European Union Committee of Experts on Rare Diseases

EUCERD/EMA WORKSHOP REPORT

Towards a public-private partnership for registries in the field of rare diseases

London, 4 October 2011

INTRODUCTION

This workshop was organised in the context of the ongoing scientific activities of the EU Committee of Experts on Rare Diseases (EUCERD) dedicated to registries in the field of rare diseases.

It builds on:

- The Rare Diseases Task Force Report "Patient registries in the field of rare diseases", based on outcomes of the 2008 RDTF workshop on this field, updated in 2011 http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf
- The report in preparation on the "Creation of a mechanism for the exchange of knowledge between Member States and European authorities on the clinical added-value of orphan drugs (CAVOD)"
- The Orphanet Report Series "Disease registries in Europe" http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

It aimed at establishing the principles for public/private partnerships for the registration of patient data for diseases for which treatment options are in development or already developed.

The objectives were:

- to foster the establishment of quality data repositories
  - to ease and speed up clinical research in the field of RD and OD
  - to provide data to regulatory bodies, to bodies in charge of assessing the CAVOD and to reimbursement bodies
- to avoid any duplication of efforts so as not to waste resources and expertise in a field where resources are scarce; and
- to provide unified sources of data for diseases where several products are available, the aim being to favour disease registries over product registries.

ABSTRACT

On 4 October 2011, over 60 participants representing all stakeholder groups met at the European Medicines Agency (EMA) in London to discuss the subject of public-private partnering for rare disease registries. The workshop was organised by the European Union Committee of Experts on Rare Diseases (EUCERD) with the support of the EMA. It was the fruit of previous work on the subject of registries conducted by the EC Rare Diseases Task Force (RDTF) and Scientific Secretariat of the RDTF/EUCERD, including the RDTF reports on "Patient registries in the field of rare diseases" (2008/2011) and "Health indicators for rare diseases (2010, 2011)", as well as the Orphanet Report "Disease registries in Europe" (2011).

The objectives were to avoid the duplication of work in this field, to maximise the output, to discuss sustainability issues. The focus was on the burning issue of organising registries by disease and not longer by product, to better deal with the requests of regulators and payers to access data for the assessment of the clinical utility of new drugs for which registers are excellent source.

A consensus was established amongst the gathered stakeholders that it is imperative that fragmentation of data sources be avoided: public/private partnership is necessary and, although it cannot be made mandatory, it can be suggested by the EMA to companies that they should consider joining existing registration systems or establishing a new one in partnership with an academic team and patient organisations. It was also suggested that technical and methodological support be provided as should rules of conduct for such partnerships. Regulatory frameworks and standards must be assured. Open-access to data should be promoted. Management by academia was identified as a solution to ensuring long term sustainability with the financial support of the regulatory bodies and of the payers, jointly with the concerned companies.

Finally, it was proposed that a small working group of stakeholders be established to work on the next steps, in order to move forward and concentrate on future opportunities (i.e. HTA requirements for MS). Liaison with CAVOD plans should be assured with the EUCERD as right forum to discuss issues of clinical utility. The potential opportunities and/or threats posed by the revision of the data protection legislation must also be carefully considered.

The outcomes of this workshop will serve as the basis for the elaboration of a EUCERD recommendation in this field.

The full public report of this meeting can be found here :

http://www.eucerd.eu/upload/file/Meeting/EUCERD/EUCERDWorkshopRegistries2011.pdf

WORKSHOP REPORT

Session 1: Overview of the current situation and identified issues for discussion between stakeholders

1. State of the art of disease and product registries in the EU – *Ségolène Aymé*

Ségolène Aymé presented an overview of the current situation in the field of disease and product registries for rare diseases in the EU. It was highlighted that registries are a crucial element in the R & D process and that they are often reliant on academically initiated registries with various forms of funding, e.g. government, patient organisations etc. Registries are currently supported at EU level for both research and public health purposes: recently two important initiatives have been funded by the EC, the EPIRAREEPIRARE project and the PARENT joint action. The EUCERD has also issued a number of reports on this subject: "Patient registries in the field of RD" (2008, 2011), "Health indicators for rare diseases I: Conceptual framework and development of indicators from existing sources" (2010) and "Health indicators for rare diseases II: Conceptual framework for monitoring quality of care" (2011). Orphanet also provides a list of "Disease registries in Europe" (2011) in the Orphanet Report Series. There also exists a useful guide by N. Dreyer and R. Glicklich entitled "Evaluating patient outcomes: A user guide" (2nd edition, 2010). The geographic distribution of the 569 registries in the Orphanet database was then presented, as were their breakdown by medical area (i.e. the majority of registries are in the fields of neurology and oncology). Most registries are national and academically governed.

A number of common issues were highlighted: the scarcity of cases and complexity of diseases imposes a large geographical, transnational coverage; resources are often limited and funding is for limited time periods only; resources can be wasted in developing tools for each registry and in duplicating efforts; data can be wasted as clinicians are not epidemiologists; expertise can be wasted; and opportunities can be wasted due to the presence of both disease and drug registries.

The objectives in the field of registries for the collection of data on orphan drugs and diseases pre- and post-drug development were underlined: the establishment of quality data repositories should be fostered to ease and speed up clinical research, to provide data to regulatory and reimbursement bodies; duplication of efforts should be avoided so as to not waste resources and expertise; unified sources of data should be provided for diseases where several products are available, and advantage should be taken of technology to share data repositories.

2. Issues identified: Point of view of academic registry leaders – *Carla Hollak*

Carla Hollak presented the issues identified in this field by the academic registry leaders present at the workshop: it was highlighted that registries have many different uses (public health, health service research, health promotion, patient care, clinical research and regulatory purposes) and that the purpose of a registry must be clarified when establishing it. In the case of registries for regulatory purposes, complete follow-up data is indispensable. It was highlighted that, since the advent of the European Orphan Medicinal Products Regulation in 2000, 40% of the drugs granted authorisqation have been gratnted authorisation under "Exceptional Circumstances", which implies that there is a lack of data: registries should capture long-term outcomes data. The example of enzyme replacement therapies for Fabry disease was given: two enzymes were authorised in the EU in 2001, both under exceptional circumstances, which led to the establishment of two post-marketing registries. The International Collaborative Gaucher Group (ICGG) Gaucher Registry was launched in 1991 and has data from over 5800 patients collected by physicians in 62 countries. This type of registry can be used to determine the long term benefit of the drug, whom to treat and when, when to stop treatment, effect of antibodies and cost effectiveness. A number of other products for Gaucher disease have been developed, presenting a risk of further multiplication of efforts and registries. With the increasing number of drugs for Gaucher disease, the launch of a separate drug registry as part of post-marketing commitments may become a reality. This hampers comparison of drugs, leads to fragmentation of data and thus should be avoided[1].

It is important to recall the purpose of registries for the evaluation of orphan drugs: they permit the evaluation of the appropriate use of all treatments, cost-effectiveness (comparison with no treatment/other treatments), the safety/side-effects, and the long-term complications. The requirements for the evaluation of orphan drugs on these registries are as follows: the assessment of patients, not drugs; an analysis independent from industry, and complete and detailed data on diagnosis, natural course, clinically meaningful outcome (i.e., quality of life), safety and side effects, factors that may influence outcome, and long term complications.

Possible models for rare disease registries were described: in the first model, registries are run by academia, with industry providing data to report to the EMA on long-term outcomes (in this case, companies request data from the academic registries, an independent board determines whether the request is feasible; and, if agreed, data is provided to industry which then analyses the data, and payment is made to a central fund which is used to sustain the registry). In the second model the registry is run by academia; and the industry and academia report to the EMA on long-term outcomes (the registry being set up before market authorisation as a disease registry, and an independent board discusses outcomes data with EMA and industry, the submission of treatment data to the registry is mandatory, academia analyses the effectiveness

[1] N.B., It may be important to note that one of the products has been able to build up its market authorisation from "Exceptional Circumstances" to a full authorisation based on this follow-up work to gather long-term outcomes, highlighting the contribution that a disease registry can make to gathering and consolidating long-term outcomes data.

data, industry analyses the safety data; and payment is made by government and industry to a central fund, which is used to sustain the registry).

Data in registries can vary in quality and completeness, mostly due to a lack of time on the part of physicians. It should be considered how to improve this situation: perhaps obliging physicians to report for costly drugs is an option.

3. Point of view of Industry – *Samantha Parker*

Samantha Parker presented the issues identified by the EUCERD industry representatives and members of the EBE-EuropaBio Joint Task Force on RD and OD. For this workshop, a short survey was sent to members of the joint EBE-EuropaBio group: Companies involved in the research and development of orphan drugs, which were running 25 registries, were identified (this accounts for over 50% of industry-run registries for orphan drug post marketing surveillance). The majority were European or global registries. The primary goal of these registries is shaped by post-marketing obligations: i.e., post-marketing surveillance for regulatory purposes. The secondary objective of these registries is to carry out a longitudinal survey. Just over 50% the registry is not the only registry in the particular disease area, and the study director is from industry in most cases. One major consideration for industry is research ethics committees: a significant quantity of work is involved to gain ethical approval in all MS, either country-by-country or centre-by-centre. In addition, post-marketing evaluation is interpreted in some countries as a phase IV trial, with the specific requirements that such a classification entails. Patients whose data is entered into an academically governed registry would need to re-consent if data is to be shared with industry

Other issues in this area include off-label drug use, and the current revision of data protection legislation at EU level. In terms of data access, rules are needed on data transfer, publications, ownership and data access (i.e., if a model where one registry is managed by academia is in place, it must be ensured that the specific drug data of Company A is not available to Company B, in the case of there being two companies with a different drug for a single rare disease). The question of how much data should be collected (drug registries record less data typically than disease registries) was raised, as well as at what and whose cost, and who has the responsibility for the quality assurance of this data. In terms of funding and sustainability, disease registries are dependent on the commitment of those who provide the financing, and industry registries have unsustainable high costs. In this scope, collaboration makes sense, but post-marketing commitments are typically for a much longer period than the current funding provided by the EC for disease registries. Industry and academic partners need to plan for the worst case scenario. Another possibility pointed out was that of patient self-populated data entry, which could be a mechanism for entering adverse events, whilst empowering patients.

In conclusion, there is a need for a communication from the EMA/EUCERD to stress the need for academics and ethical committee members to support public/private partnerships in the development of registries and collaboration for post-marketing surveillance. Guidelines on the requirements for research ethics committees in each member state for non-interventional post-marketing surveillance and the off-label use of drugs should also be created. A discussion

on patient self-populated data entry should be initiated. The discussions around the creation of the so-called "CAVOD" process also imply the set-up of registries before marketing authorisation and the collection of HTA data in such a model.

4. Point of view of patient representatives – *Fabrizia Bignami*

Fabrizia Bignami gave a view of the issues identified by patient representatives in the area. Overall, there is optimism concerning the developments for RD registries, with big pharma entering the field, many innovative products and a growing RD patient community. However it was highlighted that only minority of patients has a good understanding of registries. Patients do not want resources to be squandered in this field through the creation of a new registry for each new product, indeed this could increase distrust among patients.

Patients invite all stakeholders and in particular policy makers and regulators to create the conditions to allow the creation of disease registries that would also serve the post- marketing requirements and maintain high standards for quality. This would be an appropriate solution now that effectiveness and safety data will be more frequently requested by EU and National Competent Authorities (NCA). Logically these registries could be built and managed by the disease specific centres of expertise (or specialised centres) and data shared across EU networks when they exist.

Patients wish to be involved and can concretely contribute to the definition of the content and specific purposes of the registry (evaluation of quality of life and quality of care), governance (definition of best practices), preparation of the general information for patients and the public in general, giving feedback on the scope of the registry and the use of data, preparation of specific information to be provided to patients to be registered prior to their consent, and recruitment of patients and medical experts.

Three strategies that RD patients consider highly promising to improve use of the limited available resources and to accelerate progress are: (1) the organisation and funding of data collection at national level (included in the RD National Plans), (2) the constitution of a EU registry platform offering services for existing and new registries and linking EU wide important data on rare diseases (EPIRARE), (3) the linkage of registry data to other research resources such as biological samples and –omics data (FP7 RD call). These RD specific strategies should take advantage of existing international initiatives ensuring visibility of registries respecting high quality standards (EUCTR, ENCePP). In all cases the intent is to share data and other resources taking into consideration the needs of all stakeholders including patients who expect these initiatives to involve them in a concrete way.

In particular, in order to increase public trust and, the awareness of registries,as well as to increase long-term financial support, patients expect registries to provide transparent information about the use of the data and results of the research performed with these data. In several cases patient organisations could directly benefit from the analysis of data contained in registries, (e.g. to evaluate the benefits obtained by research to which they have financially contributed and which could be useful to support their advocacy actions). However if the

currently diverging national legislations do not enable a real exchange of information and samples while maintaining the privacy and rights of the citizen, neither of these strategies nor other networks of registries and biobanks will achieve their objectives, as RD research requires and implies cross-border exchanges and requires a real collaboration between all interested parties. Patients are ready to contribute to these efforts.

In conclusion, rare disease patient registries must respect high quality standards to be able to contribute to research and public healthcare. They should be embedded in public health institutions as infrastructures rather than projects (e.g. included in RD National Plans), should be financially sustained by public funds but with an expected and regulated contribution from private stakeholders who would benefit from rare disease product registries for their product development and surveillance, and lastly should include patients in their governance bodies and involve them in their communication/ transparency policies.

5. Point of view of regulatory agencies – *Stella Blackburn*

Stella Blackburn from the EMA presented the issues and opportunities from the point of view of the regulatory agencies. The challenges of pharmacovigilance were exposed: it must be determined what is due to the drug, what is due to the person and what is due to the disease itself. In the field of rare diseases, the challenge is more complex due to an often very limited knowledge of the safety profile at authorisation, an often deficient knowledge of the epidemiology of the disease, the small patient population per country, and the fact that patients may be treated with multiple drugs.

In terms of opportunities, registries for orphan drug pharmacovigilance provide possibly the only practical way of collecting information on patients with rare diseases. They can enable the collection of information on the epidemiology of the disease, they can enable the gathering of knowledge on the short term safety profile of the medicine, they can give long term safety and efficacy data, and they can compare different medicines used to treat the disease. However, they may need to collect information from multiple centres and may need international cooperation to achieve critical mass.

The ENCePP, an EMA-led project to bring together expertise in the fields of pharmacoepidemiology and pharmacovigilance scattered across Europe, was presented. The aim of the project is to facilitate high quality, independent and multi-centre post authorisation studies in order to strengthen the post-authorisation monitoring of medicinal products in Europe. In 2011, 93 partner organisations from 17 EEA countries are involved, including 13 networks and 17 datasources. The ENCePP database (www.encepp.eu) offers information on available sources of expertise and research experience across Europe, both for study sponsors and researchers seeking to identify collaborations for the conduct of specific pharmacoepidemiology and pharmacovigilance studies in Europe. The data is available to the general public.

In conclusion, RD pharmacovigilance present many challenges: registries are a valuable resource in orphan drug pharmacovigilance and risk management, and the EMA is trying to

increase research capabilities in Europe through ENCePP. Above all, collaboration in this field is necessary.

6. General discussion

During the discussion it was highlighted that if the EMA cannot oblige industry to collaborate with existing academic registries, it can suggest, at the time of scientific advice, to Industry to think in terms of collaboration with academia and patient organisations when thinking of establishing data collection or a data collection mechanism. In relation to the ENCePP project, it was highlighted that a code of conduct has been developed in the scope of this activity, which should be promoted more broadly. The opinion was expressed that national drug agencies should (contribute to the) fund(ing of) disease registries, as these are only tools allowing comparisons between drugs. Overall, it was highlighted that the expectations of diverse stakeholders have to be reconciled to avoid duplication of efforts, and to respond to the societal obligation of answering questions concerning efficacy and safety in the field of orphan drugs.

Session 2: Usefulness of registries for regulatory purposes: Opportunities and challenges

1. Overview of the issues – *Nancy Dreyer*

Nancy Dreyer, co-editor of "Evaluating patient outcomes: A user guide" presented an overview of the issues concerning the usefulness of registries for regulatory purposes. A number of opportunities presented by rare diseases were highlighted: indeed, inherited conditions (as is the case for many rare diseases) are easier to study than sporadic outbreaks, as it is easier to identify those who provide treatment, it is easier and less costly to set up structures for case identification and recruitment, and it is easier to build a community of interested supporters. In order to gather data on natural history of the disease, there are few inclusion/exclusion criteria, so there is a wide range of spectrum of age, severity and co-morbidities. Treatment effectiveness and safety can be potentially monitored through paths to diagnosis, real-world patterns of use and adherence, variations in treatments, alternative and adjunct/complementary therapies or treatments, and sub-groups can be used to identify treatment heterogeneity. There is also potential for long-term follow-up for delayed benefits/risks.

Challenges to design, analysis and interpretation of registries were highlighted: the focus needs to be chosen and the needed data identified; meaningful comparisons should be made (i.e. untreated patients, historical data or comparators from other regions, treatment sequencing and presumed time windows for risks and benefits); differential follow-up should be made possible; and mechanisms for reporting adverse events should be set up to allow these to be signalled by patients and/or physicians, either by stimulated or passive reporting.

Key elements for successful collaborations include: a flexible and pragmatic approach, respected leaders who can unite various parties and drive consensus, explicit and measurable expectations of all partners, and governance structures and means for dispute resolution. Operational challenges for registries are diverse: regulatory and logistical challenges, especially for multi-country studies; recruitment and retention; management of safety data when a MA holder is a sponsor; data quality and completeness, especially patient-reported outcomes, and the evolving focus of research as it progresses, requiring new data elements. Observational studies also face a range of challenges in the interpretation of safety and effectiveness data, i.e., representativeness of patients and clinicians, availability of comparable data for all treatments and treatment questions, and the validity of conclusions (e.g. bias and confounding, especially in terms of selection bias), missing and incomplete data, and measurement error).

In conclusion, the key elements for success for a registry for regulatory purposes are as follows: to generate and deliver value to all partners, to build a pragmatic and flexible process that will allow for changes in the registry over time, inflexibility in terms of management and quality, and the ability to identify a strong, respected leadership who can drive consensus.

2. Experiences from rheumatology registers and outcomes of a Swedish EU presidency project – *Nils Feltelius*

Sweden has experience in the domain of quality registries dating to the 1990s: today there are about 90 registries and 5 competence centres that receive national, central funding. However, there are substantial differences between registries in terms of coverage and performance. The government is currently aiming to improve the performance of such registries. One initiative in the field, the "Assessing Drug Effectiveness Project" of the 2009 Swedish presidency, aimed to explore ways to network effectively between registries at European level. Registry data provides information to support clinical decision making, to assess efficacy and safety, to assess cost-effectiveness, to carry out research and to make comparisons. The example of the ARTIS biologics registry in the field of rheumatology was exposed: out of 60,000 patients with rheumatoid arthritis (RA), 20'000 patients treated with biologics are registered. RA care is managed by rheumatologists, mainly in a hospital environment. The possibility to link registry data (i.e. sick leave records, disability pension records etc.) was then shown via the existence of personal ID numbers in Sweden, which, in turn, allows for the assessment of drug efficacy. An example of an anti-TNF treatment safety assessment was given, which showed an increase in the risk of TB in RA patients after TNF blockade, as well as an increased risk of lymphomas, the latter, however, explained by disease activity and not by treatment. During this work on the Swedish biologics ARTIS registry, a number of problems were identified and dealt with: data quality, compliance and endurance, the observational setting, financing, data ownership and ethics.

It was highlighted that registries are basically intended to improve knowledge and quality, not tosupervise. It should be borne in mind that only professional groups can build and maintain registries that produce good, valid outcomes data. Patient data can be aggregated and used in different ways and on different levels in the health care system, but they should be above all clinically useful.

As previously cited, current efforts to improve registries, include national financing, increased technical and methodological support, increased support to external research groups, clarified rules of conduct regarding cooperation between registries and industry, and also a national technical IT infrastructure and common, regulatory frameworks and standards. Specific challenges in this area include balancing central coordination whilst keeping local professionals engaged, and balancing open access and integrity.

More detail was given on the Assessing Drug Effectiveness (SPADE) project undertaken during the Swedish EU Presidency: this project was a survey of selected registry networks in the EU (Eurofever, EUTOS and multiple sclerosis), which included a focus on RD and from which an in-depth analysis of ethical and management aspects was conducted, alongside a comparative survey of some national rheumatology registries. The survey concentrated on data content, data handling and quality control, data analysis, safety and adverse events reporting, ethics and legal aspects, communication and risk management, and finally financing and management. The results showed that data was often not solicited for reasons of drop out/health economy issues, and that coding of diseases is not harmonised. However, regulation of data is formally organised.

The study has permitted the identification of various success factors (cooperation and collaboration between stakeholders, bottom-up approaches, the promotion of research, patient centred focus, improvement of education/clinical skills, access to own data/relevant feedback, standardised diagnostic procedures) and hurdles (ethics application, funding for local monitoring, regulatory problems, information/work overload, and national competition).

In conclusion, the following recommendations were made: bottom-up approaches when setting up and running registries are advisable, patient integrity must be safe-guarded, the involvement of industry should be transparently regulated, research opportunities are an important driving force, and advantage should be taken of new regulations.

3. Roundtable of stakeholders

Hanns Lochmüller: Academic registry perspective

Hanns Lochmüller described the experience of the Treat-NMD registries, which is a coordinated group of more than 50 national and international registries for a variety ofneuromuscular disorders such as Duchenne Muscular Dystrophy, in 'preparing the ground' for future clinical trials, even if there are not many drugs currently available. Solid registries can ensure that there is an equal base line of good clinical care to ensure that all patients start from the same level. Registries are also key elements for the recruitment of patients and for working on feasibility studies. Academics are in favour of disease registries over drug registries for these reasons. Sustainability is a key issue that needs to be addressed.

Barbara Valenta Singer: Industry perspective

Barbara Valenta Singer highlighted that there are good registries for non-interventional studies, but that post-MA studies are often without any guiding framework. If we want to provide the best data for regulators, we have to think in broader terms. We should take other regions into consideration, but the question is how to obtain a broaderrange of data if the hurdles at EU-level cannot be jumped. For regulatory purposes we need to discard the word 'registry' because registries collect all types of data, while for regulatory purposes, very specific data is needed and trying to cover all the data needed for these purposes in disease registries may be too great a task. Registries are the back-bone for the collection of future data and pragmatism is key in this area. We need a better definition of registries, perhaps to redefine them as non-interventional studies. Also, registries require better PR so that it is understood what they aim to do and how they can serve different purposes.

Stella Blackburn: Regulatory perspective

All stakeholders want registries, see their utility in the field of RD, but stakeholders come to the area with different angles, interests and needs. The main challenge is how to cooperate. Data protection remains a significant issue in this area and can prove a barrier to sharing and cooperation. Although it would be ideal to have one unique registry by disease, a more

pragmatic solution could be a federated system for subsets of data, with adequate interoperability and coding.

4. General discussion

General discussion on the focus of this session centred on examples where cooperation has worked in the field between public and private partners, and how to improve the quantity and quality of registered data.

The European CF registry, established from different roots and different national registries managed to define a minimal dataset and data quality rules, plus a governance structure in order to improve the registry without jeopardising national data sets. It was also highlighted that feedback and giving data back to the registering site is important for the improvement of clinical practice.

It was highlighted that there are now technological possibilities to allow patients to register their own data, especially when it comes to data on quality of life, and input on adjunct therapies or treatment. Patient organisations can play an important role in raising patients' awareness of their possible input. Although this will possibly increase the possibility of capturing more data, patients need internet access in order to do this – which is not always the case – and data has to be controlled for quality.

Doubts were expressed whether it was sufficient to rely on goodwill/shared objectives to ensure that data is entered into registries; it was suggested that making registration of data obligatory for orphan drug treatments could be an option.

As well as focussing on incentives for data registration, the problems of "disincentives" were cited; as professionals are sometimes blocked in their career progression when they work on RD.

Industry expressed their willingness to work with academics, highlighting that leadership is the key to success, and that study nurses can help improve the quality of data. Using existing academic registries may be just as costly, or maybe more; but they will have longevity, unlike industry-run post-marketing studies, and academics have the expertise in the field of registries that should be used. However, motivations must be clear and transparent, so not as to lose patient trust, and ethics must be a key consideration. Patients must be assured of confidentiality and be informed of how they can contribute.

The example of data submitted by patients for the PROTECT project on drug-use during pregnancy was given as a successful example of patient-submitted data. Data was compared with physician-submitted aggregated data and it was agreed that the possibility of obtaining research-quality data from patients could be a real boost to pharmacovigilance as patients are better at submitting data on adherence to medication and complementary drug use. The issue of language should also be considered in terms of consolidation of patient-submitted data, especially in free-text fields.

It was suggested that perhaps our immediate focus should be limited if we wish to obtain robust data on long-term outcomes.

Session 3: EC Initiatives to provide high quality and unified sources of data to all stakeholders

At the start of the session, Antoni Montserrat, Policy Officer for Rare Diseases and Neurodevelopment Disorders at the European Commission DG Sanco highlighted that EU funding has been provided for both research and public health registries in the field of rare diseases, covering 10% of current/past registries. The Commission Communication and Council Recommendation on RD specifically mentions RD registries, and they will be of particular focus in the context of National Plans or Strategies for RD which should be adopted before 2013, and the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare (also known as the Cross-Border Healthcare Directive.

Four important initiatives exist in the field to improve registries in the field of rare diseases: the EPIRARE project, the PARENT joint action, the EUCERD joint action and the International Rare Disease Research Consortium (IRDiRC). These initiatives are complementary to one another and should serve as instruments in gathering together efforts in the field in establishing common data sets, quality criteria and a political framework.

1. The Joint Action on Patient Registries (PARENT) perspective – Matic Meglic

The aim of the proposed Joint Action (JA) PARENT is to rationalise and harmonise the development and governance of patient registries, to enable the analysis of secondary data for public health and research purposes. The main goals of the JA are to support MS in developing comparable and coherent patient registries in fields where this need has been identified (e.g. chronic diseases, rare diseases, medical technology), and to support MS states in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy and effectiveness of health technologies. The JA will thus address issues of cross-border e-Health instruments as tools for medical information and research.

The JA will start in September 2012 with a 30 month financing of 3.4 million Euros. Partners of the project include health ministries and HTA agencies.

The specific objectives of the JA are:

- Comprehensive overview of current EU/MS situation regarding patient registries
- Coordination mechanism between PARENT and related EU projects and joint actions
- Prototype EU-level relevant source of information (Registry of Registries)
- Recommendations, guidelines and IT tools for efficient and rational governance of patient registries
- Sustainability of cross-border collaboration on secondary use of registry data

- Plan to support implementation of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare regarding patient registries.

The expected direct outcomes are :

- Provide a comprehensive overview of current EU/MS situation regarding patient registries;
- Set up a coordination mechanism to use synergies between PARENT and related EU projects and joint actions;
- Create prototype EU-level relevant source of information (Registry of Registries) regarding national patient registries;
- Develop and disseminate recommendations, guidelines and IT tools for efficient and rational governance of patient registries;
- Explore and address issues related to cross-linking and sharing of registry data. Ensure sustainability of cross-border collaboration on secondary use of registry data, incl. the Registry of Registries, Methodological and Governance Guidelines;
- Provide specific plan of activities and policies to further develop eHealth-enabled registries as a support mechanism for the implementation of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare regarding patient registries;
- Improved HTA Europe wide.

Expected indirect outcomes are:

- Sustainable reduction of resource usage for patient registries governance;
- Improved foundations for clinical and therapeutic research and development;
- New opportunities for development of public health doctrine and cross-border public health collaboration;
- Reduction of inequalities in treatment or quality of care of patients;
- Improvement of secondary registry data to help patients make an informed choice when seeking health care in other MS;
- Foundation for EU health care market consolidation.

The interrelations between DG Sanco financed projects in the field of RD and the EC eHealth projects were explained, with the JA PARENT serving as a bridge between the two areas.

In terms of collaboration between the EUCERD JA and the PARENT JA, it was suggested that the two JA discuss their possible synergies in order to avoid duplication of efforts and to exchange data when needed. There are also synergies to be sought with the upcoming EPSOS[2] project and eHealth governance initiatives. Indeed, the presence of an associated project group in the governance structure will help implement this cooperation.

[2] http://www.epsos.eu/

2. The EUCERD perspective – *Kate Bushby*

From January 2012, the EUCERD will be supported by a Joint Action to help the Committee in its work to foster exchanges of relevant experiences, practices and policies between MS and at EU level.

One issue to be tackled by the EUCERD is the field of registries, building on past work of the RDTF (EC Rare Disease Task Force) which has exposed the multiplicity and heterogeneity of existing registries in Europe to explore issues such as registries for post marketing data collection, the concept of multi-purpose registries and the sustainability of registries.

Many current activities will underpin future and ongoing registry initiatives, such as RD plans and strategies at national level, centres of expertise for RD (i.e. requirements for data collection and exchange), European Reference Networks in the context of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, and research planning. In addition to this, links with EPIRARE, IRDiRC and the PARENT joint action will be sought.

In terms of the EUCERD's actions in the Road Map and Joint Action, we need to consider issues of accreditation of EU registries for RD and also initiate cross-talk between activities of disease-specific groups/academia/industry initiatives and public health programmes to offer solutions including economies of scale and prevention of duplication of efforts, addressing issues of partnerships, and sustainability. Major communication issues should be facilitated by the structure of the EUCERD which includes MS representation. It should also be ensured that there is no duplication of effort, but that RD registries are embedded in overall planning.

3. The IRDiRC perspective – *Stuart Tanner*

On overview of the first two workshops of the International Rare Disease Research Consortium (IRDiRC) was given, and its two major goals to deliver 200 new therapies and diagnostic tests for all RD by 2020 highlighted. The great challenges of this Consortium are access to harmonised data/samples, molecular and clinical characterisation, translational/preclinical research, clinical research and cross-cutting aspects. More information can be found here: http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html.

A number of working groups have been established by the IRDiRC, including one on patient registries and biorepositories. A policy document has been drafted in this area, stating an intention to move from a passive role of planning activities to a more active role in policy development and implementation: a number of issues are highlighted:

- Consider uniform policies, e.g. for public access, standards of use, etc.
- Utilise Common Data Elements (CDEs)
- Develop Standard Operating Procedures (SOPs)
- Provide open source software
- Determine data sharing policies and requirements

- Establish procedures to provide access to data by patients, families, patient advocacy groups, IRB-approved research investigators and the pharmaceutical industry
- Resolve issue of ownership of registry and data with appropriate data protection
- Develop guarantees of privacy of individual and family
- Establish requirements to provide feedback to data providers (especially patients and their families, clinicians) of the outcomes resulting from studies conducted
- Work by groups of diseases (bundle phenotypes for treatment development)
- Include phenotype/genotype description of disorder and pathways where known
- Build a sustainability plan from the very beginning
- Open-source all information with appropriate protection of privacy for patients and families to ensure maximum use
- Enable patient/family self-entering of data and provide for the development of best practices or a guide for patients and family to enter data to a patient registry
- Develop and utilise training and educational modules about the optimal utilisation of patient registries by research investigators, health care professional, patients, families and patient advocacy groups.

The next meeting of the IRDiRC in Montréal, Canada (8-9 October 2011) will focus on: success stories ; advances in sequencing since last IRDiRC meeting ; Industry activities and programs, needs and envisaged contributions; Regulatory requirements: How could IRDiRC contribute to implementation; clinical trials; biorepositories; governance, i.e. ad hoc meeting of funding agencies; and reviewing the policy document

The IRDiRC is in its infancy and has to be schooled to a certain level. The potential and stakes are high, as are the responsibilities. Relations between EU level and IRDiRC working groups should be sought.

4. The EPIRARE perspective – *Domenica Taruscio*

An overview of the 36-month DG Sanco funded project EPIRARE (European Platform for Rare Disease Registries) was presented by Domenica Taruscio. The project has 23 partners in 14 countries. More information is available at www.epirare.eu.

The objectives of the project are:

- **To define the needs of registries and databases on RD (state of art)**
  Features of the current registries with reference, e.g. to legal basis; organisational and IT measures used; data collected; informed consent; personal data protection regulation; quality assurance, operational and financial support.
- **To identify key issues from the legal point of view**
  To assess the most suitable EU legal instruments in order to allow the registration of patients' health data in compliance with the EU Directive 45/69 and in coherence with other relevant provisions.

- **To agree on the Platform scope, governance and long-term sustainability**
  To define the scope and a governance model representing the interests of relevant stakeholders, in strategic decisions and ensuring long-term sustainability of the platform.
- **To agree on a common data set and data validation**
  A common data set, which is independent of the specific rare disease, provides information consistent with the agreed scope of the platform.
- **To identify tools and other facilities supporting the operation of the platform users**

The EPIRARE perspective was presented: registries should be single or multi-disease, population based, with full coverage. Connections between these registries with social security, reimbursement and OD prescription databases are necessary, as are connections with post-marketing surveillance. These registries need few variables, e.g. non disease-specific data (demographic data, place and date of diagnosis, mortality, treatment; prevalence, survival, QoL, ICF). The data is based on centres of expertise, whilst different information needs at regional, national and international level may necessitate different data sets.

The expectations of stakeholders were outlined. Patients expect new registries established easily through a platform, the ability to search for other patients with similar disease features or treatment, sustainability, and a tool for patients to express what patients experience (patient module, besides the clinician module). Industry expect registries to help with the assessment of OD, due to the need for a long-term follow up, efficacy (cost-effectiveness), the reduction of fragmentation, the avoidance of duplication of registration initiatives, and a strong need for quality data and criteria for quality data. Researchers and physicians expect guidelines for specific data collection, identification of best practice models, sustainability, "freedom" of research and feedback and improvement of patients' care. Public health authorities/institutions expect: a virtual database resulting from the upload of many databases, good data comparability, to include population-based registries and prospective data collection, groups of RD based on the associated health problems, to fulfill criteria for quality data, to raise awareness of the need for quality definitions, to establish connections (if not traditional linkage) with other data sources (prescriptions; disability support payments; death certificates hospital discharge records), to improve codification with a view to ICD 11, comparable data, HTA data, and disease-specific and non disease-specific data. Other stakeholders expect user-orientated products and tools.

EPIRARE will soon launch a survey aimed at registry leaders in the EU, patient organisations and EUCERD members. This questionnaire will investigate generalities concerning registries, registry aim and scope, data sources, quality of data, ethical and legal issues, informed consent, governance, communication, access to data and security, sustainability, needs and expectations.

There is a need for a discussion on governance models, finance model, control and ownership of data, access to data, platform benefits and their targets (stakeholders), types of registries in the scope of the platform and added value for "big" registries.

In the current draft documents of the project, the definition of "platform" is "a structure providing a number of services (including hosting) and tools to independent registration

activities which agree to provide data fulfilling predefined quality criteria)". The definition of "registries" is "any registration activity which agrees to provide data with predefined quality (e.g. databases, etc.)".

EPIRARE will aim to improve synergies between stakeholders and existing registries. A core dataset, alongside a target-orientated dataset and a disease-specific dataset could be envisaged as a model, with the accent placed on quality data, ultimately to make registries better.

5. General discussion

Discussion after these presentations revolved around participants' opinions of whether the tools/initiatives presented are sufficient to move forward in this field, in terms of regulatory obligations such as post-marketing surveillance. Participants discussed the differences between existing RD registries and the demands of post-marketing surveillance on registries: indeed post-marketing surveillance is a separate issue. It was suggested that the EMA could suggest that Industry go to existing registries to see if collaboration can be established: this type of public-private partnership is only conceivable when there is a product for an RD since a company would only be approaching the Agency if a product was in development. Fragmentation of data should be avoided when more than one product for a single rare disorder is authorised: disease registries are thus preferred over drug registries.

It was also highlighted that outcome measures are key to deciding whether or not a centre/expert is performing adequately: a metric can be developed to measure this (as one already developed for CF by Anil Mehta). Registries can thus serve a long term quality assurance goal, with experts defining the states of the disease very clearly for use for surveillance purposes.

Although registries should stay focused on core agreed outcomes data and indicators, it was highlighted that registries could also be used to collect data on cost-effectiveness in future. Quality-of-life measures were also highlighted as important for RD, but existing quality-of-life models are often not fit for purpose.

Session 4: Conclusions and points for action

1. Roundtable of stakeholders

EMA representative – *Stella Blackburn*
This workshop has helped bring a range of stakeholders together to see each others' viewpoint, and to consider how collaboration could possibly work and how this could be articulated. There is a need for better visibility of EU and International initiatives, as well as of individual registries, to avoid duplication of effort and increase collaboration. Initiatives outside the sphere of RD (such as ENCePP) must also be publicised in this field. Best practice issues should be addressed, and we should move forward together now these first discussions have taken place.

Patient representative – *Ulirke Pypops*
Patient organisations believe and demand that resources be optimised and expect solutions to be found in projects that already receive funding. The patients' perspective needs to be brought to these efforts, so as to assure their cooperation and avoid them not participating due to lack of confidence and transparency. RD patient organisation representatives are trained professionals with real life experience who can bring a invaluable contribution to registries.

Academic registry leader representative – *Carla Hollak*
We need a concrete definition of what is needed so as to define a dataset for evaluating cost-effectiveness. The first step is to make a simple core data set, then a second step would be to start a pilot taking a disease with multiple drugs (such as Gaucher diseases) so as to find out, through a bottom-up approach, were the real problems are.

Industry representative – *Wills Hughes-Wilson*
This workshop has been a key meeting. In no other area are registries of such value as in the field of RD. There is a strong societal impetus to have registries for RD, and all stakeholders agree they are important. Although the challenges are numerous, there are agreements on these challenges, such as the need to avoid fragmentation. Even if registries serve multiple purposes and different groups may be limited in their perspective, there are opportunities to collaborate, such as through the EUCERD, which provides a real forum for these discussions. There is a need for a flexible and pragmatic approach, with a strong leadership for consensus and governance reflecting all stakeholder groups: attention should be paid to what the payers want from registries. Now, in order to advance, we need to imagine what successful collaborations would look like from the view point of all stakeholders, and to start thinking in terms of "*we* should" rather than "*they* should": with collaborations, incentives would be less necessary. It was suggested that a working group of stakeholders should be constituted to discuss needs, outcomes, what should be done, who should pay. We need to move forward and concentrate on future opportunities rather than trying to correct the past. Attention should be paid to initiatives such as CAVOD, EPIRARE and PARENT, BURQOL-RD as should they activities of IRDiRC. Data protection legislation should also be carefully examined as it could pose a threat. The provisions of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare should also be

carefully considered. Existing legislation must be respected; we should not create extra burdens, but align with requirements. Early dialogue processes should be used at the EMA, and the CAVOD process will need to be observed.

In conclusion: common, clear definitions must be fixed, expectations and timings must be defined with all stakeholders, governance must foster collaboration, and sustainable funding sought as funding and technology advance.

National regulatory agency representative – *Patrick Salmon*
A European approach is the best solution in this area. It should be borne in mind that HTA requirements will be very different from regulatory demands. Agencies will be increasingly asked to show value for money, and registry data will be needed to do so, with more and more national requirements for additional studies.

2. General discussion and conclusions

It was highlighted that the current FP7 call includes potential projects which could possibly serve as pilots, and cross-talk should be encouraged.

Better communication around EU initiatives in the field is required and the EUCERD should be promoted as the forum for discussion of topics in this area. It was suggested that a working group at EUCERD level (possibly in the context of the Joint Action to support the EUCERD) should be planned, possibly at the start of 2012 once the results of the EPIRARE survey are in.

It was highlighted that the US Agency for Health Care Research and Quality is putting together a framework currently for a registry for registries: this is still in early stages of development.

It was suggested that the example of France (during its first National Plan for RD 2004-2008) be followed in establishing a committee in charge of designating high-quality registries in the field of RD for recognition by financing bodies. Registry operators should be trained in the field of good practices, and this process could be used in other areas to engage MS in activities at national level.

For regulatory purposes we need to think globally with the FDA and imagine what could be done in common.

Participants were advised to be vigilant when it comes to the proposed revision of the data protection directive during 2012, in particular, because this could have a negative impact in the field of registries, notably around the cross-border sharing of data. Participants were advised to engage in the process in order to ensure that the development of registries for rare diseases is not hampered by unintended consequences. The MS representatives of the EUCERD have a key role to play here.

Sustainability is a topic that needs to be dealt with: perhaps a special fund for registries could be established, or industry, MS health authorities or patient organisations could take responsibility for funding.

It was highlighted that any potential pilots need to be considered in the context of existing pilots for other, related programmes, such as the EUNetHTA, the Swedish EU Presidency project and CAVOD.

The outcomes of this workshop will serve to elaborate a set of EUCERD recommendations in the field.

Annex I: Participants

EMA & COMP

Jordi Llinares Garcia	EMA (EUCERD member)
Stella Blackburn	EMA/ENCEPP
Kerstin Westermark	COMP (EUCERD member)
Patrick Salmon	COMP
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Lesley Greene	COMP
Richard Vesely	EMA
Bruno Sepodes	COMP
János Borvendég	COMP
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Maria Mavris	COMP
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Laura Fregonese	EMA
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European Commission

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Jerome Boehm	DG Sanco
Mirjam Söderholm	DG Sanco
Catherine Berens	DG Research
Georgios Margetidis	Executive Agency for Health and Consumers

Industry representatives

Anne DE BOCK	Astra Zeneca
Katia FINCK	Shire (EUCERD member)
Wills HUGHES-WILSON	Genzyme (EUCERD member)
Samantha PARKER	OrphanEurope (EUCERD member)
Barbara VALENTA-SINGER	Baxter (EUCERD member)
Bernard DELAEY	Ablynx

EUCERD Scientific Secretariat & Bureau

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Helena Kääriäinen	National Institute for Health and Welfare, Finland, EUCERD Vice-Chair
Kate Bushby	Treat-NMD, EUCERD Vice-Chair
Charlotte Rodwell	EUCERD Scientific Secretariat

Experts/related project leaders

Nils Feltelius	MPA
Guiseppe Traversa	ENCEPP
Domenica Taruscio	EPIRARE, Istituto Superiore di Sanita (EUCERD member)
Luciano Vittozzi	EPIRARE, Istituto Superiore di Sanita (EUCERD member)

Manuel Posada	Spanish Repository**,** Instituto de Investigación de Enfermedades Raras
Matic Meglic	Institute of Public Health, Slovenia, PARENT JA on Patient Registries
Fabrizio Bianchi	Istituto di Fisiologia Clinica, Consiglio Nazionale delle Ricerche
Sabina Gainotti	Istituto Superiore di Sanita

Experts/academic registry leaders

Carla Hollak	Gaucher/Fabry registry
Stuart Tanner	Eurowilson Registry (EUCERD member)
Susan Webb	ERCUYSN Registry (EUCERD member)
Jean Donadieu	EHN EuroHistioNet Registry (EUCERD member)
Marco Gattorno	INFEVERS & EUROFEVER Registry
Christine Lavery	English MPS Registry
Anil Mehta	ECFS Registry
Guilliaume Jondeau	Marfan Cohort
Tsveta Schyns	ENRAH Registry
Hanns Lochmüller	Treat-NMD Registries
Corneila Zeidler	European severe chronic neutropenia registry (EUCERD member)

Patient representatives

Christel Nourissier	EURORDIS (EUCERD member)
Bianca Pizzera	EURORDIS (EUCERD member)
Ulrike Pypops	EURORDIS
Fabrizia Bignami	EURORDIS EPIRARE
Monica Ensini	EURORDIS EPIRARE
Andreas Reimann	ACHSE
Jeremy Manuel	European Gaucher Alliance

Other experts:

Magnus Stenbeck	Karolinska Institute, Swedish Research Council
Alric Reuther	Institute for Health Care, Germany
Nancy Dreyer	OUTCOME Chief of Scientific Affairs & Sr. Vice President