INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the 12th Executive Committee

6 November 2014

IRDiRC

EXECUTIVE SUMMARY

The Executive Committee (Exec Comm) of the International Rare Diseases Research Consortium (IRDiRC) met on 6th November 2014 in Shenzhen, China. The twelfth meeting of the Exec Comm brought together 23 participants including Exec Comm members and representatives of the three Scientific Committees (Sci Comms).

Hugh Dawkins (Health Department Western Australia) stood in for Paul Lasko to chair the meeting and present the Chair's activities report.

The Scientific Secretariat (Sci Sec) reported on their activities from the past few months and provided an analysis of the Working Group (WG) outcomes from the past two years. It was suggested that all WGs be discontinued and that Sci Comms re-focus on a smaller selection of new Task Forces (TFs) to concentrate on short- to mid-term IRDiRC deliverables.

The three Sci Comms reported on the work of their WGs.

The Exec Comm agreed to:

- Maintain all three Sci Comms and suspend the activity of WGs that have exhausted discussions on their topic.
- Implement short- to mid-term priorities, develop selected topics and organize workshops for 2015, 2016 and beyond.
- Draw up a revised IRDiRC Roadmap to be published within the next months.
- Amend the "IRDiRC Recommended" review process presented during the 9th Exec Comm meeting (Berlin, May 2014).
- Abandon the prospect of directly funding specific projects proposed by the Sci Comms. However, the Sci Comms can propose areas of research within which funding is necessary. IRDiRC will continue to fund workshops and publish results of projects.
- Approve the transition of IRDiRC as organizational partner to organization member of the Global Alliance for Genomics and Health.
- Hold the next face-to-face meetings in March 2015 in Madrid, Spain and in September 2015 in Montreal, Canada. All agreed, in principle, to organize networking sessions at face-to-face meetings.

The Chinese IRDiRC members presented the state of play of rare disease (RD) research in China, including the situation of RD patients and patient organizations as well as challenges and opportunities of RD research.

REPORT

Hugh Dawkins stood in for Paul Lasko (excused) to chair the meeting. He welcomed the participants and thanked BGI for hosting this meeting.

State-of-play of rare diseases research in China

RD patients are inadequately treated in China due to their large numbers (16 million), diagnostic challenges, lack of epidemiological studies, insufficient research funding, insufficient access to orphan medicines, inadequate social security systems and assistance, social discrimination and lack of social and political advocacy.

Four main organizations work in the field of RDs in China: the CRDRC, the Chinese Organization for Rare Disorders (CORD), BGI and WuxiApp Tech. The 53 RD patient organizations in China are relatively new and lack professional participation, social influence and resources. Focus is essentially on research. Discussions are ongoing between academic experts, patient organizations and industrial players such as BGI to build collaborations.

BGI has developed 10 next-generation sequencing (NGS) based panels, covering 1,500 RDs and over 2,000 genes. Through crowd-sourcing, data has been collected from over 6,000 patients and 62 scientific papers were published. An online platform was launched (229andme.com) to share knowledge among experts, educate patients and propose online patient activities.

Opportunities to overcome challenges to address RDs in China include development of 'omics and NGS technologies, animal models, drug repurposing, support from IRDiRC, collaboration with CORD and with government funded agencies.

The Exec Comm recommended data collection according to existing data standards. Data sharing is challenging in China due to sequencing costs and data ownership. The Exec Comm advised that even if scientists have to pay for data, they should share it in order to optimize research. It was also suggested that IRDiRC policy, which states that data will always be owned by patients regardless of who pays to generate the data, should be promoted in China thus to convince researchers to share their data. Moreover, the use of standard informed consent forms was urged in order to enable future collaborations at international level. China should also consider investing in patient organization capacity building (education, therapeutic science) to improve their contribution to research and collaboration.

Chair's activities report

Hugh Dawkins presented the Chair's activities report prepared by Paul Lasko.

Four new members recently joined IRDiRC (Chiesi Farmaceutica; WuXi AppTec; Saudi Human Genome Project; European Organisation for Research and Treatment of Cancer (EORTC)), bringing IRDiRC's total membership to over forty members.

Paul Lasko gave six public lectures on rare diseases during the second half of 2014. IRDiRC members should send in their public lectures and slides mentioning IRDiRC, presented during lectures and symposia, to continue promoting IRDiRC internationally.

Report from the Scientific Secretariat

The project coordinator reported on the Sci Sec activities and proposed a discussion on ways to advance IRDiRC activities and ensure the consortium continues to be successful.

IRDiRC's public website attracted 3,000 unique visits per month, with almost 7,000 page views. The most consulted pages are research highlights and lists of IRDiRC funded projects. Guidelines & Policy documents need to be better promoted.

The private website attracted 19 member visits (235 pages viewed) in October 2014. Most accessed pages include the Executive Committee meeting reports. Half the 252 members of the Sci Comms and WGs do not open the newsletter.

To date, 1,500 NIH research projects were introduced into Orphanet database, along with all the projects funded by other IRDiRC members. This now allows an analysis to be performed, which will be presented at the next Exec Comm meeting.

Following two years of intense brainstorming, priority should be given to topics with international scope, which are actionable with limited human means, and are not yet covered by international initiatives.

The Sci Sec proposed focusing on the following topics:

- Development of a Data Standards Clearinghouse (approved);
- Development of the Generic Consent Form (approved);
- Coordination of initiatives to identify *in silico* drugs and/or new indications (new proposal);
- Coordinate initiatives to develop patient centered outcome measures in RDs;
- Coordination of initiatives on small population trials.

The 13 WGs may now cease their activity and be thanked for achievements during this first phase. New Task Forces should be proposed to act on selected topics. The Sci Sec can manage no more than 5 to 6 topics per annum, in addition to the Data Standards

Clearinghouse, "IRDiRC Recommended" and Core Terminology of Phenome Terminologies projects which are already underway.

Changes in the composition of the Sci Sec: Ségolène Aymé; Lilian Lau (management and communication, replaces Barbara Cagniard); Antonia Mills (scientific content and communication); Sandra Peixoto (research projects and analysis of IRDiRC member-funded research); and Mariane Bellanger (assistant).

Report from the Diagnostic Scientific Committee

Chair of the Diagnostic Sci Comm reported the activities of its WGs.

The **WG on Ontologies** developed and circulated a document on the list of diseases and phenotype ontologies, to decide on what could become "IRDiRC Recommended". A minimal set of phenotype terminologies was mapped across existing ontologies and is near completion. A joint IRDiRC-Global Alliance 18-member committee will develop **Phenotype Exchange Standards** to include different phenotype ontologies and terminologies.

The **WG on Sequencing** has compared 6 or 7 existing guidelines to establish an "IRDiRC Recommended" NGS guideline. The guidelines elaborated by EuroGentest were presented at the last call and will be submitted for adoption as a recommended sequencing standard. The WG should be dissolved once this is complete.

The **WG on Model Organisms** focused on education and knowledge dissemination, ways in which clinicians and scientists interact. It identified appropriate tools and model organisms to reach IRDiRC goals for diagnosis and therapeutics. The WG can be dissolved as it has fulfilled its objective.

The **WG on Control Datasets** held two teleconference meetings to engage participants from the Middle East, China, Japan and India. Progress has been made with GEUVADIS Exome Variant Server (GEEVS) and European Variation Archive (EVA). The WG could be dissolved as soon as objectives are achieved.

The joint IRDiRC-Global Alliance **Matchmaker Exchange Project** provides data sharing tools between clinical geneticists and matches unsolved genome/exome sequence cases. Standard Operating Procedures and Application Programming Interface (API) specifications are being developed.

Conclusion: Priority funding areas should be selected to meet IRDiRC goals. Discussions with the Sci Sec should be held on how to best roll out requests.

Selected priority funding areas include:

- Variant Data-Sharing for Rare Disease Patient Discovery;
- Case-Based Matching for Gene Discovery;
- New Approaches to Solve the Unsolved Rare Diseases;
- Beyond the Exome; and
- Model Systems to Support Variant Interpretation.

Report from the Therapies Scientific Committee

The Therapies Sci Comm activities were reported by its Chair. The Therapies Sci Comm adopted the "Recommendations of the Therapies Scientific Committee to be considered by the Executive Committee to implement IRDiRC Policy 2013 and aim of new 200 therapies by 2020".

The **WG on Orphan Drug Development and Regulatory Process** followed progress of the FDA's Review Division to develop guidelines on clinical trials for orphan drugs and RDs. The EMA will revise its 2006 Guidelines on Clinical Trials in Small Populations and develop a guideline on adaptive statistical methods in small populations. The EMA and FDA have begun dialogues to coordinate.

The **WG on Chemically-Derived Products including Repurposing** is developing a concept paper and program for a 20-30 person workshop in 2015. A draft paper will be prepared and finalized during the workshop, and to be proposed for the "IRDiRC Recommended" label.

The **WG on Biomarkers for Disease Progression and Therapy Response** recommends focusing on two disease subsets: rare cancers and neurodegenerative conditions. Both therapeutic areas offer a better chance of clinical translation. A workshop will be organized in 2016.

Conclusion: The Exec Comm should provide instructions on Sci Comm focus areas. Projects initiated at the Sci Sec level should be allocated to and conducted in collaboration with relevant Sci Comms. The Therapies Sci Comm should increase face-to-face conferences and reduce teleconferences. Specific policy recommendations and papers on resource allocation should be developed.

Report from the Interdisciplinary Scientific Committee

A member of the Interdisciplinary Sci Comm reported on the activities on behalf of its Chair.

The Data Standards Clearinghouse project from the **WG on Data Sharing and Bioinformatics** is under development.

The **WG on Biobanks** discussed proposing incentives to collect samples from RD natural history studies, clinical trials and research. Catalogues and scoring systems should be developed to evaluate RD biomaterial quality.

The **WG on Registries and Natural History** recommends standardization of data collected from natural history studies for research and industry to gather sufficient and appropriate information to use with regulators. Research on how these new technologies (e.g. "unique identifier") address the objectives of registries (meet the needs/expectations of patients and researchers) should be funded.

The **WG on Ethics and Governance** highlighted the need to partner with international organizations to build consent form templates, and avoid multi-center, multinational studies being delayed or prevented by drawn-out regulatory processes.

Conclusion: International collaboration is needed on calls for funding. Patients and the public should be involved in discussions concerning data sharing, regulatory hurdles and privacy protections. Funding should be dedicated to exploring the impact of incidental findings in research. Minimum standards should be developed for consent forms.

Next steps and future plans

The presentations were followed by a general discussion to identify the areas to focus on and the next practical steps. The following conclusions and decisions were made.

IRDiRC is moving into its next phase. WGs were assembled for time limited and task specific purposes. The Exec Comm agreed to disband mature or non-priority WGs, constitute new Task Forces (TFs) and organize workshops to implement selected projects.

The Exec Comm should redefine what is expected of IRDiRC. Expectations of companies developing therapies should be defined concerning frameworks and evaluation processes to guide payers and access to medicine. Access is linked to outcome (treatment protocol, patient benefits, payer assessment of benefits, phenotype/genotype studies).

Therefore, to implement translation of IRDiRC projects into practice, Sci Comms must constitute TFs, define projects and push forward policy change. Priorities were proposed for specific mature projects and operations. Projects should involve leaders who are experts in relevant fields. Coordinators should ensure that participants liaise and share project outcomes. Industry players should be involved in the composition of new TFs in order to respond to their needs and for IRDiRC to benefit from their input.

The Exec Comm agreed to maintain the three Sci Comms (Therapies Sci Comm, Interdisciplinary Sci Comm, Diagnostics Sci Comm). The Sci Sec will propose deadlines to WGs to produce implementation documents on their specific projects.

TFs will be constituted in specific research areas according to the following criteria:

- Topics specific to rare diseases;
- High leverage projects with strong translational potential and international scope;
- Actions for international scope and relevance;
- Projects that have not been covered by international initiatives;
- Well targeted action, with potential to produce results before 2020;
- Actionable projects with secured human and financial resources;
- Clear objectives and timelines to improve participation and member motivation;
- Coordination with other organizations to identify gaps and needs;
- Utilization of projects such as RD-Connect, NeurOmics, EURenOmics and NIH projects.

The Exec Comm, Sci Comms and Sci Sec should align their objectives to improve outputs. The Exec Comm should focus activities in terms of scope (policy and recommendations) and criteria for selection of areas on which to focus.

The Sci Comms should recommend policy for implementation, identify priority areas for funding, identify actionable projects (seek investment and create *ad hoc* committees with clearly defined roles) and co-organize workshops. Sci Comms should conclude ongoing discussions of WG that have run their course. Sci Comms maintain the possibility to conduct a few *ad hoc* conference calls where necessary.

The Sci Sec will continue to support "IRDiRC Recommended" tools, guidelines, workshops and articles for publication. The Sci Sec will consult with Sci Comms to propose and circulate "IRDiRC Recommended" projects for consultation and feedback. The Sci Sec has sufficient budget to organize a number of workshops per year and cover member travel expenses.

Exec Comm proposal for short-, medium- and long-term goals

The Exec Comm agreed on the following priority outputs:

- **Recommendation of funding priorities for RD research** (short documents; publish article on recommendation to funding agencies in areas requiring funding);
- **Policy / Position Statement;**
- **Recommendation to implement IRDiRC policy** (e.g. implications of the need for more research on biomarkers, alternatives to animal models);
- **Data Standards Clearinghouse / "IRDiRC Recommended" process;**
- **Standards;**
- **Coordination among stakeholders / Link between ongoing funded projects**.

And on the following secondary outputs:

- Early-stage intervention;
- Therapeutic translation of IRDiRC knowledge;
- Outcomes with limited resources;
- Co-funding essential projects (critical size) for competitive results (alignment vs competitive force);
- Focus on short- to mid-term projects;
- Medical resource allocation, and clinician and patient education;
- Look at all RDs but concentrate on mechanisms of disease.

The Exec Comm listed the following priority topics to implement in 2015:

- **Computable consent forms**: Set up a workshop to establish elements to computerize based on standards and create clear records of what patients agree upon and which samples are usable in the future. Coordinate with the Global Alliance for Genomics and Health subcommittee (Bartha Knoppers) and other initiatives (e.g. RD-Connect).
- **Small population clinical trials**: Set up a workshop on adaptive design, statistical methods, acceptability of new methods. Coordinate with FDA, EMA, industry, IDEAL, INSPIRE, ASTERIX and other US initiatives.
- **Data Standards Clearinghouse**: Work with data banks and medical centers that do not conduct research to extract information and electronic medical records in RDs. Collect and combine industry, patient organization and clinical research case reports to provide freely available online data on data standards and data elements (e.g. NINDS).
- **Matchmaker Exchange**: A workshop is planned in January 2015.
- **Patient relevant/reported outcome measures**: Set up a workshop to make use of case studies, coordinate PCORI, ISPOR, COMET, MAPI, ICHOM, FDA, EMA, IMI and industry, and advance the HTA process. Distinguish between relevant (guidelines and objectives prior to clinical trials) and reported (outcomes reported)**.**

The Exec Comm listed the following topics to implement in 2016 and beyond:

- **Repurposing, data mining**: Set up a small workshop on data mining to gather actors working on methods to extract data, generate new hypotheses and promote tools to use known compounds or target new mechanisms.
- **Phenotype exchange standards.**
- **Functional analysis.**
- **Reference datasets** for indigenous and minority population groups.
- **Metadata requirements** (standard data elements sets to identify other data elements).

Exec Comm proposal to publish the IRDiRC Roadmap based on new directions

The Sci Comms will propose a roadmap within the next few months, based on IRDiRC's initial roadmap, the Sci Sec's proposal (workshops, defined deliverable outputs) and the present

Exec Comm's discussions. Version 1.1 should be completed to capture the current situation. Version 2.0 should be drafted to include future direction and objectives.

The new roadmap will include a '2015 Plan' to be developed at the three Sci Comm Chair levels, with the Sci Sec. The draft will be submitted to IRDiRC members for comments prior to adoption. The roadmap should highlight specific outcomes, such as expectations from workshops in 2015, in order to measure outputs from proposals.

Procedural discussions

Proposal to vote representative of Scientific Secretariat in as an official member of the Exec Comm

The nomination for the Project Coordinator of Scientific Secretariat to become an official member of the Exec Comm, with the same voting rights as that of Chairs of Sci Comms, was accepted by members present at the meeting. This will be put to a vote before all members of the Exec Comm.

Proposed "IRDiRC Recommended" procedure

"IRDiRC Recommended" was developed, following the Berlin meeting in May 2014, as a label and policy indicator to highlight tools, standards and guidelines that contribute to IRDiRC objectives. Recommended tools, standards and guidelines will be highlighted on the IRDiRC website. A logo will be displayed with a regulatory disclaimer.

Clarifications and amendments to the review process were proposed.

- For certain submissions, *ad hoc* expert committees should be set up to evaluate the recommendations and avoid conflict of interest.
- Reviews for endorsement will be introduced as standing items on all Exec Comm meetings.
- As a neutral party, the Sci Sec will manage the review process: it will provide governance, obtain a review report from the panel, provide a report to the Exec Comm for discussion with experts two weeks prior to voting deadlines, and collect votes following the report assessment.

Options to select and fund short-term project proposals from the Sci Comms

Due to the challenge to put together large funding applications, it was suggested that short project proposals could be submitted within identified calls. Proposals on specific single actions should be submitted to the Exec Comm. Successful applications can be taken forward within IRDiRC or proposed to another initiative.

IRDiRC will continue to fund workshops and publish project outcomes.

IRDiRC will not fund projects or patient representation directly. The proposal to set up a separate bank account to receive funds to support patient representation will be further explored.

Next Executive Committee Meetings

Spring 2015: National Institute of Health Carlos III will host the face-to-face Executive Committee meeting in March 2015 in Madrid, Spain. (*Post meeting note: This meeting will take place on 16 March 2015.*)

Autumn 2015: It was proposed that CIHR/McGill host a meeting in September 2015 in Montreal, Canada, coupled to an E-Rare meeting. (*Post meeting note: Paul Lasko agreed to host the meeting, and a date will be decided in due course.*)

Format of future Executive Committee meetings

The Exec Comm agreed to include networking sessions in future meetings for public bodies to facilitate exchanges on priorities for calls for proposals and ways to collaborate. A networking/matchmaking area could be created on the IRDiRC website.

Nomination for the Scientific Committee

The nomination of Dr Fowzan Alkuraya (nominated by SHGP) as a new member of the Diagnostics Sci Comm was approved by the Exec Comm for a 3-year mandate.

Outreach and international relations

IRDiRC presence in meeting

It was proposed that an IRDiRC session be organized within BIO-Europe Spring 2015, Paris, France (March 2015). (*Post-meeting note: An application will not be submitted.*)

Decision on the transition to Global Alliance for Genomics and Health

The Global Alliance for Genomics and Health requested that interested parties migrate from their expression of interest to full membership. Obligations agreed to in the expression of interest are identical to obligations as full members. The Exec Comm has agreed for IRDiRC to become a full member of the Global Alliance.

Any other business

Approximately 600 attendants are expected for IRDiRC's Shenzhen conference (7-9 November).

Acknowledgments to the host

The Exec Comm is very grateful to BGI for hosting the meeting. The Chair and the IRDiRC Secretariat wish to thank BGI for their generosity and hospitality.

Annex - List of participants

Members	**Representative**
Western Australian Department of Health, Australia	Hugh Dawkins
BGI, China	Ning Li
Chinese Rare Diseases Research Consortium, China	Qing Wang
WuXi AppTec Co. Ltd., China	Mao Mao
E-RARE-2 Consortium, EU & ANR, France	Daria Julkowska
European Commission, DG Research and Innovation, EU	Iiro Eerola
European Commission, DG Health and Consumer Protection, EU	Stefan Schreck
Academy of Finland, Finland	Heikki Vilen
AFM- French Association against Myopathies, France	Françoise Rouault
Lysogene, France	Karen Aiach
Shire Pharmaceuticals, USA	Albert Seymour
Chiesi Farmaceutici S.p.A, Italy	Andrea Chiesi
Carlos III Health Institute, Spain	Pedro Cortegoso Fernández
NIH National Center for Advancing Translational Sciences, NCATS, USA	Petra Kaufmann
National Human Genome Research Institute (NHGRI), NIH, USA	Lu Wang
PTC Therapeutics, USA	Ellen Welch
Sanford Research, USA	David Pearce
Invited Patient Advocacy Groups	
Genetic Alliance, USA	Sharon Terry
Scientific Committees	
Diagnostics	Kym Boycott
Therapies	Yann Le Cam
Interdisciplinary	Petra Kaufmann
IRDIRC Scientific Secretariat	
SUPPORT-IRDIRC Project	Ségolène Aymé, Lilian Lau, Antonia Mills

Apologies

Members	**Representative**
European Organisation for Treatment & Research on Cancer, EORTC	Denis Lacombe
Canadian Institutes of Health Research, Canada	Paul Lasko
Genome Canada	Pierre Meulien
Fondation Maladies Rares, France	Nicolas Lévy
Children's New Hospitals Management Group, Georgia	Oleg Kvlividize
Federal Ministry of Education and Research, Germany	Ralph Schuster

Istituto Superiore de Sanita, Italy	Fabriozio Oleari
Telethon Foundation, Italy	Lucia Monaco
Saudi Human Genome Project, Kingdom of Saudi Arabia	Sultan Turki Al Sedairy
The Netherlands Organisation for Health Research and Development	Sonja van Weely
Prosensa, The Netherlands	Luc Dochez
Korea National Institute of Health, Korea	Hyun-Young Park
National Institute for Health Research, UK	Willem Ouwehand
Food and Drug Administration, USA	Katherine Needleman
Genzyme, USA	Carlo Incerti
Isis Pharmaceuticals, USA	Brett Monia
National Cancer Institute, NIH, USA	Edward Trimble
National Eye Institute, NIH, USA	Santa Tumminia
National Institute of Arthritis and Muskoloskeletal and Skin Diseases, NIH, USA	Stephen Katz
National Institute of Child Health and Human Development, NIH, USA	Melissa Parisi
National Institute of Neurological Disorders and Stroke, NIH, USA	Danilo Tagle
NKT Therapeutics, USA	Robert Mashal
Office of Rare Diseases, USA	Pamela McInnes
Invited Patient Advocacy Groups	
EURORDIS (Patient Advocacy Group), Europe	Béatrice de Montleau
National Organization for Rare Diseases, NORD, USA	Peter Saltonstall

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