INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the 5th Executive Committee meeting

23-24 September 2013

IRDiRC

EXECUTIVE SUMMARY

The Executive Committee (Exec Com) of the International Rare Diseases Research Consortium (IRDiRC) met on 23-24 September 2013 in Miami, USA. The fifth meeting of the Exec Com was kindly hosted by NIH, with the support of NKT Therapeutics, PTC Therapeutics, Sanford Research and Shire, and brought together 24 participants including 17 Exec Com members and the chairs or vice-chairs of the 3 Scientific Committees (Sci Com).

Two new members were welcomed: Chinese Rare Disease Research Consortium and Korea NIH.

The chairs of the 3 Scientific Committees presented the state of play of their consultation process with their working groups. They should be in a position to propose elements for an action plan by next December. The chair of the Therapies Sci Com has resigned. The new chair will be elected through a conference call.
The members of the Exec Com provisionally agreed that the approval of new Exec Com members should remain the prerogative of the Exec Com chair. The Exec Com chair should consult the Exec Com in case of uncertainty. The objective is to be as inclusive as possible for the time being. It was also decided that a letter of motivation explaining how the applicant plans to contribute to reach IRDIRC goals, should be required for the application.

It was decided to withdraw the letter of confidentiality for members of the Sci Com as it is considered unnecessary by the chairs of the Sci Com. This decision could be reversed in the future if a confidentiality declaration is deemed necessary.

The governance document has been updated to take stock of the changes in the activities and in the organization of the consortium, and amended to take into account the past experience.

The nomination of 5 new members of the Sci Com was approved by the Exec Com for a 3-year mandate. Currently, there is no definition of how Industry could nominate Sci Com members. This should be defined in the future.

The next Exec Com meeting will be held on 7-8 May 2014, right before the European Conference on Rare Diseases meeting to be held in Berlin on May 9-10. The following Exec meeting will be held in China in October-November 2014, if the IRDiRC conference is confirmed at this date.

REPORT

Welcome of new members

The chair of the Exec Com welcomed the participants and the new members of the Exec Com:

- Prof Qing Wang, Chinese Rare Disease Research Consortium
- Dr Hyun-Young Park, Korea NIH

Introduction of the Chinese RD Research Consortium

The initiative to establish the Chinese RD research consortium was taken on 4 June 2013, and the consortium was established formally on 14 September 2014 and held its first symposium. The consortium includes Huazhong University of Science and Technology in Wuhan, the University of Hong Kong, the Peking University, the National Institute of Biological Science, Chinese Academy of Science in Beijing, Xiehe Medical School in Beijing, Beijing Yuan Tang Institute of Gene Science, the Ministry of Health in Beijing, the General Hospital of PLA in Beijing, the Sandong University in Jinan, the Shanghai Jiao Tong University, the Fudan University in Shanghai, the Shanghai Institute of Biological Science, the Chinese Academy of Science in Shanghai, the Nanjing Medical University, the Zhejiang University in Hangzhou, the Wenzhou Medical University, the Fujian Medical University in Fuzhou, the Zhongshan University in Guangzhou, the Sichuan University, the Zhongnan University in Hunan, the Nan Chang University, the Anhui Medical University, the Wuhan University, the Institute of Hydrobiology in Wuhan and the Wuhan Children's Hospital.

Action Plan

The IRDiRC action plan will be discussed by the Executive Committee when the Scientific Committees provide proposals. The chairs of the 3 Scientific Committees presented the state of play of their consultation process.

Diagnostics Scientific Committee

The Diagnostic Scientific Committee, represented by the chair of the committee, has already four active working groups (WG) in the field of Genome/Phenome, Ontologies and disease prioritization, Sequencing, and Model systems. The Genome/Phenome WG had a workshop in Dublin to discuss tools necessary for the interpretation of genetic variants. Having common ontologies, adhering to sequencing standards and opening data access for discovery were the three main ways to ease the process. The work plan overlaps with the

one from the Global Alliance. That is why IRDiRC should represent the voice of rare diseases in Global Alliance. The WG on Ontologies plans to review all existing relevant ontologies and suggests ways to support them as core infrastructures for research. An International WG is currently defining a core set of terms to describe phenomes, which could be proposed to all projects registering patients' data and to international nomenclatures. The IRDiRC should support this effort. The Sequencing WG plans to review the guidelines and identify commonalities and discrepancies. It wishes to be represented at the clinical exome meeting organized by the NIH/NHGRI in January 2014. The Model system WG expressed the wish to have a market place for model systems. One of the main messages from Diagnostic Scientific Committee was that almost all easily recognisable syndromes have been identified. Yet the work to be done is quite overwhelming: with a target of 6000 diagnostics to be available in 2020, the pace should be dramatically accelerated: some 500 novel genes should be identified on average each year from now to 2020.

Members of the Executive committee asked for the participation of the industry representatives in the working groups and underlined its importance especially for the discussions related to the clinical data sharing and involvement in Global Alliance.

Interdisciplinary Scientific Committee

The Interdisciplinary Scientific Committee, represented by the vice-chair of the Committee, has already four active working groups (WG) in the field of Ethics and governance, Registries and natural history, Data sharing and bioinformatics, and Biobanks. The Ethics WG identified several issues to consider: paediatric issues and transition through life stages; harmonization of consent access / privacy: question: What can be achieved at the international level? ; data protection / impact of data protection laws (related to new EU regulation); access (exchange) of biological resources, samples and data and incidental findings (i.e., sequencing: Discussion and elaborations of common guidelines). The Registry WG identified the topics to cover: CDEs (Common Data Elements) and MDS (minimal data set) to be defined and proposed as standards; recommendations for interoperability and patient reported outcomes; recommendations for quality assurance and data integrity, standardisation of Outcome measures; linking of registries to medical records. The Data sharing and Bioinformatics WG considered that the "sharability of data" was of primary purpose, in that, its concerns were how to ensure that data could be shared, not the actual sharing of the data. A recommendation should be issued on what to do when sharability can lead to loss of individual confidentiality. Addressing sharability across major projects or sponsoring organization, or data recipients could reveal the extent to which existing efforts have been initiated. Efforts towards developing data standards and, hence improving sharability, are underway on both sides of the Atlantic. More effort should be made to bring them together to share perspectives and make these efforts more widely known and

accessible. The Biobank WG highlighted the difficulties in material transfer between countries. There are different regulations and requirements for privacy and human subject issues in different countries. Most stored specimens lack sufficient annotation and in most cases, they are not linked to individual medical information. There is a lack of collaborations, of sharing and using existing resources leading to redundancy in many programs, and waste of resources. A Certification and Accreditation system is needed (QC procedures to identify biobanks providing high quality of samples and complying with IRDiRC objectives).

The vice-chair of the Cmitteeom concluded that, while research advances at a fast pace, these "binding actions" are essential and certain policies, e.g. data sharing, need to be clarified as soon as possible, if collaborative research is to be carried out. The Interdisciplinary Sci Com will meet in Montreal in October for "in-depth" discussions of the gap analysis and action plan and for appraising and prioritizing the output from the working groups. A full report with recommendations will be provided to the Executive Committee following the Montreal meeting. A close interaction with the diagnostics and therapeutics science committees is envisaged to harmonize the recommendations as some overlap is envisaged.

Therapies Scientific Committee

The Therapies Scientific Committee were presented by the chair of the Committee, who announced that he wishes to resign as chair, due to the situation of its department in Spain facing a severe budget cut. The Committee has not yet fully established its WGs. It was proposed to revise the name and scope of the WG to be established. The following names were agreed on: WG on biomarkers for disease progression and therapy response, WG on chemically-derived products including repurposing; WG on biotechnology-derived products including cell- and gene-based therapies; WG on orphan drug-development and regulatory processes.

The proposed next steps are to organise a teleconference of the Therapies Sci Com focusing on the completion of the WG for them to start rapidly to work on their recommendations, and on the election of a new chair. It was suggested that the experience of Yann Le Cam (EURORDIS) would bring an additional expertise to the Therapeutics Sci Com and therefore he should be invited to be a part of the committee. It was also suggested that the outcomes of the session at the IRDiRC Dublin Conference on therapies and regulatory issues should be integrated into the work of the Therapies Sci Com, in order to take stock of the progress made there.

Scientific Secretariat

The Scientific Secretariat (Sci Sec) presented a cross-sectional analysis of the WG conference calls to identify points for action. It stated that the mandate of the WG is not clear enough, most of them not understanding whether they just have to brainstorm or if they should also produce original work despite the lack of specific funding. The cross talk between the working groups should be organized. The Sci Sec proposed that, due to voluntary work only, WG are not expected to produce new work/new documents/new standards but to identify the ones produced by the research projects already funded. Any work of compilation should be provided by the Sci Sec, which has some resources. The Sci Sec also suggested that the Sci Com should provide rapid feed-back to the WG to maintain the momentum. WG calls should have well-organized agendas.

Governance issues

Approval process for IRDiRC new members

Until now, the chair of the Executive Committee was approving new members without consultation of the Exec Com. However, due to an evolution in the type of organization applying to join IRDiRC, quite different from the original research funding agencies, a possible change in the approval process was discussed. Three options for approval process were proposed following submission to the Exec Com chair:

- Dissemination to all Exec Com members and approval by mail
- Dissemination to all Exec Com members and approval at the next Exec Com meeting
- Direct approval by Exec Com chair without consultation

The members of the Exec Com provisionally agreed that the approval should be delegated to the Exec Com chair. The Exec Com chair should consult the Exec Com in case of uncertainty. The objective is to be as inclusive as possible for the time being.

It was also decided that a letter of motivation explaining how the applicant plans to contribute to reach IRDIRC goals should be required for the application. In the future, an analysis of the different types of members will have to be conducted to explore the need for establishing categories of members with different roles. The optimal number of Executive Committee members was also discussed. The Exec Com chair reminded that for the moment IRDiRC executive committee is open ended. It was agreed that the question of number of participants should be put on the agenda in the future.

The type of membership of the Exec Com was also discussed. As the IRDiRC continues receiving applications from candidate organizations, the Exec Com is growing in size and may

become less manageable. As a potential solution, some supported a multi-tier membership, i.e. a differentiation between affiliated and ordinary members. This would allow institutions whose profile is not a typical profile of a "research funder" to join IRDiRC. Others suggested that the membership should not be differentiated, but possibly a smaller group within the Executive Committee could steer the decision-making process, otherwise (with an increasingly large number of members) decisions would stall on a regular basis and no progress toward the IRDiRC objectives will be made. The proposal to exclude from membership those organizations that fund only a single RD or subgroup of diseases was voted down, as it seemed somehow discriminatory against organizations that are anyway working to increase the number of therapies for RDs or improve diagnostics. Distinguishing IRDiRC membership from Exec Com membership may be a way to explore.

Modification of the 'letter of intent' template

The present 'letter of intent' template emphasizes the past funding for rare diseases of the applicant. However, future funding is a priority and applicants do not always commit to future funding, leading to refused applications. In consequence, a new template letter with minor modifications but mentioning both future and past funding was proposed.

The members of the Exec Com agreed on the suggested modifications. However, the problem of the Policies and Guidelines cited in the letter was raised. Indeed, it is not clear if applicants sign for the current policies and future policies, which could be problematic, or only the current ones. It was specified that applicants only sign for the current policies and members of the Exec Com have to approve any change in the policies, allowing discussion. However, it was agreed to change the wording of the document to replace the link towards the Policies document by the mention 'available on the IRDiRC website'.

The question of the lack of legal status of the IRDiRC policies document was seen as a problem by an applicant from Industry. The agreement was to convey to this applicant the message that the IRDiRC is a consortium to which bodies adhere on a voluntary basis and can leave at any moment. Therefore, the documents are not legally-binding.

It was decided to create a subcommittee to write a position paper on the role of industry in IRDiRC to answer concerns of industry willing to join IRDiRC and encourage their participation. Emmanuel Chantelot (Shire), Isabel Ferreira (Prosensa), Irene Norstedt (European Commission), Diane Goetz (PTC Therapeutics), Robert Mashal (NKT Therapeutics) and Paul Lasko (chair) agreed to participate to this subcommittee, which will meet by teleconference.

Modification of 'Confidentiality and non-conflict of interest declaration'

Members of the Scientific Committees were required to sign a 'confidentiality and non-conflict of interest declaration' as they participate as individual and not as representative of their organizations. However, an issue arose when a FDA employee was nominated to join the Therapies Sci Com and declared his inability to sign the document from which the level of confidentiality is greater than the level of confidentiality required by US federal law. In agreement with the Exec Com chair, the FDA provided a modified version of the document that fit the requirement of the FDA for this type of document. Following the explanation of the modifications brought to the document by the representative of the FDA, a discussion on status of SC members as individual or representative of their organization and the possibility of special exemption for some categories was held. It was finally decided to drop the letter of confidentiality that is considered unnecessary by the chairs of the Sci Com. However Sci Coms should monitor that in the context of their and WGs work there is no confidential information that is being shared or should be protected. The above-mentioned decision could be reversed in the future if a confidentiality declaration was needed.

A confidentiality agreement may be required for Executive Committee members. This issue will be revisited at a future date but in the event such an agreement is required, adjustments to that agreement may be made to accommodate level of confidentiality required by national laws.

Update of the governance document

The governance document has been updated to take stock of the changes in the activities and in the organization of the consortium and amended to take into account the past experience. It was decided that new nominations for the Sci Com can be proposed by the Sci Com themselves but should be decided by the Exec Com as to ensure the new members have the opportunity to propose nominees. It was reminded that the Sci Com members are appointed for their personal expertise; therefore they cannot delegate their role. It was suggested that members of the Sci Com should be a part of each WG. However, to decrease the amount of work demanded to the Sci Com members, their role in the WGs could be limited to participation only and not necessarily the role of the WG chair. The WG are no longer in charge of promoting collaborations but should now present to the Sci Com the opportunities, gaps and possible actions in their field.

The question of participation/presence of the Exec Com members at the conference calls or meetings of the WGs and/or scientific Committees was raised. Representatives of the Sci Com stated that they do not see necessarily an added value in assistance to the meetings of the WGs since their work should be integrated and resumed by the Sci Com. However, a

member of the Exec Com is always free to express his/her interest in the work of the Sci Coms and ask Sci Com chair to participate in Sci Com meetings or conference calls.

EURORDIS asked to contribute to the debate on the governance of IRDiRC, as clarifying the governance is important for patients as they wish to see the Consortium speed up its pace and reach its objectives. It was suggested supporting the Exec Com chair with a bureau, but this was declined by the Exec Com chair as the Sci Sec fulfills this role. It also called for an operating committee including the 3 Sci Com chairs, the Exec chair and the Sci Sec, to formalize the activities. The Chairs of the Sci Com explained that indeed the 3 Sci Com Chairs, the Exec Com chair and the Sci Sec agreed to establish regular contacts for a better coordination amongst themselves. EURORDIS also invited to clarify the role of the different bodies and committees in IRDiRC and to bring the discussions held during this and previous Exec Com meetings to a conclusion that clarifies mandates and reciprocal expectations amongst bodies, thus enabling the Consortium to function and work on reaching its objectives.

Nominations for the Scientific Committees

The nomination of 5 new members of the Sci Com was approved by the Exec Com for a 3-year mandate. The new members are:

Diagnostics Sci Com:

- Dr Woong-Yang Park (nomination by KNIH)
- Prof Pak-Chung Sham (nomination by CRDC)

Interdisciplinary Sci Com:

- Dr Petra Kaufman (nomination by NINDS)

Therapies Sci Com

- Prof Asla Pitkänen (nomination by Academy of Finland)

Currently there is no definition of the way Industry can nominate Sci Com members. This should be defined in the future.

Next Executive Committee meeting

Attendance to the Exec Com meeting depends on the convenience of the location and the possibility for the members to justify the necessity of traveling. To improve attendance, it

was proposed to couple the Exec Com meeting with existing scientific conferences, but also to intercalate 1-2 teleconferences between the face-to-face meetings to be able to convene more often. The possibility was raised to organize a single face-to-face meeting instead of 2 per years if teleconferences were more convenient.

The suggested plan for the coming year is to organize the next Exec Com meeting on 7-8 May 2014, right before the European Conference on Rare Diseases meeting to be held in Berlin on May 9-10. A session of the Conference will be dedicated to the IRDiRC achievements and the Exec chair will be invited to the opening session.

The following Exec meeting will be held in China in October-November 2014 if the IRDiRC conference is confirmed at this date. In the meantime, a teleconference will be scheduled on the last week of November 2013 focusing on a report by the Sci Com to the Exec Com.

Scientific Secretariat update

The Sci Sec reported on its activity of organizer of the Sci Com meetings and WG teleconferences, which includes writing of the minutes and searching for documentation when needed. It proposed to enlarge this activity to a real support to the WG by preparing actively the agenda with the chairs, and proactively identifying projects and resources of interest for the WG.

In terms of communication, the website was modified to better highlight some important research projects and major scientific achievements. The website was visited during the last month by 1,402 unique visitors. A private section for members only was created where all the documents will be posted, including those in development. The Exec Com members requested to have a personal login and password, when the Sci Com opted for a common password as the level of confidentiality of their documents is lower.

An internal newsletter has been implemented to keep everyone informed regularly.

The Sci Sec reminded the Exec Com that there is no budget for scientific conferences except for the support of the scientific organising committee meetings.

The Sci Sec is supposed to analyse the current landscape of on-going research projects, which is difficult to achieve if the Exec Com Members do not provide the list of the funded projects.

The Sci Sec wishes to have the opportunity to have a formal exchange with the Exec Com chair and the three chairs of the Sci Com on a regular basis. This was accepted and will be done through teleconferences when necessary.

IRDiRC conference

Debriefing of the Dublin Conference

The IRDiRC conference held in Dublin attracted more than 400 participants from Europe, North America, Asia and Australia. The organization and the scientific program, with more than 45 speakers and 5 panel discussions over two days, were excellent. Feedback from participants was positive.

Next IRDiRC conference

BGI proposed to host the next IRDiRC conference in Shenzhen in fall 2014. This proposal is of interest as the funding to organize such a meeting is low and it would help promote IRDiRC in Asia. The lack of funding could be compensated by setting up an exhibition and/or implementing a registration fee. These possibilities should be discussed with the conference organizer. The possibility was raised to hold the conference in Hong Kong, where BGI has a branch, rather than continental China. The Scientific Secretariat will contact BGI to obtain a more detailed proposal before approbation.

The following conference could then be planned in 2016 in Europe or North America.

Outreach efforts and recruitment of new members

Outreach efforts are necessary to increase the visibility of IRDiRC, which requires funding. For example, the Diagnostics Scientific Committee is planning to organize a workshop that will increase the visibility of IRDiRC in Eastern European countries. In addition, IRDiRC WG would need funding to work on specific action. In principle, members of the Exec Com may consider participating in such efforts if the outcomes are worth the contribution and promote networking. A proposal on the type of action, their outcomes and the investment necessary should be presented to the Exec Com.

Relationship with other international initiatives

Global Alliance on Genomic and Clinical Data Sharing is identified as an organization of great relevance for the IRDiRC. However it is still at the visionary level. IRDiRC supports the spirit but is not committed to support the activities requiring funding. It is judged likely that Global Alliance will achieve the goals of IRDiRC in the field of data sharing.

Human Variome Project is organizing good meetings contributing to the issue of the production and interpretation of sequencing data. In order to be connected with its activities, HVP was invited to nominate someone to the Diagnostics Sci Com.

ICORD (International Conference on Rare Diseases) is a small organization holding annually a meeting in a different country where rare diseases are not yet on the forefront. These meetings are not seen as in competition with the IRDiRC ones but rather complementary as their focus is mainly political, not scientific.

Acknowledgments to the host

The Exec Com is very grateful to the NIH for hosting the meeting. The Chair and the IRDiRC Secretariat wish to thank the NIH, NKT Therapeutics, PTC Therapeutics, Sanford Research and Shire for their generosity.

Annex - List of participants

Members	**Representative**
IRDiRC Chair Executive Committee, Canadian Institutes of Health Research, Canada	Paul Lasko
Genome Canada, Canada	Pierre Meulien
Chinese Rare Disease Research Consortium, China	Qing Wang
E-RARE-2 (E-Rare Group of Funders), Europe	Daria Julkowska
European Commission, (DG Health and Consumer Protection), EU	Stefan Schreck
European Commission, (DG Research and Innovation), EU	Irene Norstedt and Iiro Eerola
EURORDIS (Patient Advocacy Group), Europe	Valentina Bottarelli
Shire, Ireland	Emmanuel Chantelot
Telethon Foundation, Italy	Lucia Monaco
Carlos III Health Institute, Spain	Juan Riese
Prosensa, The Netherlands	Isabel Ferreira
Food and Drug Administration, USA	Gayatri Rao
National Cancer Institute, NIH, USA	Thomas Gross
National Eye Institute, NIH, USA	Santa Tumminia
National Human Genome Research Institute, NIH, USA	Jeff Schloss
NKT Therapeutics, USA	Robert Mashal
PTC Therapeutics, USA	Diane Goetz
Sanford Research, USA	David Pearce
Scientific Committees	
Chair Therapies Sci Com	Josep Torrent-Farnell
Co-Chair Interdisciplinary Sci Com	Jamel Chelly
Chair Diagnostics Sci Com	Kym Boycott
IRDIRC Scientific Secretariat	
SUPPORT-IRDiRC project	Ségolène Aymé and Barbara Cagniard

Apologies

Members	**Representative**
Western Australian Department of Health, Australia	Hugh Dawkins
BGI, China	Ning Li
ANR- French National Research Agency, France	Bertrand Schwartz
AFM- French Association against Myopathies, France	Marie-Christine Ouillade

Lysogene, France	Karen Aiach
Federal Ministry of Education and Research, Germany	Ralph Schuster
Instituto Superiore de Sanita, Italy	Enrico Garaci
Korea National Institute of Health	Hyun-Young Park
The Netherlands Organisation for Health Research and Development, The Netherlands	Sonja van Weely
National Institute for Health Research, United Kingdom	Willem Ouwehand
Genetic Alliance, USA	Terry Sharon
National Center for Advancing Translational Sciences, NIH, USA	Christopher Austin
National Institute of Arthritis and Muskoloskeletal and Skin Diseases, NIH, USA	Stephen Katz
National Institute of Child Health and Human Development, NIH, USA	Alan Guttmacher
National Institute of Neurological Disorders and Stroke, NIH, USA	DaniloTagle
NORD, USA	Peter Saltonstall
Office of Rare Diseases, USA	Stephen Groft

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