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PATIENT REGISTRIES FOR RARE DISEASES

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SUMMARY:

Rare diseases are diseases with a particularly low prevalence. The specificities of rare diseases - limited number of patients and scarcity of relevant knowledge and expertise - single them out as a distinctive domain of very high added value. The international reference for classification of diseases and conditions is the International Classification of Diseases (ICD), coordinated by the World Health Organization (WHO).

Patient registries and databases constitute key instruments for the development of clinical research in the field of rare diseases. Rare disease registries include not only diseases that are inherently rare, but also common diseases that are rare in specific populations, especially those defined by demographics.

Disease registries create the possibility of assessing the long-term safety and benefit of different treatments, perhaps leading to treatment algorithms that allow more choices for patients and clinicians.

Keywords: Rare diseases, Register, Objectives, Public health

Rare diseases are diseases with a particularly low prevalence. The specificities of rare diseases - limited number of patients and scarcity of relevant knowledge and expertise - single them out as a distinctive domain of very high added value. The key to improve overall strategies for rare diseases is to ensure that they are recognized, so that all the other linked actions can follow appropriately. To improve diagnosis and care in the field of rare diseases, appropriate identification needs to be accompanied by accurate information, provided and disseminated in inventory and repertory formats adapted to the needs of professionals and of affected persons.

Rare diseases are significant contributors to a number of population health outcomes in terms of their high associated mortality, morbidity and disability. In particular, rare diseases are a significant contributor to early fetal loss and perinatal mortality, as well as infant and child mortality.

The impact of each disease is limited: collectively, however they represent a true challenge for public health authorities when it comes to developing a public health policy. Policies were also developed to support research and research networks, registries, databases and knowledge bases.

Most rare diseases are genetic diseases, the others being rare cancers, autoimmune diseases, congenital malformations, toxic and infectious diseases among other categories. Research on rare diseases has proved to be very useful to better understand the mechanism of common conditions such as obesity and diabetes, as they often represent a model of dysfunction of a single biological pathway.

There are very few rare diseases for which a primary prevention is possible. Still, primary preventive measures for rare diseases need to be taken when possible (e.g. prevention of neural tube defects by Folic Acid supplementation).

The international reference for classification of diseases and conditions is the International Classification of Diseases (ICD), coordinated by the World Health Organization (WHO). Many rare diseases can be diagnosed using a biological test, which is often a genetic test. These tests are major elements of an appropriate patient's management as they allow an early diagnosis, sometimes a familial cascade screening or a prenatal test.

Most rare diseases are unknown to health care professionals outside the field of genetics. In 1997 Orphanet was established, jointly by the French Ministry of Health and the Institute of Health and Medical Research (INSERM).

Patient registries and databases constitute key instruments for the development of clinical research in the field of rare diseases (RD), and the improvement of patient care and healthcare planning as well as social, economical and quality of life outcomes.

Rare diseases were identified as a public health priority as early as 1993. However, it was in 2008 that the European commission took action with the adoption of an overall policy framework, in the form of a communication – "Rare diseases: Europe's challenge". The aim of the communication was to support member states in their efforts to improve diagnosing, treating and caring for rare disease patients in the European union (EU). Alongside the communication, member states committed to putting national strategies in place, in accordance with the council recommendation on action on rare diseases.

The Commission published in 2014 a report [1] that considered the extent to which the proposed measures of the Commission Communication and Council Recommendation are working effectively to make improvements in the field. The report takes stock of the successes to date, and outlines the EU's intention to maintain a coordinative role in the development of the EU policy on rare diseases and to support Member States in their national activities in this field.

Rare diseases were also specifically addressed in Directive 2011/24/EU on the application of patients' rights in the cross-border healthcare [2], approved in 2011. This Di-

rective seeks to facilitate access to health care for EU citizens and encourage cooperation between EU Members States in the field of health, of particular interest in the field of rare diseases where patients and expertise are rare and scattered across the EU. In particular, the Directive encourages the establishment of European Reference Networks in the field of rare diseases to pool expertise and improve care for patients.

Patient registries have been in place for several decades in sectors such as cancer, birth defects and cardiovascular diseases. The European Commission, in its Communication: "Rare diseases: Europe's challenge" emphasizes the strategic importance of patient registries in the field rare diseases, stating that "collaborative efforts to establish and maintain data collection should be supported, providing that these resources are accessible through agreed upon rules".

When established, databases should be maintained and their use optimized through exchange of data between interested parties. However, the status of such databases is not well defined and most institutions have no written policies or agreements regarding this activity.

Rare disease registries are initiated by many organizations, such as patients and their families, patient advocacy groups, clinicians, national health systems, and biopharmaceutical product manufacturers, for many reasons. The scope of these registries may evolve over time, maturing from an outreach/community-building effort or a means for a basic understanding of patient and disease characteristics, to a supportive mechanism for research funding and attracting health care providers.

Rare disease registries include not only diseases that are inherently rare, but also common diseases that are rare in specific populations, especially those defined by demographics. Thus, plaque psoriasis - common among adults - is rare in children, and breast cancer - common among women - is rare among men.

Registries can be developed to serve multiple purposes. The design of the registry depends upon the maturity of the research plan around the disease, the availability and duration of funding, and to some extent, the number of patients affected. For rare diseases, the perception of relative importance of research often correlates with the number of patients affected or the number of empowered disease advocates.

The specific objectives of rare disease registries typically cluster into the following categories:

• To connect affected patients, families, and clinicians.

Patients and families of affected individuals are often interested in knowing about others who share their disease. Many rare diseases have a genetic basis. However, even if multiple family members are affected with the condition, the motivation to be connected to others may be quite strong, driven by their personal desire to know more about the condition, its natural history, alternative coping mechanisms and treatment options, and the diversity of clinical courses and outcomes. The need to connect is enhanced if the patient or family has difficulty in finding an expert to provide advice or the doctor or genetic counselor points out how little is known about the rare condition.

• To learn the natural history, evolution, risk, and outcomes of specific diseases.

Stakeholders often initiate registries to learn the natural history of a rare disease. Typically rare diseases are described in a general way based on their symptoms at the time of diagnosis. As general and specific therapies emerge, the natural history often changes and the "classical description" may no longer apply. With better therapies for treatment and supportive care, new complications may also be recognized. For treatments that extend life expectancy, what is known about the trajectory of disease can change drastically. A disease registry incorporating patients with rare diseases from many centers allows for gathering stronger and more generalizable safety, diagnostic, and prognostic information.

• To support research on genetic, molecular, and physiological basis of rare diseases.

Research on features of disease, both clinical and basic, is a common objective of a registry. Clinical research depends on having a representative population for determining the timing and frequency of natural events and complications, such as development of autoimmune complications, unusual infections, and related or unrelated malignancies. For this reason, rare disease registries benefit from a comprehensive database that is sufficient to address critical clinical questions.

• To establish a patient base for evaluating drugs, medical devices, and orphan products.

Stakeholders are vitally interested in developing drugs, devices and other therapies for rare diseases, and many rare disease registries have been developed to support the drug development process. Patient registries for rare diseases may emerge from suggestion, pressure, or advocacy of affected patients and/or families. Direct influence can be seen when patients and their caregivers decide they want a registry, raise the funds, and push for its creation. Indirect influence can be seen when patients or special interest groups drive government to make research on that disease a priority.

Patient registries are a key aspect of national plans/strategies for rare diseases and are cited as a crucial source of information on rare diseases, in terms of basic and clinical research as well for epidemiological and public health purposes, to be supported at national and European levels in the Council Recommendation. Patient registries are a key tool for gathering the scarce knowledge relevant to rare diseases so as to improve the understanding of these conditions and the treatment available to patients, as well as the planning of healthcare services for these diseases.

In January 2016 there were around 690 disease registries in Europe registered in the Orphanet database, of which 59 were European, 74 were international, 482 were national, and 75 were regional). [3]

At the national level many countries are considering in the scope of their national plans/strategies the best way to collect data relative to rare disease patients, and at the Community level the EC is in the process of establishing a European Platform for Rare Disease Registration.

Currently in Bulgaria there are total of 11 national rare disease registries, as follows:

- Bulgarian cystic fibrosis patient registry - contributes to the EUROCARE CF registry

- Duchenne and Becker muscular dystrophy and spinal muscular atrophy patient registries in Bulgaria - part of the TREAT-NMD network

- National registry of adult patients with chronic myeloid leukemia

- National registry of patients with Crohn disease

- National registry of patients with Gaucher disease

- National registry of patients with mucopolysaccharidosis type II (MPS2)

- National registry of patients with phenylketonuria

- National registry of patients with primary immunodeficiencies (PID)

- National registry of patients with thalassaemia major

- National registry of patients with Wilson disease

- The Bulgarian genetic registry of monogenic disorders

The European Union Committee of Experts on Rare Diseases (EUCERD) adopted a set of Recommendations on Rare Disease Patient Registration and Data Collection [4] in 2013 with the aim of setting down the consensus reached to date and to guide all stakeholders into discussions on data collection and registration.

To resolve the issue of information dispersion, Orphanet provides direct online access to an inventory and encyclopaedia of rare diseases. Orphanet attributes a unique identifier to each disease and places them in a polyhierarchical classification of rare diseases. Orphanet provides expert validated information on expert services in its 37 partner countries with the input of national partner teams. These services include expert centres, clinical laboratories, research projects, registries, biobanks, and patient organizations. An inventory of orphan drugs is also maintained. Orphanet is available in 7 languages (English, French, Spanish, German, Italian, Portuguese, and Dutch).

To support policy makers, Orphanet regularly publishes reports in a collection entitled "Orphanet Report Series", including lists of rare diseases with their prevalence, lists of orphan drugs in Europe and lists of rare disease registries in Europe. [5]

A number of Orphanet datasets are also directly accessible in a number of re-usable formats via Orphadata in order to ensure the dissemination of the Orphanet nomenclature of rare diseases and maximize the use of Orphanet's data for research and policy-making purposes.

Disease registries create the possibility of assessing the long-term safety and benefit of different treatments, perhaps leading to treatment algorithms that allow more choices for patients and clinicians. The lack of information reflects the uncertainties in diagnostic criteria and perhaps even inadequacies in data gathering procedures. As the patient community continues to grow throughout the world, fostered by electronic communication and social media, knowledge of the prevalence of rare diseases will increase and access to patients will be more readily available. Improved access to information on rare diseases continues to expand as rare diseases are addressed on a global basis and more people are aware of the informational needs of the rare diseases community.

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