IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the Joint Executive and Scientific Committees 2016 Meeting

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Organization

Organized and hosted by: Scientific Secretariat and AFM-Téléthon

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REPORT

1. Welcome and introduction

The Joint IRDiRC Executive (Exec Comm) and Scientific Committees (Sci Comms) meeting, chaired by Prof Hanns Lochmüller, brought together 47 participants: 7 members of each of the Diagnostics Sci Comm (DSC) and Interdisciplinary Sci Comm (ISC), 8 members of the Therapies Sci Comm (TSC); 18 members of the Exec Comm together with 4 observers, and 3 members of the Scientific Secretariat (Sci Sec). Everyone briefly introduced themselves and stated their participation in IRDiRC.

2. Updates of the Scientific Committees

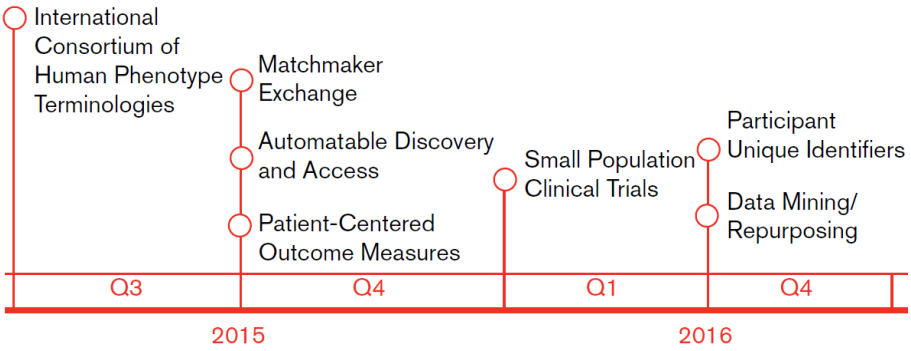
DSC: There are 14 members on the DSC, which focuses on the IRDiRC goal of providing means to diagnose most rare diseases by 2020. Technology shift is enabling discovery, on average 225 new genes per year (cause of approximately 325 diseases). It is expected that about 5,000 genes underlie the 8,000 rare diseases, therefore by 2020, it is possible to come close to achieving the diagnostic goal. However, as research moves into clinical space, the DSC urged the need to prepare for that transition and ensure gene discovery continues beyond 2020 through secondary use of clinical data.

ISC: The ISC consists of 11 members, and has elected Petra Kaufmann as its Co-Chair. Following review of its composition, the ISC is looking into recruiting a new member with expertise in research on burden of illness and health technology assessment (HTA), in order to support researchers involved in drug development processes producing affordable treatments for patients. The DSC has also been discussing HTA with regards to clinical implementation of genomic sequencing; this topic touches more than therapy development, and there is scope for potential Task Force development. Edmond Jessop has been suggested as a potential member of the ISC with knowledge of HTA.

TSC: The TSC currently consists of 14 members. From the inception of IRDiRC to the end of 2015, 183 medicinal products with orphan designation have been approved for the treatment of rare diseases in the US and/or Europe. The pace of development has doubled the trend expected and by the end of 2016, the therapies goal will be achieved. IRDiRC should consider its future objectives in this area and look beyond drug approvals.

3. Current IRDiRC Task Forces

A number of Task Forces have been launched in 2015-2016 (described below). The Task Forces are time-limited, task-specific expert committees focused on actionable topics and research areas with agreed outcomes. The Task Forces are in various stages of implementation, some operate as collaborative efforts with Global Alliance for Genomic and Health (GA4GH), some led by a group of experts which form the Steering Committee (Steering Comm). Their work is supported by the Sci Sec.



3.1 International Consortium of Human Phenotype Ontologies (ICHPT)

The ICHPT initiative started in 2014 and was completed prior to the current Task Forces. Its members compared a number of disease nomenclatures and ontologies describing rare diseases and produced a core set of terms that cross-map across different ontologies. These terms are available on the IRDiRC website as a fixed list but have limited visibility. ***A publication should be planned to disseminate this product more widely beyond the IRDiRC website.***

3.2 Matchmaker Exchange (MME)

The MME, linked to both IRDiRC and GA4GH, has been ongoing for several years. It is a federated network of databases aimed at finding genetic causes of rare diseases by matching similar genotypic and phenotypic profiles. A number of databases are involved and the MME API is currently connected to 3 databases – PhenomeCentral, DECIPHER and Gene Matcher – and collectively they represent about 4,000 patients without a definitive diagnosis. The first inter-database matches have occurred and the outcomes evaluated. A special issue of Human Mutation dedicated to MME was published in October 2015.

The API is straight forward to implement but faces a number of technical challenges as each database holds slightly different data and matches are made based on the lowest common denominator, i.e. matching only by gene, which has high false positive rate. It is currently being further refined to match with higher specificity. There is also a plan to extend the MME, currently a 2-sided hypothesis-based matchmaker, to enable 1-sided hypothesis and free-hypothesis matchmaking. These will require different frameworks, thus more time to build, and these different approaches will each maximize the utility in uncovering rare disease genes.

3.3 Automatable Discovery and Access (ADA), formerly Machine Readable Consent (MRC)

This is a collaborative IRDiRC-GA4GH effort. The underlying objective of ADA is enabling dynamic connection between research, dataset and consent parameters, thus identification if a dataset is available for discovery and the conditions for access. Progress has been rapid in the 3-months following an IRDiRC-funded workshop. An ADA-matrix (ADA-M) has been developed to describe 22 use categories in 3 sections (i.e. conditions of resource use, terms of agreement, and meta conditions) in a

standardized, computer-readable manner. The alpha release of ADA-M has generated interest and software is being built around it. The Task Force hopes the use of ADA-M will reduce the cost and burden of data stewardship, and increase the efficiency of responsible data access (e.g. if dataset is discovered, know what can be accessed or not, and automate request without having to go through committees and the slow process it involves).

3.4 Patient-Centered Outcome Measures (PCOM)

The post-workshop report and recommendations of the PCOM are being finalized. The outcome and recommendations will be organized to address regulators, drug developers, funders, and patient organizations, and the final product is expected by the end of Q2 of 2016.

A number of key messages emerged: (1) the expectation of drugs being developed with meaningful outcomes to patients and providing endpoints for regulators, for use in health technology assessments (HTAs) and for payers; (2) PCOM should be considered not only in the context of drug development but also registry; (3) early dialogue between developers of outcome measures and regulators to obtain scientific advice thus ensure relevance of measures and confidence on data collected; (4) ensure robustness of PCOM through publication in peer-review journal and validation by regulatory agencies; (5) dissemination PCOM widely through publication, and (6) the utility of a public database of PCOM used in drug approvals or rejections, if they can be reused or refined.

The European Medicines Agency (EMA) has developed a qualification process, and a check is needed to see if such a process has been developed by the US Food and Drug Administration (FDA). The ideal is to have PCOM discussed at a scientific level and be validated in parallel by EMA/FDA for use across a spectrum of rare disease research at a global level.

3.5 Small Population Clinical Trials (SPCT)

A white paper was prepared by the Sci Sec, enriched by members of the Task Force, and used as basis for discussions at a workshop recently held at the EMA in London, UK. The post-workshop report is in preparation, together with recommendations, and will be circulated to Task Force members for review and finalization.

Key elements from the workshop discussions: (1) significant changes are needed to be more daring or radical when running clinical trials as there may be other designs other than the gold standard model which may be more appropriate to answer the research questions while involving fewer patients and reducing cost; (2) well-validated elements of innovative designs should not be a topic of debate; and (3) emphasis on the importance of early scientific dialogue with regulators and HTAs after proof-of-concept and before clinical phases. The name of this Task Force may be changed to Small Population Studies (SPS) for broader impact and recognition of the utility of the methodologies/tools to be developed.

SPS methods can be applied not only in rare diseases but also in pediatrics and personalized medicine; it's a question of population size. In the era of precision medicine, the analogy may help to push for additional funding for rare disease research.

3.6 Data Mining and Repurposing (DMR)

This Task Force has just commenced its work and a background document has been drafted. The DMR Steering Comm has elected to meet monthly by teleconference, and the draft background document is undergoing integration and refinement. A workshop is planned in November 2016 in Barcelona, Spain, and a post-workshop report and development of recommendations will be produced. [*Post-meeting report: the workshop will take place on 16 November 2016.*]

3.7 Participant Unique Identifiers (PUID)

PUID is the most recent Task Force approved by the Exec Comm and will develop participant unique identifiers for research data sharing across multiple projects and institutions. A joint IRDiRC-GA4GH collaboration, it is co-chaired by Petra Kaufmann and Bartha Knoppers. The invitation of participants is expected to be issued in the coming days, followed by relevant discussions and a workshop to take place in December 2016, although this timeline is not yet fixed. [*Post-meeting note: invitations have been sent.*]

The products of this Task Force are (1) guidelines on the technical and ethical-legal requirements of patient identifiers in rare disease research; and (2) recommendations for the most practical, streamlined and minimalistic approach to implementation that optimizes uptake while complying with relevant legal regulations. Moreover, Mats Hansson *et al.*, have written research paper, currently under review at a journal, on risks and benefits of identifiers, and agreed to provide this manuscript to be used as background document of this Task Force.

4. Future Task Force proposals

The Sci Comms have been discussing a number of topics as proposals of future Task Forces:

- Strategies to Solve the Unsolved
- Clinical Sharing for Gene Discovery
- Patient Engagement in Rare Diseases Research
- Independent Orphan Drug Post-Marketing Registries
- Clinical Research Networks of Rare Diseases

4.1 Strategies to Solve the Unsolved

There are many reasons why “intractable” rare diseases could not be solved through exome/genome sequencing as there are other mechanisms outside of exome, e.g. splicing, methylation. As groups start pilot projects on other technologies, this Task Force’s objective is to gather these players to develop approaches on how to unravel the mechanism of disease, identify tools and resources, and how to share knowledge in order to move things forward. One strategy could be to bring together people who work in the space of rare diseases often cited in core textbooks which remain unsolved.

4.2 Clinical Sharing for Gene Discovery

As exome sequencing moves into the space of clinical care, funding provenance will shift from research funders to public healthcare funders. This Task Force will organize a workshop to look into ways to maximize secondary use of data generated and paid for by public health funder before clinical genome wide sequencing becomes very widespread and the opportunity is lost. Among the priorities are secondary research use of data (i.e. beyond specific purpose of patient clinical care), strategies of data sharing, and interface and consent for sharing. This will be a multi-stakeholder initiative, and key members are being identified to populate the Task Force. A potential partner for this Task Force is the Centers for Medicare and Medicaid Services (CMS).

There is a parallel opportunity in therapeutics. After translation from research to clinical use, there is a need for continuous data and sample collection. All along the therapeutic development cycle, there is a blurring line between research and healthcare. When it comes to funding strategies, there is a need to consider the capacity available in the context of healthcare to ensure data collection is correctly managed.

4.3 Patient Engagement in Rare Diseases Research

Patient engagement is a way to de-risk development of therapeutics. This Task Force would identify good practices; map patients' or patient groups' engagement, expectations and highlight their experiences; emphasize broader participation of patients in therapeutic development; reduce barriers to participation including missed opportunities, bad practices and shortcut solutions; and identify conflict of interest. Developing a framework will ensure patient participations will not be undermined through trust issues and patient representatives will be fully involved in the development of assessments and informing the decision making process. Information and educational materials are essential, not only for patient groups but also to pharmaceutical/biotech companies, HTAs, etc, and these instruments should be developed to guide and inform strong engagement processes.

Engagements at individual vs collective level (through patient organizations) are needed at different points of development (e.g. consulting individuals in the development of PCOM and involving patient organizations to design clinical trials). However, there is a significant growing issue of patients without group representations, and it also needs to be addressed. The Clinical Trials Transformation Initiative (CTTI) has developed a map for stakeholder engagement between advocacy, academia and industry (http://www.ctti-clinicaltrials.org/node/546) – there may be opportunity for IRDiRC to work with CTTI.

This topic should be approached as a scientific problem. Currently, when, who, and how to engage is unclear. Funders would benefit from knowing what the evidentiary standards are for the benefits of engagement, e.g. if you involve patient at phase X, the study will be done quicker and cheaper.

4.4 Independent Orphan Drug Post-Marketing Registries

Clinical trials for orphan drugs are complicated by the paucity of available patients, thus data, to resolve a multitude of therapeutic dilemmas, even as the drugs receive marketing approvals. Although some

regulatory agencies request post-marketing data, usually on safety and efficacy, the data generated is often done on a single-drug basis and not per disease basis (e.g. 6 different drugs available for Gaucher but no collective disease treatment data available) and proprietary to the specific companies which set up the registries. Registries should be developed in a process that is collaborative, industry-independent, and sustainable. The scope may even be expanded to go further back, from burden of disease through to treatment, therefore supporting patients from the beginning to the end. There is a changing philosophy being taken up throughout drug development space and not confined to post-marketing authorization space. A couple of points to bear in mind when developing this proposal further: companies developing compounds need to understand the new model and who is accountable for data quality, compliance and accuracy; the role regulators play in this context is very important.

4.5 Clinical Research Networks of Rare Diseases

The intention for this Task Force is to build on experiences of the NIH/NCATS' model of Rare Diseases Clinical Research Network (RD-CRN), the EU-funded Clinical Research Networks (CRN), and the new EU-funded European Reference Network (ERN) and see what can be derived in terms of recommendations and criteria in order to develop an European RD-CRN, embedded as a subgroup in the ERN, and connect to its counterpart in the US. Through identification of common function, approaches, structure, etc, it will be possible to synergize activities from both sides of the Atlantic and beyond to create better environment for global development of therapeutics.

4.6 Other considerations

A key lesson learned from Task Force implementations is the importance of stakeholders to team up and collaborate whenever possible. Sci Comm members who propose initiatives should be committed to driving the projects forward. Passionate experts' participation in the Task Forces ensures success, and early identification of individuals to work on articles will push the translation of Task Force products beyond recommendations into scientific publications.

5. The Toolkit Project

The Toolkit Project is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, NIH.

Patient involvement and community engagement are vital throughout the translational research process. While there exists a wealth of tools developed by various groups in rare diseases space, there is often no user friendly overview and access to these resources, and some may be difficult to discover.

The Toolkit Project convenes partners to create a well-designed source for online resources and provide a single portal that patient groups can readily access. The goal is not to re-create existing resources but to better coordinate them and make it easier for people to come together, identify gaps in online resources, and disseminate information to patient groups.

The planning group of this project is driven by patient group representatives and aims to be inclusive, transparent and collaborative. The needs of patient groups will be ascertained, and the landscape of available tools be surveyed. A small workshop will be held to organize tools based on use cases and identify gaps and opportunities. The end product is to disseminate this effort (e.g. via larger meetings and webinars) thus to educate and inform rare disease community.

The next steps will be to organize therapeutic development process in 4 bins: discovery and pre-clinical R&D, trial readiness, clinical trials, and post-marketing. The project aims for synergy with IRDiRC and other stakeholders, including coordination with Patient Engagement Task Force.

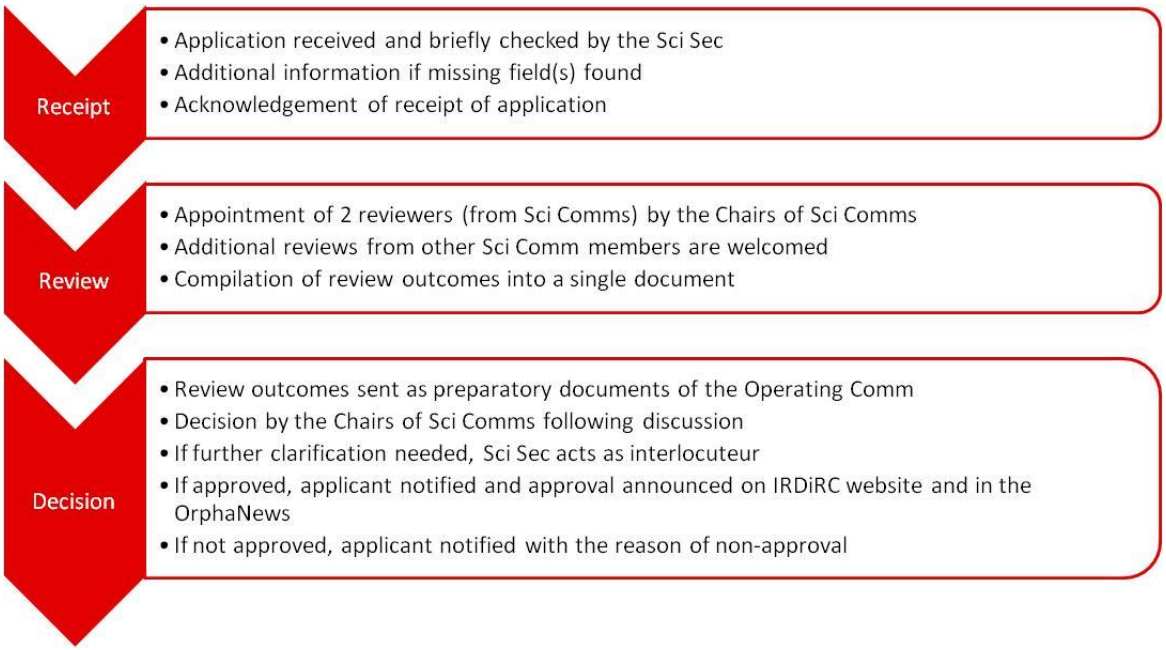
IRDiRC members could assist and support the Toolkit Project through:

- Expansion of landscaping process: please reach out to resource developers and ask them to be made known to the NIH for consideration of inclusion (note: English language tools for now)
- Dissemination: products will be made available online, and for further recognition, the Toolkit Project may look into being recommended

6. "IRDiRC Recommended"

"IRDiRC Recommended" is a label intended to highlight tools, standards, platforms and guidelines which contribute directly to IRDiRC objectives. It helps identify key resources for research communities to use to accelerate the pace of discoveries and clinical translation.

6.1 The procedure of "IRDiRC Recommended"



Resources which have received "IRDiRC Recommended" label are listed on the IRDiRC website. Noting the resources have different life term and some may become obsolete with time, the label is awarded

for a period of 3 years, after which it may be considered for renewal. (Applicants are also asked on sustainability of their resources in the application form.)

6.2 "IRDiRC Recommended" implementation

Views of members of the Sci Comms who have been involved in the review process to date:

- It is good to have this streamline process to identify useful resources
- The review process is straight-forward and guided by criteria listed in the review form
- The most difficult part is reviewing function, thus easier to review based on criteria which are now firmly established
- Reviewing based on criteria is similar to reviewing journal based on guidelines, can be objective
- The process in general is rigorous without being too heavy on both applicants and reviewers
- The Sci Sec and members of the Sci Comms have presented on and discussed "IRDiRC Recommended" at various conferences and meetings and have received support from the wider rare disease scientific community; very little, if any, criticism was raised

Cautions raised and potential solutions:

- The review process seems subjective as initially there wasn't a set of standards fully defined. With different type of resources eligible to apply, setting the standards may not be trivial. However, for certain type of resources with different quality of standards, suggestions are welcomed on standards to apply as part of the review process.
- The resources recommended to date may raise concern that this is a self-serving initiative. In the initial period, this may be unavoidable as those aware of the initiative are likely involved in IRDiRC and its activities. Nonetheless, it is imperative that the list of resources expand to include some which were not developed by people already involved in IRDiRC.
- The initiative may be taking up a lot of effort without knowing if having the approval will have any impact to the resources or the users. It is expected that resources get increased visibility and users are pointed towards resources that have been tested, found useful and reviewed. Method(s) to measure the impact of the label should be identified (e.g. website referral, survey).

[*Post-meeting note: "IRDiRC Recommended" page is the 4th most consulted page on the IRDiRC website since its launch in March 2015, with 2,606 views. For the same period of March 2015-March 2016, the most viewed page is the landing page with 21,487 views, followed by Members page with 5,237 views, IRDiRC goals page with 3,220 views, and the fifth is IRDiRC-Related calls page with 2,056 views.*]

6.3 Potential re-branding of "IRDiRC Recommended"

This initiative was born out of a consortium wishing to move rare disease research objective forward, and not specifically endorsement of a particular funder. The IRDiRC website states the Scientific Committee members review these applications, but this leaves an ambiguity on who exactly is recommending the resources. This point needs to be made clearer. Members of the Exec and Sci Comm should consider this issue, bearing in mind these questions: Who is, and/or what is IRDiRC? How is IRDiRC externally perceived or understood to be?

[*Post-meeting note: An additional subtitle/disclaimer may be added to reinforce the statement in relation to Scientific Committees reviewing the applications. For example, "Recommended by the three Scientific Committees serving IRDiRC through an independent peer-review process."*]

As an international consortium, IRDiRC should have a process to highlight useful tools for the rare diseases community. There is a positive reflection with the mention of "IRDiRC". Over time, "IRDiRC Recommended" has also earned name recognition so giving it up at this point is risky and it also represents a loss of a dissemination tool. A renaming may be considered.

[*Post-meeting note: the Operating Committee proposes a change of name to "IRDiRC Recognized Resources". This will be brought forth to the next Exec Comm meeting for discussion and approval.*]

6.4 Increasing visibility of "IRDiRC Recommended" resources

It was raised how this initiative could be more visible thus bring attention to the resources identified that contribute to IRDiRC goals and to get more people to use these resources. This would, in turn, encourage other resources – including those not already linked to IRDiRC – to apply for the label, in particular if they see benefits of getting their resources "IRDiRC Recommended" and be used more widely.

Some suggestions:

- Write a commentary on the "IRDiRC Recommended" process for peer-reviewed publication
- Funders to insert language that encourage the discovery and use of these resources

There is a role for funders to play in getting the message out to grantees that these tools are available. This can assist researchers not only in terms of leading them to valuable resources but also allow them to compare their resource with another similar resource, and ideally encourage interoperability and standardization.

6.5 Potential collaboration with "HVP Recommended"

The Human Variome Project (HVP) has a similar endorsement system and it was proposed that IRDiRC and HVP can work in collaborative manner, so resources which have been approved by one consortium don't have to go through another similar process but could simply indicate on the application form to obtain evaluation information from the collaborating consortium.

While the idea is similar, in term of content, "IRDiRC Recommended" has a rare disease-specific mandate. To enable collaboration, it is necessary to first map out the overlap in terms of process and criteria, then identify what can be done jointly.

7. Publication and dissemination plan

Members of Exec and Sci Comms were encouraged to think about publications and wider dissemination of IRDiRC's work products. Funders were also asked to consider way to encourage grant recipients to acknowledge their work in context of IRDiRC.

7.1 Annual State-of-Play report

The annual State-of-Play (SoP) report is a deliverable of the SUPPORT-IRDiRC contract and is drafted by the Sci Sec. The first SoP report was fairly Europe-centric, and while the second report was much improved, it is not yet truly comprehensive for use of global trends. Nonetheless, the SoP report serves the need of some funders, and industry members found it a useful, tangible product to show to their organizations the impact they are making when contributing to IRDiRC goals and the value of being an IRDiRC member.

The Sci Sec will draft its third SoP report in mid-2016 and has asked that members of the Exec and Sci Comms provide feedback on how the report may be improved (e.g. if there are sections to expand or to remove, what kind of analysis they would like to see included). The SoP report should be adapted for publication, perhaps as a commentary, in order to disseminate it more widely.

7.2 International Cooperation to Enable the Diagnosis of Most Rare Genetic Diseases by 2020

The DSC has drafted a commentary which discusses the IRDiRC diagnostic goal, the bottlenecks in discovery pipeline and strategies to enable progress in this regard. This article is planned for joint publication in the AJHG and the EJHG for most impact with respect to audience. It will be co-authored by DSC members and other contributing individuals.

7.3 Task Forces output

It is important that each Task Force not only produces recommendations but also works toward a scientific publication as its end output.

7.4 IRDiRC policy and guidelines

Many global initiatives (e.g. GA4GH, UDNI, G2MC) have published their policy and guidelines. IRDiRC should consider publishing its policy and guidelines, reformatting into a publication format if needed. Full engagement is needed to get this out in reasonable time frame; the ISC and the DSC will take a lead.

7.5 Encouragement to acknowledge IRDiRC

Funders are acknowledged in publications but projects funded under IRDiRC-related calls may not mention IRDiRC. This makes it harder to measure the impact of IRDiRC and identify projects published under IRDiRC-related funding. Suggestion was made that grantees be encouraged to mention "This work

contributes towards IRDiRC goals" or something similar. The Operating Comm will suggest the phrasing for consideration by the Exec Comm.

7.6 Wider dissemination

IRDiRC members should also help to disseminate the products as there are other stakeholders attentive to their activities. Actions may include displaying the products on their respective websites and bringing to attention of the products through social media accounts.

8. Proposal of IRDiRC Conference

IRDiRC Sci Comm members who met in Glasgow last year voiced their support for an IRDiRC Conference. It can be used as a forum to showcase what IRDiRC has been and is doing, bring stakeholders together for their vision, forge collaborations, celebrate achievements, and define new objectives.

Some suggestions for consideration:

- To run in parallel to other rare diseases meeting(s) to optimize time and leverage travel costs
- To explore beyond the usual attendees and focus on attracting young researchers
- To have sessions around IRDiRC active work, e.g. case study and panel discussion on PCOM, engagement with stakeholders following Task Force recommendations
- To look beyond therapy approvals and into research activities along the life cycle of treatment development, e.g. outcome-based research, impact of fast-track approvals, access for patients, post-marketing authorization research, economic impact of patient health outcomes
- To host specific workshops, e.g. at RE(ACT), EMA workshop dedicate to orphan drugs and protocol assistance
- To provide training workshops, e.g. to train more clinical geneticist/counselors to deal with personalized medicine and sequencing results
- To hold strategic discussions on transformations in rare disease space and what kind of changes will be required to get the impacts wanted and/or needed

9. Any other business

9.1 Potential collaborations

A number of global initiatives have been identified (e.g. GA4GH, G2MC, UDNI, HVP) to date for potential collaborations. Members of Exec and Sci Comms were asked to point out if there are other initiatives on that IRDiRC should make contact with. ICORD was suggested as a potential collaborator. [*Post-meeting note: it was strongly proposed that IRDiRC discuss with the leaders of G2MC on the role of each organization and potential collaboration specifically on rare diseases.*]

9.2 Definition of ultra-rare

Caution was raised in the definition of certain terms, e.g. disease prevalence to describe “ultra-rare” due to its arbitrary nature. The figure changes from one body of authority to another, and there may be unintended consequences, e.g. legislators looking at reducing incentive of orphan drug development given a prevalence stated and they opined it to be not that rare since profits can be made.

9.3 Rare Disease Day 2017

A selection on the theme for Rare Disease Day 2017 will be taking place in coming weeks. There is a consideration for focus on research, e.g. patient participation in research, and this could be a good opportunity to align IRDiRC actions with Rare Disease Day to gain more visibility and public communications. A proposal can be made to the National Alliances who make the final decision.

Main actions

- Refine future Task Force proposals and submit to Exec Comm for consideration
- Consideration of “IRDiRC Recommended” re-name and send feedback
- Mapping overlap of “IRDiRC Recommended” and “HVP Recommended”
- Provide feedback on how the State-of-Play report may be improved
- Identify opportunities for publication and act on them
- Prepare draft publication for ICHPT
- IRDiRC policy and guidelines write up for publication

Acknowledgements to the host

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