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On the Creation, Utility and Sustaining of Rare Diseases Research Networks: Lessons learned from the Urea Cycle Disorders Consortium, the Japanese Urea Cycle Disorders Consortium and the European Registry and Network for Intoxication Type Metabolic Diseases

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A B S T R A C T

The past two decades has seen a rapid expansion in the scientific and public interest in rare diseases and their treatment. One consequence of this has been the formation of registries/longitudinal natural history studies for these disorders. Given the expense and effort needed to develop and maintain such programs, we describe our experience with three linked registries on the same disease group, urea cycle disorders. The Urea Cycle Disorders Consortium (UCDC) was formed in the U.S. in 2003 in response to a request for application from the National Institutes of Health (NIH); the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) was formed in 2011 in response to a request for applications from the Directorate-General for Health and Consumers (DG SANCO) of the EU; and the Japanese Urea Cycle Disorders Consortium (JUCDC) was founded in 2012 as a sister organization to the UCDC and E-IMD. The functions of these groups are to collect natural history data, educate the professional and lay population, develop and test new treatments, and establish networks of excellence for the care for these disorders. The UCDC and JUCDC focus exclusively on urea cycle disorders while the E-IMD includes patients with urea cycle disorders and organic acidurias. More than 1400 patients have been enrolled in the three consortia, and numerous projects have been developed and joint meetings held including an international UCDC/E-IMD/JUCDC Urea Cycle meeting in Barcelona in 2013. This article summarizes some of the experiences from the three groups regarding formation, funding, and models for sustainability.

1. Introduction

2013 marked the 30th anniversary of the United States' Orphan Drugs Act, the 20th anniversary for Japan's Orphan Drug policy, and the 14th anniversary of the European Union's Regulation (EC) No 141/2000 on Orphan Medicinal Products. As a result of these governmental actions growth in the therapeutic development of rare disease compounds has accelerated. The compound annual growth rate (cagR) of the orphan drug market between 2001 and 2010 was an impressive 25.8 percent, compared to only 20.1 percent for a matched control group of non-orphan drugs [1]. Lichtenberg noted in a 2013 economic impact paper: "Our estimates indicate that, in the United States, potential years of life lost to rare diseases before age 65 (PYLL65) declined at an average annual rate of 3.3% and that, in the absence of new drug approvals, PYLL65 would have increased at a rate of 0.9%." [2]

In 2002 the United States passed The Rare Disease Act of 2002, which provided the statutory authorization for the Office of Rare Diseases (ORD) of the Office of the Director of the National Institutes of Health (NIH) to act as the federal entity able to recommend a national research agenda, coordinate research, and provide educational activities for researchers in the field of rare diseases. (ORD's name was changed to the Office of Rare Diseases Research (ORDR) and is now a section of the National Center for Advancing Translational Sciences (NCATS) of the NIH.) Numerous published and public statements have emphasized the need to bridge the knowledge gap in the field of rare diseases to improve the care of patients and facilitate the development of new treatments. The patient organizations the National Organization for Rare Diseases (NORD) and The European Organization for Rare Diseases

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(EURORDIS) have stated that patient registries must be a fundamental research effort to ensure the welfare of patients with rare diseases (see EORORDIS-NORD-CORD Joint Declaration of 10 Key Principles for Rare Disease Patient Registries). These agencies, laws, and organizations have led to an enhanced interest in the creation and utility of registries in rare disease patient populations.

The World Health Organizations definition of "patient registry" is "a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a pre-determined scientific, clinical or policy purpose." It does not prejudge the amount of collected data, which can be minimal or extensive, but implies continuity (longitudinality) as distinct from a cross-sectional survey. The U.S. National Committee on Vital and Health Statistics defines registries as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes (them) to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects". These definitions often result in some confusion when referring to a "patient registry" and differ in common usage between Europe and the United States. This article will use the term "registry" to denote a collection of longitudinal natural history data on patients with a specific condition or set of related conditions rather than a database of contact information for patients with a particular condition.

2. History of the UCDC, EIMD and JUCDC

In 2001, a group of urea cycle disorder (UCD) clinical experts met in Washington D.C. along with the National Urea Cycle Disorders Foundation (NUCDF, a patient advocacy organization), and representatives from the NIH ORD to develop consensus treatment guidelines for UCD [3]. One result of this conference was the recognition that there was a knowledge gap that significantly compromised the abilities to formulate "best practices" in the field [4]. What resulted from this conference was a series of articles based on the limited available data and the expert opinion of the group [3,5–10]. On February 27, 2003, the ORD, in response to the Rare Diseases Act of 2002 (P.L. 107–280), released a Request for Applications (RFA) for a Rare Diseases Clinical Research Network in collaboration with the National Center for Research Resources (NCRR) and other NIH Institutes and centers. The group that first met in 2001 formed the core of a successful U54 application forming the Urea Cycle Disorders Consortium (UCDC) with 5 sites in the U.S. Part of the strength of the UCDC was the subsequent identification of philanthropic donors who basically matched the NIH grant, permitting the expansion of sites in the UCDC to its current 14, including one in Canada and two in Europe (which are also part of the E-IMD). Several articles have been published on the progress of this consortium and its success in recruitment and retention of subjects [11,12]. The UCDC has been funded for three cycles (currently through 2019) and has received mention in hearings in the U.S. House of Representatives as a model for this type of work (U.S. House of Representatives Health subcommittee hearings on 21st Century Cures). It has also served as a model system for bringing rare disease therapeutic agents rapidly to market, with three new compounds receiving FDA approval in the past decade. The ecosystem responsible for sustaining a dispersed collaborative network for over 10 years in a competitive funding environment is part of the subject of this article.

3. E-IMD

The partners of the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) have already successfully collaborated for many years in various projects on UCD and organic acidurias (OAD). Thus the E-IMD formalized and extended a previously existing informal network. Multidisciplinary collaborations (biochemistry, radiology, psychology) existed previously on inborn errors which included natural history studies of glutaric aciduria type 1 and methylmalonic aciduria and guideline development for glutaric aciduria type 1 and UCDs [13].

In 2010, a strategic decision was made to formalize this cooperation by establishing the E-IMD in an application for funding within the E-Rare Call 2009 (for UCD) and the FP7-HEALTH-2009 Call (for organic acidurias). This brought together the OAD and UCD groups which had previously acted independently.. E-IMD was established to extend the information technology and data warehouse expertise developed by these groups to other IMDs and new applications, and to foster a collaboration with patient advocacy organizations, the pharmaceutical organizations, industry, and other scientific consortia.

E-IMD has been partially funded from 2011 to 2014 by the European Union (via the European Agency for Health and Consumers [EAHC]), in the framework of the Health Programme 2008–2013. It is coordinated by the University Hospital Heidelberg and started with 28 project partners (a coordinating center, 12 associated sites and 15 collaborating partners) in 15 European countries. Associated partners received on average 60% EU co-funding from the grant whilst collaborating partners participated on a voluntary basis. The network has developed beyond expectations and now includes 87 partners from 25 countries on four continents. Sixteen patient advocacy organizations, four industry partners and 67 clinical partners currently form the network. Representatives of UCDC, JUCDC, and the adult metabolic and dieticians' groups of the Society for the Study of Inborn Errors of Metabolism (SSIEM) are also E-IMD partners. Funding from the Kindness for Kids Foundation helps to sustain the E-IMD registry.

In 2013, the data warehouse platform of the E-IMD was extended to homocystinuria, methylation defects, and folate cycle disorders. In 2014, disorders of biogenic amine and tetrahydrobiopterin metabolism were added. In conclusion, the network has been continuously extended, and new IMD groups have been successfully added to the modular information technology platform.

4. JUCDC

Members of the Japanese Society for Inherited Metabolic Disease (JSIMD) have collaborated to form the Japanese UCD consortium in 2012 under the conduct of Fumio Endo, who was the Chairperson of JSIMD from 2010 to 2014. Previously, numerous research programs had been established, such as the long term follow up and new medication survey for IMD in Japan as well as the development of guidelines and establishment of new therapies for organic acidurias, urea cycle disorders, and glycogen storage disorders supported by the Japanese Ministry of Health, Labour and Welfare. These studies revealed the outcomes, complications and remaining problems for Japanese UCD, OA and GSD patients. The next step for this field survey was to determine how to accumulate scientific knowledge about the effectiveness of new drugs, and how our guidelines impacted quality of life. The goal was also to collaborate with patient organizations, industries and government organizations. We used the template that was successfully deployed by the E-IMD to accomplish this. In 2012, the National Center for Child Health and Development (NCCHD) in Tokyo, established a registration system that not only clinicians but also patients can register themselves, and the accumulated data are stored at NCCHD, supported by the Ministry of Health, Labour and Welfare from 2012 to 2014. This registration system will be maintained and supported by the JSIMD from 2014. In conclusion, JUCDC has collaborated with other research groups and is continuously developing.

5. Results

5.1. Patient Enrollment

As of August 1, 2014, the UCDC has registered 701 cumulative patients in its longitudinal study, with 680 eligible patients having