IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 9th Therapies Scientific Committee Meeting

Paris, France
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Participants

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Dr Michela Gabaldo, Milan, Italy
Dr Virginie Hivert, Paris, France
Mr Yann Le Cam, Paris, France
Dr Sandrine Marreaud, Brussels, Belgium
Dr Akifumi Matsuyama, Osaka, Japan
Prof Gert-Jan van Ommen, Leiden, the Netherlands
Prof Josep Torrent i Farnell, Barcelona, Spain

Dr Anneliene Jonker, Scientific Secretariat, Paris, France
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Apologies

Dr Karin Rademaker, Utrecht, the Netherlands
Dr Adam Heathfield, Sandwich, UK
Dr Anne Zajicek, Bethesda, USA
Dr Seng H. Cheng, Framingham, USA
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REPORT

1. TSC membership

Michela Gabaldo was approved by the Consortium Assembly (CA) as a new TSC member and attended her first Therapies Scientific Committee (TSC) meeting. Annemieke Aarstma-Rus replaced Gert-Jan van Ommen, who will retire after this meeting; her nomination had been approved by the CA. Seng Cheng's mandate was renewed by the CA for another term. Anne Zajicek has arrived at the end of her term, and received many thanks for her contribution.

2. Roundtable and introductions

Diego Ardigo, the new Chair of the TSC, welcomed all participants and invited them to introduce themselves. He is Project Leader at Chiesi Farmaceutici, which also focuses on rare diseases (RDs).

Annemieke Aartsma-Rus is a Professor at the Department of Human Genetics of Leiden University Medical Center, and is involved in the development of therapies for Duchenne Muscular Dystrophy. She will serve out the rest of the term of Gert-Jan van Ommen.

Michela Gabaldo is Head of Alliance Management & Regulatory Affairs Manager at San Rafaele Telethon Institute for Gene Therapy (SR-TIGET), and has been highly involved in the development of Strimvelis, approved last year for the treatment of ADA-SCID.

Virginie Hivert is the Therapeutic Development Director of EURORDIS, and previously worked at Orphanet, based in Paris, France; she has been involved in IRDiRC in various roles since its beginning.

Anneliene Jonker is the Communication Manager of the IRDiRC Scientific Secretariat (Sci Sec).

Sandrine Marreaud is the Head of EORTC's Medical Department, and she is the coordinator of their fellowship program.

Akifumi Matsuyama is the Director of the Platform of Therapeutics for Rare Diseases at NIBIOHN, and the Head of their Office of Policy and Ethics Research.

Yann Le Cam is the Chief Executive Officer of EURORDIS, and former Chair of TSC. He is also involved in the Rare Diseases International (RDI), the UN CoNGO for RDs, and sits on the management board of the European Medicines Agency (EMA).

Gert-Jan van Ommen is an Emeritus Professor of Human Genetics, and the former Head of Department of Genetics at Leiden University. He is also the Editor of EJHG, and the Coordinator of Orphanet Netherlands. He will retire as an IRDiRC TSC member after this meeting.

Ana Rath is the Coordinator of the IRDiRC Sci Sec and the Director of Orphanet.

Josep Torrent i Farnell is a Professor of Clinical Pharmacology and Therapeutics with an interest in orphan drugs, and has been involved in IRDiRC since the start. He was a former Chair of the TSC, and has also previously served on the EMA's Committee for Orphan Medicinal Products (COMP).

3. Dissemination of TSC Recommendations

The TSC members had agreed on recommendations for doing and funding therapeutics research, and metrics to keep track on the progress. These recommendations are published online, but in order to give a higher visibility to them, a small commentary has been prepared and submitted for peer-review publication, so far unsuccessfully.

Several suggestions were made to improve submission success:

- Contact the editor prior to the submission to see if there is interest and better target the article
- Not have the authors who wrote the recommendations be author on the paper
- Update the recommendations in order to assure timely publication

4. "IRDiRC Recognized Resources" update

After the last Joint Scientific Committees (SCs) meeting in Lyon, IRDiRC's quality label, previously called "IRDiRC Recommended," was renamed "IRDiRC Recognized Resources." In order to get more visibility on this label, an article has been published in the EJHG.[1] This article was an update and further elaboration of a previous short commentary by Ségolène Aymé.

5. Discussion on Orphan Drug Counter

Based on information obtained from the EMA and the Food and Drug Administration (FDA) websites and using the current established count methodology, i.e. orphan medicinal products (OMPs) with a marketing authorization (MA) and an orphan designation (OD) – see preparatory document – 222 new indications have been approved by the end of 2016, fulfilling one of the IRDiRC's goals.

This achievement is good news, and led to several discussion points:

- What will the next therapeutic goal be?
- How can this count be refined and expanded, and if so, in which direction?

[1] Lochmüller *et al.*, "IRDiRC Recognized Resources": a new mechanism to support scientists to conduct efficient, high-quality research for rare diseases. EJHG 2016, 25:162-165. http://www.nature.com/ejhg/journal/v25/n2/full/ejhg2016137a.html

- What are the other discussion points on the current count?

There is a wish to refine the current count. A set of secondary metrics were suggested.

- Primary count: based on current count methodology
- Secondary count: includes OMPs with a MA but without OD (see below)
- Extension I: the number of RD that have become treatable
- Extension II: the number of unique OMPs
- Extension III: curative OMPs vs symptomatic OMPs

Firstly, at present, only OMPs with an MA and an OD are included in the primary count. However, numerous drugs intended for the treatment of RDs without OD have obtained MA. In Europe, such list is available through EMA and collected by the Orphanet. However, in the US, the FDA does not currently provide such a list. If available, these drugs will be added to a secondary counter, with the inclusion criteria clearly specified.

Secondly, there is overall a wish to extend the current count to more countries. Country-wise, Japan is a logical candidate to expand the count to, as they have a clear orphan drug policy in place and maintain a list of OMPs. However, it is not easy to access this list. The Sci Sec will contact EMA and AMED to assist in provision of a list of Japanese OMPs.

Furthermore, a number of discussion points have arisen from the counting of the number of OMPs. Some OMPs have multiple indications; some have one indication but linked to several conditions. Additionally, the diseases to be treated are not clear for all OMPs, as some are intended to treat symptoms and not necessarily linked to a specific disease. A couple of possible extensions therefore lie in the count of number of RD addressed by these OMPs and in the count of unique OMPs, although further discussion is needed. It would also be preferable if it is possible to differentiate curative OMPs and OMPs that are treating symptoms.

Proposed actions:

- Prepare a list of complicated cases and OMPs for which there is doubt on inclusion in the count
- Following clarification, prepare a statement to highlight the achievement of the 200 OMP goal
- Prepare a commentary/scientific article where these 222 new OMPs are analyzed

6. Discussion on new IRDiRC goals

The IRDiRC Conference Planning Committee (CPC) has proposed a set of new IRDiRC goals, based on feedback from members of CA and SCs.

The goal related to therapies is formulated as “the rate of rare disease therapy approvals will have increased 10-fold, against the 2016 data.” That translates to, with a current rate of about 35 new OMPs reaching the market yearly, 350 new OMPs per year should reach the market in 2027. TSC members opined this is a little bit overambitious, as 5 fold (175 new drugs a year) would already be a fantastic

improvement! Counter proposal: to aim for 5 more drugs every year, so 85 drugs in 2027, **and** that these drugs are collectively five times cheaper than the drugs currently reaching the market.

Some considerations for the next therapy goal and accounting for factors influencing development:

- How can the time from trial to approval be reduced? (Theoretically: shorter development timeline → reduced development cost → reduced drug price)
- How can the pattern of development be changed in order to accelerate development timeline?
- Exhaustion of easy targets: have the low-hanging fruits already been picked and future therapeutics face tougher development process?
- To what extent can new therapeutic platforms (e.g. theragnostics) speed up development pipeline?
- What regulatory changes can assist speeding up of therapy development?
- Can horizon scanning into new therapies be carried out to help formulate development strategy, e.g. number of new publications on certain compounds or targets, or number of new initiatives around certain diseases, as metrics on how the field advances and how to advance the field?

Overall consensus: set IRDiRC's new therapy goal to 1,000 new OMPs approved in major geographical regions by 2027.

Regarding the metrics, the same primary assessment principle should be kept. The count should be expanded geographically and with secondary metrics established (see Section 5 above). It would be ideal to be able to quantify the number of RD patients who receive diagnosis and treatment, to ensure that the research actually reaches and benefits the patients.

7. Update: recommendations from the Patient-Centered Outcome Measures (PCOM) Task Force

The recommendations from the PCOM Task Force have been re-classified and published online on the IRDiRC website. Due to changes at the Sci Sec, its publication has taken a little longer than expected; it is currently in preparation for submission to the OJRD.

8. Update: recommendations from the Small Population Clinical Trials (SPCT) Task Force

The recommendations from the SPCT Task Force have been finalized and published online on the IRDiRC website. Simon Day, with assistance of the Sci Sec, has submitted an article to the OJRD that is currently under review.

A follow-up meeting, organized by IDeAL, AsteriX and InSPiRe will be held at the EMA premises in London, UK, on March 29-30. Interested participants are welcome to participate. For more information, please contact the Sci Sec.

9. Update: the Data-Mining and Repurposing (DMR) Task Force

The DMR workshop took place in Barcelona, Spain, on November 16 and was attended by 15 Task Force members and members of the Sci Sec. Task Force was chaired by Noel Southall and Madhu Natarajan.

Data mining and drug repurposing hold enormous potential for rare diseases. The purpose of this Task Force was to review past drug repurposing and data mining successes, to plan for future biomedical research capacity using data mining, and to identify where to target research and development investments to best realize the potential of these approaches. A further aim of the Task Force was to discuss strategic infrastructure investments needed to maximize RD therapy development.

The workshop was built around several topics:

- Current state-of-art / major successes to date
- Current gaps in data and analysis
- Tools for assessing validity / uncertainty of new clinical hypotheses
- Combining *in silico* / experimental approaches
- Sharing strategies / providing guidance to researchers and advocacy groups
- Improved data sharing to help focus limited resources
- Supporting incremental improvements for small patient populations

The conclusions and recommendations resulted from the workshop are currently in draft format. Four key areas emerge as opportunities for accelerating rare disease research productivity:

- Improving the capture and sharing of patient data
- Better integrating existing research data
- Increasing experimental testing capacity
- Nurturing rare disease research and development expertise

It is thought that this infrastructure would benefit not only data mining and repurposing efforts, but the entire ecosystem of rare disease drug development. Strategic business models are very important in order to see DMR advance. The workshop report and draft recommendations will soon be open for comments, after which the Chairs of the Task Force will further shape. TSC members are invited to send in their feedback to the Sci Sec for inclusion. A scientific publication is also expected.

10. Start of Patient Engagement in Research Task Force

The Patient Engagement in Research Task Force was initiated both by the TSC and Interdisciplinary SC (ISC) from the Joint SCs Meeting in Glasgow. Last year in Lyon, this Task Force proposal was brought to the CA for discussion. The proposal was subsequently refined and approved by the CA in Catania; it is now ready to start after the IRDiRC Conference. This Task Force is aimed at promoting patient engagement in RD research activities and health product development, and providing guiding principles for the engagement of patient groups or patient experts in research activities.

The Task Force is expected to start in the second semester of 2017, with a bibliographical study and analysis of past and ongoing initiatives as sources of policy and funding recommendations. In this phase, the Steering Committee of the Task Force would also be composed, a Chair identified, and the general members appointed. The workshop would be planned in the last quarter of 2017, or the first quarter of 2018. The final report and publication are aimed for completion in mid-2018.

11. Proposal: Clinical Research Networks for Rare Diseases Task Force

This Task Force will build on experience gained and ongoing initiatives, and is aimed to identify policy recommendations for the development and adoption of new diagnostic tools and therapies, and to establish findable, usable protocols for data collection, cost sharing, infrastructures, centralized data repository, longitudinal studies, clinical trials, natural history studies.

This proposal still needs to be finalized and sent to the CA for deliberation and approval, either at the next CA meeting or by written procedure. If approved, the work is expected to start in the last quarter of 2017, with a workshop in early 2018, and a finalized report in the fall of 2018.

Several reasons make it a good time to launch and finish this Task Force relatively quickly: (1) the Clinical Research Networks (CRN) program in the US is currently undergoing review, and they are planning for the next phase that is expected to start in 2019; (2) in Europe, the European Reference Networks (ERNs) will be legally created this year, and the Commission's Joint Research Center of EU Platform on Rare Diseases Patient has started last year; (3) the new H2020 Work Program will be adopted mid-2017, with preparation of the EU funding programs for 2021-2025 starting soon; and (4) there is currently an ongoing discussion for a European Joint Program on Rare Diseases.

To provide some setting for this Task Force, there are several major pillars. The Rare Diseases Clinical Research Network (RDCRN) in the US is an initiative of the Office of Rare Diseases Research, NCATS. It is made up of about research consortia and a Data Management and Coordinating Center that work together to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. Each consortium covers at least 3 diseases in the same group of related diseases.

In Europe, the creation of ERNs will provide for the first time a unique opportunity for clinicians to work across borders in healthcare, and facilitate the sharing of knowledge, experience, medical research, teaching, training and resources. Although these centers of expertise in Europe are intended for healthcare, there can be benefits gained from the clustering of diseases and use it for clinical research.

In this context, the purpose of the Task Force on Clinical Research Networks for Rare Diseases will not only be built on the experience gained and ongoing initiatives in the US and EU, but also Australia, Japan and other countries willing to take an active part in identifying policy recommendations as well as

recommendations to funders in support of the development and adoption of new diagnostic tools and new therapies for rare diseases. The outcome will be to develop recommendations on guiding principles for national policies on clinical research networks within an international context for collaboration and interoperability, and the related funding recommendations.

Possible key questions for this Task Force are:

- What are the recommended functions for the Clinical Research networks? Which functions could benefit from international alignment?
- What are the tools used in the different Clinical research Networks? Which resource, tool or standards could be shared and adopted across the USA / EU / Australia / more
- Which key policy elements so to link up these national or continental clinical research network at international level
- What are the common goals, functions and selection criteria to include in all public funding strategies?

12. Topics for future Task Forces

The TSC brainstormed on additional Task Force topics that may be of interest. The goal of these topics is to speed up drug development, leading to an increased number of RD therapies. Some of these topics may overlap with those considered by the ISC or the Patient Advocates Constituent Committee.

Topics for a Task Force proposal are:

- Requirements and recommendations for public-private partnerships aiming at developing shared registry-like studies enabling continuum of research collaboration throughout drug development ("from NHS to PASS")
- Horizon scanning for identifying initiatives and gaps to the achievement of 2027 IRDiRC new therapies goal (see also Section 6)
- Requirements and recommendations for initiatives of open innovation in drug development
- Define and support specificities for advanced therapies and one-off treatments for rare diseases
    - Manufacturing trends, delivery model, pre-/post-approval data collection

Next steps and actions

- Resubmit TSC Recommendations
- Finalize and submit PCOM recommendations to OJRD
- Review and feedback on DMR recommendations and conclusions
- Publish DMR outcomes
- Contact FDA for list of OMPs without OD
- Contact EMA/PMDA for list of Japanese OMPs
- Create secondary metrics for the orphan drug count
- Create list and discuss complicated cases of OMPs

- Draft and review press release of 200 new therapies
- Draft and review article of 200 new therapies
- Start work on Patient Engagement Task Force
- Finalize proposal on Clinical Research Networks for Rare Diseases Task Force

Document history

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