Meeting Report

Joint IRDiRC Consortium Assembly and Scientific Committees Meeting

14-15 March 2023
Berlin, Germany

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

ACRONYMS

AI	Artificial Intelligence
ASGCT	American Society of Gene & Cell Therapy
ASOs	Antisense Oligonucleotides
CCC	Companies Constituent Committee
CCE	Common Condition of Use Elements
CORD	Chinese Organization for Rare Disorders
COST	European Cooperation in Science and Technology
CRN	Clinical Research Network
DIA	Drug Information Association
DLQI	Dermatology Life Quality Index
DSC	Diagnostics Scientific Committee
DUC	Digital Use Conditions
EATRIS	European Advanced Translational Research Infrastructure
EHDS	European Health Data Space
EJP RD	European Joint Programme on Rare Diseases
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EPND	European Platform for Neurodegenerative Disorders
ERICA	European Rare Disease Research Coordination and Support Action
ERN	European Reference Networks
EU	European Union
FCC	Funders Constituent Committee
FDA	Food and Drug Administration
GA4GH	Global Alliance for Genomics and Health
HTA	Health Technology Assessment
HUGO International	Human Genome Organization International
IMI	Innovative Medicines Initiative
IRDiRC	International Rare Diseases Research Consortium
ISC	Interdisciplinary Scientific Committee
KOL	Key Opinion Leader
LOI	Letter of intent
MHRA	Medicines and Healthcare products Regulatory Agency
ML	Machine Learning
NCATS	National Center for Advancing Translational Sciences
NGO	Non-Governmental Organization
NIH	National Institutes of Health
NIH	National Institutes of Health
NLP	Natural Language Processing
PACC	Patient Advocates Constituent Committee

PAGs	Patient Advocacy Groups
PCOM	Patient-Centered Outcome Measures
PROM	Patient Reported Outcome Measures
RD	Rare Disease
RDI	Rare Disease International
RSC	Regulatory Scientific Committee
SEO	Search Engine Optimization
TF	Task Force
TSC	Therapies Scientific Committee
ULEIC	University of Leicester
UMCG	University Medical Center of Groningen
WG	Working Group
WHO	World Health Organization

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THE REPORT

The International Rare Diseases Research Consortium (IRDiRC) recently held a 1.5 day of hybrid meeting for the Joint IRDiRC Consortium Assembly (CA) and Scientific Committees (SC) Meeting on 14-15 March 2023. The meeting took place through a combination of teleconference and Face-to-Face (F2F) in Berlin, Germany. A total of 25 participants representing CA and SC members attended online, while 53 participants representing 16 members of the CA, 8 members of the DSC, 7 members of the TSC, 6 members of the RSC, 7 members of the ISC, 6 members of the Scientific Secretariat (Sci Sec), and 3 project managers from the EJP RD Coordination Team attended on-site in Berlin.

1. Presentation of New IRDiRC Members, Leaders, and Representatives

IRDiRC is pleased to announce the addition of new members, leaders, and representatives to the Consortium. We extend a warm welcome to all.

- **New Members of IRDiRC Constituent Committee (2)**
  - **European Federation of Pharmaceutical Industries and Associations (EFPIA)**
    - Official Representative: Magda Chlebus, Executive Director Science Policy and Regulatory Affairs, Belgium
  - **GlobalSkin**
    - Official Representative: Tammi Shipowick, Programs Director, Canada

- **New Members of IRDiRC Scientific Committees (4)**
  - **TSC**
    - Emilio J.A. Roldan, Scientific Director at Qualix DoT, Argentina
    - Michelle Farrar, Professor of Neurology at School of Clinical Medicine/Sydney Children's Hospital, Australia
    - Trudy Nyakambangwe, Founder of Child and Youth Care Zimbabwe, Zimbabwe
  - **RSC**
    - Caroline Pothet, Head of Advanced Therapies, Human Medicines Division at the European Medicines Agency (EMA), The Netherlands

- **Change of Leadership (2)**
  - **DSC**
    - Newly elected DSC Chair: David Adams, Senior Clinician at the National Human Genome Research Institute (NHGRI) of the US National Institutes of Health (NIH), USA
    - Newly elected DSC Vice Chair: Clara van Karnebeek, Principal Investigator at Emma Children's Hospital, The Netherlands

- **Change of Representation (1)**
  - **FCC**
    - Eva Bermejo-Sanchez, Director of the National Institute of Health Carlos III (ISCIII), Spain - replaced Prof. Manuel Posada

2. Summary of Parallel Sessions

- **FCC Parallel Session**

  - **FCC Leadership:** FCC Chair and Vice Chair roles will be open for nomination in May.
  - **Continuous Information Exchange Between FCC Members:** This could be done during FCC meetings and on MS Teams. Information can be archived and shared sequentially or in real-time. The platform can be used to propose ideas, share ongoing work, and discuss commonalities and differences. Discussions can be maintained despite having different time zones. Conferences can also be shared through this platform. A training session was requested to teach FCC members how to use MS Teams.
  - **Funded Projects Database Platform:** Members discussed interest in increasing participation in the funded projects database platform. A consensus on whether to make the platform available to the public was requested by the FCC members. A survey on how many funders are using it, how many are submitting data and accessing the platform, and whether members are willing to open it to the public was requested to be created.
  - **FCC Membership:** The group aims to increase membership and believes that every member of IRDiRC should be responsible for promoting the group.
  - **Public-Private Partnership:** The group identified this as a potential Task Force topic. The US FDA recently announced a similar Moonshot initiative that will be launched soon. It was mentioned that private sectors rely on academics, but recently the industry has been divesting from rare disease. In the US last year, most of the small biotech companies involved in gene therapy had cut their workforce by about 50%. Private investment has been a challenge.
  - **Impact/Outcome Measurement:** The IRDiRC Chair emphasized the importance of a continuum of research that ultimately leads to practical use and highlights the need to address the clinical impact and improvement of quality of life. The goal is not always to cure but to improve the quality of life, which requires a different type of measurement. Economics is also a consideration in rare diseases. There is potential for partnering with TSC in terms of outcomes assessments for clinical trials and research. The group also discussed potentially an extension of Working Group 3 with a focus on measuring the overall RD burden and impact on society and the families of the RD patients to have a holistic overview.
  - **Recommendations to Create a Process for Global Strategic Research Decisions for Underrepresented RD:** It was mentioned that France has dedicated funding for the ultra-rare disease. The FCC Chair raised the challenges faced by organizations regarding funding priorities and suggested collecting information on what is being done around

the world within IRDiRC constituencies in regard to ultra-rare RD. There was some debate about the use of the term "ultra-rare" and its potential impact on drug development, with some suggesting a focus on therapeutic platforms rather than specific diseases that can impact the US Orphan Drug Act and the funds for rare disease research. In addressing the engagement and investment by industry, if the focus is instead on the therapy platforms, the industry could potentially treat large numbers of the patient population, and it would be a whole different conversation. ISCIII mentioned a federation of patients in Spain is committed to ultra-rare RD. The group also raised the need to make recommendations to funding priorities from the IRDiRC Committees either through Task Forces or by internally sharing it within the Consortium.

- **Other Discussions:** Members discussed increasing synergies between IRDiRC Committees and Task Forces to share recommendations and outputs that can guide the funders on funding priorities and strategies.

➢ **PACC Parallel Session:**

- **Some PACC Members Update:**
  - GlobalSkin is an international patient organization with over 200 members in 65 countries. They conduct research projects for rare skin diseases (such as PROMs research for dermatology, which currently they are working with the University of Hamburg, to take on the Dermatology Life Quality Index (DLQI), with a target of 10,000 patients). They will have the measurement translated into 15 different languages to increase reach. GlobalSkin mentioned that they continuously struggle in terms of funding.
  - Rare Disease South Africa is an organization with 6,000 patient members (including corporate members). The organization has four pillars focused on advocacy, patient engagement, and research covering congenital disorders. South Africa is based on the UK system in terms of the evidence-based healthcare system, but they have a dual healthcare system that has about 15% of the population accessing private healthcare and then the majority of the population accessing state healthcare services. Rare Disease South Africa has the largest patient registry, working together with Northwest University, with ethics coverage (privacy, security, and access to personal information). The organization is also developing a hub where clinicians can get information on available tests in South Africa, but also it serves as a safe place for patients to hold their own data. There are currently no electronic health records in South Africa. Newborn Screening for South Africa is centralized, but only less than 5% of people have access to it, which the RD South Africa team is working on improving. China CORD, officially represented by Kevin Huang, launched a new foundation called Hope for Rare Foundation in 2022 with involvement of 11 scientists.
- **Role of PACC Members:** They emphasized the role of patients and patient advocates in research, and the need to increase involvement and collaboration of patient advocacy groups (PAGs) and industries. The role of PAGs within IRDiRC was also discussed, along

with the need for skill development. PACC plans to conduct a survey within IRDiRC to better understand the role of PACC in IRDiRC and will also include questions on how to improve patient participation in research and outcomes. The PACC Chair raised questions about what does "patient advocate" really mean, and how to ensure that the experiences of patients are genuinely recognized and valued, and whether we are effectively bringing them into the research process. PACC Chair also mentioned an interest to evaluate outcomes of research when patient advocates are directly involved as partners.

- **Other Discussions:** PACC members discussed the need for patients who are topic experts to contribute to research, with a focus on patient-centricity. The group also discussed about increasing PACC members.

➢ **DSC Parallel Session**

- **General Discussion:** During the meeting, the DSC discussed plans for future meetings and the various resources available to them within IRDiRC, such as SharePoint, Miro, and support from the Scientific Secretariat. The DSC also shared its intention to submit a task force proposal for IRDiRC's Roadmap 2024. Additionally, the DSC Chair presented the process for reviewing applications for IRDiRC Recognized Resources, and the group agreed to hold separate online meetings with the TSC and ISC to discuss relevant topics.
- **Review of Area of Focus:** The DSC Chair presented previous DSC topics of discussion and asked the group members for feedback on their areas of focus, including any potential task force ideas. Some of the identified areas of focus is about the transition of diagnosis to therapy, and how to meet the IRDiRC goal on getting the diagnosed patients to therapy, and the undiagnosed patients to be involved in research. Transition of diagnosis to therapy was identified as a potential task force proposal that will be collaborated with other IRDiRC Committees. Other previous topics of discussion included phenotyping, the safety of diagnosis, equity, diagnostic stigma, language barriers, access, trends and roadblocks, new technologies, interoperability of initiatives, and a compendium of global diagnostic resources. The group highly advocated for RD multistakeholder education, raising awareness of existing initiatives that link diagnosis with treatment and identifying different ways of linking them at the gene and variant level. Additional discussion was on the ethics in terms of diagnosing rare disease, and how the diagnostic field is moving fast where some diagnosis previously could now be a different diagnosis.
- **Agreed Future Actions:** The group discussed potentially refining and resubmitting the phenotyping task force proposal or submitting a new proposal on multigenic/polygenic diseases or a topic on best practices for matching diagnosed persons to treatments and/or relevant translational research. The DSC Chair emphasized the importance of communicating global projects and checking for duplication of efforts before starting new projects. The group also agreed to create a high-level review of the preeminent diagnostic challenges and new solutions annually as a white paper to be submitted to a journal or published on the IRDiRC website and will also be disseminated internally in IRDiRC. The publication can then be periodically revisited and updated as a deliverable of the DSC. The DSC agreed to focus on general topics for discussion and submit a task

force or working group proposal for a more specific area and action. Comments from the Consortium related to the need for an increase in natural history studies are highlighted. It was also mentioned that funding resources are difficult to find when the disease is less researched.

- **Approaches to Maximizing Impact and Evaluating the Impact of Task Forces:** The DSC members emphasized the need to share the outcomes of IRDiRC Task Forces and Working Groups. The group discussed various ideas for maximizing impact, including partnering with institutions to disseminate outputs, monitoring citations and the number of downloads, ensuring high-impact papers produced by IRDiRC, and involving experts in evaluation and advancing implementation. The group also proposed conducting surveys to assess the impact.
- **Other Potential DSC Initiatives:** The DSC identified other potential initiatives, such as yearly publications on barriers and opportunities in diagnostics, participating in symposiums/conferences, and increased collaboration with external organizations, such as GA4GH, Human Genome Organization (HUGO) International, WHO, and the United Nations

➢ **TSC Parallel Session**

- **Registries and AI:** TSC discussed the exponential role of AI in all aspects of clinical research, including target validation, screening molecules for drug repurposing, and clinical validation for diagnostics and endpoint validation. The impact of AI in rare conditions is significant, as it maximizes data processing for these conditions. There are different approaches to Artificial Intelligence (AI), including Machine Learning (ML) and in-silico trials being of particular interest, with the digital twin making predictions on clinical outcomes by testing different scenarios. This is a fast-evolving field. In terms of our practice today, we are still on a learning curve. Some issues have arisen in dealing with unexpected artifacts, such as towels in imagery, and in ensuring inclusivity in the data, particularly for women and children. Although we have had moderate success, some projects have been funded. Looking to the future, AI is expected to influence our practice significantly, particularly in small data, with a focus on PK, anesthesiology, and rare diseases. There is a need to consider clinician education around AI, particularly impacting the breadth of data collection and quality. There are implications for the work of the TSC and other committees, and TSC thinks that a sub-group should be created to explore these identified areas. A call of interest should be launched in IRDiRC. TSC would like to consider looking at Horizon Calls for AI in rare conditions in addition to a literature review to stay abreast of the latest advances that could disproportionately influence RD research. In terms of regulatory guidelines, EMA is still developing guidelines for AI. However, the Swedish regulatory agency has experience using AI for pharmacovigilance signal detection to train models properly for Covid-19 vaccine adverse event detection and evaluation. They are also using NLP in EPAR to look at the conformity of assessment. Whether AI is best suited for primary care or specialized areas, there is a huge

opportunity from a diagnostic perspective, and primary care can leverage these areas. When repurposing a drug for an RD affecting different organs than the initial organ target, a tool is needed to have different specialists interact. When no therapy is available, AI can improve the quality of life, as seen in disabilities, leveraging AI tools such as metaverse applications. A company called Helix is using AI for repurposing in RD. Results from RD can also be upscaled to non-rare conditions.

- **COST Action Preparation and Roadmap for Development:** IRDiRC has developed guidebooks such as "Run an ODDG" and "Drug Repurposing Guidebook," with more guidebooks and results expected for the n of 1 approach. However, it is worth exploring how far we can go with IRDiRC and outside of it. One option is to consider a COST action, which is an EU-funded program that focuses on building networks and exchanging information through working groups. Researchers, industries, and NGOs from Europe and additional countries outside of Europe can apply. The groups are divided equally among young, middle, and senior careers, with a combination of researchers, industries, and NGOs. A 15-pages document as application is required to be submitted that discusses scientific excellence, impact, implementation, and networking excellence. The next deadline for applications is October 25, and the funding can be used for meetings, networking, and exercises. The TSC is considering exploring this option and discussing which topics to focus on, such as guidebook methodology and additional guidebooks. Additionally, the TSC is interested in providing courses through the COST action. The TSC will identify topics to focus on within the COST action, including those involving a broad range of countries. Finally, the TSC will discuss with EATRIS to learn from their experience using the COST action for training and avoid double funding.
- **Future Task Force/Working Group:** The TSC discussed the potential benefits of combining device and medication development to improve patient care and identified key areas for collaboration. These included developing better medications using devices, improving medication delivery methods, leveraging eHealth to enhance patient care, and identifying RD-specific solutions. To further this collaboration, TSC proposed working with CCC and EFPIA to prioritize topics and identify potential gaps in research and development. Several task force topics were considered, including Drug-Device Combination, Patient Engagement in Therapy Development, Guidance for Small Population Clinical Trial Sequel, Pre-Competitive Space Working, Guideline Digital Biomarkers for RD, Patient-Relevant Regulatory-Endorsed Endpoint (PCOM) Sequel, Developing Cost-Effective Drugs for RD Patients, Improving Medication Access for Patients by Involving Payment Leaders, Developing Patient-Relevant Regulatory-Endorsed Endpoints for Drug-Device Combination, De-implementing Current Practices for New Practices, Interface Between Phase 3 and 4 and Conditional Approval, Biomarkers for RD Research, Leveraging AI to Enhance RD Research and Development, and Digital Biomarkers and Endpoints for RD Research. To move forward, TSC aims to define its value proposition and identify potential external collaborators. The committee is considering reaching out to the RD Moonshot initiative and ERICA for collaboration on future task force topics.

- **RSC Parallel Session**
  - **Summary:** The entire meeting was devoted to a working whiteboard session to develop the mission statement for the RSC and to identify key goals for the committee. RSC's work-to-date on the mission statement, gap identification, and fact-finding information were reviewed. Thus far, guest speakers have been heard on:
    - Shared Molecular Etiologies (SaME) and the Bespoke Gene Therapy consortium, inclusive of many diseases at a time and platform approaches
    - Pluto Project: Under-research diseases defined by the 4 zeros of: 1) no publications, 2) no therapy approval, 3) no marketing approval, 4) no orphan or other designations
  - **Regulatory Science Working Definition:** The following were identified from the literature
    - Wikipedia "Regulatory science is the scientific and technical foundation upon which regulations are based. In contrast to "…regulatory affairs and regulatory law which refer to the administratve or legal aspects of regulation…"
    - EMA "Regulatory science refers to the range of scientific disciplines that are applied to quality, safety and efficacy of medicinal products and that inform regulatory decision making throughout the lifecycle of a medicine"
  - **Goals of Regulatory Science:**
    1) Catalyzing the Integration of Science and Technology
    2) Driving Collaborative Evidence Generation to Improve the Scientific Quality of Evaluations
    3) Advancing Patient-Centered Access to Medicines
    4) Addressing Emerging Threats
    5) Enabling and Leveraging Research Innovation
  - **RSC Key Points:**

Foundational Science	Key Points
Complying with regional authorities	Evolving – FDA pilots, such as Rare Disease Endpoint pilot
Flexibility and judgment for rare diseases, standard setting through examples	Why do drugs fail? What has worked? Data collection - catalogue experience
Communication, education	Information sharing, influence best practices through examples and recommendations

  - **Results:** The following **draft mission statement** is being proposed:

    "The mission of the RSSC is to benefit all rare disease patients through the development, communication and transparency of Regulatory Science"
  - **Proposed Key Areas for RSC Development:**
    - Influence regulatory science environment through publications
    - Share the process of development through summaries and case studies
    - Influence/recommend best practices through examples: What works, What doesn't work, and Communication flexibility
    - Define gaps

➢ **ISC Parallel Session**

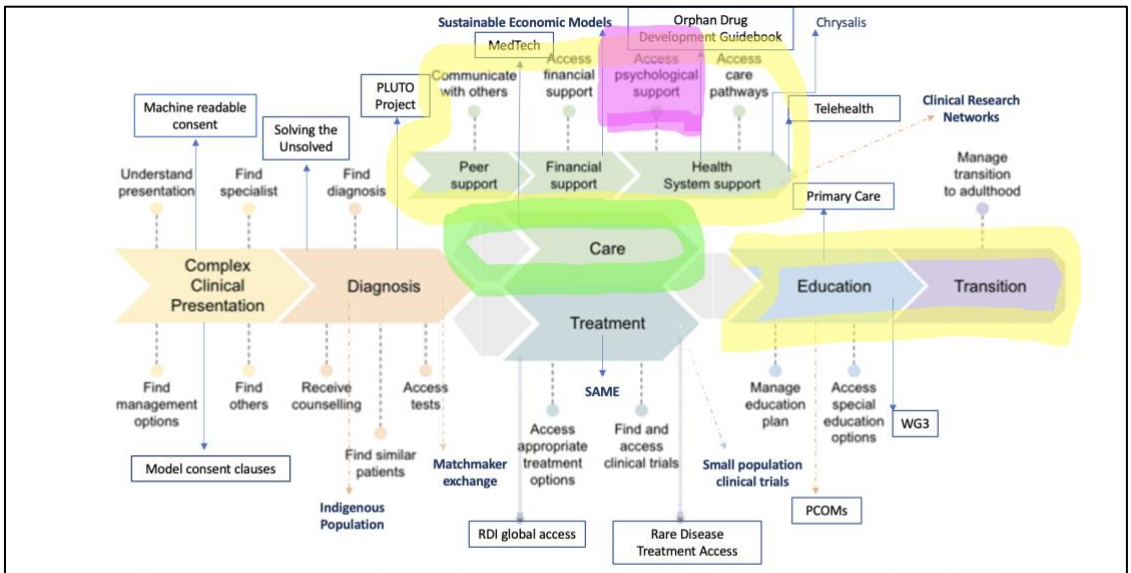


Figure 1. A conceptual view over the patient journey constructed by patient representatives of ERN ITHACA augmented with the most relevant associated actions.

- The ISC Chair highlighted several areas that the International Rare Diseases Research Consortium (IRDiRC) had yet to focus on and proposed some potential directions for future Task Forces or Working Groups. These included the idea on “Care”, “Mental Health”, “Education”, and "Stigma”. To address the social stigma faced by patients with rare diseases, the involvement of a multidisciplinary research team that includes sociologists and data scientists, including exploring a potential extension of IRDiRC's work with a focus on mental health and social environments that includes beliefs and religion. The group also discussed the potential use of generative AI along the patient journey and the development of phenotypic clusters. In addition, the group emphasized the importance of standards and regulations for implementation. To broaden the representation of the committee, there was a suggestion to increase patient advocacy participation, and an open call was proposed to target data scientists and experts in ontologies. The ISC Chair also highlighted the example of Singapore, which engaged with legislators first before implementing new screening measures as part of their strategy. The patient journey was suggested as a framework for future work. Overall, there was an agreement on the need to explore these areas and expand the focus of IRDiRC to benefit rare disease patients.

3. Summary of Cross-Committee Exchange

➢ **Exchange 1**

FCC and PACC: During the meeting, the participants discussed the need to develop metrics to measure the success of patient advocates' involvement in clinical trial design (what works, what did not work, etc.). They highlighted the importance of identifying what works and what does not work in patients directly being involved in research and potentially

integrating these findings into best practices or recommendations. This would include evaluating the patient engagement in research and understanding the burden of unmet needs for rare disease patients. Magda Chlebus, the EFPIA representative, suggested looking into the metrics for patient engagement developed in PARADIGM, an Innovative Medicines Initiative (IMI) project (https://imi-paradigm.eu).

- **DSC and ISC:** During the meeting, the group discussed the topic of transitioning from diagnosis, including the potential implications of the successful or unsuccessful diagnosis and the availability and unavailability of therapies. It was suggested that cross-committee collaboration could be beneficial in addressing this complex issue. In addition, the DSC Chair suggested that social aspects should also be considered to encompass all aspects of the transition process fully.

➢ **Exchange 2**

- **FCC and DSC:** The group discussed the potential for funders to focus on shared molecular etiologies and shared clinical phenotypes and fund research around that idea based on the "The Treatabolome initiative" (https://solve-rd.eu/the-treatabolome/). Sergi Beltran presented the concept of The Treatabolome by Solve-RD project, which links genes and genetic variants to available treatments or even tracks them to those that have been tested by capturing information in the publications about drugs that were tested or proven to be useful for specific diseases and link those to genes and genetic variants. The involvement of various therapeutic platforms and approach were discussed (nutritional therapy, medical device, drugs, care, etc.). The importance of natural history studies for novel rare diseases was also emphasized. Participants suggested that outcome measures may be necessary for continued work in this area and pointed to existing platforms for monogenic diseases. The involvement of ontologists was seen as crucial for accurate and comprehensive data collection. A concern of what happens when a disease is not part of the Treatabolome and how patients may be affected when they know they have a disease but no treatment is available was raised.

- **TSC and RSC:** The group discussed the concept of personalized medicine and how it could lead to splitting many rare diseases into subsets. They noted that in the EU, there are currently no biomarker-defined subsets that are considered separate conditions, and there is still a difference between the definitions of rare diseases and personalized medicine. The group also raised questions about how shared molecular alterations could impact the incentive for drug development and how reimbursement works if a therapy works for one type of inherited retinal dystrophy over another. The discussion also touched on the difficulties of defining diseases based on pathophysiology, etiology, etc., and the possibility of new disease definitions. The group noted that the traditional definition of diseases leads to over 10,000 diseases, and with the increasing complexity of genetic mutations, drug development becomes more difficult. The group attempted to write a paper on the differences between rare diseases and personalized medicine, focusing on accelerating

research and development as new legislation is coming. They also discussed the need to reflect on the complexity of determining biomarkers and how this contributes to transparency and communication for reviews. Finally, the group discussed the example of a CT platform approach for developing drugs for rare diseases, which raises questions about whether a full toxicology package is necessary for a development targeting a single person and the potential use of non-rare conditions for toxicology testing or alleviating costs when a transgene is changed. The regulatory may identify other use cases to feed the paper.

- **ISC and PACC:** During the cross-committee exchange, the role of PACC within IRDiRC was brought to attention, together with the role of diagnosis and access to approved therapies, but by whom and for who designed. It was suggested that IRDiRC could facilitate the patients' discussions on the symptoms experienced by creating dedicated forum. Another topic of interest was how to better connect the health and education systems to maximize patient impact. It was suggested that having community advisory boards (like the ones created for HIV) would help in this sense.

- **TSC and RSC:** The group discussed how to define RD in the era of precision medicine and why it matters. The TSC will share the manuscript on RD in the era of personalized medicine with the RSC to receive their feedback. From a regulatory perspective, many RD could be subdivided through the concept of personalized medicine. The group raised the question of using shared molecular etiologies to group RDs but also concerned that this may impact the incentive for drug development. It was raised that a lot of difficulties come from definitions. The topic on N-of-1 was discussed.

➢ **Exchange 3**

- **PACC, RSC, and DSC:** The meeting discussed the barriers to diagnosis from the patient perspective, including issues related to education, access, and infrastructure. It was suggested that systemic solutions such as AI and incentives may be necessary to move providers beyond a first pass differential diagnosis. The importance of making the case for the value of early diagnosis was also emphasized. Equity in diagnostic approaches was highlighted. Infrastructure to support patients before, during, and after complex diagnostic procedures was also discussed. This includes providing resources to help patients prepare for complex diagnostic procedures and support services to help them cope with the emotional and psychological impact of a potential diagnosis. The DSC Chair emphasized the importance of early diagnosis as a driver for economic models and the need for infrastructures to support patient groups such as screening. Finally, Marc Dooms (ISC Vice Chair) mentioned a paper related to ethics and equity in diagnosis.

- **TSC, ISC, and FCC:** Participants focused on the role of Genomic AI in RD and identified key issues that need to be addressed. The group discussed the need for more incentives to support undiagnosed RD cases and the importance of considering the patient journey and transition between services/places. They also emphasized the need to identify changes and

opportunities for regulatory changes and leveraging on data standards. One of the main topics of discussion was the successful application of AI from a healthcare provider perspective. Examples were given of combining phenotypes with available datasets and the use of AI throughout the life cycle of developments. The group noted that successful AI applications tend to involve small data. The group also discussed the use of AI in the diagnostic odyssey and the example of the Swedish Medical Products Agency, which has appointed a Head of AI to use NLP to check drug authorization applications and follow-up. The potential use of AI to develop communication materials for patients was also discussed, including in various areas of healthcare, such as logo creation, medical notes, patient leaflets, and data standards. A project to gather medical records and identify similarities between patients through AI analysis was presented, with the aim of identifying shared molecular patterns for ultra-rare disorders. However, the quality of data was acknowledged as a potential issue, with the maxim "garbage in, garbage out" being cited. Emphasis on the potential for AI to make a significant contribution to the field of RD, but also the need for careful consideration of data quality and the patient journey. Participants discussed the importance of natural language processing, regulatory guidelines, and having the right model for successful AI implementation, with a particular focus on the patient journey and the use of AI in diagnostic odysseys.

4. Summary of Featured Session Topics

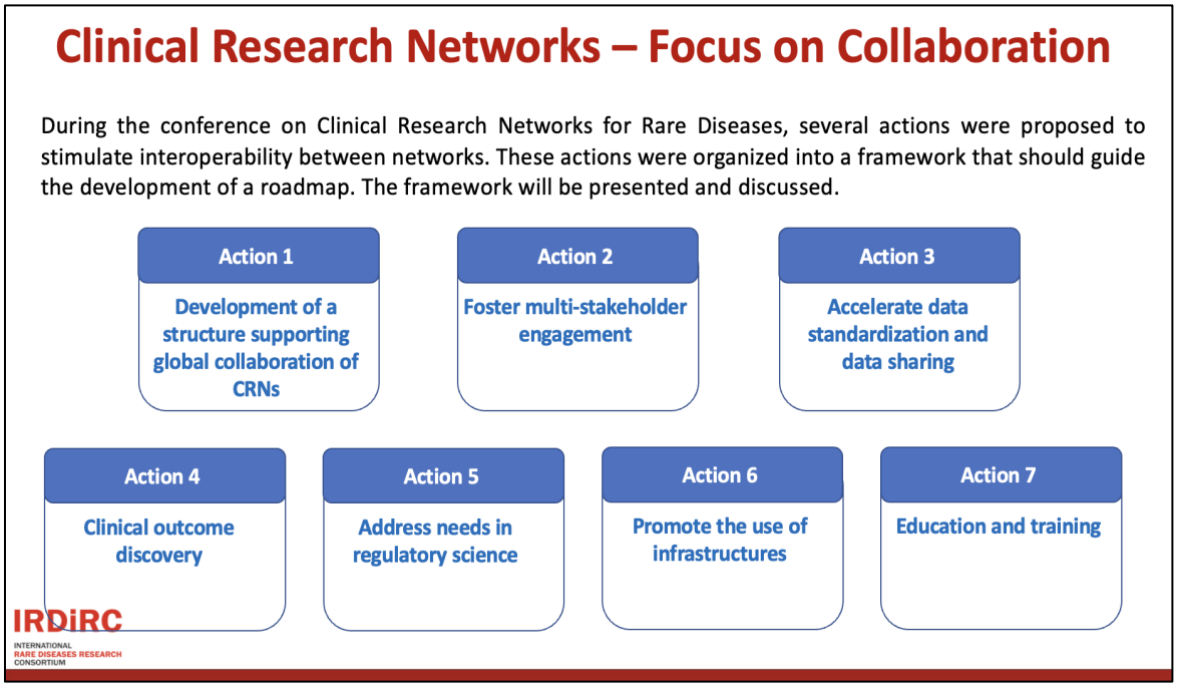
- **Parallels of COVID19 and RD**

  The session discussed various aspects related to the development of cancer therapies, particularly using mRNA and viral mechanisms. It was noted that basic science research on mRNA vaccines led to accelerated development during the COVID-19 pandemic, with regulatory authorities prioritizing the process. The group suggested that the lessons learned from COVID-19 could be applied to the development of therapies for rare diseases. Participants highlighted the importance of addressing the social aspects that RD patients experience daily and promoting trust among underserved populations. Additionally, there was discussion around the definition and nomenclature of rare diseases, as well as triage practices and discrimination in healthcare. Other topics included the mental health impact on patients and caregivers, decentralized measurements, community education and engagement, and accelerated data sharing and analysis. The group emphasized the importance of addressing these issues in the development of therapies for rare diseases, with a focus on promoting equity, inclusivity, and patient-centered care. As an output of this session, the group will publish a white paper led by Anne Pariser, Gareth Baynam, and PJ Brooks.

- **Models for Data and Registries Support Within Regular Funding Mechanisms**

  The session was introduced by presenting the Task Force proposal, drug discovery development phase, resources needed to consider when establishing or sustaining a registry, and types of funders of data registries. The group discussed the importance of continuously evolving and reassessing data in registries and the need for a sustainable model of funding for data registries. The discussion also touched on disease registries, EMA guidelines for registries, and the need to involve patients in sustaining a registry. The group raised concerns about establishing trust between public and private entities and the importance of interoperability. The group talked about the need for quality control and the use of patient-reported outcome measures (PROMS) and artificial intelligence (AI). Available funding tools, such as national budgets, financial incentives, and Return-On-Investment (ROI) were also discussed. During the meeting, concern was expressed that most of the platforms being discussed are focused on Europe, including the European Reference Networks (ERNs) and EU databases. Participants highlighted the importance of considering the international perspective, with a recommendation for different types of funders tailored to the different needs of regions. The group emphasized the need for a tailored approach to data registries and the importance of conceptualizing a registry that considers what is missing globally rather than just what exists in the EU. The group also discussed the use of PROMS and AI in data registries. Finally, they talked about the idea of having the post-its online and sharing them with the participants to continue the discussion.

- **Clinical Research Networks – Focus on Collaboration**



Daria Julkowska presented the session background based on the survey developed in the Clinical Research Networks for Rare Diseases Task Force (TF). The mentioned Task Force identified gaps in Clinical Research Networks (CRN) interoperability. Participants felt the need to define what CRN meant and its scope and highlighted the need for information to be shared regarding a mapping to capture the commonalities and differences of existing CRNs globally. The group also identified the need to bring all competencies together and work with the industry to advance research. The US model of a joint evaluation committee, a common data infrastructure, and a coordination center was shared, while in Europe, different models exist, and there needs to be more collaboration with industry. The session also discussed the importance of creating an environment where people could share protocols and best practices, advocating for standard harmonization and governance, and identifying gaps in Rare Disease (RD) spaces. The group emphasized the need to strengthen patient organizations, standardize the data collection, and set a framework for development. The meeting also discussed the involvement of patients in CRNs and the importance of mutual understanding and training. Additionally, data ownership and the sharing of protocols, as well as how to design clinical trials and outcomes, were raised. China CORD shared that they had similar issues in China and suggested exploring the possibility of cooperation with Europe and the US. Overall, the meeting identified the need for better coordination and collaboration between CRNs and highlighted the importance of involving patients in the process. The group also emphasized the importance of standardization and governance in Rare Disease spaces and the need to establish a framework for development.

- **Demystifying Gene Therapies (Terminology/Nomenclature and Method of Delivery) for Better Understanding and Accessibility**

  During the session, a participant expressed concern about people's fear towards gene therapy in France. IRDiRC Chair suggested creating educational resources, such as videos or documents, through IRDiRC. A participant questioned whether the problem was related to education or understanding the different terms, while another suggested that experts should agree on a common understanding before informing the public. The creation of short videos for informational purposes was suggested. A participant asked if prevention was a part of the conversation, and others suggested grouping therapies and explaining them to people and those affected by rare disease. The uncontrolled use of the word "cure" instead of "treatment" were raised and emphasized the importance of being vigilant with advertising. Comments about companies tend to hype up genetic therapies, but they can also help prevent diseases. A participant brought up the importance of making a distinction between cure and therapy. Some suggested not using the word "cure" due to people's overly optimistic thinking. The IRDiRC Chair asked if they should define therapy and treatment for the rare disease community, and participants questioned its importance for the wider audience. Some suggested borrowing definitions from other societies and mentioned books on gene therapy written in easy-to-understand terms. The IRDiRC Chair clarified that IRDiRC is not making a definition but highlighting different platforms. The group shared that the WHO started descriptions of gene therapy in 2005, but it was not continued, and someone proposed nomenclature last year. The group suggested ASGCT as a resource and clarified that ASO treatments do not damage genes. The group proposed a "Why series," like what the EMA did for vaccines. The IRDiRC Chair suggested providing links to different resources on the IRDiRC website and creating resources for different stakeholders as the organization grows. A participant suggested creating a library of resources for families. The session discussed the varying levels of knowledge about gene therapy among populations at a regional/country level, which depends on education. IRDiRC was suggested to contribute to providing educational help in the form of sharing links or references to diagrams, videos, and other resources to align the nomenclature used. Misconceptions from families about gene therapy were also discussed, especially when referring to 'replacement gene therapy'. Language barriers were also highlighted, and it was noted that most patients do not speak English. The meaning of being in a clinical trial and receiving investigational therapy from an ethical perspective was also discussed. To further address misconceptions on gene therapies, the group proposed to clarify about antisense oligonucleotides (ASOs) and mRNA. A list of useful links related to gene therapy was proposed to be published on the IRDiRC website. It was also suggested to have a section for patients/caregivers on the IRDiRC website, as the current website is more oriented toward researchers.

5. IRDiRC Task Forces, Working Groups, and Initiatives

Fourteen Activities are Ongoing for the Year 2023 (Task Forces, Working Groups, and Initiative):

- Newborn Screening Initiative
- IRDiRC-RDI Global Access Working Group (in collaboration with RDI)
- Machine Readable Consent and Use Conditions (led by the ISC and ULEIC)
- 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 – Disregarded Rare Diseases (led by the CCC and TSC)
- Drug Repurposing Guidebook (led by the TSC)
- Operationalizing a Comprehensive Framework to Assess the Impacts of Diagnosis and Therapies in Rare Disease Patients (led by the PACC) - *new*
- Functional Analysis Task Force (led by the DSC) - *new*
- Funding Models to Support the Spectrum of Rare Disease Research and Development (led by the FCC) - *new*
- Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations (led by the TSC) - *new*

➢ **Newborn Screening Initiative**

- **Progress Update:** Currently involving approximately 30 volunteers grouped in two major thematic areas: “Real World Applications and Technologies” (led by Virginie Bros-Facer, DSC member) and “Policy, Ethics and Patient Perspectives” (led by Helen Malherbe, ISC member). David Pearce and Helen Malherbe presented the progress updates. The “Policy, Ethics and Patient Perspectives” is a special edition categorized into international, regional, national, and thematic focus. One of the main objectives is to bridge the gap between low- and middle-income countries with the high-income countries. The timeline for this project is end of Q2. Daniel Scherman invited everyone, including task forces members, to participate, and emphasized that the articles will be with open access, covering topics from basic science to patient advocacy. David Pearce expressed his passion for increasing IRDiRC initiatives, outputs, and publications. One online participant, Michelle Farrar (an ethicist), showed interest in contributing to the project.

➢ **IRDiRC-RDI Global Access Working Group**

- **Presentation:** David Pearce, the Chair of IRDiRC (International Rare Diseases Research Consortium), provided a brief update on the working group's progress (WG). This WG is a collaborative effort with RDI (Rare Diseases International).
- **Objective:** The WG aims to enhance access to medicines for rare diseases by developing a list of standard-of-care medications, exploring innovative approaches, and identifying both systemic and idiosyncratic barriers to access. These barriers may include issues

related to screening, treatment, aftercare, cost, and exclusivity expiration, particularly in low- and middle-income countries. The WG also aims to potentially include rare disease medicines in the WHO's Essential Medicines List and explore how different healthcare systems can incorporate them.

- **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.
- **Progress Update:** The WG utilized cystinosis as a use case and circulated a paper among the members of the working group for comments. A second use case on cystic fibrosis was also examined, and common challenges and barriers observed in different country settings were incorporated into the framework. This WG was also presented at the World Orphan Drug Congress Europe last year.
- **Summary:** David Pearce reported that the group had conducted case studies on cystinosis and believes that the findings will be valuable in informing approaches to rare disease treatment by companies. The group is currently working on framing the implications of the findings, and a survey was conducted to identify commonalities. The group discussed the initiative's next steps, including exploring a philanthropic model and potential sponsorships. Daniel Scherman offered to connect with the Cystic Fibrosis Foundation in the US, and Helene Le Borgne offered to connect with the European Reference Networks (ERN) in the EU for issues related to access and care. Christina Kyriakopoulou inquired about the trend of combinatorial therapy, and David Pearce expressed the opinion that combinatorial therapy would likely be necessary for the effective treatment of rare diseases like cystinosis.

➢ **Machine Readable Consent and Use Conditions**

- **Presentation:** Esther van Enckevort from the University Medical Center Groningen (UMCG) presented the updates and progress summary online. The Task Force, led by Esther van Enckevort (from ISC) and Anthony Brookes (from the University of Leicester (ULEIC)), consists of approximately 40 international scientists.
- **Objectives:** The objective of the Task Force is to create machine-readable profiles for consent and use for registries and biobanks, building on the data structures and semantics of the Global Alliance for Genomics and Health (GA4GH) + IRDiRC standards.
- **Expected Output:** The Task Force aims to work with ontology developers to define new classes and properties that fill gaps identified in the ontologies. They also plan to extend the concepts of the Consent Codes Exchange (CCE) to provide a basis for consent and use conditions at the record level, in Data Use Consent (DUC) format.
- **Progress Update:** The Task Force has two papers on DUC and CCEs that are almost ready for submission. They are currently working on creating an individual-level consent template that is mapped to the DUC-CCE structure and verifying its applicability and compatibility with different parts of the record-level approach. They are also evaluating the need for consent and use conditions at the record level for biobanking data and defining the objectives. The development of Real-World Pilots has started, but it is still in the early phases.

- **Summary:** The Task Force plans to submit two papers to the same journal. These papers will provide guidance to registries in creating profiles and will include the development of an individual-level consent template mapped to the DUC-CCE structure for record-level consent for biobanks. Real-World Pilots are also being developed for discovery at the resource level, including the BBMRI-ERIC Directory, MOLGENIS component for RD Registries, a stand-alone generic software solution by ULEIC, and integration into the EJP-RD Virtual Platform. The potential adoption of these initiatives in other projects and infrastructures, such as BBMRI-ERIC, Health-RI, EHDS, and IMI-EPND, was also discussed during the meeting. The audience asked questions about national-level initiatives, open access, and integration with different systems. The speakers mentioned that some ontologies have already been created in this space and discussed the potential for synergizing with other initiatives, such as GA4GH.

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

- **Presentation:** Clara van Karnebeek delivered a comprehensive overview of the Task Force objectives, timeline, updates, and progress summary. As the DSC Vice Chair, she leads the Task Force in collaboration with Co-Chairs Bekim Sadikovic and Anne O'Donnell-Luria.
- **Objectives:** The Task Force aims to identify cutting-edge technologies in development or experimental use that can enhance the diagnostic rate of rare disease patients. Additionally, they are working towards developing a clinical framework or guideline for the implementation of a combined diagnostic approach utilizing metabolomics, genomics, and AI.
- **Expected Output:** The publication titled "Leaving No Patient Behind! Expert Recommendation for the Use of Innovative Technologies in the Diagnosis of Rare Diseases" has garnered interest from Nature Medicine.
- **Progress Update:** The manuscript is currently in its finalization stage, and the Task Force is collaborating with an external illustrator to incorporate graphics for the publication.

➢ **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 Gareth Baynam (ISC Chair), Adam Hartman (FCC Chair), and Stephen Groft (NIH/NCATS).
- **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.
- **Expected Output:** Publication Title: Empowering Rare Disease Patients, Patient Advocates, and Primary Care Providers to Improve and Optimize Patient Care Pathways.
- **Progress Update:** Manuscript completed and currently being edited by the Task Force Chairs.

- **Enabling and Enhancing Telehealth for Rare Diseases Across the Globe**
  - **Presentation:** Mary Catherine Letinturier, member of the Scientific Secretariat, presented the updates and summary of progress. This Task Force is led by Melissa Parisi, Faye Chen, and Adam Hartman from the FCC.
  - **Objectives:** The Task Force aims to conduct interviews and perform a systematic review of existing telehealth models to identify barriers and opportunities for improving access to rare disease diagnosis, care, and research. The findings will be leveraged to develop best practices for introducing telehealth services into the rare disease community.
  - **Expected Output:** The Task Force will identify barriers, facilitators, and best practices for introducing telehealth services into rare disease communities. This will culminate in a publication summarizing the literature search and key stakeholder interviews.
  - **Progress Update:** The Task Force will release two papers: (1) A manuscript summarizing findings from the review and collation of 400 literature sources, and (2) A manuscript summarizing the findings from the Telehealth Key Opinion Leader (KOL) interviews. The Task Force is currently in the process of writing the summary of findings from both the literature review and KOL interviews.

- **Working Group on MedTech for Rare Diseases**
  - **Presentation:** Anneliene Jonker from the University of Twente provided updates and a progress summary on behalf of the Working Group. This Task Force was initiated by the University of Twente in the Netherlands.
  - **Objectives:** The Working Group aims to understand and map the current incentives, supportive frameworks, and unmet technical and functional needs for developing medical devices for rare diseases. They also seek to identify the regulatory landscape in 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 preparing 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.
  - **Summary:** The Working Group highlighted that there is currently no specific Health Technology Assessment (HTA) for medical devices, but they have been gradually building a collection of information. They also mentioned their participation in discussions on EU medical device regulation and the introduction of medical devices for rare diseases. The Working Group has created videos on patients' device needs and discussed the regulatory landscape, legislation, and the need for further development. Anneliene Jonker expressed the group's hope for real legislation for orphan devices and raised the question of making the working group global to ensure equality. They also discussed the different definitions of orphan devices in the US, Japan, and the EU, and how it could impact their purposes or indications. It was mentioned that in the US, the orphan device definition is based on less

than 8,000 patients, while in Japan they have a similar definition for orphan drug and orphan device. Samantha Parker added that it's important to note that one device may not be suitable for treating multiple diseases in the same way.

- **Pluto Project on Disregarded Rare Diseases**
  - **Presentation:** Daniel O'Connor from MHRA presented the Task Force updates and summary of progress.
  - **Objectives:** The objectives of the Task Force are to identify rare diseases that have received little attention from academic researchers and industrial developers, determine common characteristics among these diseases, and understand the roadblocks in developing effective treatments for them.
  - **Expected Output:** The Task Force aims to produce a recommendation paper that describes the commonalities identified among disregarded rare diseases, identifies roadblocks to therapy development, and highlights opportunities to overcome these challenges and foster research and development.
  - **Progress Update:** A workshop was held last 28-29 November 2022, where three streams of discussion took place: (1) Planet 4 Zeros - Why do so many Rare Diseases have no publications, no trials, no Orphan Drug Designations, and no Market Authorizations?; (2) Indexes and Outliers: Creation of indexes to better define under-researched Rare Diseases and understanding why so many Rare Diseases are under-researched; and (3) Agreement on the definition of under-researched rare diseases and methodological approach to studying them.

- **Drug Repurposing Guidebook**
  - **Presentation:** Anneliene Jonker from the University of Twente presented the Task Force updates and summary of progress.
  - **Objectives:** The objective of the Task Force is to create a guidebook that focuses on repurposing approaches, including incentives, regulatory tools, initiatives, and development tools, among others.
  - **Expected Output:** The Task Force aims to create a comprehensive guidebook that describes the available tools and initiatives for drug repurposing and provides guidance on how to utilize them effectively.
  - **Progress Update:** A workshop was organized last 13-14 October 2022, which included discussions on the definition of drug repurposing, investigation of three cases and their variations, validation of clusters of building blocks specific to drug repurposing, and the development of a Gantt chart, checklist, and decision tree to support the process.

- **Operationalizing a Comprehensive Framework to Assess the Impacts of Diagnoses and Therapies in Rare Disease Patients** *(new)*
  - **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, (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

- **Planned Output:** Framework to assess impacts; White Paper
- **Progress Update:** 35 applications received; 20 members were selected.
- **Kick-Off Meeting:** 20 March 2023

- **Functional Analysis** *(new)*
  - **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 rare diseases.
  - **Planned Output:** Framework for the robust and effective ecosystem of functional analysis in rare diseases; White Paper
  - **Progress Update:** 24 applications received; 20 members were selected.
  - **Kick-Off Meeting:** 03 April 2023

- **Funding Models to Support the Spectrum of Rare Disease Research and Development** *(new)*
  - **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; 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:** Summary Paper of Findings and Funding Model/Good Practices Toolbox
  - **Progress Update:** 26 applications received; 20 members were selected.
  - **Kick-Off Meeting:** 19 April 2023

- **Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations** *(new)*
  - **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.
  - **Planned Output:** Two White Papers on (1) Summary of Analysis, and (2) Recommendations on the development for N-of-1 therapies.
  - Progress Update: 45 applications received; 19 candidates were selected.
  - **Kick-Off Meeting:** 11 April 2023

6. IRDiRC Priorities and Strategies

- **Upcoming IRDiRC Meetings**
  - 07-08 June 2023: Online Consortium Assembly Meeting at 15:00-16:00 CEST
  - 03-04 October 2023: In person Consortium Assembly Meeting in Montreal (Canada)
  - 06-07 December 2023: Online Consortium Assembly Meeting at 15:00-16:00 CET
  - 27-28 March 2024: In person Consortium Assembly Meeting in Shanghai/Hangzhou/Suzhou (China)

- **Previous Task Forces and Working Groups**

  The IRDiRC Chair expressed concern regarding the recurrence of task force proposals submitted by the same proposers and with the same people being involved. He encouraged all members of the Consortium to increase their activity participation and not hesitate to take the lead in proposing activities or task forces. Dissemination of Task Force or Working Group outputs was also highly encouraged.

- **Presentations of IRDiRC**

  The IRDiRC Chair urged the Consortium to present IRDiRC at conferences or symposiums they attend and inform the Scientific Secretariat. The Scientific Secretariat can provide IRDiRC presentation slides to support these efforts. Raising visibility and awareness of IRDiRC was highlighted as an important goal, and identifying strategic activities to enhance this was discussed.

- **IRDiRC Governance**

  The IRDiRC Chair presented the need to add quorums and voting rules in the Governance. Daria Julkowska, the Scientific Secretariat Coordinator, reminded the Consortium of previous discussions on the IRDiRC Governance and importance of defining processes related to the mandate of the Operating Committee, including the addition of voting rules as mentioned by the IRDiRC Chair.

7. Summary of Planned Actions and Deliverables

- **IRDiRC Membership**

  All IRDiRC Constituent and Scientific Committee members are highly encouraged to invite new members and increase dissemination of the work of IRDiRC, including Task Forces and Working Groups outputs. Revamping of the CCC membership was raised by Samantha Parker. The IRDiRC Letter of Intent (LOI) for Industry has been improved and revised. David Pearce and Samantha Parker continuously participates in meetings with industry and organizations who are interested in applying to IRDiRC.

- **Future Task Forces Proposals**

  The IRDiRC Chair highly encouraged cross-committee collaborations in preparing task force proposals, especially on the topic of AI.

- **Communication Strategy Sub-Committee**

  A sub-committee composed of IRDiRC members will be established to review IRDiRC's current and future communication strategy. This sub-committee will be led by Samantha Parker, the IRDiRC Vice Chair. The IRDiRC Chair also encouraged the IRDiRC Constituent and Scientific Committee members to continuously share information through the Scientific Secretariat whether it is about funding calls, research projects, or others. Using social media for dissemination of information and participation in various conferences such as Drug Information Association (DIA) was suggested. Improvement of the IRDiRC website was also suggested, making sure that access to publications can be reached within two to three clicks. Resource navigator or Search Engine Optimization (SEO) tools on web search engines such as Google/Bing/Safari was also suggested to improve access to IRDiRC resources and publications.

- **Parallels of COVID19 and RD**

  A white paper will be published from this group and will be led by Anne Pariser, Gareth Baynam, and PJ Brooks.

- **Demystifying Gene Therapies (Terminology/Nomenclature and Method of Delivery) for Better Understanding and Accessibility**

  Participants of this session will be submitting list of recommended links and references that the Scientific Secretariat will collate and publish on the IRDiRC website. A folder will be created on the IRDiRC website dedicated for this topic.