

Meeting report series

Report of the 8th Therapies Scientific Committee Meeting

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Agenda

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3. Recommendations from the Patient-Centered Outcome Measures (PCOM) Task Force
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5. Update on the Data Mining and Repurposing (DMR) Task Force

6. Discussion of new Task Force proposals
7. Topics for future Task Forces/IRDiRC Conference

REPORT

1. Roundtable and introductions

The Chair of the Therapies Scientific Committee (TSC) opened the meeting and each participant briefly introduced themselves. The Chair of the Executive Committee (Exec Comm) partially attended this meeting and took the opportunity to meet the TSC members and become acquainted with their work.

2. Method of work of TSC Task Forces

The work methodology of TSC Task Forces can be summarized as follows:

- ▶ Proposal of Task Force by the Scientific Committee (Sci Comm)
- ▶ Evaluation/decision of the proposal by the Exec Comm
- ▶ If approved, nomination of experts to constitute Steering Committee (Steering Comm) and general Task Force members
- ▶ Writing of background/pre-workshop document through bibliographic research by the Sci Sec
- ▶ Organization of teleconference calls of the Task Force Steering Comm
- ▶ Organization of workshop of the Task Force (where general members also attend)
- ▶ Workshop discussions and development of recommendations
- ▶ Preparation of post-workshop report, which include Task Force recommendations
- ▶ Dissemination of workshop outcome

After a year of working with Task Forces, the TSC concludes that, overall, it has been a positive development. Positively evaluated points include the short-term duration of the Task Forces, strong presence of nominated experts, dynamic workshops, and the production of tangible elements (e.g. background paper and post-workshop publication), thus concrete output has been produced by the Task Forces. Clear goals and outcomes are needed to move the work of Task Forces forward and a potential future IRDiRC conference can be used to disseminate their outcomes.

A number of positive practical points adopted include appointment of Task Force leaders to be reference point (e.g. SPCT and DMR Task Forces), the formation of Steering Comms consist of highly engaged experts, adapted one-on-one calls with Steering Comm members to improve the background paper (e.g. for PCOM Task Force), and full involvement of Steering Comms to set up workshop agenda.

In order to finalize the recommendations, a conference call of the Steering Comm should be organized. Case studies from the European Medicine Authority (EMA), US Food and Drug Administration (FDA) and/or Pharmaceuticals and Medical Devices Agency (PMDA) should be added for real life examples. One of the ways to obtain acknowledgement of recommendations at the regulatory level is to invite representation from the regulators at an early stage for participation.

Additional points for consideration: tracking the implementation of Task Force recommendations by members of IRDiRC, follow-up work focused on operationalization of the recommendations and conclusions from the Task Forces.

3. Recommendations from the Patient-Centered Outcome Measures (PCOM) Task Force

3.1 Patient-Centered Outcome Measures workshop

The workshop took place in Paris, France, on November 30, 2015, and was attended by about 20 members; members unable to attend contributed in writing. The post-workshop report with its recommendations has been finalized.

The workshop had different objectives, some general and some more specific:

- ▶ Define experience of existing communities already active in the field of common health events;
- ▶ Benefit from the existing knowledge and processes, and explore what is directly transferable from this existing knowledge and among the outcome measures that have been developed and tested in more common diseases;
- ▶ Identify areas for initiatives likely to ease and accelerate the development of PCOM;
- ▶ Identify major gaps in instruments (intellectual disability, quality of life, etc) which should be prioritized for funding;
- ▶ Agree on a collaborative effort to develop standard tool sets and thus to decrease the cost and time length of development of PCOMs;
- ▶ Raise awareness within rare disease community of methods to set up PCOMs, and educate and train researchers, doctors, nurses and patients.

To set the stage of the PCOM workshop, the five types of clinical outcome assessment are:

- ▶ Patient-reported outcomes measures;
- ▶ Clinician-reported outcomes;
- ▶ Observer-reported outcomes;
- ▶ Performance outcome;
- ▶ Biomarkers.

The scope of patient-centered outcome measures is thus larger than only patient-reported outcome measures.

3.2 Summary of recommendations

The development of PCOM in rare diseases is a necessity that is of importance for research purposes, to monitor / evaluate trial results, and for evaluation by health technology assessment (HTA), regulators, and

other decision makers. For patients, they are the instruments can be used to measure real benefits from their perspective.

The main recommendations that have resulted from the workshop are:

- ▶ Clearly define:
 - What to measure, based on qualitative research
 - Why we measure, for what purpose
 - Where measuring takes place
 - Who is qualified to measure (a critical element)
 - How to measure (instrument, scale, etc)
- ▶ PCOM need to be relevant, useful and feasible for the assessment for health care providers in clinical practice;
- ▶ If it is possible, adaptation of existing tools to the specificities of a rare disease is preferable over the development of a new tool. Recommendations on how to apply existing PCOM to the rare disease field have been included. In the context of the transfer of existing outcome measures to a new field, the outcome measures should be re-validated;
- ▶ PCOM could be applied across several rare diseases; some PCOM can easily be adapted from one disease to another one;
- ▶ If existing measures are used, qualitative efforts to establish content validity is crucial to ensure that patient' most pressing concerns are properly captured;
- ▶ Fund the development of outcome measures. Better resources for the development of PCOM should be made available, as well as a mechanism to foster collaboration. All funders need to consider how they can support the development of PCOM;
- ▶ The recommendations should be taken into account by all stakeholders; in order to ensure this, an early discussion with all stakeholders is necessary. Awareness for outcomes should be spread to all involved stakeholders, e.g. through sessions in summer schools, training sessions, etc;
- ▶ In the development of new outcome measures, regulatory bodies should be involved early on to ensure the outcome measures can be used for benefit-risk assessment;
- ▶ PCOM should be used in a much more systematic, more complete way.

Awareness of best practices is necessary. All existing guidelines must be highlighted, promoted, and disseminated as a support to the rare disease community. Early dialogue with the regulators is essential to validate outcome measures for regulatory use. In addition, the regulatory bodies should disclose the outcome measures on which they granted marketing authorization. Also, publication of new tools in peer-review journals is highly recommended.

It is proposed to structure the recommendations by stakeholders and by reader (drug developers, regulators, etc.). The recommendations should be divided into two parts, recommendations about the reinforcement of existing PCOM and their adaptations, and recommendations on the development of new PCOM. The recommendations in both sections could be graded, with recommendations that are meaningful for all, and recommendations that are more experimental. This ranking should also be kept in mind for a future publication.

3.3 Concluding remarks

The recommendations will be restructured to facilitate readability. Thereafter, the finalized version will be send back to the Task Force members for comments. After the restructuration, the post-workshop document is complete and it will be made available for adoption to the Exec Comm.

A scientific publication is planned and a Steering Comm member will be asked to shape the publication, with assistance of the Sci Sec to write a first draft and with input from the Task Force members. An additional point to be kept in mind for the scientific publication is the use of case studies from the EMA/FDA. Retro perspective studies on how the regulators took PCOM into account can be essential to highlight the correct us of PCOM.

The recommendations may be integrated into that of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Task Force in the future.

4. Recommendations from the Small Population Clinical Trials (SPCT) Task Force

4.1 The SPCT workshop

The workshop took place in London, UK, on March 3, 2016, and was attended by around 35 members. This workshop was organized to discuss technical solutions to make the best use of scarce clinical data in the context of small population trials and to identify points of agreement between the different stakeholders regarding non-classical designs. The workshop was also aimed at identifying further areas where research is needed.

The workshop started with a plenary session to establish the objectives of the workshop, followed by several breakout sessions, and a final plenary session to discuss and conclude on the outcomes of the breakout sessions. The first draft post-workshop report has been prepared.

The six topics explored during breakout sessions are:

- ▶ Different study methods/designs vs types of conditions;
- ▶ Adequate safety data;
- ▶ Multi-arm designs or platform trial designs;
- ▶ Decision analytic approaches and rational approaches to adjusting levels of evidence;
- ▶ Extrapolation problems and opportunities;
- ▶ Patients' engagement in study design and patient-centered outcomes.

4.2 SPCT: Conclusions and recommendations

The recommendations resulted from the workshop are for general policy, drug development, public funding bodies, regulators and research bodies. To briefly summarize the main recommendations:

- ▶ Innovative design and new statistical methods have a tremendous potential to decrease the number of patients and the time involved and in trials
- ▶ It is advised to also look, next to the randomized control trial study, at different trial designs when setting up a clinical trial for rare diseases, creating an environment of affordable and accessible rare disease trials. Not every rare disease trial is as challenging, but if the burden for patients is too high using a randomized control design, or when a randomized control design is not feasible, or the benefit/risk ratio is not acceptable, other trial options should be considered;
- ▶ Better use of scientific advice regarding small population clinical trials of the regulators should be promoted. Regulators are often very accepting and supportive for new clinical trial designs, and welcome discussions and questions on this topic. Scientific advice is best requested at the early phases, directly after the proof of concept studies.

4.3 Concluding remarks

Final point to consider is the need for specific pilot examples; case study examples from the regulatory authorities should be asked to benefit from the experience. In addition, the alternative title of small population studies, rather than small population clinical trials was suggested.

To finalize the Task Force, the post-workshop report is currently being worked on by the Sci Sec, after which the Chair of the Task Force will further shape. Hereafter, the Steering Comm and general members will be asked for input. A scientific publication, shaped by the Chair of the Task Force and the Sci Sec, together with input from the Steering Comm, is also expected.

5. Update on the Data-Mining and Repurposing (DMR) Task Force

The Steering Comm is composed of seven nominated experts and three IRDiRC Sci Comm liaising members. The first draft of the background document has been written by the Sci Sec and is currently being reshaped by the Steering Comm. The Steering Comm also decided to have standing monthly conference calls to discuss their work plan and to prepare the workshop that will most likely take place in Barcelona, Spain, on November 16, 2016.

6. New Task Force proposals

6.1 Patient Engagement in Rare Diseases Research and Health Product Development

This is a joint TSC/ISC proposal intended to provide guidelines on where the views of patients are needed, when they are useful, and to provide existing examples of the experiences. It was proposed that the Task Forces members should include academic members, industry representatives, patient representatives and regulators. The Task Force work methodology used to date will be applied. The Task Force is not

requested to develop new tools or best practice guidelines, although these should be kept in mind for a later stage. The process and timelines may change with input from the ISC.

The background document should provide an overview of patient engagement so far, based on bibliography and existing examples. The following information is considered essential:

- ▶ Ways to de-risk the development of medicine;
- ▶ Identification of good practices;
- ▶ A map for patient groups, that is not disease specific, with the experience and existing framework in different patient organizations;
- ▶ 'Good' and 'bad' examples of patient engagement, to highlight experiences;
- ▶ Broader participation of patients in therapeutic development including ethics committees is not always there, but should be emphasized;
- ▶ Lack of patient engagement create barriers, missed opportunities, bad practices, shortcut solutions;
- ▶ Gap of communication, information and education between patients and clinical centers, which leads to missed opportunities when being involved in clinical trials.

A number of obstacles that could emerge are:

- ▶ Conflict of interest: if patient engagement becomes more regular, does it become more professional?;
- ▶ Individual patients/value of patient organizations?;
- ▶ Patient smart work: can we measure what the impact and success of patient involvement is?;
- ▶ How to get away from the 'tick the box' setting;
- ▶ Confidentiality of patients;
- ▶ Patients not on regulator-side or the industry-side but essential in multi-stakeholders meetings.
- ▶ Difficulty identifying and accessing the center of expertise

The next steps are the discussion of this proposal with the ISC and its restructuring. It will then be submitted to the Exec Comm for discussion and decision. If approved, a Steering Comm will be set up to lead the Task Force.

6.2 Clinical Research Networks of Rare Diseases

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 30 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. In Australia, health networks and health pathways such as the Genetic and Rare Disease Network have been developed. These networks are for health professionals and the wider community.

In Europe, there are already a number of Centers of Reference for Rare Diseases and other EU research funded activity consortia. Under the direction of funding of DG Santé, this is at present being developed further, to the European Networks of Reference of Centers of expertise for Rare Diseases. Although these centers of expertise in Europe are intended for healthcare, there can be benefitted from the clustering of diseases, and use it for clinical research.

In the new context, a Task Force could be set up to look at the experience so far in the US, Australia and Europe, and with this experience to look towards the future, thereby linking the past experiences of the US, Australia and Europe, also with the future experience of Europe.

The Task Force should investigate:

- ▶ What are these quality criteria intended for the therapeutic spectrum?
- ▶ What are the functions of the different Clinical Research Networks?
- ▶ What are the tools used in the different Clinical Research Networks?
- ▶ What could be done in order to use the European Reference Networks, or a subset of their members, as clinical research networks?
- ▶ What would be the key function of the European Reference Networks?
- ▶ Can we align the functions of the US/ Australia/ EU Clinical Research Networks?
- ▶ What could these networks do in terms of drug development, what type of incentives are needed?

After this investigational phase, recommendations should be developed to optimize the global outreach to patient, in terms of registries (interoperability, common datasets), facilitating the development of clinical studies, and developing the best practices of care. Recommendations should also be made on the coordination of policy expectations; looking for broader international collaboration might be feasible but challenging. It should be kept in mind that the systems are different, for cultural, historical, geographical and other reasons. Additionally, there are challenges due to the differences in regulation to consider.

7. Topics for future Task Forces/IRDiRC Conference

The TSC had a short brainstorming session on additional topics that can either be of interest for a Task Force, or as a topic for a future IRDiRC conference. The goal of these topics is to speed up drug development, leading to an increased number of therapies for rare diseases. Some of these topics may overlap with the topics considered by the ISC. In order to progress towards setting up a Task Force, it is important to determine what realistic questions are to be asked, and whether they can be answered.

Topics for a Task Force proposal or IRDiRC Conference session are:

- ▶ The identification and recruitment of rare disease patients in studies
- ▶ Natural history studies
- ▶ Alternative to animal models (in vitro/ in silico (*maybe part of the Data-mining and Repurposing Task Force, could also be as a follow up*))

- ▶ Manufacturing of advanced therapies – accepted level of risk for the community – post-approval phase for GeneT/CellT (*maybe as follow up from the SPCT Task Force*)
- ▶ Looking beyond approval into the Research activities all along the life cycle:
 - Outcomes based research
 - Fast-track approval – rapid access to drugs for RD
 - Economic impact of patient health outcomes
- ▶ Personalized medicines – common molecular markers – concept of rarity will change
- ▶ New incentives to engage in therapeutic development: how to attract investment. Investment despite uncertainty? This is an issue that is too large, and that cannot be solved, and therefore might not be suitable for a Task Force.

Next steps and actions

- ▶ Restructure PCOM recommendations
- ▶ Re-submit PCOM recommendations to Task Force members
- ▶ Send request to shape the PCOM publication
- ▶ Finish SPCT post-workshop report, including recommendations
- ▶ Review and feedback on SPCT post-workshop report
- ▶ Publish outcomes of SPCT
- ▶ Merge and restructure Patient Engagement Task Force proposal
- ▶ Brainstorm at Joint Exec/Sci Comm meeting about future Task Force topics