Meeting report series

Report of the16thInterdisciplinary Scientific Committee Meeting

Paris, France
6 February 2017

Participants

Prof Hanns Lochmüller, Newcastle, UK (Chair)
Dr Petra Kaufmann, Bethesda, USA (Co-Chair)
Dr Angel Carracedo, Santiago de Compostela, Spain
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Prof Jack Goldblatt, Perth, Australia
Dr Stephen Groft, Bethesda, USA
Prof Ken Ishii, Tokyo, Japan
Dr Edmund Jessop, London, UK
Dr Jeffrey Krischer, Tampa, USA
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Apologies

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Agenda

1. Welcome and introduction
2. ISC membership
3. IRDiRC new goals and area of focus
4. Draft IRDiRC activities 2017-2027
5. Metrics
6. Any other business

REPORT

1. Welcome and introduction

The Chair of the Interdisciplinary Scientific Committee (ISC) welcomed its members to the meeting, and extended the apologies of members unable to attend due to prior commitments. A roundtable took place for members to introduce themselves to the committee.

The Chair expressed gratitude of having new members who will bring experience on issues such as access, and Japanese perspective on the issues dealt with by the ISC.

2. ISC membership

The term of Rumen Stefanov as ISC member is extended for one year to complement his first term of 2 years (norm: 3 years, renewable once). His term will end in February 2018.

Petra Kaufmann was voted to be the Chair of the ISC, as Hanns Lochmüller stepped down from this position. She will be assisted by Domenica Taruscio in her position as the Vice Chair of the ISC. [*Post-meeting note: this change of leadership was announced to the Consortium Assembly (CA) and other Scientific Committees (SCs) during the Joint CA/SC meeting.*]

3. IRDiRC new goals and area of focus

3.1 Background

- Original overarching goals were established in 2011, that by 2020
  - Contribute to the development of 200 new therapies, and
  - Means to diagnose most rare diseases
- These goals largely achieved after 6 years
  - Provides need/opportunity to establish new goals for next decade (i.e. 2017-2027)
  - New goals also needed to maintain dynamic
- Conference centres around this theme of new objectives
  - CA and SC members have contributed to the consultation process
  - SMART criteria used to choose goals
  - Must be within scope of IRDiRC mission, and can be effected by IRDiRC

3.2 Framework

The ISC works on transversal themes and the original goals didn't have an interdisciplinary goals; one may be included with this new set of goals.

- Three levels in the draft goals:
  - Overarching goals
  - Critical activities that will support the achievement of these goals
  - Metrics to measure progress

3.3 IRDiRC goals 2017-2027

3.3.1 Goal 1: Diagnosis of all RD patients within one year of diagnostic assessment

- Is this within a year of seeing a specialist, or just first suspicion, or from symptoms appearing?
  - Situation very different from country to country
- Is this implying better diagnostic tools?
  - Is this stated clearly enough as a research goal?
- Moving towards realising not all RD are genetic
  - Implies other routes of diagnoses apart from genetic diagnoses
  - What about undiagnosed diseases and environmental causes?
- What is the common definition off RD?
  - Currently "rare" because diseases not prevalent enough to invest time and money in
  - Cut-off: US < 200,000; EU < 1 in 2,000 → HIV/AIDS, CFS, MS fell out
  - Not "scientific" definition; market-size orientated
  - In future, common diseases could become rare with genetic causes being known

3.3.2 Goal 2: Rate of RD therapy approvals will have increased 10-fold

- Rate of 10 fold, i.e. 35 per year in 2016 to 250 per year in 2027, is overoptimistic
  - Is it preferable to set too high or too low? →Too high at least motivates
- A range of different definitions of therapy could be applied
  - Does a new therapy treat a symptom or does it need to be curative?
  - Does approval mean 1 indication?
  - What is a RD, in context of precision medicine, so single diseases have sub-types?
- What to include under this 10-fold figure?
  - Only new therapies?
  - And repurposing/repositioning? → need massive global effort to fund and support
  - Any specificity, e.g. directed at underlying defect?

→**Recommendation: describe what is "10-fold" in numbers.**

3.3.3 Goal 3: All RD patients will receive available treatment within 1 year of diagnosis

- Is this an activity rather than a (real research) goal?
- Strong communication needed
  - Driven by patient advocacy
  - Inspire to move diagnostic and therapy goals forward in order to move this goal

- How to measure or what metrics to use?
  - T0 starting point mapping exercise needed
  - Situation will vary very differently from country to country
  - Some information from regulatory agencies but how close to real situation?
- Other considerations
  - Must be transdisciplinary work
  - How to identify patients who before weren't diagnosed are the ones diagnosed now?
  - Need information from companies and health services to see number of patients getting treatment → possible avenue to use data from ERNs
  - Need right diagnostic codes to identify patients and get more data
  - Need to discuss with companies on penetrance into the market
  - Importance of identifying red-flags at primary care level to increase early diagnosis

3.3.4 Goals 1 and 3 on access and healthcare

- These goals are 10-year, long term goals; the ISC is ready to take on work for parts of the goal when requested by the DSC and TSC
  - Data sharing is a massive topic to be worked on, with legal aspects to consider
  - Trials data in particular is currently inaccessible

- Some questions
  - Are other countries considering population screening and early diagnosis, in particular psycho-social aspects, to obtain medically actionable results?
    - Screening of variants in children via WGS in US and some other countries
    - Actionable findings from the UK 100,000 Genomes Project are expected
    - Similar large cohort study in Fukishima, Japan
  - What could the impact be on families and possible willingness for early diagnosis?
  - Concerns in some countries that this knowledge could cause problems regarding health insurance coverage: pre-existing dispositions ruling out coverage

- Suggestion of a topic to work on: diagnostic treatments
  - In Japan, there is a use of treatments to diagnose the disease and see patient reaction
    - Elsewhere, may be known as off-licence treatment
    - In the UK, known as therapeutic trial – would have problem following up
  - This becomes more difficult to do with reimbursement restrictions

- Activities that could help reach these new goals
  - White paper to raise awareness of goals, identify a problem and propose solutions
    - Identify blocking points, e.g. treatment in adults and children, moving biological samples across borders
    - Solutions need to be taken on by the right type of audience
  - Work on samples and biobanks (note: this has not been solved by BBMRI)
  - New approaches to consent/protocols needed – different between countries
    - Including contracting, consent templates, guidelines, common core

- Note: overarching committee is not envisageable

4. Draft IRDiRC activities 2017-2027

Four key activities were focused on and discussed by the ISC.

4.1 Promote RD biomarker and modifier discovery validation

- Increasingly important: how will patient individually respond to a treatment?
  - Need for correct ontologies and interoperability considerations
  - Biomarker screening could lead to quicker diagnostics for some diseases
- What does "promote" mean practically?
  - Could take inspiration from biomarker qualification group and FDA guidance
  - Could be good to have a central biobanks for testing biomarkers on specimens
- DNA banks of cancer research trial
  - Patients give consent to work on research on a wide number of topics
  - How to make this more visible and provide rules of access?
- Regulatory perspective
  - Different understanding of the term biomarker
  - Confirmed biomarkers is not easy to accomplish; act as companion diagnostics
  - Guidelines and supporting structures that provide access could be a topic ISC could contribute to

4.2 Improve (industry-independent) post-approval real world data collection

- Resonates with the TSC but concerns ISC; expensive but necessary to do
  - Many agencies interested in toxicity/side effects but not clinical effectiveness
    - Note: in EU, have conditional approval which requires this
  - In the UK, blocked by legal issues; patient identifiable data is tricky to deal with – don't need data per se but anonymised metrics
  - In the US, talk of pre-approval data; more pragmatic trials with real-world evidence, where investigational new drugs use extended to population not in clinical trials
    - Need to generate evidence in a way that is scalable: applicable to RD with small populations/numbers
- Draft paper recently written
  - International post-marketing surveillance registries satisfying regulatory agencies are needed → could be run by WHO, potential to promote continuity of such initiative
  - Promote registries to be independent of companies
    - Industry could put money into a pool rather than paying for single registries
  - Disease-specific registries needed
- Potential white paper with recommendations from the ISC

4.3 Promote RD health technology assessment (HTA) and health economics research

- Missed opportunities to use patient trial data for health economics research
  - Sticking point: economists want to translate this into measures of quality of life
    - There is nothing validated for children
    - Current measures of utility need to be improved
    - What sequence of tests to do to arrive at a decision of imposing a public health measure to improve quality of life?
  - Sequence of tests often leads to increase in cost of product
    - Assessment motivated by how much we are willing to pay to prevent one case of a disease
- Potential Task Force to work on a proposal
  - Develop needs for funding, projects
  - Focus: "problems of assessing utility in RD"
    - Currently proxy diseases as used
  - Global guidelines/general principles in health technology assessment
- Health economics vs ethics/moral assessment: care for the most vulnerable
  - In EU: newborn screening based on national decisions on possible cost-saving HTA
  - In UK: drugs funded come in at 10 times the cost per quality adjusted life year (QALY)
  - In US: reaching a level of advancement of a disease/disability, qualify for aide
- Additional information sources
  - ERNs for data
  - EUnetHTA for methodologies and identify what is adaptable to RD

4.4 Formulate and disseminate standards and guidelines to enable the goals of IRDiRC

Depending on discussion outcomes by the CA, the DSC and the TSC, the ISC could work on formulation and dissemination of standards and guidelines to enable IRDiRC goals.

5. Metrics

Diagnostics and therapeutics metrics are collected by the Scientific Secretariat (Sci Sec) and Orphanet.

- Therapies
  - Current metrics largely EU and US-centric
    - Would be nice to make this a truly global metric
    - Scope to integrate data from other countries, e.g. Japan
    - In Japan, exchange of information with Taiwan and Korean FDA recently started
  - A strong regulatory presence in IRDiRC needed to have greater insights

- Metrics on patients receiving diagnosis and treatment
  - Need a global collaboration with labs and clinicians
    - Overcomplicated by the need to have a temporal data of delay to diagnosis

- Problem on data collection: need to facilitate clinicians' work, not requiring double entry of data
- Patients may not want or have the right diagnosis on file
  - Stigma associated with RD in some societies – do not want such label
  - Reimbursement issues with off-label use
- Potential piloting in a country/region using electronic health records
  - E.g. in Finland or Sweden, may be possible
  - Question of coding could be a stumbling block
  - In UK, payment and treatment is not linked
  - Use of "sentinel" diseases to see if carrier rate corresponds to rate picked up or diagnosed
- Involvement of patient organisations
  - Demand for good coding and diagnostic criteria
  - Development of treatment will bring out additional patients, leading to improved diagnostic tests and/or more diagnosis
  - Patient collaboration with industry to enable tracking and collection of post-treatment data
- Model for identifying, tracking and treating RD patients
  - Based on WHO model for infectious diseases → identification/qualification by WHO to get approval for a drug
  - Approach Anders Olauson, Yann Le Cam with proposal for UN CoNGO for RD
  - Another model: Global Alliance for Chronic Diseases, supported by World Bank

6. Any other business

6.1 BBMRI-ERIC

- Data protection rules at European level
  - In past years, EU Directive with unequal transposition across member states (MS)
  - New EU General Data Protection Regulation (GDPR) will come into effect in 2018
  - Some sections left open as MS couldn't agree on all
- Challenges
  - Fear of inhibition of data sharing for research, in particular patient re-contact
  - Additional challenges with changes in technology and internet
- Opportunity
  - Proposal of Code of Conduct from BBMRI on the GDPR to be taken on by the MS
  - Suggest how research infrastructures be implemented while integrating EU GDPR
  - BBMRI reach out to other research projects but not IRDiRC
    - Excellent initiative but European-specific issue
    - Would the ISC recommend the CA to consider?
  - Code of Conduct to be sent to the EC for validation in May 2017

6.2 Feedback from the Task Forces

- Automatable Discovery and Access (ADA) Task Force
  - Previously Machine Readable Consent (MRC) Task Force
  - Presentation would be given by ADA Co-Chair at the Joint SC meeting
  - Essence: to understand under which conditions dataset can be coded as per consent given, and the possibility for automated access and data use
  - ADA-Matrix software available: concept to be applied for use in real life scenario
- Privacy-Preserving Record Linkage (PPRL) Task Force
  - Previously Participant Unique Identifiers (PUID) Task Force
  - Workshop in Paris in December 2016 to discuss ethical/legal and technical issues
  - Ethical/legal article will be drafted shortly
  - Technical group exploring EUPID model and will make recommendations

6.3 Scientific Secretariat

- The Sci Sec is supported on a limited funding which will end in September 2018
  - Collect and provide information on metrics and research activities
  - Provide logistics and communication assistance
- The ISC voiced its support that IRDiRC funders continue to the Sci Sec