IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the Joint DSC/ISC/TSC 2015 Meeting

Glasgow, Scotland, UK
6 June 2015

Organization

Organized and hosted by: Scientific Secretariat

Participants

Diagnostics Scientific Committee (DSC)

Dr Kym Boycott, Ottawa, Canada (Chair)
Prof Xavier Estivill, Barcelona, Spain
Prof Johan den Dunnen, Leiden, Netherlands
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Dr Feng Zhang, Shanghai, China

Interdisciplinary Scientific Committee (ISC)

Prof Hanns Lochmüller, Newcastle, UK (Chair)
Dr Stephen Groft, Bethesda, USA
Dr Petra Kaufmann, Bethesda, USA
Prof Bartha Maria Knoppers, Montreal, Canada
Dr Jeffrey Krischer, Tampa, USA
Ms Samantha Parker, Paris, France
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Therapies Scientific Committee (TSC)

Mr Yann Le Cam, Paris, France (Chair)
Dr Diego Ardigò, Parma, Italy
Dr Adam Heathfield, Sandwich, UK
Dr Elizabeth McNeil, Bethesda, USA
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Executive Committee (Exec Comm)

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Agenda

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REPORT

1. Introduction

The Joint IRDiRC Scientific Committees (Sci Comms) meeting, chaired by Prof Hanns Lochmüller, brought together 23 participants: 5 members of the Diagnostics Sci Comm (DSC), 8 members of the Interdisciplinary Sci Comm (ISC), 6 members of the Therapies Sci Comm (TSC), Chair of the IRDiRC Executive Committee (Exec Comm), and 3 members of the Scientific Secretariat (Sci Sec). Everyone briefly introduced themselves and stated their participation in IRDiRC.

2. Presentation by the Chair of the Exec Comm

The Chair of the Exec Comm thanked all members for their efforts in working towards IRDiRC's goals and gave a brief presentation of the direction the consortium is moving towards. Launched in April 2011, the mandate of the consortium lies at the level of research, with an aim to improve international collaboration and coordination to better facilitate research with the concomitant benefit of reducing inequities for patients.

The consortium's diagnostics goal is to develop means to diagnose most rare diseases by 2020. About 3,400 and 2,400 genes were linked to rare diseases respectively towards the end of 2014 and 2010, and about 3,300 and 2,200 rare diseases have a genetic test available for the same time points respectively. [*Post-meeting note: the number of rare diseases with a genetic test available is based on data collected in 37 European countries by Orphanet.*] While nearly 7,000 rare diseases are recognised to date, not all are genetic diseases. The 1,000 or so genes discovered between 2010 and 2014 had been largely driven by exome sequencing, which may be reaching its plateau. Additional genes and disease-mechanisms may be ultra-rare and more challenging to identify, with technical challenges to overcome.

In terms of the consortium's therapies goal, which is to deliver 200 new therapies by 2020, the count as of June 2015 was 144. If the rate of approximately 30 new therapies delivered per year is maintained, this goal will be achieved by the end of 2016.

The focus of IRDiRC in the coming years could shift to the demonstration of the added value it brought to the rare disease research community. In order to do that, IRDiRC has to have as high a profile as possible and be strongly linked to the community. IRDiRC conferences – in Dublin in 2013 and in Shenzhen in 2014 – have raised its visibility. Collaborative work (e.g. Matchmaker Exchange, in partnership with Global Alliance for Genomics and Health, GA4GH) also helps to promote its presence.

Suggested goals for 2015-16 are:

- to increase dissemination of what IRDiRC members are doing and their achievements
- to widen community involvement in IRDiRC activities (e.g. participation in Task Forces)
- to add visibility of activity deliverables (e.g. public consultation on Task Forces' outcomes)
- to be involved and/or co-sponsor conferences/meetings (e.g. co-sponsoring RE(ACT) 2016 in Barcelona, planning an IRDiRC session during the ICHG 2016 in Kyoto)
- to continue recruiting new members

The Chair of the Exec Comm was asked of the opportunities for the Sci Comms to guide or suggest funding opportunities, and the practicality in the uptake. While IRDiRC does not have a formal mechanism to coordinate funding centrally, the Chair nonetheless encouraged Sci Comms to make their suggestions to the Exec Comm, as these may be picked up by some funders for implementation in their jurisdictions.

The future of IRDiRC beyond 2020 was also discussed. The hope is that IRDiRC continues to exist, which will depend on the demonstration of the added value of the consortium. Recommendations to funders, policy recommendations, reference for good practices, and linking academic teams to industry partners were proposed as ways to demonstrate added value. Members were also reminded that the funding supporting the Sci Sec will end in September 2018.

Collaboratively, IRDiRC has also contributed to the GA4GH's *Framework for Responsible Sharing of Genomic and Health-Related Data* which provides a principled and practical framework for the responsible sharing of genomic and health-related data. It is available in 10 languages and should be capitalised to facilitate responsible research conduct in data sharing.

3. Update on current Task Forces

A number of Task Forces have been launched for action in 2015-2016 and briefly described below. For more information and details, please consult the Glasgow meeting report of indicated Sci Comm. (Please note that while Task Force proposals originate from particular Sci Comm, the Task Forces implemented are/will be collective efforts across all Sci Comms.)

For each Task Force, selected core group members (i.e. Steering Committee members), based on nominations from the Exec and Sci Comms, will lead these projects; non-selected nominees will be eligible for general Task Force membership. Each Steering Committee will decide on the participant list of its invitation-only workshop, based on participants proposed by the Sci Comms, the Steering Committee and other Task Force members. The Sci Comms also recommended opening the general membership of Task Forces to any interested volunteer by way of announcements on IRDiRC website/newsletter.

Sci Comms will be sent a background paper of each Task Force, where applicable, in due course, and members were asked to actively review them and provide their input. Sci Comms will also nominate member(s) to sit in each Task Force and to report back to the Sci Comms.

3.1 Matchmaker Exchange (MME) – DSC

The MME is a federated network of databases aimed at finding genetic causes of rare diseases by matching similar genotypic and phenotypic profiles. Launched in October 2013, the MME faces the technical challenge in that each database holds slightly different data. The first version of the API was created based on the lowest common denominator of databases involved and runs point-to-point queries.

The MME Task Force is working towards two meetings in conjunction with the ASHG 2015 in Baltimore. There will be a full-day meeting geared for (1) investigators implementing or about to implement the API, and (2) next set of adopters, to discuss the nuts and bolts of the API. There will also be a 2-hour community-based meeting to show how the MME works etc. A special issue of Human Mutation containing 16 articles which describe MME, the API, each of the databases involved and success stories – is due for publication ahead of the meetings – and will facilitate communication of this project.

3.2 Patient-Relevant Outcome Measures (PROM) – TSC

The background paper was circulated to all members of Exec Comm on 27 April, and Sci Comms on 1 June (ISC) and 2 June (DSC and TSC). The draft report synthesises projects and initiatives conducted in the area. Methods in this area have reached a certain level of maturity, with significant investment in best practices, for common and specific diseases. The planned workshop will look into extending the development of methodology and guidelines, best practices and experience into the area of rare diseases. The Task Force has been composed.

[*Post-meeting note: the steering committee members have been contacted individually to review the background paper and its scope, add references, identify topics for discussion at the workshop and draft policy recommendations. Task Force members involved in the initiatives highlighted in the background paper have been invited to review their section – most have sent their feedback and the paper has been updated accordingly. A new draft of background paper following integration of reviews by Task Force members will be circulated in due course. The workshop will be held in Paris, end of November 2015.*]

3.3 Small Population Clinical Trials (SPCT) – TSC

A first version of the SPCT background paper has been prepared and the Task Force composed, consisting of regulators (i.e. EMA, FDA) and leaders of major EU-funded projects (i.e. ASTERIX, IDEAL, InSPIRe). Sci Comm members were asked to inform the Sci Sec of any other project leaders which may be missing, especially in the USA, so they can be invited to participate. The EMA has indicated their intention to host the workshop; the date has not yet been identified. The outcomes the TSC would like to see from this workshop are: (1) State-of-Play of different types of design and statistical methods in small populations, and (2) recommendations from IRDiRC. In parallel, IRDiRC could (a) identify what may be translated as recommendations to funders for integration into calls to ensure cost effective studies involving less patients, and (b) suggest to FDA and EMA to push forward their guidance documents to convey this message of adaptiveness to applicants/developers of medicinal products, such as in the Guidelines for Clinical Trials in Small Populations/Orphan Medicinal Products/Paediatric.

3.4 Data Mining and Repurposing (DMR) – TSC

Several groups have recently published successful identification of new therapy targets using data mining tools. This Task Force engages these key players to identify tools which are mature enough for use by academic researchers to accelerate therapies research and to forge collaborations that integrate different research domains to benefit rare diseases research. The key members contacted have agreed

to participate in the Steering Committee. The workshop is planned for the end of 2015 or early 2016 and not yet set.

3.5 Machine Readable Consent (MRC) – ISC

This is a collaborative project with GA4GH, which was due to have its first teleconference recently to validate the mandate and membership of the Task Team, but didn't go as planned as both Co-Chairs were unexpectedly called away. It was hoped that this group will have a face-to-face meeting/workshop in Paris in the coming months.

4. Future Task Force proposals

Future Task Force proposals to the Exec Comm should contain the following information (1 page):

- Title
- Background
- Objective
- Process and/or timeline
- Product/output
- Budget requirement
- People involved

The proposing Sci Comm(s) is(are) responsible for task force presentations to the Exec Comm at the next face-to-face meeting in September in Montreal. Below is a list of suggestions that will be discussed by the Sci Comms, and for further discussion details, please consult the Glasgow meeting reports of indicated Sci Comms.

Suggestions from the DSC:

- MME v2: the second version will enable centralised hub-point matches
- Ontologies: aims at increasing utilities and uptake on ontologies
- Strategy for diagnostic approach and translation
- "Solving the unsolved": beyond the exome
- Variant data sharing for rare disease patient diagnosis
- Model systems to support high throughput variant interpretations

Suggestions from the ISC:

- Integration of electronic health records and clinical research data
- Best practices in patient group/stakeholder engagement
- Medical devices for rare diseases
- Development of participant unique identifiers for research data sharing
- Paediatrics gene therapy research

Suggestions from the TSC:

- Best practices in patient representatives engagement in medicine development

- Authorisation and adaptive approached in data collection
- Regulatory issues in gene and cell therapy
- Patenting and bridging translational research gap

Innovative approach to catalyse progress

A TSC member suggested the use of intellectual challenges in order to come up with new solutions to catalyse progress in rare diseases research. For example, NINDS held a competition among statistical modellers to find the best model to predict seizure frequencies and found a winning model with 95% accuracy. Similar approach may be adapted, say, to model optimal small clinical trial design; winning statistician/modellers will be invited to the workshop to explain their model. Concrete proposals may garner plenty of support, be it to raise prize money or to raise the profile of IRDiRC, in addition to benefiting the rare disease research community.

5. "IRDiRC Recommended" procedure

The initial "IRDiRC Recommended" work step was discussed at the Exec Comm face-to-face meeting in Shenzhen and further refined during a teleconference call in January 2015. The process was as follows:

- Receipt of submission of resource for review
- Appointment of *ad-hoc* experts to review the submission
- Rapporteur's report from the Sci Comm following experts' review
- Assessment of experts' and rapporteur's reports by the Exec Comm
- Vote for acceptance or rejection of application by Exec Comm

Sci Comm members discussed the practicality of this methodology. Members opined that it should be within the mandate of the Sci Comm to review what IRDiRC should recommend, given their knowledge of IRDiRC's mission, policies and guidelines. Moreover, appointment of external experts could possibly delay the process and/or their input may not be aligned with IRDiRC's goals.

The process was therefore modified:

- Receipt of submission of resource for review
- Appointment of at least 2 members from the Sci Comms to review the submission
- Circulation of submission to all Sci Comm members for additional engagement
- Presentation of reviews to the Exec Comm for vote to accept or reject the application

Sci Comm members were also asked to identify resources which should be "IRDiRC Recommended" and encourage their respective principal investigators to put in their submissions.

6. State-of-Play Report 2015

The first State-of-Play Report was prepared in 2014 and followed a methodology that was publication-based to demonstrate the role of research and its achievements in rare diseases. The Sci Sec tried to be

as comprehensive as possible but could not rule out the possibility that some information may have been missed (e.g. initiatives that were not (yet) published may be missed).

The preparation of the next report is scheduled for July 2015. In addition to literature searches, the Sci Sec will analyse data from the NIH, EU and E-Rare to identify trends of investment and highlight funding areas since 2010 to date. This report should be completed by August 2015.

The role of the Sci Comm in aiding the writing of this, and subsequent, report(s):

- Review the draft circulated by the Sci Sec in due course and provide feedback
- Pro-actively forward information of rare disease initiatives to the Sci Sec
- Pro-actively notify the Sci Sec of publications targeted to rare diseases (but not on individual genes nor disease studies)
- Pinpointing any significant change in the past 4-5 years given the momentum created by IRDiRC

As background documents are being prepared for various Task Forces, they also capture the state of play in these specific areas; this information may be incorporated into subsequent year reports.

7. Mandate of the Scientific Committees

The mandate of the Sci Comms agreed upon, following discussion:

- Act as scientific coordinating bodies
- Propose research priorities for consideration by Exec Comm
- Propose policies and guidelines for adoption by Exec Comm
- Identify actionable projects and contribute to the organisation of workshops
- Contribute to the establishment of Task Forces to advance selected projects, nominate members and help populate the workshop
- Evaluate, validate and make recommendations based on project workshop outcomes
- Review submissions for "IRDiRC Recommended"
- Address emerging issues of scientific nature
- Contribute to the preparation of annual State-of-Play Report
- Organise scientific programme of IRDiRC conferences
- Encourage exchange of protocols and best practices, and agree on standard operating procedures, quality standards, roadmap to reach IRDiRC goals in their scientific area

8. Publication plans (to facilitate dissemination of IRDiRC activities)

8.1 Marker paper

The State-of-Play report may be adapted as a marker paper for publication. It will include emerging areas to move the state of art forward and highlight some of the scientific outputs. This will also be an opportunity to highlight IRDiRC's contribution to rare disease research (e.g. implementation of Task Forces and their recommendations) and demonstrate added value of IRDiRC (e.g. improved funding level since the creation of IRDiRC). IRDiRC needs to start strategising for "IRDiRC 2" with new goals.

8.2 Beyond the exome: enabling diagnosis of most rare genetic diseases by 2020

The DSC has drafted a paper which discusses the IRDiRC objective to diagnose most rare diseases by 2020 and will submit this position/opinion paper, ideally to both AJHG and EJHG, and perhaps also an Asian equivalent. It will look at everything that is needed beyond exome sequencing to identify disease genes; e.g. the need for matchmaking, ontologies, the way forward etc. It will be co-authored by DSC members and other contributing individuals.

8.3 TSC Recommendations

The TSC has produced a recommendation document but this has been delayed due to disclaimer text which FDA wishes to include. Additionally, the TSC will rewrite the summary of this recommendation document for publication, possibly in the OJRD. [*Post-meeting note: a disclaimer text has been received by the Sci Sec.*]

8.4 IRDiRC achieving its goal: 200 therapies

An event and/or paper to celebrate IRDiRC meeting its 200 therapies milestone was suggested.

9. Any other business

9.1 New therapies count

The current methodology involves counting therapies with orphan designation, but there are other products indicated for rare disease treatment that do not have orphan designation. It was suggested that the therapy count list should list both categories, in addition to identification of therapies approved in either the EU or the USA, but not both, to identify the gaps. However, this is not in line with the decision taken when IRDiRC defined its goals. The indicator will therefore still be based on orphan products with marketing authorisation, while a more complete picture will be provided in the relevant pages of IRDiRC website.

9.2 Funding for patent maintenance

Sci Comm members discussed the problem faced by researchers involved in translational research who lack funding to maintain important patents held beyond research grant periods. Funding agencies should be made more aware of this issue, and consider provision of additional patent maintenance support for promising therapies. If not, the funds awarded for the research work in the first place may be lost when patents expire. This could potentially be a workshop topic, to explore ways to bridge the gap and reduce attrition and project failures. It could touch upon commercialisation, venture funding, co-patenting by families, etc. This subject should be further scoped, and perhaps also be organised as a forum session of the IRDiRC meeting in conjunction with the 200 therapies milestone.

9.3 IRDiRC Conference 2016/2017

Sci Comm members indicated their keenness to plan another dedicated IRDiRC conference, which may be organised to coincide with the achievement of its therapies milestone. The issue lies in resources and a meeting in conjunction with a milestone will be more likely to attract external funding. This topic will be discussed during the Exec Comm meeting in Montreal.

9.4 Future meetings of Sci Comms

Members agreed that a joint meeting like this has been a very useful forum for discussion, thus Sci Comm members should try to meet together at least once a year.

Main actions

- Nomination of Sci Comm members to Task Forces
- Identification of key investigators in small population trials in the USA
- 1-pagers on future Task Force proposals
- Forward information of rare disease initiatives and key publications to the Sci Sec
- Review State-of-Play Report following its circulation in July 2015
- Discussion about the next IRDiRC conference
- Planning of a joint meeting of the three Sci Comms in 2016