

Meeting report series

Report of the 2nd Interdisciplinary Scientific Committee (ISC) Meeting

Paris, Plateforme Maladies Rares
9th and 10th November 2012

Participants

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Prof Jamel Chelly, Paris, France (vice-chair)
Prof Jack Goldblatt, Perth, Australia
Prof Hanns Lochmüller, Newcastle, UK (chair)
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Apologies (input by email)

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Mr Alastair Kent, London, UK
Dr Jeffrey Krischer, Tampa, USA

Agenda

Friday, November 9th

09.00 Welcome and Introduction to SUPPORT-IRDiRC (S. Aymé)
09.30 Feedback from the Executive Committee, discussion (H. Lochmüller)
10.00 IRDiRC policies and guidelines document, discussion and finalizing ISC sections (all)
13.00 Lunch on site (group photograph)
14.00 Dublin meeting: sessions and speakers, discussion (all)
18.00 End of meeting, joint dinner

Saturday, November 10th

09.00 Working groups associated to the ISC: remit and composition, discussion (all)
11.00 Further work, suggestions to the executive committee (all)
12.30 Lunch on site, end of meeting

EXECUTIVE SUMMARY

The IRDiRC Interdisciplinary Scientific Committee (ISC) met in Paris hosted by SUPPORT-IRDiRC on November 9/10, 2012. Four sections of the IRDiRC “policies and guidelines” (generalized principles, registries and biobanks, publication and intellectual property, communication) were revised and are now ready for review by the Diagnostics and Therapies Scientific Committees. Target is to provide the Executive Committee with a final draft of the document by the end of the year for review and adoption. The ISC had received feedback from the Executive Committee regarding funded projects, suggested working group members and suggested speakers for the conference in Dublin. This information was reviewed at the ISC meeting. The tasks and objectives for the four working groups that the ISC is asked to set up (ethics and governance, biobanks, registries and natural history, data sharing and bioinformatics) were discussed and refined. A list of potential members was generated for each of the 4 working groups which are ready for review and approval by the executive committee. The ISC has agreed on the basic structure of the sessions at the IRDiRC April conference in Dublin, organized by the European Commission. The 3 interdisciplinary sessions will be themed as follows: (i) building the tools (ii) ensuring the collaboration (iii) facing the challenges. Session (iii) is programmed in collaboration with Eurordis. Speakers have been suggested for all 3 sessions and further refinements will be made in discussion with the 2 other Scientific Committees and the European Commission.

Specific enquiries for the Executive Committee

- ▶ Review and approve working group members. This needs to be expedited to allow the new working groups to meet in Dublin (April IRDiRC conference)
- ▶ Who is inviting the working group members? Should a standard letter be used for all invitations?
- ▶ Consider a presentation on the new EU privacy regulation for one of the plenary sessions at the Dublin conference. This may have major implications on IRDiRC research in Europe.
- ▶ The ISC would benefit from additional US (NIH) input, as the ISC currently has only one US member. Would the Executive Committee consider a individual with a clinical research background?
- ▶ The ISC was interested to hear how small associations addressing small disorders could be involved in IRDiRC as they may not have the means to become Executive Committee members.
- ▶ The ISC was interested to hear whether there are any exit strategies for IRDiRC members that do not comply to the “guidelines and policies” of the IRDiRC.

REPORT

Welcome and Introduction to SUPPORT-IRDiRC

The SUPPORT-IRDiRC project, its organisation and main objectives were introduced. SUPPORT-IRDiRC is constituted of a team of two partners: ORPHANET, who acts as the Project Coordinator and the French Rare Diseases Foundation. SUPPORT-IRDiRC aims at facilitating the implementation of the project (including the organisation of all meetings). ORPHANET will facilitate the dissemination and collection of information. As of today, 40 countries are included in the ORPHANET network (Australia joined a few months ago). Through IRDiRC, the USA will join the network. The ORPHANET database includes a list of drugs for rare diseases; this list included EMA approved Orphan Drugs, FDA approved and also drugs for rare diseases that do not necessarily have an ODD. The SUPPORT-IRDiRC team has the capacity to summarize literature and that the project aims at acting both as a scientific and administrative secretariat.

As far as dissemination is concerned, external communication will include communication to the general public and in lay-terms as an important milestone. Orphanews (14 000 readers already) will enable dissemination of information related to IRDiRC. The dissemination material already developed by the project was presented. It is important to use the logo when relevant. With regard to the internal dissemination, a secure collaborative platform will be created.

An annual conference will be organised with the support of the project, except for 2013, the Conference being organised by the European Commission, under the Irish EU Presidency. In addition to the organisation of annual conferences, dedicated sessions should be held at major conferences (not only targeting genetics conferences). At least two sessions should be held over the year. For 2013, this might be compromised as most programmes are almost finalised. A list was started (to be shared with ISC members). A metabolic meeting next year in Barcelona (12th International Congress of Inborn errors of metabolism – ICIEM 2013 September 3rd – 6th) that would be an excellent opportunity for dissemination was mentioned. The ISC members agreed that other domains such as bioinformatics (incl. data sharing) and policy meetings should be targeted as well. It was pointed out that this is a win-win situation both for the IRDiRC representatives and for the hosting organisations. Some of the ISC members might already be involved as organizers, or as members of a programme committee, for some conferences, and they were encouraged to include additional input related to IRDiRC whenever possible. As for USA participation, it was mentioned that the NIH committed to support activities if they happen in the USA. As part of SUPPORT-IRDiRC activities, an annual public report should also be released describing the state-of-the-art of rare disease research in the world.

As far as the team is concerned, four new people will join the SUPPORT-IRDiRC team: a Project Manager (from December 2012), a Communication Manager (from December 2012), an Information Scientist (from January) and an Assistant and Financial Manager (from January). With regard to reporting, SUPPORT-IRDiRC will report to the Executive Committee and his Chair.

Feedback from the Executive Committee, discussion

The ISC members were welcomed to be in touch directly with SUPPORT-IRDiRC (with the ISC chair being copied). With regard to practical aspects, all receipts for travel reimbursements should be sent to INSERM.

The ISC chair has been active in communicating with the two other Committees over recent months. The opportunity to have a joint session with other scientific committees was discussed in order to ensure the best connections. Nevertheless, the respective timelines of the SC may not match up to allow a face-to-face meeting before the Dublin conference.

Additional members can still be involved in the ISC, but this would need to be proposed to and agreed by the Executive Committee. The ISC work has progressed well and is relatively advanced with regard to its mandate. A few expectations of the Executive Committee with regard to the Working Groups (WG) have already been refined. Twelve working groups have been defined in IRDiRC, four of them depending on and reporting to the ISC as follows: (i) Ethics and governance; (ii) Biobanks; (iii) Registries and natural history; (iv) Data sharing and bioinformatics. Many issues addressed by the twelve WG being cross-cutting and transversal issues, the ISC will closely link with the two other scientific committees. The WG should ideally be constituted of 5 to 10 people.

The Executive Committee would like the IRDiRC policies and guidelines document to be finalised by the end of 2012. The rationale for speeding up the process and delivering the policies and guidelines document by the end of the year is related to the fact that some research projects – funded by the European Commission – are obliged to develop links and adhere to IRDiRC policies. Consequently, the IRDiRC policies should be finalized and made available as soon as possible. The Executive Committee anticipates reviewing the document in January in order to have a final document endorsed before the April Conference. Further developments and refinements of the guidelines will be discussed by the WG in the future. The policy document should remain general and high level. Data sharing was one of the policies' sections that the diagnostics committee was keen on starting.

Some principles were emphasised with regard to the policy document. The rare diseases field should be well identified. Defining a consistent way of giving results is underlined as a critical issue. For example, in Canada, the policy for paediatrics is that results should be returned (which doesn't apply equally for adults). In Western Australia, only the information that is related to the investigated disease is given back. Informed consent is a very critical point that was discussed within the ISC. Two different situations can be distinguished:

- ▶ **Retrospective situation:** while nothing can be changed in the way of collecting the information, this remains an issue since science has progressed (should former patients and families be contacted? If a new gene is found: should families be contacted again? Do you have an obligation?). There was a consensus that the norms of today's research should be applied.
- ▶ **Prospective situation:** different policies apply (for instance, in Belgium and in the Netherlands, people are asked if they want information other than the information related to the disorder

investigated). It has to be clearly defined which information is given back, being careful with false promises. From a practical point of view, patients' organisations and patients' wishes couldn't be ignored.

IRDiRC policies and guidelines document: discussion and finalizing ISC sections

A draft was circulated prior to the meeting of the four sections that are the responsibility of the ISC. The format was standardized and agreed with the 2 other Scientific Committees and the Executive Committee: one page per section should not be exceeded and no more than 2 policies and 4 guidelines per topic should be included. Agreement or revisions/additions from the group are needed in order to pass the document to the two other SC. The revisions were discussed in detail by the Committee and are included in the Appendix 2.

General issues relating to the policies document were discussed:

- ▶ In the context of genomic environment: what is "rare" today?
- ▶ With regard to the involvement of small associations addressing small disorders, it could be interesting finding a way of involving them in IRDiRC. So far the commitment to IRDiRC is from big organisations. Nevertheless, small associations have acquired substantial knowledge about some specific rare diseases. This may be important to discuss with the Executive Committee. Big funders involved in IRDiRC may only cover 10-20% of the research on rare diseases. Smaller groups of diseases should not be forgotten in the wider scope.
- ▶ How to make IRDiRC visible? A pilot study could be done in order to see from a practical point of view what is IRDiRC about and how it can speed up research. If the objective is to convince more countries to join the initiative and to commit funding, IRDiRC should be visible during congresses for instance. In that respect, it was emphasised that one of the IRDiRC objectives is to set up a framework. For instance, RD-CONNECT in the framework of IRDiRC is setting-up a platform at the international level with respect to registries, databases and data collection in order to facilitate and increase research activities in this field.
- ▶ Policy language should be harmonized in the document (favour 'should', 'would' against 'must' as it is not a legal document; use carefully 'may' and 'might').
- ▶ Guidelines are context-dependant.
- ▶ The document needs to be generic (but not as far as being meaningless).
- ▶ Some ISC members sought clarification on the policy document's main objective. It was answered that it was a roadmap.
- ▶ IRDiRC is not a legal entity.

Discussion on ISC sections of the policies and guidelines document

D1 – General Principles

Debate on prevention: Prevention is impossible for rare diseases. In addition, it is not an IRDiRC objective. Nevertheless, prevention is important as a method and it could be put to the question of the Executive Committee. Prevention is easily misinterpreted as eugenics. In rare diseases research

consortia, this may not be the right place to discuss this. The EC wants IRDiRC to be “research focused”. Yet, it was agreed that in the introduction/background of the document, it was important to identify the support systems which may include a paragraph on prevention. It was concluded that the ISC would not include “prevention” in a guideline or policy directly.

D6a – Patients registries

Question: rare diseases registries: what is the status in the US? The NIH participation in IRDiRC is not monolithic as different institutes of the NIH are represented in the Executive Committee. RD-HUB (link in the US biobanks) was mentioned as an equivalent to EuroBioBank. “Patients Crossroads” is a company setting-up registries helping patients’ organisation, feeding into the GRDR.

Updating of the registries is a key point to be addressed. In the long run, it is natural that records are managed (like other disease-specific registers) by the health system. Therefore, thoughts about the transition/transmission of rare diseases records from research to health care system should be discussed in order to anticipate potential difficulties.

D6b – Biobanks

What we do with many old samples for which there are not the right consent. What should be the guideline for use? Issue of legacy collection will be addressed in the Ethics WG. Particular attention will be paid to this issue. Australian ethics committees may provide a “waiver” of the need for consent, in accordance with the relevant guidelines in the 1999 National Health and Medical Research Council (NHMRC) National statement on ethical conduct in research involving humans, and in the guidelines under section 95 of the Privacy Act 1988 (Cwlth) and the guidelines approved under Section 95A (private sector amendment effective from 21 December 2001) of this Act.

D10 – Publication and Intellectual Property

Exclusivity licensing was identified as an issue, not the patenting *per se*.

Other points

A sentence may be included to explain how new IRDiRC members are included and how members would leave the consortium. Funders should also make sure that if they adopt this policy document they ensure that funding is used accordingly. While no formal discussion at the ISC level was held on the Governance document, ISC members stressed that the breach of requirements may apply not only to the Steering Committee but also to the Executive Committee.

Working groups associated to the ISC: remit and composition, discussion

Nominations for the working groups were taken from information that Executive Committee members have provided to the 3 committee chairs prior to the ISC committee meeting (Shire, Lysogene, European Commission, NIH-NHGRI, E-Rare, Genome Canada and CIHR, DLR/BMBF, ZONMW, AFM, Fondazione Telethon, Carlos III, Sanford Health, NIHR, Eurordis, Genetic Alliance). Some additional nominations have been received after the meeting, circulated by email and included where appropriate. In addition, ISC Committee members included some individuals based on their expertise or standing in the field. It was not possible to determine whether these individuals receive funding by an IRDiRC organization.

Action point: Send list of suggested WG members to Executive Committee for approval (and to other Committees for cross-check, double nominations should be avoided). Clarify who will be in charge of inviting the nominated individuals. Clarify who is paying their participation at the Dublin meeting, in case they do not have dedicated funding.

WG Meeting in Dublin

Slot in the afternoon April 15th (2-6 pm).

Chairing the WG sessions: ISC Members agreed to chairing the WG to make sure that the Group was working in the right direction. ISC representatives on the WG will also report.

Invitation: WG have to receive a mandate letter: → Compare our minutes with the minutes of SC Therapies and Diagnostics → Check with Exec Committee on the wording. Invitation letters to be sent in December 2012 the latest.

WG Funding

WG members' organisations should fund their participation. Since WG members are expected to be part of already funded IRDiRC projects, those projects should support their attendance. Electronic communication should be organised and structured.

WG Meeting

WG members could be contacted by SUPPORT-IRDiRC prior to the organisation of a conference call to facilitate the calls. SUPPORT-IRDiRC will provide call-in numbers and teleconferencing services. A detailed and straightforward questionnaire is to be defined.

The ISC refined the remit, tasks and objectives of the 4 working groups, based on the suggestions that have been made at the first meeting of the Committee in June (*See Appendix 1 for the final agreed list of tasks and topics to be addressed per working group*).

WG objectives (general, for all WG)

- ▶ Identify opportunities and gaps
- ▶ Point out the problems and opportunities, flag up the issues
- ▶ Advise on the format of future funded projects
- ▶ Suggest new topics
- ▶ Make suggestions to the Executive Committee; the funders decide afterwards

Specific topics to be addressed

WG on ethics and governance

- ▶ Paediatric issues and transition through life stages / Phenotype delineation (disease trajectory)
- ▶ Harmonization of consent access / privacy: question: What can be achieved at international level?
- ▶ Data protection (related to new EU regulation)
- ▶ Access to samples and data

Rationale for topics not included:

- ▶ Patient representation' is an overarching issue. Patients' representation topic goes to the Biobanks and Registries WG.
- ▶ Intra-familial communication' is an important issue but not directly linked to research.
- ▶ Return of research results moves to the Biobanks WG.

To be noted:

- ▶ It would be important to link with ethics groups working on active funded projects to see practically how it works and in order to defined guidelines on these topics for future funded projects.
- ▶ So far, consenting is considered at national level, international issues should be further addressed. Samples could be used internationally. Otherwise, requests for sharing have to be done anytime an international cooperation is sought. For example, in Canada, three components are already included in the consent: after death use / commercial opportunity industry use / internationally sharing. Usually, there is no refusal from patients. As far as research projects are concerned, it is doubtful that this could be applied in France for instance (although with the current regulation international transfer of biological resources for diagnostic purposes is possible). But, it is all about information. Generic information should be produced for patients and their representatives.

WG on biobanks

- ▶ Networking (Sharing practices/Quality assurance practices/Certification)
- ▶ Communication: Feedback/Websites/Return of research results and unsolicited findings
- ▶ Cataloguing / International transfer
- ▶ Biobanks legacy samples

Rationale for topics not included:

Former topics 1 and 4 ('Access to samples and data'; 'Harmonization of consenting issues') are already addressed in the ethics and governance WG.

WG on registries and natural history

- ▶ CDEs: need for interoperability / MDS: minimal data set to be defined.
- ▶ Sustainability plan enabling patients self entry and PPP / Interoperability and clustering of registries

- ▶ Quality assurance and data integrity (linked to the core MDS)
- ▶ Standardisation of Outcome measures
- ▶ Linking to medical records

Rationale for topics not included:

- ▶ Phenotype / Genotype → Other WG will address this issues
- ▶ Consider policies → Ethics WG will address this issue
- ▶ Custodianship of registries and data → Ethics will address
- ▶ Privacy → Ethics WG will address
- ▶ Feedback → Biobank WG will address
- ▶ Registry and Natural History: Innovative trial designs (for very small populations) such as observational trials would speed up the process for drug development → for therapeutic groups
- ▶ Groups of diseases → this is more a policy statement: registry of registries (biobanks and registries) not directly linked to research activities. Coding catalogue OMIM and ORPHANET used as international reference. Promotion and encouragement to use such coding will be important. More a guideline than a topic *per se*.

WG on data sharing and bioinformatics

- ▶ Provide Open Source Software
- ▶ Harmonization
- ▶ Core data sets
- ▶ Data release
- ▶ Technical software and security aspects

NB: ISC members pointed out the necessity for care with regard to the composition of the group and to make sure that rare diseases aspects are covered.

Dublin meeting (April 16th and 17th): Interdisciplinary Scientific Committee (ISC)

The aims and the layout of the Dublin conference were explained. The ISC was asked to help with the programme for 3 sessions that run in parallel with the diagnostics and therapies strand (thematic tracks). Two sessions are on the 16th of April in the afternoon (each about 2-2.5 hours), the third session is on the 17th of April in the morning (about 3 hours). To allow people to move from a lecture in one strand to the next lecture in another strand, we agreed to use 30 minutes slots throughout the 3 sessions (generally a speaker would have 20-25 minutes time for the presentation). Platform discussions can be used (as another 30 minutes slot), but are not mandatory for each session.

The European Commission is the convener of the conference and suggests the following framework: they expect the conference to be attended by approximately 500 people, majority of them are scientists. They want us to respect gender issues and geographical distribution of speakers. The Executive Committee will program the plenary sessions. A general theme was “taking stock” of RD research with respect to the programme and objectives of IRDiRC.

Nominations for speakers were taken from information that Executive Committee members have provided to the 3 Committee chairs prior to the ISC committee meeting (Shire, Lysogene, European Commission, NIH-NHGRI, E-Rare, Genome Canada and CIHR, DLR/BMBF, ZONMW, AFM, Fondazione Telethon, Carlos III, Sanford Health, NIHR, Eurordis, Genetic Alliance). Some additional nominations have been received after the meeting, circulated by email and included where appropriate. In addition, ISC committee members included some speakers based on their expertise or standing in the field or specific relevance to the suggested topic.

SUB-SESSION 1 | “Building the tools”

This session is focusing on tools (registries, databases, trial networks, novel cell models). Rather than just describing the tool itself, the lectures will focus on a particular success story, where significant breakthroughs have been achieved or are expected in an RD by using a research tool. This session should help researchers to get a better understanding of tools that they could use towards reaching IRDiRC objectives in their RD area.

SUB-SESSION 2 | “Ensuring the collaboration”

This session is focusing on collaborations (clinicians and scientists from academia, scientists from industry, patient organizations, regulators). Rather than just describing the collaboration itself, the lectures will focus on a particular success story, where significant breakthroughs have been achieved or are expected in a RD through a collaborative mechanism. This session should help researchers to get a better understanding of collaborations that they could use towards reaching IRDiRC objectives in their RD area.

SUB-SESSION 3 I “Facing the challenges” (up to 5 speakers)

Objective for this session: The ISC suggests that the joint session should focus on “challenges” that go beyond the “pure science”, but are relevant and interesting for scientists. We would want to encourage discussion and debate around some of the most important ethical, economic and political questions that are directly related to IRDiRC research. The way these challenges are addressed will, at least in part, determine whether the ambitious IRDiRC objectives can be reached and implemented. It was agreed that this session will be jointly programmed with Eurordis.

To be noted and further discussion:

- ▶ It would be key to have speakers from NIH.
- ▶ RD and science aspects to be addressed.
- ▶ RDCRN is the equivalent to the network of EU reference centres.
- ▶ In Italy, there is mention of the national registries for rare diseases (RD) in privacy law. To send to ISC members the exception related to RD in the Italian law. In Canada, there is such mention for Cancer but not for RD. Registry: once it is declared an exception, it will facilitate collaborations.
- ▶ Someone in the opening/plenary session could speak on the EU directive on Privacy. RD are an exception with regard to privacy. As this is a new EU directive, we don't need the national laws.
- ▶ That would be an important signal that IRDiRC existed by lobbying for the inclusion of such collaboration between Industry and registries in the regulation of the Directive on privacy. Momentum to be sought at EU level.
- ▶ Epirare and EUCERD are currently working on a position paper supported by many stakeholders.

Next ISC Meetings

Dublin Conference in April 2013 (lunch break)

October 17th-18th, 2013 in Montreal (tbc)

Other issues

Reminder

While in the Executive Committee, organisations are represented, in the Scientific Committees, in person representation is considered.

Additional ISC member

Clinical background is needed.

Appendix 1 – Topics addressed by the Working Groups

WG on ethics and governance

- ▶ Paediatric issues and transition through life stages / Phenotype delineation (disease trajectory)
- ▶ Harmonization of consent access / privacy: question: What can be achieved at international level?
- ▶ Data protection (related to new EU regulation)
- ▶ Access to samples and data

WG on biobanks

- ▶ Networking (Sharing practices/Quality assurance practices/Certification)
- ▶ Communication: Feedback/Websites/Return of research results and unsolicited findings
- ▶ Cataloguing / International transfer
- ▶ Biobanks legacy samples

WG on registries and natural history

- ▶ CDEs: need for interoperability / MDS: minimal data set to be defined.
- ▶ Sustainability plan enabling patients self entry and PPP / Interoperability and clustering of registries
- ▶ Quality assurance and data integrity (linked to the core MDS)
- ▶ Standardisation of Outcome measures
- ▶ Linking to medical records

WG on data sharing and bioinformatics

- ▶ Provide Open Source Software
- ▶ Harmonization
- ▶ Core data sets
- ▶ Data release
- ▶ Technical software and security aspects

Appendix 2 – IRDiRC Consortium Policies and Guidelines – draft as of 30th November 2012 (ISC sections)

D. CONSORTIUM POLICIES AND GUIDELINES

The IRDiRC policies and guidelines document should be communicated widely, and contain sufficient information to allow funding bodies and scientists in many countries to make decisions on future participation.

Incomplete scientific knowledge (e.g. pathophysiology of rare diseases), rapidly evolving technologies (e.g. next generation sequencing technologies), diversity of funding mechanisms, and differences across nations in regards to informed consent and/or sharing of samples across international boundaries are examples of issues that need to be considered.

What is a Consortium policy?

A consortium policy is a principle which consortium members agree to follow, during the course of the project. Although policies will likely be long-lasting, the IRDiRC will periodically review its policies. POLICIES are highlighted in grey in this document.

What is a Consortium guideline?

Consortium guidelines refer to recommendations made by IRDiRC scientific committees/working groups that offer advice as to “best practices” at a given time. Considering the rapid evolution in technologies and new knowledge gained, guidelines are likely to evolve in the coming years.

It is also expected that approaches will need to vary based on disease type, local laws, or other factors. In such cases, comparisons and clarifications of different approaches, relative to IRDiRC guidelines should be presented.

In this document, guidelines are written in blue-shaded boxes.

The IRDiRC Scientific Committees will be the "guardians" of updating this policy document, and propose changes to the Executive Committee for adoption. The Scientific Committees will work closely with the working groups to ensure that policies and guidelines are relevant and implemented.

D.1 Generalized Principles – HL

D.2. Data Sharing and Standards – KB

D.3. Ontologies – KB

D.4. Diagnostics – KB

D.5. Biomarkers – JT

D.6. Patient Registries and Biobanks – HL

D.7. Natural History – JT

D.8. Therapeutics – JT

D.9. Models – KB

D.10. Publication and Intellectual Property – HL

D. 11. Communication – HL

One page for each

2 policies and 4 guidelines max

Format:

Intro paragraph with need and definitions

Context

Policies and Guidelines

D.1 Generalized Principles -HL

The overarching goals of the IRDiRC are diagnosing all RD and developing 200 new RD treatments by 2020. RD research is currently fragmented and compartmentalized. This leads to lack of integration, duplication of efforts, lack of critical mass, thinking in “silos” and waste of resources. It also hinders progress towards better diagnosis and therapy for RD patients both in research and in healthcare. Current regulatory and ethical systems can be a barrier to collaboration, which increases the disadvantage and vulnerability of RD patients. RD are seen as very diverse and different from one another, but commonalities between different RD exist that can be utilized and exploited: Most RD are: inherited and chronic, leading to disabilities, difficult to diagnose, lack effective treatment, and require specialist care and access to expert centres. Many RD share common pathogenic pathways and require the same type of research to better understand their pathogenesis and identify therapeutic targets. RD often use the same model systems to elucidate these mechanisms and test new therapies. RD are developing targeted treatments (individualized medicine) based on a better, molecular understanding. All face the same difficulties in clinical trials (small numbers and lack of well defined outcomes, for example). There is an urgent need for better integration of RD research, in particular with a view to sharing approaches that will enhance the development of better diagnosis and therapies. Integration and increased collaboration through IRDiRC will accelerate these developments, avoid wasting money and other resources and provide efficiency gains. This integration requires a change in mindset and direct involvement of all relevant stakeholders (scientists, doctors, patients, industry, regulators), but promises a quantum leap that is required to meet the ambitious IRDiRC objectives. Therefore, it is important to recognize and address the needs and concerns of all stakeholders and ensure their commitment. The key outcome is improved health (through better diagnosis and therapies) for people living with RD worldwide.

Policy1: RD research should be collaborative. Resources, data and results should be shared among IRDiRC research projects and made publicly available to the broader community through existing IRDiRC platforms and other suitable means.

Policy 2: IRDiRC research should involve patients and their representatives in all relevant aspects of the research. Adequate information, benefit sharing, empowerment, governance and advisory aspects should be considered.

Guideline 1: Best ethical practices for balancing patient-related interests associated with RD research shall be applied. Patients’ preferences for RD research and global linking of medical and personal data should be considered.

Guideline 2: The impact of IRDiRC research on people living with a RD should be a key consideration for each project. Early implementation into health care systems should be targeted whenever possible.

Guideline 3: Public-private partnerships should be encouraged to accelerate research. Sustainability of IRDiRC resources should be considered for each research project as early as the application stage and monitored during and after the project.

Guideline 4: (i) Information about IRDiRC and associated research projects should be disseminated and made available to the RD communities and the lay public. (ii) Clinicians and researchers should receive training and education on RD research.

D.6a. Patient Registries – HL

Patient registries are organized databases where patient information, including demographic, medical and family history information are collected, stored and available for retrieval via standardized and secure methods. Patient registries are increasingly recognised as crucial tools for RD research. For most RD, no single institution, and in many cases no single country, has sufficient numbers of patients and resources to conduct clinical and translational research. Identifying patients with specific genotypes and phenotypes is a major constraint to patient recruitment into research and clinical trials. Therefore, international collaboration is absolutely essential to ascertain pathogenicity or rare genotypes, achieve a unified collection of RD phenotypic data, foster natural history studies, facilitate studies to identify appropriate clinical endpoints or biomarkers, identify participants for research and clinical trials and support the safety and efficacy evaluation of potential therapies. Patient registries are often used as part of regulatory decisions and post-marketing surveillance requirements. In addition, they may play an important role in providing health care to RD patients in the context of reference centres and specialist networks.

While patient registries are considered important tools for RD research, there remains a clear need for standardisation, coordination and further development. In particular patient registries need to overcome the following challenges to develop their full potential in RD research: a) lack of harmonisation due to the high variability among registries according to RD coding systems, geographical coverage and type of data collected b) lack of data sharing since only a minority share data with other databases, biobanks or centres of expertise c) lack of sustainability since RD patient registries often expire due to lack of commitment from data providers, lack of funding or study termination leading to loss of data and loss of investment, and d) lack of utility for research owing to absence of quality control, standardised data elements, and genetic data.

Please note that several Policies and Guidelines under D1 (General Principles) and D2 (Data sharing and standards) are directly relevant to D6 (patient registries) and are therefore not restated here.

Policy 1: Interoperability and harmonization between RD patient registries should be consistently pursued. Linking and transferring data into existing IRDiRC platforms should be considered “best practice” for RD patient registries.

Policy 2: Registries should be built around a disease or grouping diseases, i.e. not exclusively around a therapeutic intervention or a single product. RD patient registries should be global in geographic scope whenever possible.

Guideline 1: Registries need to take into account long-term funding mechanisms. The sustainability plan should include the embedding of the registry into expert networks and public-private partnerships.

Guideline 2: Data should be directly reported by health care professionals as well as by patients to improve the completeness and robustness of data collection in RD patient registries. Measures of quality control and updating should be implemented.

Guideline 3: RD patient registries should be linked with data and biological specimens in biobanks, natural history studies and clinical trials whenever possible.

Guideline 4: Patients and their representatives should be involved in the governance of RD patient registries. RD patient registries should consider feedback, dialogue and benefit sharing with RD patients and their representatives.

D.6b. Biobanks – HL

Biobanks are collections of biomaterials with associated data. Biobanking is an essential tool to provide access to high quality human biomaterial for fundamental and translational research. RD research benefits from the provision of human biomaterials through biobanks, and each human sample from a person with a RD has a high value as it may hold the key to answer an important research question. The rarity and diversity of RD and their associated biomaterials harbour specific challenges and opportunities for biobanking requiring transnational collaboration and harmonization. Legacy samples, small collections or even individual samples, may be extremely precious for RD research, including primary cells, tissue, DNA, RNA, serum, urine, CSF, human induced pluripotent stem cell (hiPSC) lines, and others. Collection, storage and dissemination of biomaterials often requires specialist input and appropriate quality standards. RD biobanks rely on the active participation of patients and patient organizations. Providing and managing information and access to valuable biological samples through a simple and reliable process is crucial for RD research. It underpins the development of new diagnostic techniques, biomarker development, identification of potential therapeutic targets and testing therapeutic response.

Biobanks are important tools for RD research. There remains a clear need for policy interoperability, standardisation, coordination and further development of RD biobanks. They need to overcome the following challenges to develop their full potential in RD research: a) lack of policy and IT harmonisation b) lack of biomaterial and data sharing c) lack of sustainability and d) lack of utility for research (see also D.6a).

Please note that several Policies and Guidelines under D1 (General Principles) and D2 (Data sharing and standards) are directly relevant to D6 (patient registries) and are therefore not restated here.

Policy 1: Policy interoperability and harmonization between RD biobanks should be consistently pursued. Linking and data transfer into existing IRDiRC platforms (utilization of common catalogues) should be considered “best practice” for RD biobanks.

Policy 2: RD biobanks should share and distribute biomaterials to IRDiRC research projects. RD biobanks should be global in geographic scope and practice whenever possible.

Guideline 1: IRDiRC research projects requiring biomaterials and associated data from biobanks should support sustainability of the biobank (cost recovery). IRDiRC studies (natural history, clinical trials) should utilize biobanks for processing and storage of biomaterials whenever possible.

Guideline 2: Data should be directly reported by health care professionals; measures of quality control and updating should be implemented.

Guideline 3: RD biobanks should retrieve data from RD patient registries, natural history studies and clinical trials whenever possible.

Guideline 4: RD biobanks should involve patients and patient representatives in their governance and promote feedback, dialogue and benefit sharing.

D.10. Publication and Intellectual Property – HL

IRDiRC research results should be rapidly shared and be made highly visible to the scientific, health care, patient and pharma communities. Their utility must be clearly demonstrated and potential users must have the opportunity to receive training in the techniques and tools developed. This includes negative results, which are equally important for the RD field as new scientific breakthroughs (see D2 in relation to data sharing policies and guidelines). A high level of visibility in scientific meetings and through scientific publications is mandated. The scientific impact of IRDiRC research projects should be maximised by pursuing opportunities for publication. Online publication of the research results after peer-review will be pursued in full respect of international copyright law. Where the most suitable journal for the results offers the possibility of paying a publication fee to ensure free access to all, this option will be strongly encouraged. IRDiRC members already mandate open-access publication for all projects they fund and cover fees where required. In addition, journals might allow the author to post an electronic copy of the publication on their website. Publications in lay journals may be prepared in order to attract maximum attention to rare diseases.

Intellectual Property (IP) is an important factor for the public and the private sector, in particular to cover the significant cost of developing new therapies. Issues related to IP rights need to be assessed and handled in accordance with fundamental ethical rules and principles. Tools to handle IP issues may include exploitation and technological implementation plans, non-exclusive licensing, patenting, knowledge property rights and pre-existing know-how. In many instances, confidentiality agreements may be required between the parties involved.

Policy1: IRDiRC research projects should publish their results in peer-reviewed scientific journals. Research publication related to IRDiRC research objectives should refer to IRDiRC whenever possible. Funders should encourage open access and fund it whenever possible. Publication in a scientific journal does not negate the need to share full data sets and data not used in publications, which should also be deposited in publicly accessible repositories (see D2).

Policy 2: IRDiRC research should be published in a timely way. For most research, this should not be later than 12 months after the completion of the experiment; for clinical trials it should be not later than 18 months following the last patient completed (including trials with a negative result).

Guideline 1: Research publications related to IRDiRC research projects should acknowledge research funding in an appropriate way.

Guideline 2: The contribution of patients and their representatives should be acknowledged in research publications related to IRDiRC research projects in an appropriate way.

Guideline 3: IP issues should be considered to ensure the financial viability for the development of programmes and of IRDiRC resources. However, IP issues and confidentiality agreements need to be balanced with the need to share information for the benefit of research and the patient community. In general, all IRDiRC research outcomes should be freely accessible unless a clear need for protection can be demonstrated.

Guideline 4: IRDiRC research should be published even where its outcomes are negative or do not show convincing results.

D. 11. Communication on IRDiRC – HL

Through its research projects, IRDiRC will generate new knowledge, tools and resources and stimulate debate. Its outputs require high visibility to a range of stakeholders and a clear strategy to train and educate a next generation of scientists and other users. Target groups include the global scientific community both within and outside the RD field, professionals involved in the delivery of healthcare including diagnostics and delivery of new therapies, policymakers involved in health care planning at national and international levels, the pharmaceutical industry, and the RD patient communities. In addition, there is a strong imperative to raise awareness of this area with the general public and increase its profile in the media. The goals of an external dissemination strategy are to promote international academic and industrial cross-fertilisation, both within and outside IRDiRC, and to provide information on IRDiRC research to other research projects, the scientific community, industrial groups, government bodies, policymakers and the general public, including patients.

Communication from the IRDiRC will be built on the principles of openness, public accessibility, transparency, inclusivity and timeliness. The IRDiRC will communicate through various means, in particular through electronic communications and the internet.

Policy 1: IRDiRC members should be required to disseminate relevant information on their research through adequate and timely measures (in particular the IRDiRC website). IRDiRC research projects shall provide information on: disorders under study; name and organization of investigators; objectives of the research project; key collaborators and partners; scientific, non-confidential abstracts; financial contribution; anticipated impact; and participation of patients.

Policy 2: IRDiRC should promote the translation of relevant RD research information in plain language accessible to a wide audience in as many languages as possible. For each IRDiRC research project, a lay summary should be made publicly available at the beginning and end of the project.

Guideline 1: IRDiRC members will update publicly available information at regular intervals, at least annually. Updates should include significant results of the research (scientific publications), and a final report (including lay-friendly version) at the end of the project.

Guideline 2: IRDiRC will publish their mission statement, their list of member organisations and list of funded projects. IRDiRC will publish non-confidential proceedings, minutes and documents of its executive committee, the scientific committees and the working groups.

Guideline 3: IRDiRC will publish regular information on the achievements of the proposed objectives and milestones (RD policy, diagnoses and therapies). An electronic copy of each publication arising from IRDiRC research shall be provided to the IRDiRC secretariat for archival and impact-monitoring purposes and may be linked from the IRDiRC website if appropriate and if open-access.

Guideline 4: IRDiRC research projects and IRDiRC member organizations will make reference to IRDiRC on organizational websites, information material and presentations, and make use of the IRDiRC logo.