IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 7th Therapies Scientific Committee Meeting

Glasgow, UK
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Participants

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Apologies

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Agenda

1. Roundtable and introductions
2. Review of TSC progress and activities
3. Role of the TSC
4. Update on Patient Relevant (Centred) Outcome Measures (PROM) Task Force
5. Update on Small Population Clinical Trials (SPCT) Task Force
6. Action planned on Data Mining and Repurposing (DMR) Task Force
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8. Planning of the workshops
9. Suggestions of potential Task Forces for future action in 2016 and beyond

REPORT

1. Introduction

The Chair of the Therapies Scientific Committee (TSC) opened the meeting and members introduced themselves.

1. Review of TSC progress and activities

2.1 IRDiRC Policy

The policy was adopted in 2013.

2.2 TSC Recommendations to funders

The TSC recommendation document was finalised end of 2014, but has not been published as it still requires an FDA disclaimer. To avoid further delay to publish the recommendations, the TSC chair suggests adding a disclaimer, stating that the document has not been officially endorsed by the FDA. The FDA can propose a disclaimer at a later stage if necessary.

The Scientific Secretariat will publish and highlight the recommendations on the IRDiRC website. The TSC should publish a short editorial in a journal, summarising and highlighting the main recommendations and their impact. The increase in the number of applicants seeking scientific advice from the FDA or EMA has had a positive high impact on the number of applications, from academia in particular.

The TSC should target journals of their choice. It is suggested that Orphanet Journal of Rare Disease would be appropriate as it is an open access journal and balances research and policy issues. All present members second the proposal.

TSC members are invited to candidate as editorial writers. Following no proposals, all agree to appoint Virginie Hivert and Josep Torrent Farnell. Once written, the article will be circulated to all TSC members for review. Support IRDiRC will cover the fees for publication (contributing authors pay the open access journal fee to publish).

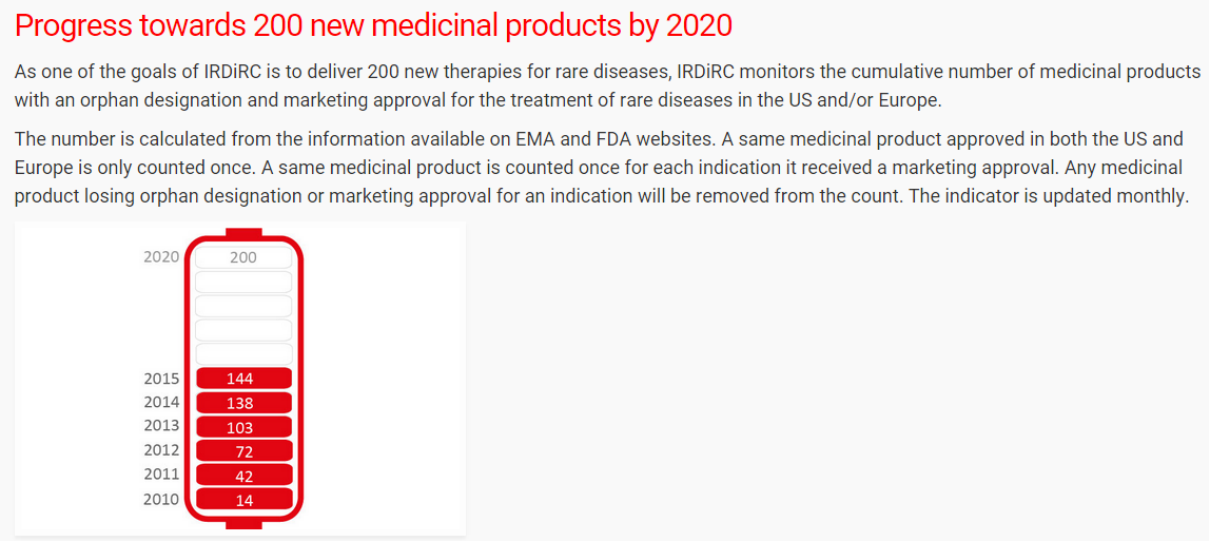
Ongoing topics include regulatory process flexibility. A number of projects at the FDA, EMA and IMI focus on adaptive licensing, approval, and earlier and progressive patient access.

The TSC needs to revisit the gap analysis to identify what can be carried out with current available resources and where additional funding is required to go further. Identified gaps to address at a future stage include unmet medical needs and regulatory hurdles, and the impact of breakthrough and adaptive licensing.

2.3 Progress towards 2020 goal

The Scientific Secretariat presented the Exec Comm-approved methodology to count new therapies for RD. The strategy and methodology were approved by the Exec Comm at the outset of Support IRDiRC.

New orphan drug market approvals are extracted from FDA and EMA websites monthly. Double EMA/FDA approvals for the same product and indication are counted only once. The cumulative total is presented in the IRDiRC counter. Overall, new orphan products have increased roughly by 30 a year.



EMA: Data is retrieved from the European public assessment reports (EPAR) for human medicines published by the European Medicines Agency (EMA)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

FDA: Data is retrieved from the US Food and Drug Designations and Approvals
http://www.accessdata.fda.gov/scripts/opdlisting/oopd/

- New therapies are counted if:
  - ✓ No prior indications or market authorisations exist for this product
  - ✓ Marketing authorisations exist for different indications to the latest one

- Orphan therapies are not counted if:
  - ✗ Marketing authorisations exist for the same indication as the latest
  - ✗ The new marketing authorisation is a label extension or a label change
  - ✗ The FDA has granted marketing authorisation prior to EMA's authorisation, or vice versa.

2.4 FDA & EMA statistics on Orphan Drug designations and market authorisations, scientific advice/protocol assistance and other RD therapy market authorisations

A lag in figures during the first half of each year is not unusual. The trend is fairly high with approvals and designations growing at a constant annual rate. Results indicate that the goal of 200 new therapies will be reached by 2020.

The number of designations continues to increase and the transformation of designations into market authorisations has been stable over the past 20 years. While the effect of academia seeking early policy and scientific advice may increase the designation rate, the overall authorisation success rate remains stable.

The balance of EU and USA market approvals must take into account that a number of orphan products are registered first in the USA, then in the EU, sometimes one or two days apart only. This first to register filter may suggest a higher approval rate in the USA, but EU and USA authorisations are frequently filed almost simultaneous. Approval dates are reported on IRDiRC website, in orphan drug authorisation lists.

The chair suggests engaging someone from the office of COMP to analyse USA and EU approvals and identify gaps in authorisations.

The question of counting drugs approved for RD, but without orphan designation, is raised. Many drugs with RD indication have not been approved as orphan drugs. Furthermore, some orphan drugs approved in the USA may be non-orphan drugs approved in the EU or on the point of losing their orphan status because they don't meet the EU-specific Significant Benefit criteria and vice versa. It is suggested that all drugs with RD indication (orphan drug approved or not) should be counted. It is also suggested that IRDiRC's method of counting new drugs attempts to capture all drugs for RD, with or without orphan status.

- Decisions taken:
  - For the period 2010 to 2020, continue to count only orphan RD therapies for the main counter; the two reasons for maintaining this counter are (a) to have a continuum of method and counting and (b) to encourage orphan status of rare disease therapies.
  - Try to collect data on RD drugs without orphan designation and display this information on the website with a second counter; the three reasons to create this counter are (a) the official goal of IRDiRC is "to deliver 200 new therapies for rare diseases" not 200 orphan medicinal products and (b) all medicines approved for rare disease indications are used in the treatment of patients which is the aim of IRDiRC, and (c) the reasons for having or not having an orphan status are mostly exogen to scientific and medical considerations.
  - Try to collect data on RD medicines approved without orphan designation in EU or USA to create this second counter (update the counter since 2010). This should be easily done from existing data in Orphanet and tables from EURORDIS for the EU, and by asking the office of OMPs at EMA and OOPD at FDA for the USA.
  - Identify gaps where drugs are approved in either EU or USA, and highlight drugs approved in both;
- Objectives:
  - Indicate where IRDiRC should push funding for research.

2. Role of the TSC

3.1 Revised TSC mandate

- Act as scientific coordinating bodies
- Propose research priorities for consideration by the Executive Committee
- Propose policies and guidelines for adoption by the Executive Committee
- Identify actionable projects and contribute to the organisation of workshops
- Contribute to the establishment of Task Forces to advance selected projects, to appoint their members and populate the task force workshops
- Evaluate, validate and make recommendations based on the outcomes of project workshops
- Propose reviewers to review submissions for "IRDiRC Recommended" and receive these reviews
- Endorse and present the Rapporteur's report for "IRDiRC Recommended"
- Address emerging issues of scientific nature
- Organise the scientific programme of IRDiRC conferences as they occur
- Encourage exchange of protocols and best practices, and agree on standard operating procedures, quality standards, roadmap to reach IRDiRC goals in their scientific area

3.2 Role of TSC and method of work with Task Forces

It is reminded that the Scientific Committee Working Group activities have ended, according to decisions adopted by the Executive Committee in Shenzhen in November 2014. Task Forces are being developed to act on past discussions and identified priority projects.

The time limited Task Forces have a focused approach to address priorities. They are composed based on nominations from the Executive and Scientific Committees. The Scientific Committees can still propose names for the three Task Forces Patient Centred Outcome Measures (PROM), Small Population Clinical Trials (SPCT) and Data Mining & Repurposing (DMR) being launched and for future Task Forces.

- For each Task Force:
  - A mandate has been written and approved by the Executive Committee
  - The Scientific Secretariat prepares the first draft of the background document for the Task Force: compilation of the literature and existing research projects in each field; identification of issues to discuss with the Task Force members and during the workshop
  - The document is circulated to members of the Scientific and Executive Committees for feedback
  - The Scientific Secretariat will call each Task Force member to discuss and review the paper, identify reference gaps, questions to discuss in the workshop, expectations from the workshop in terms of recommendations to funders
  - Develop workshop content with members
  - Write post workshop paper highlighting recommendations to funders

Specific messages are expected to result from the workshops, and the primary objective of the Task Forces is to translate workshop outcomes into policy for funding bodies. Depending on the Task Force topic however, other essential objectives will be sought, presented below.

3. Update on Patient Relevant (Centred) Outcome Measures (PROM) Task Force

4.1 Mandate and objectives of the Task Force

Several large players (PCORI, Genetic Alliance, ISPOR, COMET, ICHOM, PROMIS, etc.) have developed measures for common diseases, but not for RD. The Task Force and workshop will need to convince them to invest in RD, based on the needs in the field. The objective of the Task Force is not to recommend funding, but that these organisations invest in the field of RD.

The Scientific Secretariat highlights that the concept of the background report is to avoid discussions among workshop attendees on what is already known regarding ongoing initiatives in the field. While it is not comprehensive, the background document aims to remind participants of basic definitions, establish an equal level of knowledge and avoid repeating known concepts during the workshop. The Task Force will identify and define the topics of focus for the workshop, based on actionable issues.

The Task Force steering committee has been composed and consists of six expert members.

Further suggestions are made to include additional members in the general membership list.

4.2 Feedback and discussion on draft background paper and workshop programme

It is agreed that the title be modified to **Patient Centred Outcome Measures**.

The increase in number of patient monitoring devices provides greater capability to measure patient centred outcomes. The typing test, to assess hand dexterity, is suggested as an example of a tool to be validated as a measure in neurological disorders. It is further suggested that the Task Force assess different existing measures from various initiatives and organisations to be merged into standardised measures.

It is suggested that recommendations be made as soon as orphan drug designation clusters emerge for one or several RD. Funders should encourage the development of guidelines for outcome measures for individual or groups of diseases.

The issue of pre-competitiveness is addressed with the examples of data and biomarker sharing. Many clusters of several biomarkers are developed in parallel to assess patient outcomes. It is suggested that if researchers and developers shared their validated biomarkers, greater standardisation and more widespread use of biomarkers would be achieved. IRDiRC could incentivise academic institutions as well as pharma and biotech companies to share their data.

4.3 Next steps & expected output

It is suggested that Task Force members and workshop participants identify tools from the background work and workshop outcomes that should become IRDiRC Recommended.

- A database of validated outcome measures was to be set up, but the project requires funding and should be discussed with industry and IMI. An outcome of the workshop could be to compile EMA or FDA validated measures for specific RD or groups of RD and extract measures for common diseases that may be applied to RD.
- Standard outcome measure development methodologies from initiatives such as ICHOM and PCORI could be proposed for IRDiRC Recommended as tools to help develop outcome measures in RD.

The TSC members are asked to send their feedback and comments on the background document for the Scientific Secretariat to update this first draft. Version 2 of the background paper will be sent to all scientific committee members.

4. Update on Small Population Clinical Trials (SPCT) Task Force

5.1 Mandate and objectives of Task Force

The aim of this Task Force is to reach an agreement between FDA and EMA on policy and regulation in the field. The two regulatory agencies and large projects working on methods will be invited to the workshop. The EMA has accepted to host the workshop.

Following the lack of progress with both FDA and EMA guidelines, this Task Force needs to help advance the field of small population clinical trials. The FDA's review of guidelines, designs and statistical methods, due for public consultation in September 2014, was never presented. The EMA's guideline on adaptive statistical methods of 2006 is due for revision, with the aim of merging it with new knowledge to produce one comparative guideline. Because no progress has been made on this project, the EMA is seeking impetus from outside.

The Task Force steering committee has been composed and consists of five expert members.

Further suggestions are made to include additional members in the general membership list.

5.4 Feedback and discussion on draft background paper and workshop programme

The Task Force should address what needs to be done before studies are designed and ways of approaching pre-clinical development to design specific studies. The lack of interaction between pre-clinical research and RD communities must be addressed to improve the use of pre-clinical studies and the development of phase II and III clinical trials.

The issue of patient expectations and follow up from therapy is raised. Following one or two years in trials, patients may subsequently become enrolled in another trial for a different treatment run by another sponsor. This generates a situation in which no one has the entire picture of those patients. The succession of trials may also confuse patients and carers about which studies to join.

The Task Force must therefore address the issue of patient engagement. The more trials become adaptive, the more patients need to become engaged due to potential risks and the small number of patients in RD trials. Furthermore, becoming involved in trials is an essential question as once patients are enrolled they

will no longer be treatment naïve for subsequent trials. The issue of patient engagement must also distinguish between patients and their parents/carers in order to identify the point at which the patient's wishes override the clinician's advice.

There is a need to harmonise independent committee decision making processes, particularly concerning dose selection. A standard charter should be established to help decision making when it is not in the hands of (academic or industrial) sponsors.

The choice of clinical trial methods must be addressed. Choice of methods should not be independent of post-marketing considerations. When adaptive methods are promoted, attention to evidence collection and data generation is shifted from pre-marketing to post-marketing, particularly in RD. The various trial methods and approaches should be linked to pre- and post-marketing, and homogeneity and heterogeneity considerations.

It is proposed that IRDiRC write to EMA and FDA offering to contribute workshop output to revise and harmonise their guidelines, with input from industry and patient groups. A proposal to FDA must, however, avoid making direct recommendations as IRDiRC is not a legal entity and FDA is a member of IRDiRC. Consensus from all IRDiRC members will need to be sought before sending any proposal to FDA. As FDA representative, Ilan Irony, has accepted to become a member of the Task Force steering committee, talks should be held at the workshop on the possibility to coordinate efforts.

The 2006 EMA guidelines were positively received by industry, who would welcome, in principle, a guideline revision on adaptiveness and flexibility. Furthermore, based on EMA pilots on adaptive licensing, the agency wishes companies to submit more ambitious plans. A phase II study (not in a company portfolio) could be used at the workshop to propose an alternative 'real case' trial design to increase recognition of different study models.

The NINDS competition award for best algorithm to predict seizure frequency is proposed as an example of ways to draw attention to alternative methods. In the field of RD, a competition on adaptive designs could be proposed to study a chosen RD. Statisticians would be invited to come up with a design, the best of which would be presented at the workshop and assessed by FDA and EMA statisticians. The winner would gain exposure, be covered for workshop attendance expenses and present their work.

5.6 Next steps & expected output

The TSC members are asked to send their feedback and comments on the background document for the Scientific Secretariat to update this first draft. Version 2 of the background paper will be sent to all scientific committee members.

5. Action planned on Data Mining and Repurposing (DMR) Task Force

Many academic and industrial initiatives exist in this area and are showing results. A workshop will bring together players finding new targets and indications: to learn from their experience, identify projects open to academic researchers, discuss how this field can be organised and build up a community of stakeholders. The eight people contacted have agreed to be part of the Task Force Steering Committee.

Further suggestions are made to include additional members in the general membership list.

6.2 Next steps

Work on the background document will begin in the next weeks, based on published experiences.

6. Task Force organisation

The Task Forces are transversal and are not attributed to any one Scientific Committee. [*Post-meeting note: following discussions at the joint Sci Comms meeting, one or more Sci Comm members closest to the field of each project will represent all three Sci Comm on each Task Force*.]

[*Post-meeting note: non-core group nominees will be invited as general members of the Task Force. 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 and relevant Sci Comm members will decide on the list of participants invited to the workshop, based on Exec and Sci Comm, scientific secretariat and Task Force steering committee proposals.*]

[*Post-meeting note: the core group was renamed 'Steering Committee'.*]

Version 2 of the Task Force background documents will be send to members of all three Scientific Committees, following review of the first draft including their input.

Scientific Committee member feedback on background papers should include any further questions, additional references, gaps in information and suggestions of additional names to become members of the Task Force or to attend the workshops.

7. Planning of the workshops

Workshop attendance will be on invitation only. PROM and SPCT workshops must be organised before end of 2015.
The Scientific Secretariat will identify workshop dates with the steering committee members, depending on their availability. The first conference call with the PROM Task Force Steering Committee will take place on 15 June, during which content and dates of the workshop will be discussed. [*Post-meeting note: the PROM workshop will be organised in Paris end of November 2015. Three members of the steering committee were contacted individually on 6-7 July, following the joint teleconference of 15 June, to discuss the background paper and its scope, add references, identify topics for discussion at the workshop and draft policy recommendations. Task Force members involved in the initiatives highlighted in the background paper have been invited to review their section – most have sent their feedback and the paper has been updated accordingly.*]

A conference call will be set up shortly with the SPCT Task Force steering committee, and subsequently with DMR once the steering committees have been constituted. The EMA initially confirmed they would

host the workshop. The EMA must re-confirm this and Jordi Linares must nominate a representative. Bruno Sepodes is suggested as an additional contact at EMA.

A workshop on DMR is less urgent, but a date will be discussed shortly to avoid delay, possibly early 2016.

8. Suggestions of potential Task Forces for future action in 2016 and beyond

9.1 Task Force on multiple endpoints

This Task Force should bring in industrials and statisticians.

9.2 A knowledge-building tool-independent Task Force

This Task Force would address the issue of collecting data on all existing patients, ways to consider real world observations on all patients treated, and pre-marketing approval to evidence based therapy. Adaptive pathways are important in RD to learn about treatment effects over time and build knowledge on RD. Adaptive processes allow post-marketing evidence or post-trial data collection to homogenise and stratify patients for future trials, as illustrated in phase III trials in Duchenne Muscular Dystrophy.

This Task Force could address how investigators should identify key questions to build up knowledge and allow them to advance to subsequent stages of clinical investigations. In most diseases, all patients are involved in one form of research or other at any one time. This raises the question of how to collect all the data generated from research. Paediatric oncology is one model of this type of research. All children with cancer in the USA are part of research, the nature of which depends on the patient or family choice. Patients and their family can elect to receive standard of care only or standard of care plus investigational therapy. Generated data serves to build up research knowledge.

9.3 Real-world evidence

This Task Force would explore data mining, i.e. real life data consisting of what can be generated from available (web based) data, as opposed to data retrieved from organised systems.

9.4 Gene/cell therapy

This Task Force would analyse gaps and identify roadblocks in funded projects on gene and cell therapy, and identify the lessons learnt from what has been achieved so far. The Task Force could analyse the quality of approaches in terms of drug development, compared with traditional methods, as well as the business model for gene therapy.

Several companies developing gene/cell therapy could be brought together to discuss the model for access to patients, from approval to clinical use. The business model must be associated with an analysis of cross-border healthcare, payment for additional or future treatment and treatment respondent patients, among other health economy issues.