations; it should have the same flexibility that was provided for COVID-19;
  - Support the social investment, promote solidarity by creating common platforms for treatments that have no economic business models in patient's benefit;
  - Using Telehealth for health services and support, but also for educational purposes and community mobilization of resources and capabilities;
  - Reducing the fragmentation of the market, by adapting the treatment prices between countries and ensuring pricing negotiations; improving accessibility to treatments;
  - Undiagnosed patients and stigma of being diagnosed as rare disease;
  - Government-private partnerships;
  - Ensure public workforce: evaluate and research for new insights and innovations that can be applied in the development of therapies; checking where the RD use cases could fit in the frameworks that have been used in COVID-19 management.
- The IRDiRC Chair proposed to the Consortium to write a manuscript on this topic.

4. Priorities and Strategies

- **IRDiRC Events and Communication Activities**
  - Upcoming CA Meetings
    1. 14-15 March 2023 Joint Meeting with Scientific Committees (Hybrid) in Berlin, Germany
    2. 07-08 June 2023 (Online)
    3. October 2023 (Hybrid) in Toronto (Canada)
    4. December 2023 (Online)
  - Upcoming Events
    1. IRDiRC-EJPRD-RE(ACT) Congress on 15-18 March 2023 in Berlin, Germany, in collaboration with BlackSwan Foundation and the European Joint Programme on Rare Disease.
  - IRDiRC Communication Activities
    1. Statistics of IRDiRC's Communication Platforms for Year 2022
       1. Twitter: +266.4% visits and 287 new followers for a total of 2790 followers
       2. Newsletter: 133 new subscribers for a total of 932 subscribers
    2. IRDiRC Communication Activities in a Nutshell for Year 2022
       1. New IRDiRC Website (more modern and more visible information).
       2. Rare Disease Day Campaign: New IRDiRC Introduction Video published on YouTube with 744 views and 2561 impressions.
       3. Short interview videos of IRDiRC members supported by the European Commission with over 13,000 views on Twitter.
       4. State of Play of Rare Diseases Research Initiatives 2019-2021, with over 3,900 views, 234 downloads, and 1937 impressions on Twitter.
       5. Commentary paper on Nature Reviews Drug Discovery Journal - "Ten years of Progress and Challenges at IRDiRC", with 3373 impressions on Twitter.
       6. New Videos called "IRDiRC Interview Series" published on YouTube where IRDiRC members shared their experience in IRDiRC and its added value to the community.

- **IRDiRC Initiatives**
  - Newborn Screening

    Two special issues are currently being prepared and will be published at the Rare Disease and Orphan Drug Journal. Each of the special editions involves contributions from IRDiRC members, along with external experts. First publications are planned to be ready in Q1/Q2 of 2023.
    - Real World Applications and Technologies: Virginie Bros-Facer (Illumina, DSC member) as the Associate Editor
    - Policy, Ethics and Patient Perspectives: Helen Malherbe (Rare Diseases South Africa, ISC member) as the Associate Editor

- **IRDiRC Governance and Procedures**
  - **Revision of IRDiRC Governance**: The IRDiRC Chair presented the different changes incorporated into the newly revised version of the IRDiRC Governance for the review and validation of the CA. The revised version was distributed to the CA one month before the meeting for review, with the edits and changes indicated in the copy. The Scientific Secretariat will distribute an online form to get the CA's validation regarding the new version. Listed below were the changes made to the IRDiRC Governance:
    1. Changes to the mandate of the Consortium Assembly
       - Validates new members to the CA that are reviewed and recommended by Operating Committee;
       - Validates new members to the Scientific Committees that are reviewed and recommended by the Operating Committee;
       - Validates new Task Forces and Working Groups that are reviewed and recommended by the Operating Committee;
       - Nominates Task Forces and Working Group members.
    2. Changes to the mandate of the Operating Committee
       - Reviews new Constituent and Scientific Committee membership applications and/or nominations and provides propositions for the final validation by the Consortium Assembly.
    3. Changes to the Constituent and Scientific Committees
       - Constituent Committees propose Task Forces and Working Groups, publications and other actions;
       - The number of Scientific Committees has changed from three to four, the Regulatory Scientific Committee was created in September 2022.
       - Other changes include to the contribution to Working Groups.
    4. Changes to the Nomination and Membership Procedure for Scientific Committees
       - New Scientific Committee members nominations are reviewed by the respective Scientific Committee Chairs, who make recommendations to the Operating Committee for a final proposition, and are validated by the Consortium Assembly. The Chairs of the Scientific Committee must propose an appropriate composition of the committee membership from the nominations received ensuring member diversity and inclusion that reflects a broad global stakeholder group and is fully representative of the rare diseases community.
    5. Addition of the Regulatory Scientific Committee (RSC)
    6. Addition of Working Groups
    7. Addition to the Expected number of members for Task Forces and Working Groups
       - Each Task Force will be composed of approximately 20 members, and the Working Groups of approximately 10 members.
    8. Addition of information regarding meetings and activity timeline of Task Forces and Working Groups

- Each Task Force and Working Group will meet several times through teleconferences. Travel organization and expenses for one in-person Task Force workshop is provided by the Scientific Secretariat.
- Task Forces are mandated to run their activities for one-year period, with possibility of three to six months extension. Working Groups are mandated to run their activities for six-months period, with a possibility of three months extension.

- **Task Force (TF)/Working Group (WG) Proposal Submission and Validation:** The IRDiRC Chair re-iterated the new submission and validation process to the Consortium, including the methodology used for the review and recommendation of Task Force proposals by the OpComm.
  1. **January to September 2022:** Submission of TF/WG proposals
  2. **October 2022:** Analysis and recommendation of proposals by the OpComm, including polishing of proposals by the proposers, if requested by the OpComm.
  3. **November 2022:** All proposals were shared to the CA members with four identified as "OpComm-recommended and reviewed".
  4. **December 2022:** Official presentations of the OpComm-recommended TF proposals to the CA during the December CA meeting.
  5. **15 days** after the official TF proposal presentation: Validation by the CA
  6. **16 December 2022:** Result of the validation by the CA was released.

➢ **IRDiRC Roadmap 2023**

- Four OpComm-recommended Task Force proposals submitted by IRDiRC Constituent and Scientific Committees were presented by the Task Force proposers.
  1. **Framework to Assess Impacts Associated with Diagnosis, Treatment, Support, and Community Integration that Can Capture Changes Along the Rare Disease Patient and Family History** was presented online by Durhane Wong-Rieger (PACC Chair).
     Proposers: PACC
     Background: This research project builds upon the work of the "IRDiRC Working Group on methodologies to assess the impact of diagnoses and therapies on rare disease patients." It draws upon the models/flowcharts developed by the WG.
     Objectives:
     - Develop, operationalize, and test a comprehensive framework of holistic, multidimensional, and evolving life-long experiences of patients and families living with a rare disease (derived from or leading to a natural history study);
     - 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";
     - Develop tools and processes for fully integrating patients and families as research partners and to assure that the outcomes are meaningful and empowering;

- Develop, operationalize, and test indicators of access to diagnosis and treatment impact on health systems and other societal sectors .

Comments from the Audience: Very long proposal for one year. There should be possibilities to connect with groups working on measure of impacts and patient empowerment. Maybe refine by picking up 1-2 diseases and going through the points. The specificity of this proposal is to create a common framework/metrics for all RD and not individual metrics. This will be more valuables for health care systems.

2. **Functional Analysis Task Force** was presented in-person by Biruté Tumiene (former DSC Vice Chair).
   Proposers: DSC
   Background: Functional impact of less than 1% of genetic variation in the 1-2% of our DNA has only been assessed to date. Recently, the development of high-throughput methods of large-scale mutagenesis was followed by the large-scale functional assessment of induced variation and supported by computational methods. This development allows for proactive, large-scale, indiscriminative functional assessment of genome functional elements and their variation, and development of variant effect maps for the basic and clinical research communities. However, there is a lack of guidance on the application of these novel (incl. traditional) methods and on the required infrastructure and standards.
   Objectives:
   - Further development, standardization, and quality improvement of the experimental and computational methods of functional assays;
   - Foster ecosystem building, infrastructure development, and partnerships for the effective chain from fundamental research to clinical applications of functional assays;
   - 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 rare diseases.

   Output: Framework for the robust and effective ecosystem of functional analyses in rare diseases as a white paper.
   Comments from the Audience: Some fetal abnormalities are not well covered by Human Phenotype Ontology (HPO) terms. Difficulty to assess the evolution of the phenotype across the time where an HPO can be presented at some point, but not in other time points of the disease. Some work is done on "phenotype trajectories" to accommodate this point.
3. **Funding Models to Support the Spectrum of Rare Disease Research and Development Task Force** was presented online by Adam Hartman (FCC Chair).
   Proposers: FCC
   Background: Successful development of therapies requires support of early stages through clinical stages. How different types of funders make decisions about when to fund at a given stage in a treatment's development is fairly opaque. Knowledge of the factors that contribute to this process might help others understand better how to facilitate the development of these treatments. The IRDiRC Chrysalis Task Force addressed some of these questions for companies but this led to the realization that this knowledge was lacking for other types of funders.
   Objectives:

- Identify key motivating factors for different types of rare disease research funders;
- Identify how different types of funders decide at which point in a research study's lifecycle they will provide support;
- Identify key influencing factors for effective public-private partnerships (PPP) of late-stage clinical research;
- Identify models of public-private partnerships, including means of sharing information.

Output: White Paper of Findings and Funding Model/Good Practices Toolbox

Comments from the Audience: The most value would be in early-stage funding (e.g., validate endpoints, NHS). It is important to understand the expectations around data at various time points and timing to work in PPP. Partnership should be supported beyond commercialization (partnership with patients).

4. **Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations Task Force** was presented by Anneliene Jonker (TSC Vice Chair)
   Proposers: TSC

   Background: There is little commercial interest from pharmaceutical companies to develop therapies for these very small numbers (N-of-1+). Formal clinical trials are not possible in most cases, field is at a pivotal point and IRDiRC could take the lead on bringing multiple interested parties together.

   Objectives: The overall goal is 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.

   - Raise awareness of the N-of-1+ concept and challenges with all stakeholders;
   - Identify major challenges hampering N-of-1+ therapy development and timely patient access;
   - Allow for development of proposed solutions and create better opportunities for strategic planning and delivery.

   Output: Two white papers (1) Summary of Analysis; (2) Recommendations on development for N-of-1 therapies.

   Comments from the Audience: The companies didn't respond to this initiative because it doesn't serve their interest; Consider including commercialization of platform therapies to interest/integrate companies.