

Meeting report series

Report of the 10th Interdisciplinary Scientific Committee Meeting

Glasgow, Scotland, UK
5 June 2015

Organization

Organized and hosted by: Scientific Secretariat

Participants

Prof Hanns Lochmüller, Newcastle, UK (Chair)
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Dr Petra Kaufmann, Bethesda, USA (from 12:30)
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Apologies

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Agenda

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REPORT

1. Introduction

The Chair of the Interdisciplinary Scientific Committee (ISC) welcomed its members and the Chair of the Executive Committee (Exec Comm) to the meeting.

2. ISC membership and renewals

The ISC has good continuity since its formation, with good meeting attendance. Several of its members have been renewed for a second term while a few will be up for renewal next year. However, the ISC has lost a member for the first time, as Alastair Kent resigned from his position.

Suggestions of replacement (and/or additional member):

- ▶ Someone from a patient organisation
- ▶ Someone from the health economics sector
- ▶ Someone from RD appraisal

The former Chair of Genome/Phenome WG and member of Data Sharing and Bioinformatics WG was also suggested as a possible addition to the ISC for research-to-healthcare point of view, but he may be better placed in the Diagnostics Sci Comm (DSC); this will be discussed with the Chair of the DSC. Generally, it was felt important to have the patient voice represented at the ISC. Further suggestions are welcome (including suggestions from ISC members who were unable to attend).

3. ISC meetings

The ISC meets in person once per year, and by *ad hoc* teleconferences at other times. Members were happy to maintain this arrangement, although it may be adapted accordingly as needs arise following implementation of Task Forces. [*Post-meeting note: members agreed to the coordination of individual face-to-face Sci Comm meetings to enable joint Sci Comm meetings in the future.*]

Suggestions of events to potentially couple the ISC face-to-face 2016 meeting with:

- ▶ RE(ACT) in Barcelona, 7-10 March
- ▶ RD-CONNECT in Barcelona, 9 March
- ▶ InSPiRe in Germany
- ▶ ESHG in Barcelona, 21-24 May
- ▶ ECRD in Edinburgh, 26-28 May
- ▶ Paris (standalone, Lysogene could host the meeting)

4. Current IRDiRC Task Forces

4.1 Task Force formation

The steps involved in IRDiRC Task Force formation defined at the Exec Comm meeting in Madrid:

- ▶ Nominations of experts by the Exec and Sci Comms
- ▶ Selection of core group members by the Exec Comm
- ▶ Contact and formation of core group by the Sci Sec
- ▶ Provision of non-selected names (from initial nomination stage) to the core group
- ▶ Selection of additional members, from the list or otherwise, by the core group to complete Task Force membership
- ▶ Selection of one Sci Comm member to liaise between Sci Comms and Task Force

This process is adaptable, especially when a project with a specific team is in place through collaborative effort with another organisation, e.g. Global Alliance for Genomics and Health (GA4GH).

The members would like the Sci Comm participation in Task Forces to be open and not restricted to one selected representative. *[Post-meeting note: This was brought up for discussion during the joint Sci Comms meeting. Sci Comms may nominate more than one member to participate in Task Forces.]*

4.2 Task Force participation

As core group members will drive the activities of the Task Forces, it is important that the right people with required expertise and availability to really participate be nominated. Members were informed that the Sci Sec continues to accept nominations until the names are turned over to the core group. It was also suggested that the Sci Sec contact nominees not selected for the core group to keep the information flow open and to engage their interest in subsequent actions (e.g. reviewing workshop paper).

[Post-meeting note: following discussion at the joint Sci Comms meeting, non-core group nominees will be admitted for general Task Force membership. The general membership will also be open to any individual who is interested in relevant topics to maximise contribution and engagement from the community. However, the core group – henceforth known as steering committee – will decide on the list of invitation-only participants for the planned workshop.]

Members suggested several mechanisms for interchange between Sci Comms and Task Forces:

- ▶ Chairs/representatives of Task Forces attending teleconferences/meeting of Sci Comms
- ▶ Sci Comm members attending teleconferences of Task Forces and report back to Sci Comms
- ▶ Sci Comm representatives attending planned workshops

4.3 Machine Readable Consent (MRC)

The MRC Task Force straddles IRDiRC and GA4GH, and it aims to complete its work by April 2016. The ISC is represented. The composition of this group is not yet finalised but it will be a unique one, involving different expertise including informatics and legal.

The first teleconference of this Task Force took place recently as planned but there was an unexpected unavailability of the co-chairs. Both wish to have a face-to-face meeting of the Task Force (in Paris) to

define what machine readable is, how to deal with consent, etc., with emphasis on interoperability and international data sharing. This meeting will be supported by the Sci Sec. Contacts between IRDiRC and GA4GH coordinators should move things along. Subsequent work can be completed via teleconferences.

4.4 Patient Relevant Outcome Measures (PROM)

The draft background paper has been circulated to all members. Questions were raised about the work that can be realistically carried out by this Task Force as end points and dimensions of disease change, and it is unclear which of the many complex issues will/can be addressed. There is a large battery of tests and functional tasks, with parameters that need to be differently interpreted in different populations, ceiling effects and insensitive scales to address, etc.

The background paper will soon be updated and refined with the help of experts in the Task Force to produce a clearer landscape and objectives to achieve. Once the paper has been circulated, Sci Comm members are encouraged to provide their feedback and make recommendations.

4.5 Small Population Clinical Trials (SPCT)

The FDA and the EMA are, respectively, developing and updating guidelines on clinical trials in small populations. Concurrently, the European Commission has invested in three projects specifically on this theme. This workshop will bring together these key players to discuss adaptive designs, statistical methods and acceptability of new methods.

There are other aspects to consider, including (1) restrictions in data sharing, which means IRDiRC also needs to consider the implication of the policy developed, and (2) addressing measures that could not necessarily be extrapolated from treated patient groups into target patient groups. Similarly, members are encouraged to provide their feedback when the background paper of this Task Force is circulated.

5. Future Task Force proposals

ISC members were previously asked to scope a few key topics for proposal of Task Forces to the Exec Comm. They should be rare disease specific with an international reach, with objectives and final products clearly defined. A document listing ISC Task Force proposals was circulated to all attending members. All proposals were discussed to identify the best way forward.

5.1 Integration of electronic health records (EHR) and clinical research data (CRD)

EHRs are increasingly penetrating the healthcare system and they should be integrated with CRD to accelerate rare disease research and treatments. Current processes are inefficient, for a number of reasons including: (1) clinical data not available/accessible for research purposes, (2) the need to re-enter data collected in different systems, and (3) technical and policy gaps.

This project will bring together researchers, informaticians, healthcare professionals and policy experts:

- ▶ to share experiences and discuss case studies on using EHR for research
- ▶ to examine development and maintenance of research data warehouses
- ▶ to define the use of standard terminologies to enable downstream data integration
- ▶ to disseminate new terminologies for rare diseases
- ▶ to discuss research data sharing best practices

Case example (in common condition): Data from EHR of Scandinavian populations were used to study the use of aspirin to treat patients with multiple myocardial infarctions and their survival, at a cost of less than €30 per patient. PCORnet also recently started their first trial to determine aspirin dosage for preventive use against coronary artery disease. EHR is used as one of the data sources.

There are systems set up with some common data elements and standard terminologies but commercial products, designed primarily to allow for claims, clinical operation and billing dominate the market. Systems that integrate international terms (e.g. international classification of diseases, ICD) would not only help research queries and improve diagnosis, they also have financial implications (e.g. there is great value for the private sector to quickly identify where patients are and could be recruited for trials). Moreover, there are areas where EHR systems are not in place, thus it is an opportunity to transform the way they handle medical records.

The timeframe estimated for work of this Task Force is 6-12 months, to study use cases of EHR and make recommendations on how to potentially gather data and access to patients faster and cost-effectively, which does not necessarily have to be specific only to rare diseases. This is a multi-dimensional project, involving technical, legal, ethical, sociological and economical considerations. Among the people to be invited for participation are players within the European eHealth Network, IMI's Electronic Health Records for Clinical Research (EHR4CR), and Expanding Health Data Interoperability Services (EXPAND).

Concern was raised about pushback to EHR integration due to data and privacy concern, but this is being addressed by advancing privacy technology. Adoption of EHR systems is occurring, like online banking has over time, and addressing this now and making recommendations is crucial. Best practices and experience should be shared.

A scope for integration of patient-reported outcome measures into EHR via a research-based tool (e.g. an app on smartphone) was also raised, for patient engagement in different research endeavours. However, access to personal health/medical data varies from one system to another, one place to another, often due to legal concerns. Patients' perspective is key if this aspect is also to be integrated. The proposal was welcomed by the ISC and will be further developed by its proposer.

5.2 Best Practices in Patient Group/Stakeholder Engagement

The objectives of this Task Force are to develop guiding principles of patient group engagement in clinical trials and consensus recommendations for best practices.

For successful trials, partnerships are critical. It is important for successful partnerships that:

- ▶ the research questions asked or issues to be addressed matter to patients

- ▶ the protocol is feasible and avoids undue burden to participants
- ▶ the outcome measures are clinically meaningful
- ▶ communications, consent forms and other materials are clear, transparent and user-friendly
- ▶ participants are aware of the trials and can be enrolled quickly
- ▶ any conflict of interest is understood and addressed

The issue regarding conflict of interest is particularly important. Some patient groups are funding research and recruiting patients for these studies, and alignments of patient groups with company or research investigators, as well as funding sources, are not always clearly specified. Moreover, when patient groups start to invest in potential products, transparency becomes even more important given issues related to access to patients, who form the limiting resource. Complications also arise from gene patent aspects, when patient organisations are co-patent holders (e.g. when members may or may not be aware of it).

This Task Force will operate for 6 months, to get stakeholders (industry, academia, research funders, patient groups) around the table and discuss the opportunities and barriers to partnership, gain an understanding and raise awareness of rules governing conflict of interest, and solicit feedback to form recommendations of best practices and guiding principles. The Task Force will publish a paper with recommendations.

This initiative should be co-led by someone from the US and someone from Europe. A Clinical Trials Transformation Initiative (CTTI) at Duke, funded by the FDA, may be invited to share their insights as their work focuses on patient engagement and the different related perspectives, even if they are neither international nor rare disease focused.

The adoption of best practices then needs to come from patient groups. IRDiRC provides the forum for discussion, and could get its patient organisation members and other international groups together to solve this problem. Therefore, the TF should be initiated and led by patient organisations such as EURORDIS. The proposing member will discuss ways forward with the CEO of EURORDIS.

5.3 Medical Devices for Paediatric and Adult Rare Diseases

Data standards and regulation change extensively, but there remain few standards in the world on medical devices. Active and expansive work is ongoing, but certain required collaborations are difficult to put into action as engineers, researcher and clinicians not only think differently but have different knowledge and understanding regarding regulation or clinical trials. In the USA, various initiatives are emphasising medical devices, including a specific one on paediatric medical devices for rare diseases by FDA/OOPD and NIH/NCATS/ORDR.

Medical devices, like drugs and biologics, utilise high level data standards and need interoperability of systems to integrate data collected, stored, analysed and redistributed from global sources. Efforts are also needed to develop critical information on protecting intellectual property, regulatory requirements, commercialisation procedures and reimbursement requirements. There are varied expertises according to the categories of medical devices (e.g. assistive technology such as cochlear implants, diagnostic and

monitoring devices such as biosensors, medical imaging devices such as MRI, etc). Partnerships to increase the focus on medical devices for rare diseases are needed between engineers, clinicians, academics, patients and medical devices industry.

Moreover, the increasing development of sensors (e.g. in watches, adapted clothing) that are widely available is collecting health information from everyday users and there is room to integrate data from these devices and/or adapt some of the technologies for medical devices development.

This Task Force will bring together these key players to think globally and collaboratively on bringing in medical devices for rare diseases, to bridge the disconnect between prototype development and clinical application. The Task Force will refine the focus of their work, identify related current initiatives and potential future development opportunities, identify influences and obstacles to device development, and train/educate the stakeholders. The proposal was welcomed by the ISC and will be further refined by its proposer.

5.4 Development of Participant Unique Identifiers for Research Data Sharing

Rare disease patients are often participants in multiple independent research projects. The value of the datasets generated is dramatically increased if they can be linked at the level of the individual patient. The objective of this Task Force is to develop guiding principles to generate patient-specific identifiers enabling data from the same individual to be connected across multiple projects without revealing the patient's identity.

The NIH created the Global Unique Identifier (GUID), which uses personal identifying information (PII) to generate a code identifier. However, the identifiers are not globally unique, but project-specific and by disease (e.g. an autistic patient with Parkinson's disease would have 2 GUIDs), due to protection concerns.

One way to push things forward is through the use of federated UIDs, with the collection of recommended PII elements and language harmonisation, and interoperable systems at an international level. Lessons from current GUID efforts will guide the building of this federated system, and other issues to explore, and will include geographical barriers (e.g. jurisdiction governing existing legislation and cloud storage) and technical requirements. The key to this project is to think globally and act locally.

The Task Force will, following discussion among interested parties, propose recommendations for the most practical, streamlined and minimalistic approach that maximises uptake whilst complying with relevant legal regulations. The proposal was welcomed by the ISC and will be submitted to the Exec Comm by the proposing member. *[Post-meeting note: This proposal was also discussed in more detail at the joint Sci Comms meeting, and has the support of the Diagnostic and Therapeutic Sci Comms.]*

5.5 Paediatric Gene Therapy Research

The objective of this Task Force would be to investigate gene therapy in children, to see what is needed in terms of policy, to examine new safety issues, the ethics involved, etc. Rare diseases in children are often very severe, with no alternative treatment and small numbers of patients.

At present, only a small number of gene therapy studies involved children (206 out of 3950, from <https://clinicaltrials.gov>) and additional information on paediatric studies are difficult to obtain. The Journal of Gene Medicine Clinical Trial site (<http://www.abedia.com/wiley/>) reported 2,142 trials to date, indicating a substantial number of follow-up studies. Among all gene therapy studies, 64.2% address cancer diseases where patients are often terminally ill with a short life expectancy, and in regions where gene therapy trials are taking place, they are concentrated in certain countries and others are completely missing from the picture.

It is very difficult to establish clinical efficacy of novel therapeutics, and if damage has been quite extensive (e.g. in neurodegenerative conditions), minor changes are difficult to pick up but would have been more beneficial if treatment has been given at an earlier stage. Approvals for paediatrics gene therapy in rare diseases are very low, and the seriousness of rare diseases needs to be better conveyed to push policy change by regulators. Outdated regulations need to be revised, an international policy specific to paediatrics gene therapy clinical trials is needed, development of methods to assess quality of life is essential and the issue of access to therapy must be addressed. Multiple issues arise: ethics, safety, treatment delivery device, long term risks and benefits.

Collaborative efforts are needed to clarify the regulators' guidelines for small population trials and their sets of endpoints in innovative therapies and/or complex diseases; extend marketing authorisation to related population subsets that could benefit from the treatment; and tackle ethical and policy impacts with a convergence of ethical standards (e.g. foundation of EUnetETHICS).

Paediatrics is also still missing largely from IRDiRC and should be worked into it as most rare diseases start during childhood. There is a scope to revisit the policy and identify what can be renewed and what should be restructured. The proposal was welcomed by the ISC and will be further refined by its proposers.

6. Defining the role of Interdisciplinary Scientific Committee

Members reviewed the change of mandate of the Sci Comms and the question was raised on the review process for "IRDiRC Recommended". As the aim of "IRDiRC Recommended" is not to perform another scientific review but to identify resources that contribute towards the goals of IRDiRC, the Sci Comm members would be better placed to review the applications. [*Post-meeting note: This was brought up for discussion during the joint Sci Comms meeting. Members of Sci Comms will review future applications.*]

7. The future of IRDiRC

7.1 Therapies goal

The IRDiRC therapies goal is progressing steadily and should be attained by end 2016/early 2017. This milestone should be celebrated, and the events and activities that propel things forward be emphasised.

In considering future therapies goal, members would like to first understand how the therapies indicator is counted and have requested for the related methodology document from the Sci Sec. There was also interest to investigate the following:

- ▶ Has the rate of repurposing changed when comparing periods before and after IRDiRC?
- ▶ An analysis of cancer/non-cancer therapy and quantify the gap in rare oncology

7.2 IRDiRC conference

Members agreed that another IRDiRC conference should be organised, preferably to coincide with the achievement of its goals. IRDiRC lacks resources to host the conference on its own but with focused planning and good content, should be able to attract partners to co-sponsor the conference.

7.3 Added value of IRDiRC

Specific rare disease funding calls are waning and being replaced by precision medicine. As IRDiRC is not a health consortium, the Exec Comm faces the challenge in identifying IRDiRC's added value and predicting the direction in which research will go in order to adapt IRDiRC accordingly.

The publication of a marker paper capturing IRDiRC's background (i.e. steps and changes that affect and lend to success in rare disease research), activities and successes would be a way to set the stage for the next steps and goals of IRDiRC for its existence beyond 2020.

8. Any other business

Members were invited to a dinner on the same evening with members of the other Sci Comms.

Main actions

- ▶ To identify potential new ISC member(s) and suggest to the Exec Comm
- ▶ To identify venue/date of face-to-face meetings 2016
- ▶ To contact GA4GH and coordinate actions of MRC Task Force
- ▶ To fully scope Task Force proposals for submission to the Exec Comm