The pooling of manpower and resources through the establishment of European reference networks and rare disease patient registries is a necessary area of collaboration for rare renal disorders

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ABSTRACT

This review aims to provide guidance on emerging concepts and policy related to European reference networks (ERNs) for rare diseases (RDs) and the development and management of RD patient registries. A major problem facing many RDs including rare renal disorders is that patients do not have a specialist centre that they can attend where clinicians, working as a multidisciplinary team, are experts in the particular disease. Furthermore, for most RDs, no single centre, and in many cases no single country, has sufficient numbers of patients and resources to fully understand the natural history or to conduct clinical and translational research. Therefore, the pooling of manpower and resources through the establishment of ERN and RD patient registries is a common and necessary area of collaboration. The concept of European networks for RDs dates back to the early 2000s and the Commission launch of a call for European pilot reference networks for RDs. These networks of expert centres have been brought together through the desire for further knowledge and innovation in RD areas. Networks demand a holistic approach and long-term vision with close collaboration between clinicians, diagnostic laboratories, scientists, patients and their families. The development of legal measures for ERNs is in progress at the Commission and these networks will be a shared responsibility of the Commission and member states. In the context of ERNs, an essential activity is the patient registries. Patient registries are organized databases where patient information, including demographic, medical and family history, are collected, stored and available for retrieval via standardized and secure methods. Patient registries are increasingly recognized as crucial tools for RD research for which international collaboration is absolutely essential to understand the pathogenesis of rare genotypes, achieve a unified collection of phenotypic data, foster natural history studies providing the foundation for successful orphan drug development, facilitate studies to identify appropriate clinical endpoints or biomarkers, identify participants for research and clinical trials and support discussions with regulators including the safety and efficacy evaluation of potential therapies. Furthermore, patient registries are often used as part of regulatory decisions and post-marketing surveillance requirements. Data can be entered into a registry by patients, clinicians, researchers or directly imported from patient’s health records. The major concern in maintaining the dynamic of these networks and registries is sustainability, as the infrastructures and coordination have a cost.

Keywords: European reference networks, improved diagnosis, patient outcome, rare disorders, registries

INTRODUCTION

The term ‘rare diseases’ (RDs) has been in growing use in the fields of research, public health and patient advocacy for the past four decades. The term appeared initially as a by-product of the orphan drug act in the USA. The orphan drug act of 1983 was the result of sustained advocacy efforts driven by patient organizations to make RDs a health priority. The act provides regulatory and economic incentives for industry to
develop drugs for these diseases, known as orphan drugs. These incentives were subsequently enacted in regulations in Japan, Taiwan, Europe and elsewhere.

The regulations provide statistical definitions for an RD that vary between countries; for example in the USA, a condition is considered ‘rare’ if it affects fewer than 200,000 persons and in Europe, a disease is considered rare if it affects fewer than 5 per 10,000 persons. Orphan drugs are also granted for use in a medially plausible subset or for a disease such as malaria that is rare in the USA but common in some parts of the world. For acute diseases, the incidence rather than prevalence may be used. Some definitions, such as the European legislation, include other factors, such as the existence of adequate treatments or the severity of the disease. The orphan drug sponsor must demonstrate prevalence through a variation of sources, including published literature, registries and experts. For example, the FDA accepted ADPKD as an orphan indication based on large hospital data, even though the allele frequency is as high as 1 in 1000. The sheer number of individual RDs, estimated between 5000 and 7000 [1], means that millions of people will be affected during their lifetime.

Rare kidney diseases represent a group of >100 different disorders [2], collectively affecting a significant number of individuals. Given the size of the RD problem, these regulatory developments have triggered several questions, from the definition of rarity to the pricing of orphan drugs and their impact on health-care systems.

RDs share common issues requiring special combined efforts to address them: few or no effective treatment, most often evidence-based guidelines do not exist and there is a lack of uniformity in clinical practice; there is wide variation in the infrastructure, expertise, resources, access and time to diagnosis, treatment and outcome of patients between individual centres and countries. These specificities single them out as a distinctive domain, where international collaboration can have a very high added-value. The pooling of manpower and resources through the establishment of European reference networks (ERNs) and RD patient registries is a common and necessary area of collaboration.

In addition to information and clinical networks, the rational pooling of science and research into sophisticated networks can be achieved, such as the newly instigated European Commission funded EuRENoMics project, which will develop novel tools to make more accurate diagnoses, predict the disease course, ensure efficacy of available treatments and help develop new and better therapies for rare kidney diseases. Further information on EuRENoMics can be found on their website www.eurenomics.eu.

EUROPEAN REFERENCE NETWORKS

Article 12.4 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 requires the Commission to support the development of ERNs. Commission members have been working with member states (MS) since January 2012 to define the criteria and conditions to be fulfilled by the network and methods for evaluating compliance with these criteria. The development of networks will be a shared responsibility between MS and the Commission. The legal measures for ERN will be adopted in 2014, and in 2015 the Commission will launch a call for candidatures of ERNs. By this time MS should decide how they will promote the participation of centres in the networks. The European Committee for Experts on Rare Diseases has produced Recommendations to the European Commission and MS on ERNs for RDs [3]. These provide the structure and content of an RD ERN. They recommend that ‘the overall vision of RD ERNs is that they will provide the framework for health-care pathways for RD patients through a high level of integrated expertise [that] nationally designated centres of expertise are the core participants in RD ERNs’. A particular concern is the care pathway for undiagnosed patients. Therefore, ‘an RD ERN should have the capacity to follow patients with an unclear diagnosis and manage their care’. An area of consideration when thinking about an ERN is the ‘possible economies of scale of developing shared platforms across RD ERNs such as core components for registries, data collection and quality assurance’. As it will only be possible to establish a limited number of RD ERNs at the beginning of the process, it is recommended to give priority to RD ERNs which meet the following priority criteria as a robust starting point: (i) preferentially formal or informal networks of experts that have reached maturity and have the scope to expand; (ii) there are patient registries established and willing to interoperate; (iii) there are existing networks of patient groups and (iv) there are sufficient existing activities of research output. Each thematic RD ERN would still need to expand over the course of its first 5 years of designation to include other centres, expert groups, patient groups and ultimately diseases.

The concept of European networks for RDs dates back to the early 2000s and the Commission launch of a call for European pilot reference networks for RDs. These networks of expert centres have been brought together through the desire to further knowledge and innovation in RD areas. Central is also the participation and empowerment of patients and families.

Networks demand a holistic approach and long-term vision with close collaboration between clinicians, diagnostic laboratories, scientists, patients and their families. Networks should consider needs of governments, health authorities, health-care professionals and national RD centres of expertise. Another stakeholder group is the pharmaceutical industry, which can have a supporting role in co-funding specific activities, such as registries, through public–private partnerships. This partner also has the knowledge base for the development of potential new therapies.

About 15 pilot reference networks have received funding from the Commission since 2006. They were, mostly, networks for isolated RD, that is Wilson’s disease or the porphyrias. However, their sustainability is threatened as, from an economical perspective, it is not possible to fund networks for the total number of different RDs. The patient federation Eurordis states in its position paper that all RD patients should be covered by at least one ERN and no patient should be excluded.
from the system. It is therefore expected that ERNs will cluster groups of RDs based around the concept of medical specialties and body systems, diagnostic and therapeutic areas, as described in the European Committee of Experts in Rare Diseases (EUCERD) recommendations. The Eurodis position paper is available at www.eurordis.eu.

In the area of inborn errors of metabolism, an initial group of 16 centres of expertise has established funding for a network and registry for the organic acidurias and urea cycle disorders (E-IMD [4]: European network and registry for intoxication type metabolic disorders). In 2013, homocystinurias, methyl-ation and folate defects were added to the network by achieving funding for the E-HOD project. In 2014, it is expected to add neurometabolic disorders to make a total of 50 diseases followed by the network. The network is organized into specific groups each with a coordinator and management committee; while the registry is located in one centre. This project currently brings together 68 partners from 24 countries.

EuroCYST is another example of an European Initiative that has established a network of reference centres across Europe and a registry that includes a central biobank. Euro-CYST is an academic multinational action to build an European network of autosomal dominant polycystic kidney disease (ADPKD) reference centres and to establish a large-scale pan-European ADPKD cohort serving as a versatile and powerful clinical research platform. EuroCYST will set up a large, well-characterized cohort of 1100 ADPKD subjects who are followed in a longitudinal observational cohort for at least 3 years at 14 ADPKD reference centres across Europe.

For rare kidney diseases, 5–7 subgroups, under one or two ERNs, could be envisioned for tubular disorders, genetic glomerular diseases or ciliopathies, for example.

European networks for RDs should serve as information, research and knowledge centres, updating and contributing to the latest scientific findings, managing patients from other European countries, when no expert is available, and ensuring the availability of subsequent laboratory and treatment facilities where necessary. Some of the main activities will include the following:

(i) **Identifying expertise:** Rare, often multisystem, diseases require a multidisciplinary approach. This is increasingly important as patients with RDs are now being seen as adults, due to improved paediatric care or because some RDs present in adulthood. The network should bring together the different specialists who might not meet in any other forum.

(ii) **Coordination of the network:** A network should have different levels of management and coordination. This should include a lead coordinator who must be supported locally by a project manager and local team, a small executive group which will be the strategic decision-making body, writing grant applications, reports and checking progress against objectives. All members of the network should meet at least annually. A network charter should be agreed. Team working and keeping up enthusiasm in a network is one of the most time-consuming occupations for the coordinator.

(iii) **Dissemination:** An ERN overarching aim is to promote the care of patients with an RD and patient’s access to information. To achieve this ERN’s should be visible to the wider public. Public relations and communication managers are useful to ensure this visibility, but they have a cost. There are many websites that have been set up by the pilot networks: e-imd.org, porphyria-europe.org, e-hod.org and treat-nmd.eu.

(iv) **Telemedicine and tele-expertise:** Telemedicine and tele-expertise are two distinct concepts. Telemedicine is a relationship between a health-care professional and a patient in a different location, whereas tele-expertise is the relationship between two or more health-care professionals in different locations. Tele-expertise has been very successful within networks. Members will make personal contact with other network members to ask for advice or services. Some networks provide tools that allow sharing of images and data. All network meetings provide time for experts to share clinical conundrums. Medical and clinical care questions from patients are received via the website (telemedicine), and the network will provide information back in the patient’s own language.

(v) **Empowering patients and encouraging the establishment of patient groups.**

(vi) **Offering training opportunities to health-care professionals through live training, fellowship opportunities and e-learning activities.**

(vii) **New-born screening, diagnostic and clinical guidelines:** Developing, translating and disseminating evidence-based best practice guidelines for diagnosis and management are a core activity. Including the provision of recommendations for effective practice in clinical situations where variations in practice are known to occur and where effective care may not be delivered uniformly.

(viii) **Setting up independent laboratory external quality assurance schemes or partnering with existing schemes, such as the EMQN or ERNDIM.**

(ix) **One of the essential activities of an RD ERN is patient registries which play an important role in improving knowledge of healthcare to RD patients.**

Many of these activities will require significant, on-going funding to support the management and delivery of the network (Figure 1).

**PATIENT REGISTRIES**

Patient registries are organized databases where patient information, including demographic, medical and family history, are collected, stored and available for retrieval via standardized and secure methods. Patient registries are increasingly recognized as crucial tools for RD research for which international collaboration is absolutely essential to understand the pathogenesis of
rare genotypes, achieve a unified collection of phenotypic data, foster natural history studies providing the foundation for successful orphan drug development, facilitate studies to identify appropriate clinical endpoints or biomarkers, identify participants for research and clinical trials and support discussions with regulators including the safety and efficacy evaluation of potential therapies. Furthermore, patient registries are often used as part of regulatory decisions and post-marketing surveillance requirements. Data can be entered into a registry by patients, clinicians, researchers or directly imported from patient’s health records.

New technologies and open information such as 'big data' so called, not for its sheer volume, but for its complexity, diversity and timeliness will transform the way we collect data into registries, and how RD patients get involved in research. Data entry may become less of an issue when data will be automatically retrieved from electronic health records. Research on how these new technologies address the objectives of registries will need to be developed. In the meantime, this is not operational and initiatives in RD patient registries continue to increase. The Orphanet database shows that there are well over 500 registries for RDs in Europe. These registries are using different technology and platforms; there are no uniform standards for collecting data. Most often centres work in isolation in different disease areas and country-specific registries capture different data points in different languages complicating data consolidation. Approximately 40% of orphan medicinal products are granted under exceptional circumstances; therefore, pharmaceutical companies are required to set up their own post-marketing registries. These registries for an isolated RD or stakeholder objective are becoming increasingly complex to sustain. In some countries, there is a national approach to establishing registries for common core data elements across all RDs (i.e. in France, Spain, Italy and Bulgaria, for example), but there is still little crosstalk with disease-specific registries and between different countries. In addition to these challenges, the proposed new European Data Protection Regulation could seriously impede on European-wide data collection and exchange.

Given these challenges, there is a clear need for the standardization of registries, coordination and a structure to ensure that these invaluable resources are sustainable for the future. One proposed solution is the strategic objective of the European Commission to create a European platform on RD registration providing common services and tools for existing and future RD registries in the EU. Although this platform could optimize some resources through a common technical, regulatory and ethical framework, it will not solve the main cost of the registry which is defining disease-specific data elements and most importantly source data entry.

EUCERD provides guiding principles on RD patient registration and data collection. The International Rare Disease Research Consortium has developed policies and guidelines for researchers in the development and funding of RD research. Overarching policies relevant to patient registries and databases include the following:
(i) RD research should be collaborative. Resources, data and results should be shared among IRDiRC research projects and made publicly available to the broader community, and duplication should be avoided.

(ii) RD research should involve patients and/or their representatives in all relevant aspects of the research.

(iii) International, national, regional and local legislation/regulations need to be adhered to with respect to data protection and ethical approvals.

(iv) IRDiRC members will promote the harmonization, interoperability and open access of ontologies to be applied to databases, registries and biobanks.

(v) RD patient registries should aim to be global in geographic scope and practice. Interoperability and harmonization between RD patient registries should be consistently pursued. Linking and data transfer into existing platforms should be considered ‘best practice’. Registries should be broad and not focused exclusively around a single therapeutic intervention or product.

The IRDiRC guidelines relevant to registries include:

(i) The impact of research on people living with an RD should be a key consideration for each project. Best ethical practices for ensuring the interest of the individuals living with RD should be applied.

(ii) RD patient registries should be linked with data and biological specimens in biobanks, natural history studies and clinical trials and should also include measures of quality control and updating.

(iii) Patients and/or their representatives should be involved in the governance of RD registries.

The European Commission funded RD-Connect project, started in 2013, to develop an integrated platform for sharing between funded projects by connecting databases, registries, biobanks and clinical bioinformatics. RD-Connect will work towards the development of data standards and hence improve the way we share data. Efforts are on the way to developing ‘unique identifiers’, to enable linking different datasets (biobanks, registries, biomarker experiments, clinical trial data and -omics data) from the same RD patient across institutions and countries. For this to be successful, effective public engagement will be required.

Multicentre registries are often delayed or even prevented by drawn-out regulatory processes (ethics approval not harmonized) and highly variable institutional governance processes. Work is required to distinguish between informational risks and interventional risks.

CASE STUDY OF A REGISTRY
PUBLIC-PRIVATE PARTNERSHIP

Pharmaceutical industry collaboration with existing registries and studies that are collecting longitudinal data on a specific patient population can reduce the burden on participants and streamline the running of a registry.

The Longitudinal Study of homocystinurias is operated by the European Network and Registry for homocystinurias, methylation and folate defects (E-HOD). Its primary purpose is to collect data on the natural history, disease progression, treatment and outcomes of individuals with these disorders. E-HOD links with the E-1MD registry and network sharing the same platform. The Cystadane Surveillance Protocol is a mandated post-approval registry that is collaborating with the study to monitor the long-term safety and effectiveness of cystadane, a treatment for homocystinuria.

The marketing authorization holder (MAH) of Cystadane is required by the European Medicines Agency, in its risk management plan, to develop a registry for patients treated with Cystadane. The sponsor recognized that data collection for this RD would be difficult because of the small number of patients and the extended time frame for data collection; thus, the sponsor sought to meet their commitment while avoiding redundancy in research efforts and over burdening the small patient population.

E-HOD is governed by a steering committee and maintains relationships with over 12 clinical sites, a data monitoring and coordinating centre, and patient advocacy groups. The data elements to be collected in the E-HOD registry only needed to be supplemented by a few additional elements in order to fulfil the sponsor’s post-marketing registry commitment. A protocol was written for the registry to specify which study data the sponsor would have access to in their registry and which new data elements would be added to the study for registry purposes. One challenge encountered early on related to executing a legal agreement on which to base the collaboration. Because E-HOD does not have a legal entity, it was not possible to contract directly with them.

By collaborating with E-HOD, the MAH is able to set up the registry in a quicker time frame and more efficiently than building a new, independent registry. Collaboration with E-HOD also resulted in only a few more data elements required from sites and patients participating in the E-HOD study; this represents a smaller data collection burden on the already limited patient population. One limitation of this partnership has been in relation to the registry ethical applications in certain countries. Either the post-marketing surveillance was included in the original E-HOD application or requested as an amendment. As an amendment there has been confusion over who is the sponsor of the registry which is linked to data control and custodianship. In some countries, a post-marketing survey does not follow the same type of ethical application as an academically led study. The lesson learned is that it would be better to make one application for the study and sub-study with an additional patient information and patient consent form for the patients treated with the orphan drug (OD) in question.

CONCLUSIONS

ERNs unite scarce manpower and resources to improve information, knowledge and learning of RD. They should be a
one-stop shop for a patient looking for a specialist, a healthcare professional looking for best practice, research scientists and industry developing new therapies or running post-marketing surveillance studies. They cover essential tools and activities in RD including patient registries. ERNs can succeed beyond expectations in the objective of improving healthcare for patients with an RD and their families. The network of participating centres is often larger than planned for with a geographical coverage that extends beyond Europe. Partners enthusiastically embrace the principles of widening access to and improving quality of diagnostic and clinical services. Information for patients, families and non-expert clinicians in a variety of European languages is a priority for networks, and there is often a commitment from partners to expand this library to include more international languages where possible. Audit and assessment of the quality of laboratory diagnosis allows for key diagnostic criteria to be defined and services to be measured against these standards which enhance quality. Collection of detailed biological, genetic and clinical data into a registry builds knowledge on the incidence and prevalence, provides a platform for research and defines the level of disease burden. Finally, ERNs and registries engender a momentum and enthusiasm among professionals working in this field. RD-ERNs require legal measures to be adopted and the Commission launch for a call for ERN candidatures in 2014/2015. The network and activities will require significant, ongoing funding to support the management and delivery of the network.

CONFLICT OF INTEREST STATEMENT

The author’s expertise has evolved from her central role in the development and implementation of rare disease networks and registries and her expert role at the European Commission on the EUCERD and IRDiRC committees. She has been directly involved in the development of recommendations and guidelines. The author represents the industry in her role on the expert boards and networks. She is employed by the pharmaceutical company Orphan Europe, part of the Recordati group. Orphan Europe is developing orphan medicinal products related to research described in this review.

REFERENCES

3. Aymé S, Rodwell C. The European Union Committee of Experts on Rare Diseases: three productive years at the service of the rare disease community. Orphanet J Rare Dis 2014; 9: 30

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