

Meeting report series

Report of the 4th Funders Constituent Committee Meeting

Tokyo, Japan
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Participants

In person

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Agenda

1. Welcome of participants to Funders Constituent Committee
2. Platform for FCC members to coordinate and prioritize efforts on research funding
 - a. Presentation on status of Orphanet/IRDiRC/Uber Research platform collaboration

- i. Update on progress of the contract with Uber Research
 - ii. Data that will be incorporated into the planned platform
 - iii. Capabilities of the planned platform
 - iv. Timeline
3. How FCC members tackle the new goals: focus on future initiatives
 - a. Presentation and discussion on the European Joint Programme on Rare Diseases
4. International collaboration on rare diseases Clinical Research Networks
 - a. Presentation of existing networks:
 - i. US CRN
 - ii. ERNs
 - iii. IRUD
 - b. FCC point of view
 - i. Barriers and opportunities for global collaboration
 - ii. Possibilities to incentivize global collaboration
5. Ethical, legal and social implications (ELSI) of rare diseases research funding, rare diseases healthcare and therapies
 - a. Extant funding opportunities
 - b. Funding-related notices
 - c. Gaps to be covered by ELSI-related funding calls

EXECUTIVE SUMMARY

- ▶ The Funders Constituent Committee (FCC) would like to get a better overview of the full rare diseases funding landscape, in order to build a coordinated, strategic research funding agenda. A potential collaborative platform, between Orphanet and Uber Research was presented, which, if approved by the IRDiRC Consortium Assembly (CA), could be included in the current SUPPORT-IRDiRC contract, in order to better collect and analyse rare diseases funding.
- ▶ The European Joint Programme Cofund (EJP) on Rare Diseases was presented, as one of the future big projects in rare diseases research coordination and research funding. The IRDiRC Scientific Secretariat will be part of the future EJP
- ▶ A Task Force on international collaboration for clinical research networks is proposed for approval by the CA. The FCC discussed current initiatives, such as the US CRN, the EU ERN, and the Japanese IRUD, and on what this Task Force should focus.
- ▶ Ethical, legal and social implications (ELSI) are aspects of rare diseases research that has recently received increased attention. The FCC discussed current funding opportunities for ELSI research, and potential gaps to overcome in the future.

REPORT

1. Welcome of Participants Funders Constituent Committee

The Chair of the Funders Constituent Committee (FCC) thanked and welcomed participating members to the face-to-face FCC meeting. Main agenda items included: discussion on a potential platform to coordinate and prioritize research funding efforts, how FCC members tackle the goals, international collaboration on rare diseases clinical research networks, and ethical, legal and social implications of rare disease funding.

2. Platform for FCC members to coordinate and prioritize efforts on research funding

2.1 Presentation on status of research funding platform collaboration

A collaboration with a research funding platform is being considered, in order to:

- ▶ Better capture the overall rare diseases research funding landscape
- ▶ To build a coordinated, strategic research agenda
- ▶ Avoid unnecessary duplication of funding
- ▶ To fulfill the need for data, that is both accurate, complete, specific for rare diseases, exploitable, and provides a global coverage of rare diseases projects and clinical trials

A small working group investigated if such a platform already exists for this purpose and how useful one might be by asking a number of questions and doing a limited number of analyses. Useful data points and queries centered around:

- ▶ The type of funding:
 - Public/ private/ alternative funding instrument
- ▶ Data analysis
 - Per disease/ per country/ over time/ in developing countries
- ▶ To identify gaps and overlaps
 - Disease/group of diseases (the most studied, the never studied...)
 - Categories of projects (basic/pre-clinical/clinical... and more granular categories)
 - Phases for clinical trials

In addition, questions asked on the existing databases:

- ▶ How is the collection done?
- ▶ How is the curation is done?
- ▶ Are the results of funding collected?
 - Deliverables
 - Publications
- ▶ Are the links to drugs in development collected?

- ▶ Are the number of recruited patients collected?

In order to make best use of the data, data definition is important, for example:

- ▶ What definition of rare diseases should be used?
 - Per continent, overall definition?
- ▶ Which rare disease nomenclature should be used (interoperability)?
 - Orphanet nomenclature, OMIM, etc
- ▶ What definition of a research project should be used?
 - For example, a different definition of translational research is used in the EU and the US
 - Some research projects are funded by several funding organizations
- ▶ What definition of a clinical trial should be used?
- ▶ How should a year be defined?
 - Fiscal year, academic year, calendar year
- ▶ How should the cost of a project be defined?
 - How is overhead defined everywhere, and how can we deal with it?
 - For example, EC projects have 25% indirect costs, NIH 50%, other EU projects 20%, so the percentage is variable
 - Mostly, total cost is defined, so including overhead

2.2 Data that will be incorporated into the planned platform

For IRDiRC, the data collection results would be better if the collection was done in a more systematic fashion:

- ▶ Complying with the necessary dataset
- ▶ Including information on funding amounts, which is currently not done
- ▶ Providing a larger overview of rare diseases funding and clinical trials

2.3 Capabilities of the planned platform

For the potential platform, studies that what will be included are:

- ▶ Ongoing and unpublished research projects explicitly focused on a rare disease or on a group of rare diseases
- ▶ Coverage: single-center and national or international multi-centric research projects, thereby creating a global RD focused platform
 - In countries in the Orphanet consortium
 - Funded by a member agency of the IRDiRC consortium

Studies that will be excluded from the platform are:

- ▶ Studies on general aspects of a common disease which has rare forms
- ▶ Studies that could one day be applicable in the field of rare diseases but without explicit intention
- ▶ Studies already published with the label of the study being the title of the article in Pubmed

- ▶ Studies that are too fundamental: no specific disease or general title including some rare diseases as examples

Clinical trials that will be included in the platform are:

- ▶ Interventional clinical trials
- ▶ Clinical trials conducted in patients with a rare disease
- ▶ Clinical trials evaluating a drug or a medical device
- ▶ Conducted in at least one country of the Orphanet consortium or funded by an IRDiRC member
- ▶ Clinical trials approved by competent authorities

Clinical trials that will be excluded from the platform are:

- ▶ Non-interventional/Observational clinical study: when identified, they must be registered as research projects.
- ▶ Pre-clinical studies
- ▶ Clinical trial on a common disease which has rare forms
- ▶ Clinical trials on non-rare diseases
- ▶ Clinical trials evaluating an intervention other than a drug or a medical device
- ▶ Terminated clinical trial that started before 2010.
- ▶ Clinical trials entirely conducted outside the Orphanet consortium unless they are sponsored/funded by an IRDiRC member.
- ▶ Non-authorized clinical trials by competent authorities.

2.4 Timeline and budget

- ▶ The collaboration will cost 50,000 euros in the first year; 20,000 euros in consequent years
- ▶ The collaboration will take approximately 1 year to develop, afterwards data can be integrated and requested on a systematic basis
- ▶ The decision to request the contract amendment needs to be a common decision from the Consortium Assembly (CA)

Current status quo of the collaboration

- ▶ Several meetings have been held to explore aspects of the collaboration
- ▶ Next (all or some):
 - Internal use
 - Development of a data analyzer
 - Development of a curation web interface to ease and speed-up the curation process and the results

Until this collaboration has been approved, a more systematic way of data collection is proposed, with the category of the funding included in the data that funders should send. Some objections were raised:

- ▶ Automatically check off boxes: mistakes can be made easily
- ▶ Time consuming on part of funder
- ▶ Applicants often check off boxes that they think are required, so not very reliable

Ideally, the data will be collected in a more structured way, so that data analysis can be done more easily.

At present, the limiting factor is the collection. Ideally in the future:

- ▶ Automated procedure
 - ▶ When data from funder is entered, a report is prepared systematically with data from a specific funder
 - Send it to the funder for verification
 - ▶ Data will be publicly accessible afterwards
- ➔ At the suggestion of the IRDiRC Chair the discussion was continued at the CA wrap-up session regarding this addition to the contract, in order to get approval by the full CA.

3. How FCC members tackle the new goals

One of the large new initiatives for rare diseases research currently planned is the new European Joint Programme Cofund on Rare Diseases (EJP RD or EJP RD Cofund), as part of the European Commission's next Work Programme 2018-2020, that was published in October 2017. This programme is set up to create a research and innovation pipeline "from bench to bedside" ensuring rapid translation of research results into clinical applications and uptake in healthcare for the benefit of patients.

Links to IRDiRC

- ▶ Initiative should follow IRDiRC policies and contribute to IRDiRC Objectives
- ▶ Opportunity to establish strong connections across the rare diseases community
 - ERNs
 - patient organisations

Implementation of the EJP Rd will lead to four kinds of activities, including research, coordination, networking, training, demonstration and dissemination:

- ▶ Funding (Pillar 1)
- ▶ Coordinated access (Pillar 2)
- ▶ Training and capacity building (Pillar 3)
- ▶ Helpdesk and information: Virtual platform (Pillar 4)

Ideally, there is a long-term vision and business model for the EJP RD as a whole and for specific activities and products, thereby providing sustainability to this initiative in rare diseases research and funding.

4. International Collaboration on Rare Diseases Research Networks

Several clinical research network exists worldwide, with the US Rare Diseases Clinical Research Networks, the EU European Reference Networks and the Japanese IRUD Regional Alliance Hospital Network being some of the examples. How is it in different countries:

4.1 Presentation of existing networks

a) US Rare Diseases Clinical Research Network (RDCRN)

- ▶ Established in 2003
- ▶ Partnership of several NIH Institutes and Centers
- ▶ Physicians, scientists and their multi-disciplinary teams work together with patient advocacy groups (PAGs) to study rare diseases
- ▶ 21 research consortia and data management coordination center
- ▶ To date:
 - >100 active protocols
 - >43,000 patients have been enrolled
 - >350 trainees
 - >140 Patient Advocacy Groups (PAGs)

b) European Reference Networks (ERN)

- ▶ Networks of healthcare providers aiming at improving quality, and safety and access to highly specialised healthcare
- ▶ Added value at EU level
- ▶ Multidisciplinary approach
- ▶ Need of cooperation
 - Scarcity of knowledge on
 - Need of education for health care professionals
 - Complexity and high costs of RD
 - Effectiveness in the use of resources
- ▶ Knowledge travels, not the patient
- ▶ Affiliated partners will join in late 2017
- ▶ To date:
 - 24 ERNs
 - 26 countries
 - >300 hospitals
 - >900 healthcare units

c) Japanese Initiative on Rare and Undiagnosed Diseases (IRUD)

- ▶ Global data sharing for patients to terminate their diagnostic odysseys
- ▶ Improve life science, daily life and quality of life of patients and families
- ▶ Establishing new matrices to check a quality of projects
- ▶ Central IRB

- ▶ ToMMO (Tohoku University) provides rare variants of >3000 healthy Japanese to speed up for precise diagnosis
- ▶ To date:
 - >400 hospitals
 - >2200 registered families
 - 11 new disease families
 - 3 case matches with foreign countries
 - 35.2% successful diagnoses
- ▶ Next steps
 - Beyond diagnosis: Translational research to the treatment
 - Beyond genotyping: Progressive improvement of the success rate in diagnosis via cutting edge technologies
 - Beyond borders: Global data sharing and fostering young investigators through bilateral funding

4.2 FCC point of view

Currently it would be a good time for global collaboration of clinical research networks, with a unique opportunity currently representing itself:

- ▶ Rare diseases are a global burden, and portray the need for global harmonization
- ▶ The co-funding of NIH partners for the clinical research networks will have it its next round in 2019
 - Call currently in preparation
- ▶ The ERN were approved in early 2017, and, as such, have just started this year
 - Opportunity to integrate guidelines in newly created structure
- ▶ IRUD will start its IRUD Beyond program at the end of this year
- ▶ Other National Clinical Rare Disease Research Networks such as implemented in Germany should be taken into account
- ▶ Current rare diseases clinical research networks show clearly overlap and possibilities for collaboration
 - Task Force to identify how to best make connections
 - Funders can help set the stage, paving the way for future data sharing and consent use

Task Force should investigate several issues:

- ▶ How to best make connections between the different networks and how these connections could be implemented and supported within funding opportunities proposed by FCC members
- ▶ To what extent are these clinical research networks good for new gene discoveries
- ▶ Data sharing: how to best set the stage for optimal sharing, using dedicated consent language and dedicated standards
 - Opportunity to go a step further as FAIR principles
 - Joint agreement on data sharing language
 - Ethically and legally robust guidelines for data sharing
 - Expansion of common data elements and global adoption of these elements

5. Ethical, legal and social implications (ELSI) of rare diseases research funding, rare diseases healthcare and therapies

What kind of ethical, legal and social implications (ELSI) types of research can be done in the rare diseases research space?

- ▶ Not necessary on the ethics of expensive therapies, but more on the broader issues
- ▶ What is done around the world in this space?
 - How can we raise awareness for this kind of research?
 - What are the initiatives done?
 - How to we define the ELSI space from a rare disease funding perspective?

5.1 Existing funding opportunities

Different NIH institutes (NHGRI, NCI, NIA, NICHD, NIDCD, NIEHS, NINDS, NIMHD) have funding announcements for ELSI issues on genomics studies

- ▶ Solicit research projects that anticipate, analyze, and address the ethical, legal, and social implications of the discovery of new genetic technologies
- ▶ Solicit research project that study the availability and use of genetic information resulting from human genetics and genomic research.
- ▶ National Institute of Child Health and Human Development (NICHD) ELSI announcement focuses for example on new born screening and genomic sequencing.
- ▶ BRAIN initiative has a specific call for ELSI as part of this initiative, that looks at brain connectivity and network issues, but not directly related to rare diseases

5.2 Funding-related notices

Outside of the NIH, ELSI related funding opportunities in rare diseases:

- ▶ EJP RD and E-Rare also includes ethical and legal implications in funding calls
- ▶ Sometimes included as part of a larger project dedicated to ELSI work
 - RD Connect project has done significant work on this, and developed a set of common elements for informed consent together with BBMRI, as well as a code of conduct for health research
- ▶ CIHR and Genome Canada have a joint call, with a ELSI component integrated into the project
- ▶ CIHR and Genome Canada support a project, Can-SHARE, in which researchers are to develop framework for responsible, secure and effective sharing of genomic and clinical datasets across Canada and with international partners
- ▶ GA4GH has various projects related to ELSI work, some in collaboration with IRDiRC, such as the Task Forces on access and consent (Automatable Discovery and Access), and the project on the patient unique identifiers (Privacy-Preserving Record Linkage).

- ▶ German Ministry of Research has yearly calls for ELSI initiatives, with currently a call for retreats, to compare German ELSI matters to international ELSI matters
- ▶ H3Africa has 2 funding announcements on ELSI research in the African context
- ▶ Data protection in Japan is changing in 2017
- ▶ No targeted calls in Australia by the NHMRC, but currently ELSI granted project on genomics and rare diseases research

→ Prepare a table for an overview of different ELSI funding opportunities that all FCC members can complete for their own agency

→ Prepare a white paper or report on the overview of the ELSI landscape

5.3 Gaps to be covered by ELSI-related funding calls

What are the gaps to be targeted in the field of rare diseases?

- ▶ Principles of justice: should rare disease patients be prioritized
- ▶ Tension between data sharing versus privacy and confidentiality
- ▶ What are common international issues to be considered, and what are more national issues to be considered?

→ Complete table with gaps and opportunities to be covered by ELSI research