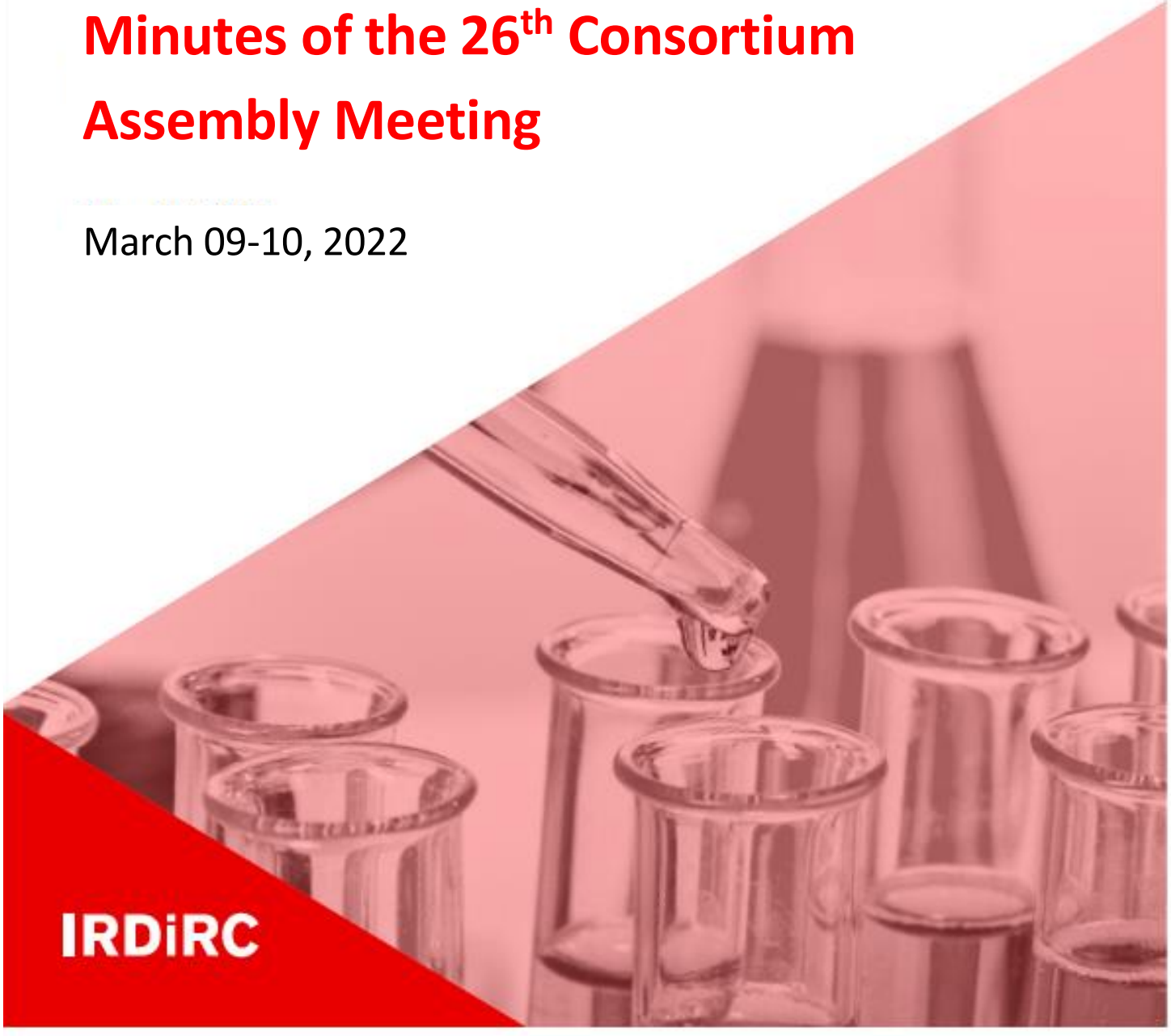
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the 26th Consortium Assembly Meeting

March 09-10, 2022



IRDiRC

EXECUTIVE SUMMARY

The Consortium Assembly (CA) of the International Rare Diseases Research Consortium (IRDiRC) held a two-days online meeting on March 09 & 10, 2022. It was attended by 47 participants representing 37 member organizations, the Scientific Committees (SC) and the Scientific Secretariat (Sci Sec).

March 09, 2022:

1. Changes in Representation and End of Mandate
   - Agence National de la Recherche (FCC) : Prof. Philippe Bouvet (Head of the Biology-Health Department) is replacing Dr. Dominique Dunon-Bluteau.
   - National Center for Advancing Translational Sciences – NIH (FCC): Dr. PJ Brooks (Deputy Director, Office of Rare Diseases Research) is replacing Dr. Anne Pariser.
   - Lysogene (CCC) : Dr. Marie Trad (Chief Medical Officer) is replacing Dr. Ralph Laufer (Chief Scientific Officer).
   - Prof. Anthony Brookes (Leicester University, UK) ended his second mandate in the Diagnostics Scientific Committee.

2. Update on IRDiRC Activities: Task Forces and Working Groups
   - Rare Diseases Treatment Access Working Group
   - Chrysalis
   - Sustainable Economic Models in Drug Repurposing
   - Machine Readable Consent and Use Conditions
   - Shared Molecular Etiologies
   - Integrating New Technologies for Rare Diseases Diagnosis
   - Primary Care
   - Enabling and Enhancing Telehealth for Rare Diseases Across the Globe
   - MedTech Working Group
   - Pluto Project on Disregarded Rare Diseases
   - Repurposing Guidebook

March 10, 2022:

3. Upcoming Events
   - Spring CA meeting: June 1-2, 2022, Paris
   - Winter CA meeting: Nov30-Dec1, 2022, Brussels (TBC)
   - International Conference on Clinical Research Networks: Back-to-back with winter CA meeting
   - EJP RD-IRDiRC-RE(ACT) Conference: March 15-18, 2023, Berlin

4. Regulatory group
   - Following an expert consultation, the potential general objectives of the regulatory group were presented and include:
     - Contribution to task forces and working groups
     - Pathways for regulatory harmonization
     - Identification of new regulatory questions
   - The group will be integrated in IRDiRC as a Regulatory Scientific Committee. This will require the modification of the IRDiRC Governance and the approval from the Consortium Assembly.

5. Summary of the Miro Board Session
   - The results of the MIRO Board Session organized during the last CA meeting (Dec 2021) were presented.
   - Key activities topics and activities have been identified and can be considered for the future IRDiRC Roadmap.

6. Member Engagement
   - The willingness to increase IRDiRC membership was expressed
   - This will require the development of a strategy for member engagement as well as a clarification of the IRDiRC roadmap to identify the organizations to contact.

7. Communication Activities
   - The new introductory IRDiRC video was presented and an update on the Scientific Secretariat communication activities was provided.

REPORT

1. Changes in Representation

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2. End-of-Mandate

- We thank Prof. Anthony Brookes (Leicester University, UK) who has ended his second mandate in the Diagnostics Scientific Committee (DSC). Prof. Brookes will remain involved in IRDiRC as co-leader of the Task Force on Machine Readable Consent and Use Conditions.

3. Updates on IRDiRC Activities: Task Forces and Working Groups

- **Eleven Activities are Ongoing and/or Foreseen for the Year 2022 (Task Forces and Working Groups):**
  - Rare Diseases Treatment Access Working Group (in collaboration with RDI)
  - Chrysalis (led by the FCC and CCC)
  - Sustainable Economic Models in Drug Repurposing (led by the TSC and PACC)
  - Machine Readable Consent and Use Conditions (led by the ISC and ULEIC)
  - Shared Molecular Etiologies (led by the ISC)
  - Integrating New Technologies for Rare Diseases Diagnosis (led by the DSC)
  - Primary Care (collaboration between FCC, ISC, and DSC)
  - Enabling and Enhancing Telehealth for Rare Diseases Across the Globe (will be led by the FCC)
  - MedTech Working Group (will be led by the University of Twente)
  - Pluto Project on Disregarded Rare Diseases (will be led by the CCC and TSC)
  - Repurposing Guidebook (will be led by the TSC)

- **Rare Diseases Treatment Access Working Group (WG)**
  - Presentation: Durhane Wong-Rieger (Rare Diseases International) presented the objectives, methodology, and summary of their progress and results. This WG is a collaboration with RDI.
  - Objective: The goal is to improve access to rare disease medicines by creating a list of standard-of-care medicines, looking at innovative schemes, and identifying the systemic and idiosyncratic barriers to access (e.g., barriers in screening, treatment,

aftercare, cost, and exclusivity expiration, etc.), especially in low-and-middle-income countries.

- Status: The group is developing two workstreams. (1) Review and update the list of essential medicinal products for RD. Include some of the medicines in the WHO's essential list. (2) Map the barriers in the drug journey from manufacturing to delivery. Possibility to select Ghana as a LMIC country case study.
- Foreseen: Updated RD medicine list and recommendation paper on the barriers to access and how to overcome them.

- **Chrysalis**
  - Presentation: Katherine Beaverson (Pfizer) presented the objectives, methodology, and summary of their progress and results. This Task Force is led by the FCC (Adam Hartman) and the CCC (Katherine Beaverson).
  - Objectives: Identify key criteria that would make Rare Diseases research more attractive to industry and find the gaps in the current funding opportunity landscape, including other non-financial factors.
  - Status: The group has sent out surveys to 70 companies and received 39 responses predominantly from large private pharma and biotech companies. Four writing groups were formed covering different themes such as commercial viability, payer/pricing models, probability of regulatory success, and collaboration with stakeholders. Writeups from the four different Writing Groups were completed last November 19, 2021. The final manuscript was expanded and reviewed by the Chairs and simultaneously edited by the different Writing Group members.
  - Result: Attitudes towards Rare Diseases research were mainly influenced by regulatory factors, return of investment, and availability of Rare Diseases natural history studies.
  - Foreseen: An inquiry to scientific journals was submitted for publication. Currently waiting for a response. The next phase of the project is Gap Analysis.

- **Sustainable Economic Models in Drug Repurposing**
  - Presentation: Virginie Hivert (Eurordis-Rare Diseases Europe) presented the objectives, methodology, and summary of their progress. This Task Force is led by the TSC (Daniel O'Connor) and Virginie Hivert (PACC, ex TSC Vice Chair).
  - Objectives: To understand the key features of successful drug repurposing projects and its corresponding business and/or funding models, and to create IRDiRC recommendations on the most successful approaches to support drug repurposing.
  - Status: The questionnaire is composed of 11 sections focused on the expert groups' repurposing research activities, sources and mechanisms of funding, barriers and challenges, sustainable economic model chosen, and recommendations for a successful drug repurposing process. Ten expert groups were selected with various economic model approaches (eight provided answers; two did not answer).
  - Result: The group analysed the results from the survey and the interviews and identified 10 key factors for developing a sustainable approach in drug repurposing for rare diseases. These findings are put together into a manuscript.

- Foreseen: The manuscript will be submitted to a peer-review journal.

- **Machine Readable Consent and Use Conditions**
  - Presentation: Esther van Enckevort (University Medical Center Groningen, ISC) presented the objectives and summary of their progress/results. This Task Force is led by Esther van Enckevort and Anthony Brookes (Leicester University, ex DSC). 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 GA4GH+IRDiRC standard data structures and semantics.
  - Status: Consent form templates were designed for the EU Clinical Patient Management System and the ERN registries and were ontologized. This group is putting this work into a flexible data structure/profile (Digital Use Conditions) for consent and use consent metadata. Many organizations (EJP RD, BBMRI, FAIR Genomes) are assessing this data structure and giving feedback.
  - In the EJPRD registries and biobanking setting, 14 core elements of consent and core conditions (Common Consent of Use - CEE) have been identified, defined, and now alpha tested. A software was established to create the profiles for these 14 CCEs.
  - Foreseen: The group plans to work with ontology developers such as Orphanet to define new classes and properties that are not yet defined in the ontologies, and to extend the Common Conditions of Use (CCE) concept for more complete description of consent and use conditions in the Digital Use Condition (DUC) format. The group aims to integrate the use of DUC and CCE as part of the European Joint Program on Rare Diseases (EJPRD) research activity.

- **Shared Molecular Etiologies (SaME)**
  - Presentation: PJ Brooks (NIH/NCATS) presented the activity's objectives, methodology, and summary of their progress and results. This Task Force is led by the ISC (PJ Brooks and Marc Dooms).
  - Objectives: To assess the global landscape of clinical trials of drugs with 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 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.
  - Status: The group is developing three work streams to address the objectives: (1) Identification of the RD that may benefit from the SaME approach, (2) challenges in clinical trial design (heterogenous phenotypes, statistical approaches), (3) regulatory route for approval.

- **Integrating New Technologies for Rare Diseases Diagnosis**
  - Presentation: Mary Catherine Letinturier (SciSec) presented the activity's objectives, methodology, and summary of their progress and results. This Task Force is led by the DSC (Sarah Bowdin, Clara van Karnebeek, and Gareth Baynam).

- Objectives: To identify new technologies in development or in experimental use that would likely increase the diagnostic rate of rare diseases patients, and develop a clinical framework or guideline for the implementation of combined diagnostic approach of metabolomics, genomics, and AI.
- Status: Two new experts joined the Task Force: Patricia Durao (Executive Director of The Cure and Action for Tay-Sachs (CATS) Foundation, UK) and Prof. Judith Jans (Associate Professor at UMC Utrecht, Netherlands). The group is currently discussing the outline of the future manuscript, state-of-play, and technology mapping accomplished through surveys. Two processes are being considered to address these tasks: (1) Clinicians will provide their current clinical care workflow, and new technology experts will provide recommendations, (2) Focus on the potentials and limitations of new technologies, and the combined diagnostic approach of metabolomics/genomics/AI
- Foreseen: Draft the outline of the future manuscript and organize the writing groups.

- **Primary Care**
  - Presentation: Mary Catherine Letinturier (SciSec) presented the activity's objectives. This Task Force is led by the DSC (Gareth Baynam), FCC (Adam Hartman), and Stephen Groft (from NIH/NCATS). The call for nominations was opened for one month and ended last October 29, 2021. The Sci Sec received 35 applicants from North and South America, Europe, Africa, Asia, the Middle East, and Australia.
  - 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.
  - Status: The group selected three workstreams to develop within the field of primary care: (1) Referral Pathway Optimization, (2) 3P Partnership: Patients-Patient Advocates-Primary Care Providers Partnership and Empowerment, (3) Awareness, Education, and Training.
  - Foreseen: The next meeting will address two topics: (1) framework & process for the mapping of literature, (2) organization of focus groups for the literature review.

- **Enabling and Enhancing Telehealth for Rare Diseases Across the Globe**
  - Presentation: Melissa Parisi (NIH/NICHD) presented the activity's objectives and background. This Task Force is led by the FCC. The call for nominations ended last November 30, 2021, and received 35 applicants from North America, Europe, the Middle East, Asia, Africa, and Australia.
  - 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.
  - Status: A kick-off meeting was organized to introduce the members, the project plan, and the timeline.
  - Foreseen: Scoping exercise and organization of focus groups for the literature review

- **MedTech Working Group**
  - Presentation: Anneliene Jonker (University of Twente, TSC) presented the activity's objectives and background. This WG is a collaboration between IRDiRC and the University of Twente (Netherlands).
  - 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 determine the possibilities for patient involvement in the medical device design process.
  - Status: Two calls were organized to present the project plan and a draft review of medical technologies initiatives and state-ot-the-art across the world.

- **Pluto Project on Disregarded Rare Diseases**
  - Presentation: Daniel O'Connor (MHRA, TSC) presented the activity's objectives and background. This activity will be open for nominations in January 2022.
  - Objectives: To use an integrated database search approach to identify and classify groups of rare diseases that are currently underrepresented by academic research and industries and to determine their common characteristics through analysis to help understand the roadblocks in developing effective treatments for such diseases.
  - Status: The Task Force group was established.

- **Drug Repurposing Guidebook**
  - Presentation: Anneliene Jonker (University of Twente, TSC) presented the activity's objectives and background. This activity will be open for nominations in February 2022.
  - Objectives: To create a guidebook focused on repurposing approaches (incentives, regulatory tools, initiatives, development tools, etc.).
  - Status: The Task Force group was established.

4. Upcoming Events

- **Joint CA-SC Meeting**
  - Date: 01-02 June 2022
  - Location: In-person (Paris, France) or Online? A form will be sent to the CA and SC to identify the number of members attending in person.
  - The meeting agenda is under development and will be shared as soon as possible

- **Conference on International Clinical Research Networks (in partnership with EJP RD)**
  - This event will be organized in Partnership with the European Commission, ERICA (European Rare Disease Research Coordination and Support Action consortium), EJP RD, and NCATS.
  - It will build on the findings of the Clinical Research Network Task Force. The objective of this event is to bring networks together (first connection), share information, network, and potential collaboration.

- It is foreseen to be organized back-to-back with the winter CA meeting (Nov 30-Dec 01, 2022, Brussels, TBC).

- **EJP RD-IRDiRC-RE(ACT) Congress**
  - Date: 15-18 March 2023
  - Location: Berlin, Germany
  - Note: The program committee will be formed soon and will include members of the IRDiRC Operating Committee
  - Organizer: Developed jointly with Black Swan Foundation and EJP RD

5. Regulatory Group

- Collaboration between regulators and other stakeholders is essential to accelerate innovative medicines development for rare diseases and translate this progress into effective, high quality and accessible therapies.

- The secretariat, chair and vice-chair of IRDiRC consulted with several members and collaborators of IRDiRC on the concept to establish a regulatory group

  - Daniel O'Connor, MHRA
  - Katherine Beaverson, Pfizer
  - Kristina Larsson, EMA
  - Katherine Needleman, FDA
  - Marjon Pasmooij, Medicines Evaluation Board NL
  - Oxana Iliach, Certara and member of BoD CORD
  - Durhane Wong-Rieger, CORD
  - Anne Pariser, ex NIH
  - David Lee, Health Canada

- There is a general agreement that the regulatory group should include multiple stakeholders i.e. regulatory bodies, patient groups, industry, public and non-for-profit funders, clinicians and scientists. Three general objectives have been pre-identified:
  - Contribution to task forces and working groups to better address regulatory questions and potentially increase the impact of IRDiRC activities
  - Multi-stakeholder interaction to identify pathways for regulatory harmonization and foster clinical reseach and therapeutic development
  - Identify new regulatory questions

- Objective 1: Contribution of IRDiRC activities: example of the Task Force on Shared Molecular Etiologies
  - What are the regulatory challenges in defining a rare disease vs personalized medicine?
  - Expanding rare disease drug trials based on shared molecular etiology

- How is the work in the task force "shared molecular etiologies" going to challenge what it means to be a rare disease versus a treatment that is disease agnostic?
- What are the key barriers of having different regulatory views?
- Deliverable: recommendations to address actionable barriers

- Objective 2: Regulatory pathway for harmonization
  - Focus on innovative clinical trial designs: How have the regulatory authorities' perspectives been included?
  - Use of natural history data in the contextualization of single-arm trials or augmentation of RCTs
  - Utility of real-world healthcare data leveraged as external control data
  - Getting better epidemiological data for decision making
  - Use of RWE in approving orphan drugs. Guidance on the use of patient-generated data or data gathered from digital/mobile health devices.
  - Use of compassionate data – how to collect and use as supportive
  - What is the best practice and standards for validation of surrogate endpoints, novel clinical outcome measures and biomarkers?
  - Deliverable: work on harmonization (ICH like guidelines)

- Objective 3: Potential supplementary objectives
  - Identified need to increase the knowledge of regulatory processes amongst academic researchers and SME.
  - State of the art – communication and access to existing tools
  - Existing materials: how to build from existing work / platforms?
  - *Deliverable: Regulatory Guidebook? Master classes?*
  - Platforms and standards to speed the development of bespoke gene therapies to treat groups of rare diseases
  - Leveraging technology to develop therapies in extremely rare diseases
  - Reduce animal testing

- Recommendation for the Integration within IRDiRC
  - The group will form a new scientific committee: Regulatory Scientific Committee (RSC)
  - It will require modification to the IRDiRC Governance document and validation/voting by the IRDiRC Consortium Assembly (CA)
  - IRDiRC will then open a call for nomination of RSC members and the final RSC members list will be validated by the CA
  - RSC members will vote to elect the RSC Chair & Vice Chair
  - Anticipate to set-up the RSC by June 2022

6. MIRO Board Summary – December 2021 CA Meeting

- In December 2021, CA members were asked "How can IRDiRC make the most of its research skills and abilities to better move in the 5 thematic areas and address the vision of the Consortium?". Three blocks were proposed in the MIRO board.

- Block 1: Expand on current activities
  - Evaluation/Follow-up of previous Task Forces and its created tools (implementation, dissemination, and continuity)
  - Increase coverage on global issues and better coordination with global multi-stakeholders and organizations
  - Promote basic structures: Registries, Biobanks
  - Increase emphasis on programs for Undiagnosed Diseases (e.g. Health Systems)
  - Increase transversal topics & expertise (ELSI, Data Sharing)

- Block 2 : Propose new ideas
  - Cross-Consortia Activities and Analyses
  - Catalog of RD with an organisational "phylogeny"
  - Education & Training
  - Research & Health (bridging the gap)
  - Governance Structure (Data Sharing & Access, EHRs)
  - Links to Global Centres of Excellence
  - Epidemiology
  - Funder + Patient Organizations Collaboration in Research Granting Cycles
  - Quality of Life (QOL) Evaluation Index
  - Global South Involvement (Latin America, Africa)

- Block 3: I need to think about it because…
  - Strategic decisions need to be made
  - Companion diagnostics and access to treatments should be considered
  - Focus more on research activities and synergies

- The responses of IRDiRC members were further grouped in different themes
  - Collaboration
    - Low and Middle Income Countries (LMIC)
    - European Reference Network (ERNs)
    - Clinical Research Networks
    - World Health Organization (WHO)
    - Health Ministries
    - Between IRDiRC Committees
    - Regulatory & Payers
    - Internal & External Dissemination

  - Disregarded RDs
    - Increase projects
    - Identify projects with unmet needs

  - Dissemination and engagement
    - Better monitoring of IRDiRC members engagement to its goals
    - Better dissemination methods & strategy of Task Forces output and access to tools

        - Transcription Regulation Therapies
        - Invite RNA vaccine biotech to look into RD therapies

    - Guidelines/Recommendations
        - Assess and update diagnosis and treatment guidelines
        - Borrow strategies and best practices from common diseases
        - Best Practices for learning healthcare system
        - Review RD policies worldwide and gather understanding of access and care

- Finally, key topics and activities have been proposed by IRDiRC members and may be considered for the implementation of future activities
    - Diagnosis and its economic value
    - Economic impact of untreated RDs
    - Telehealth
    - FAIR data
    - Linkages and knowledge transfer between cancer & rare disease
    - Mental health issues
    - Centralised information bank
    - Highly innovative research
    - List of diseases with high unmet need and no ongoing clinical trials
    - Data Harmonisation
    - Link with basic animal research to expedite to human research

7. Engagement and Recruitment of New Members

- The IRDiRC leadership with the support of IRDiRC members and the Scientific Secretariat would like to engage in the recruitment of new members
- It was noted that some types of stakeholders are not present in IRDiRC e.g. companies specialized in gene therapies
- The discussion on member engagement highlighted the need to clarify the IRDiRC roadmap prior to contact the right organizations to join the Consortium
- Regarding the engagement of companies, it was suggested to think about multiple mechanisms for companies to come in i.e. full member, consultant, ad hoc contributor, etc.

8. Communication Activities

- Progress on Website & Twitter Activity
    - The number of visits on the IRDiRC twitter is constantly increasing. Following the RD day campaign, the visits grew by 361% compared to February 2021 (803 in 2021 to 3705 in 2022). The most popular tweet is for the animated video.

- New Animated Video
    - A new video introducing IRDiRC is now accessible on the website and on YouTube https://www.youtube.com/watch?v=OSjfeZBJH2E

- Interview Videos

- Six short interviews videos were produced by the European Commission. The interviewees were asked to describe their experience in IRDiRC as well as the impact of the Consortium in their respective field. These videos will be made available on the IRDiRC YouTube channel https://www.youtube.com/channel/UCLv-c0U2CpWwKNFB0r548Yg
  - David Pearce
  - Gareth Baynam
  - Lucia Monaco
  - Irene Norstedt
  - Katherine Beaverson
  - Keving Huang