EUCERD Joint Action

EUCERD JOINT ACTION WORKSHOP

ON

RARE DISEASE REGISTRATION

SUMMARY REPORT

13 November 2012

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EUCERD Joint Action Workshop Report on Rare Disease Registration

Introduction

The workshop was organised by the EUCERD Joint Action, within the scope of Work Package 8 ('Integration'). It was held in Luxembourg on 13th November 2012, ahead of the 6th EUCERD Meeting. It was attended by over thirty experts in the field of rare disease registration, representing the various stakeholder groups (see appendix i)

Aims of the Workshop

To provide a forum to share information to EUCERD members and interested parties on the following:

- Rare disease registration developments
- The state of the art of the various on-going registry projects and initiatives
- How to optimise cooperation between rare diseases (RD) registry plans

Specific questions to be addressed

- Is it possible to create multipurpose registries for epidemiology studies, research and the post-marketing surveillance of orphan medicinal products (OMP)?
- How can we optimise the use of European funding in the next budgetary period 2014-2020?
- How can the European cooperation between registries be strengthened?
- Could a European platform on RD registration be a useful tool for RD registration?
- Can the US experiences help us to define a new model?
- Several initiatives are currently running in the EU (EPIRARE, EJA, PARENT Joint Action, RD-CONNECT). A new transatlantic dimension on RD registration has been introduced by the IRDiRC. How can the EU work effectively with this new transatlantic dimension?

The workshop was planned to be the forum for these discussions and for the establishment of a EUCERD working group to co-operate with the European Commission (EC) on moving the outputs of the different projects (EPIRARE, PARENT Joint Action, IRDiRC/RD-Connect and the EBE-EuropaBio joint task force working group in the field of RD registries) into policy and integration with other RD initiatives. This working group will work with the Member States on the development and implementation of the various recommendations that will come through these various projects and which, in time, can achieve EUCERD recommendation status. The EUCERD working group will be developed within the context of the different projects to involve EUCERD members in the key recommendations and implementation on the development of RD registries. The EUCERD Joint Action will facilitate and support these discussions and developments as required.

Agenda

Session 1: Setting the context

Welcome from EJA coordinator, Kate Bushby (Workshop Chair)

Presentation 1: EPIRARE progress update, implications for MS registry developments, expectation and current plans (Domenica Taruscio)

Presentation 2: PARENT Joint Action: aims and objectives and how they will impact on planning for RD registry development. (Matic Meglic)

Presentation 3: IRDiRC and RD-Connect: linking international/US/Canadian etc., efforts in research with epidemiological registries, biobanks, and clinical trial planning (Kate Bushby on behalf of Hanns Lochmüller)

Presentation 4: Follow-up from EUCERD/EMA Workshop in October 2011, including the role of the EBE-EuropaBIO industry working group (Samantha Parker)

Presentation 5: Patient perspective on the structure and implementation of a European Rare Disease Registry Platform (Yann Le Cam/Monica Ensini)

Presentation 6: The European Commission initial vision on the future of the RD registration in the EU: an EU platform on a new period, the role of JRC, EU funding on RD registration 2014-2020 (Stefan Schreck, Antoni Montserrat, JRC)

Session 2: The Way Forward? (Chaired by Kate Bushby & Thomas Wagner)

Discussion session to include:

- The value of an EU platform for RD registration - Why? How? Where? Funding? (Stefan Schreck, Antoni Montserrat and Domenica Taruscio)
- Common data sets for international exchange of information – is this feasible? How will this fit with national plans, ERNs, future integration with research platforms and drug surveillance (Thomas Wagner and Domenica Taruscio)
- Quality criteria in rare diseases registration (ISCIII, Spain)
- Data protection – update on legislation changes and how the RD community can influence implementation for the benefit of patients (Monica Ensini)
- Establishment and mission of the EUCERD Registry Working Group – membership and aims. It is proposed the working group will ensure documents produced by EPIRARE and the other projects can be integrated (in terms of sources of production) and presented to the EUCERD. Ensure the implementation, practicality and coherence of the various recommendations and establish processes for monitoring their impact. Facilitate the provision and coherence of RD registries in the MS (discussion facilitated by Kate Bushby and Thomas Wagner with project leads).

Session 1 – Setting the Context

The overall aims and objectives of the workshop were presented by Kate Bushby (EJA coordinator and leader of WP 8 on Integration). These included the desire to share information on the state of the art of on-going activities across the RD registries field, and build on previous workshops – particularly the EUCERD-EMA workshop of October 2011, which involved all stakeholder groups - and position papers in order to take full advantage of RD registration developments. In addition, with the current complex situation of several projects operating simultaneously, an important aim of the workshop was to fully optimise co-operation between the different initiatives.
Key questions to be addressed were highlighted, including the feasibility of creating multipurpose registries for RD, which serve the needs of epidemiology, research and post marketing surveillance, and how EU funding in this area might be optimized. In addition, the group was asked to consider whether an EU platform for RD registries is feasible at this stage, and if so, what would it look like in the context of on-going and future international initiatives?
Appendix ii provides an oversight of the on-going projects in this field - the current status of these initiatives was further described in the presentations of the workshop.

Presentation 1: EPIRARE (Domenica Taruscio and Luciano Vittozzi)
EPIRARE is a wide-ranging project on Rare Disease registration, which is involved in several areas including the legal framework for RD registries, policy scenarios, common data sets and disease-specific data collection, data quality and validation, data source integration and an assessment of the needs of current registries. The project has organised a series of collaborative activities including workshops and international meetings, and has developed a strong association with other projects in the field.
A comprehensive survey of registry holders attracted 220 responses, which are being used to identify the shared needs and other characteristics of the registries, including their aims (which predominantly fall into three main categories, namely health services planning and epidemiology, clinical research, and treatment evaluation and monitoring). Additional work has concentrated on the legal basis of RD registries, with particular emphasis on the potential implications of the upcoming changes to the European data protection legislation.
EPIRARE has in addition defined a vision for a central platform to serve RD registries, which envisages a data repository for central collection of some data from different registries, to allow their networking and interoperability, as well as separate sections to support *ad hoc* collaborative projects. With the assumption that participation in the platform is voluntary, the platform would provide tools and resources to support the operation of on-going registries and the establishment of new ones, so that the advantages of participation will counterbalance the initial effort required to adapt to the platform. The central platform would be competent to deliver predefined outputs for funding organisations and the public and promote registration and networking amongst patients. Identified outputs refer to health services assessment and planning, information on natural history, genotype/ phenotype correlations and

the safety and effectiveness of orphan medicinal products (OMP). Further utility could be envisaged within the assessment of disease costs and the monitoring of screening programmes. The platform would also be able to develop systems for external quality assurance. Participation in the platform would be granted only to registries complying with data quality criteria.

The overall impact of such a platform would be to encourage the extension of registration activities and promote their quality, standardization and extended interoperability, thus positively impacting on clinical and epidemiological research; moreover, it will result in a better exploitation of data present in the registries for health services assessment and planning. It is likely, however, that the extension of registration to those diseases drawing little research interest may require additional incentives.

Work based on the existing registries is beginning to clarify the core data elements that might usefully be shared within a registry platform. Three types of datasets are being studied: a minimum set of common data elements to be collected by all registries, necessary to interlink registries and to selectively extract basic data; other purpose-specific sets of common data elements, selected depending on the predefined outputs to be achieved by the platform; and project-specific sets of data elements, which are agreed by registries collaborating in *ad hoc* studies and/or in research on specific diseases. EPIRARE will produce a number of final reports on the different parts of its workplan over the coming months.

Presentation 2: PARENT Joint Action (Matic Meglic)

The PARENT Joint Action is a relatively new initiative (it started in May 2012). Its main aim is to support Member States in setting up and running interoperable patient registries and improving secondary usage of these data (for public health and research) in a cross-border setting. To achieve this, PARENT will prepare supporting guidelines and tools (i.e. Registry of Registries, knowledge management platform) as well as provide policy advice on the implementation of the Cross-Border Healthcare Directive. Overall, these outputs will provide support for the development, governance, comparability and interoperability of registries. PARENT is not specific to RD, and intends to work closely with EPIRARE and other projects to identify previous work in the RD field. Various scenarios will be mapped, including scenarios on drugs and sharing of information to support the efforts of the Cross-Border Healthcare Directive, and secondly in the domain of research where a cross border platform (very similar to what has been envisaged in EPIRARE) could potentially support research in a number of different ways. Again, the definition of potential common data elements provides a high degree of coherence with the EPIRARE outputs, with the proposed benefits to registry holders of increased visibility and coherence with, for example, the Cross-Border Healthcare Directive, as well as access to and comparison with other registries.

(Discussion ensued on previous problems encountered in other disease specific meta registries which had pioneered this kind of initiative. One clear steer for new

initiatives would be to have a very structured approach to ownership, custodianship and consent.)

Presentation 3: RD-Connect/the International Experience (Kate Bushby)

Kate Bushby presented an overview of the RD-Connect project on behalf of the project co-ordinator Hanns Lochmüller and registries work package leader Domenica Taruscio. RD-Connect is an infrastructure project which was initiated on November 1st 2012, funded under the FP7 programme within the IRDiRC initiative. It has a wide-ranging remit to facilitate the sharing of data in many domains relative to RD research, predominantly in the theme of handling the growing amount of –omics data, initially in close collaboration with two other FP7 funded projects, Neuromics and EUrenOMICs. In the field of registries, the major projects within RD-Connect relate to the establishment of a databases and registries core implementation group (CIG) and the implementation of a common identifier across RD research including data collection and biomaterial repositories. In summary, clinical research networks such as Cystic Fibrosis, Huntington and neuromuscular have developed a 'new generation' of gene-specific patient databases that include genotype data plus detailed, quality-controlled phenotype data, and maintain the link with the patient within a secure ethical framework and in close collaboration with patient organisations. These registries have a broader range of clinical utility than locus-specific genetic databases (which are often anonymised with no link back to the patient for trial recruitment) or registries without genetic information (which cannot facilitate cohort selection for trials). These registries have facilitated numerous studies including clinical trials, generated significant commercial investment, and contributed to the development of novel therapies. RD-Connect will bring these leading registries together in a 'core implementation group' to establish best practice, build on existing expertise, and implement new standards and recommendations.

A unique feature of the RD-Connect project is its objective to develop a globally unique identifier for each RD patient (RD ID), to be associated with patient data and samples in all IRDiRC research projects. Full and irreversible anonymisation makes it impossible to link data on the same patient from different sources (such as biobanks, patient registries and -omics experimentation), as well as leading to possible duplications of the same data set. RD patients want and expect researchers to be able to exchange data, including personal and health-related data, in a responsible and secure way and with their consent. The RD ID will build on the frameworks developed for existing systems in cancer and autism research established by the International Cancer Genome Consortium (ICGC) and the National Database for Autism Research (NDAR), to create a unique coded identifier that can track patients across all the systems they are enrolled in (registries, biobanks, trials, research projects). RD-Connect is just in the first stages of its initiation, and is committed to work closely with the other projects in the RD registry field to provide a particular emphasis on research aspects and their integration across the field.

Presentation 4: EBE-EuropaBIO industry working group (Samantha Parker)
Samantha Parker presented the recently developed industry position paper (appendix iii) and conclusions of the EBE-EuropaBIO joint task force on rare diseases and orphan medicinal products, within which there is a specific registries working group. Similarly to other groups, the industry joint task force wants a consistent framework for registries, informed by a new industry survey of 21 registries from 10 companies. From the perspective of industry working in RD, registries often have a European or global scope, and the priorities relate to post-marketing surveillance and pharmacovigilance. A shared challenge is the lack of motivation on the part of clinicians to enter long term safety data. Most registries now offer online, secured access data collection. The quality of data is absolutely fundamental for registries providing safety and other information on orphan medicinal products. It is required that quality is ensured in terms of collecting complete, consistent and credible data. Industry presented different structures and processes that have been put in place to improve the quality of data, including the possibility of automatic validation of data as well as the requirement for monitoring and validation committees.
The industry working group agreed several key points which were, for the most part, highly consistent with the presentations of the other projects: the avoidance of fragmentation; the centralization or at least harmonization of data to allow comparability; the orientation of registries around diseases as opposed to an OMP. Elements of registries relating to pharmacovigilance and the fulfilment of ENCePP guidelines will need to reside with industry and have a specific requirement for quality control. There was strong support amongst the group for the concept of a public-private partnership to enhance sustainability. The emphasis on disease specific rather than drug specific registries and the concept of registries to be built as public-private partnerships were key components of the EMA/ EUCERD workshop in 2011 (appendix iv). Further follow-up is required to ensure that this message is consistent throughout the process of drug development and to encourage collaboration with on-going initiatives. Broadening of discussion in the process of drug development to include other parties (such as disease experts) as well as the regulators and industry, will be crucial.

Presentation 5: The Patient Perspective (Yann le Cam and Monica Ensini)
Yann le Cam and Monica Ensini presented the patient perspective on RD registries, based on the EURORDIS-NORD-CORD Joint Declaration on 10 Key Principles for Rare Diseases Registries (appendix v) and the results of the EPIRARE survey on registries addressed to patients across the EU. The ten common principles articulated by the joint international patient statement are crucial as this is the first joint international statement in the field of RD.

1. Patient registries should be a global priority in the field of RD so should be inherent in CEs, ERNs and should inform health policy and standards of care.

2. RD registries should encompass the widest geographical scope possible and should be worldwide.

3. RD patient registries should be centred on a disease or group of diseases not a treatment

4. Interoperability and harmonization should be consistently pursued.

5. Minimum Common Data Elements (CDE) should be consistently used in all RD patient registries.

6. RD patient registries should be linked with corresponding biobank data.

7. RD registries should include data reported by patients as well as data reported by professionals.

8. Public/ private partnerships should be encouraged to ensure sustainability of RD patient registries.

9. Patients should be equally involved with other stakeholders in the governance of RD patient registries at all levels- from content, ethics, utilization of data, partnerships with health professionals etc.

10. RD patient registries should be key instruments in building and empowering patient communities.

As can be seen, the core principles articulated by the patient groups are highly consistent with the outcomes of the other groups and projects presented. In addition, the results of the patient survey carried out by EURORDIS within the framework of the EPIRARE project, encompassing more than 3000 responses, were presented by Monica Ensini. (More responses are anticipated over the next two or three months.) Patients give the highest priority to healthcare and social services planning as a deliverable of RD registries, together with the description of the disease and the monitoring of the efficacy of treatment, which is in contrast to the main objectives of existing RD registries. Patients would like to make decisions regarding access to data, permitting access to public institutions and authorities. They also express a desire to participate in defining the main objectives of registries. They believe that the EC, national authorities and research institutions should finance registries. In a unanimous finding, 96% of participants supported common legislation for registries, and 97% believed that there should be a common portal/platform/hub for RD registries in Europe. In contrast to the stated and overwhelming wish of patient organisations to be involved in governance, only a minority of registries currently have patients as part of their governing boards.

Presentation 6: The European Commission (Antoni Montserrat)

Antoni Montserrat presented, on behalf of the EC, a vision for the way forward for RD registries. There is a clear and longstanding commitment to RD registries illustrated by approximately €60 million of funding over the FP6 and 7 programmes and through DG SANCO. In addition, the 'umbrella' projects presented at this workshop also illustrates the commitment of the EU to this area. The projects, as

presented at the workshop, suggest a high level of enthusiasm for a RD platform to be established at EU level, and this has stimulated the discussion between DG SANCO and the Joint Research Centre (JRC, a part of the European Commission based in Ispra in Italy: see appendix vi for JRC work on the co-ordination of national cancer registries) for there to be a call in the 2013 work programme for a provisionally titled "EU Rare Disease Registration Repository Platform". The vision of such an EU platform is inspired by discussions over the last two years as well as forthcoming IRDiRC policies, and mirrors the NIH Global Rare Diseases Patient Registry and Data Repository. The feasibility of such a repository could be explored during an initial funding period at the JRC and subsequently funding could be sought via a mechanism to support the platform as an ERIC (European Research Infrastructure Consortium). This would need to be aligned with the Horizon 2020 programme as well as the new 'Health for Growth' plans.

Session 2: The Way Forward?

A lively debate ensued with contributions from all of the workshop participants. It was emphasised that patients welcome the EC's overall plan to create an EU platform, viewing it as potentially a very important structural initiative with strong long-term commitment and funding. However, some participants expressed concern over the fact that the JRC has little specific experience in the field of RD, although it was emphasised that there are important precedents for the collation of registry efforts from the infectious disease and cancer fields. The push for a hub for RD registries and the alignment of the different projects in this regard was perceived to be very positive.

Concerns were expressed, however, as to whether there were sufficient data on which to base such a development at this stage, so that calling for funding in 2013 was perhaps premature. Some participants felt that the proposals were not currently realistic and expectations should be lowered, pointing out that even having open access to a fully comprehensive Registry of Registries would constitute significant progress in itself. Concerns were raised about the realistic scope of any common dataset for multipurpose registries, with the fear this would ultimately be limited to demographic data plus a robust diagnosis. It was emphasised that the lack of incentives for medical personnel to enter data is having a profound impact on the availability and reimbursement of OMP, and this inertia should be addressed before such an ambitious project begins. Some participants felt it was important that the various component parts of the platform should be clearly defined before the EU begins to build the infrastructure. Others had questions regarding the ownership of existing registries – would the EU platform seek ownership of these, or custodianship, and would registries have the right to refuse to participate?

It was emphasised that the platform would be a secondary data collection point, (with the primary point being the country or disease-specific registries), and it is envisaged as an open platform, to allow data to be entered and distributed in any format required. Surveillance networks for rare diseases (e.g. EUROCAT, SCPE) cautioned that they would not fit directly into the platform, but were assured this would be taken into account in the planning process. Several participants voiced

concerns over the funding of such a structure – how would the current and future funding for individual registries and networks be impacted? The need to embed quality assurance procedures at every stage, from data collection to analysis, was agreed – the importance of standardized coding was emphasised here, with the aim that Orphanet codes will be used in conjunction with those from ICD-10, to provide a set of codes for rare diseases in ICD-11 (appendix vii).
Given the JRC's relative inexperience in RD, the EUCERD was suggested as the key advisory body for the development of this platform/hub. In subsequent discussion at the workshop and also at the following EUCERD plenary session, several **action points** were therefore proposed:

- The EUCERD should become the main advisory body to the JRC on the topic of developing and implementing a European RD Registration Platform

- Next steps for registries discussions :

    - Subsequent meetings of the group should ideally be chaired jointly by the EUCERD JA, EPIRARE and PARENT JA coordinators (with flexibility of the relative projects to fund the relevant work)

    - Membership is to include a broad range of experts, including those attached to current academic networks and projects (e.g. EPIRARE, RD-CONNECT, PARENT JA), Member States' representatives, EURORDIS patient representatives, industry representatives, the European Medicines Agency (EMA) and the JRC.

    - At least two follow-up meetings will be organised for 2013, to address the key issues and components of the proposed EU platform for rare diseases. Representatives from the JRC will be included in discussions within an appropriate timeframe

    - The workshops will work towards the generation of a set of EUCERD Recommendations on key principles for the registration of RD patients

- The initial workshop will advise the scope of the recommendations, which are likely to be based on points of convergence from the outcomes of this EJA Workshop 2012, the EUCERD-EMA Workshop 2011, the Joint Declaration of ten Principles by EURORDIS-NORD-CORD and the Industry EBE-EuropaBio JTF Position Paper, in the context of the EPIRARE project, Parent and IRDiRC/ RD-Connect. A concept paper will be produced for discussion at the January workshop with a timescale for EUCERD adoption to be agreed

- This discussion will also address the requirements of member states, ERNs and academic networks, and post marketing surveillance. Areas of attention will include the following:
    - Advice and facilitation of the development of the platform to support RD registration
    - The content of the proposed platform
    - Leadership discussions and governance
    - Ownership, custodianship and consent
    - Interaction with existing structures at national and disease specific level, to foster the MS initiatives which are also on-going within the context of national plans for RD
    - Working alongside other projects and initiatives including the prospects for RD ERNs.

APPENDIX

i) Participant List

Verónica Alonso	Institute of Rare Diseases Research, ISCIII Spain
Ségolène Aymé	INSERM, France
Kate Bushby	Newcastle University, UK
Silvia Comis	Novartis
Patrice Dosquet	National Directorate for Health, France
Monica Ensini	EURORDIS
Ester Garne	Hospital Lillebaelt, Kolding, Denmark
Gemma Gatta	Istituto Nazionale dei tumori, Italy
Karolina Hanslik	DG SANCO
Carla Hollack	University of Amsterdam
Helena Kääriäinen	National Institute for Health and Welfare,
Paul Landais	Centre Hospitalier Universitaire de Nimes
Yann Le Cam	EURORDIS
Stephen Lynn	Newcastle University, UK
Flaminia Macchia	EURORDIS
Georgios Margetidis	EAHC
Matic Meglic	National Institute of Public Health, Slovenia; PARENT JA
Anil Mehta	University of Dundee
Antoni Montserrat	DG SANCO
Christel Nourissier	EURORDIS
Samantha Parker	Orphan Europe Recordati
Vinciane Pirard	Genzyme
Bianca Pizzera	EURORDIS
Gábor Pogány	HUFERDIS
Charlotte Rodwell	INSERM, France
Steffan Shreck	DG SANCO
Raimund Sterz	Shire
Domenica Taruscio	Centro Nazionale Malattie Rare, ISS
Luciano Vittozzi	Centro Nazionale Malattie Rare, ISS
Thomas Wagner	Goethe University Hospital Frankfurt
Jarek Waligora	DG SANCO
Martine Zimmerman	Alexion

Apologies for Absence – Hanns Lochmüller, Manuel Posada, Bruno Sepodes and Wills Hughes-Wilson

Documents Circulated to Participants

ii) Overview of Current Registry Activities

iii) Position paper of Joint EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicines

iv) EUCERD/EMA Workshop Report (4th October 2011): Towards a Public-Private Partnership for Registries in the Field of Rare Diseases

v) EURORDIS/NORD/CORD Joint Declaration on the 10 Key Principles for Rare Disease Patient Registries

vi) JRC proposal for the European Network of Cancer Registries (ENCR) to develop a Cancer Information System for Europe (presented September 2012)

vii) EUCERD JA/EuroGentest Workshop Summary Report (27th-28th September 2012): The Cross-Referencing of Terminologies

viii) Case Study provided by Dr Anil Mehta

ix) Registry Types and Data Access Models