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Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group

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ABSTRACT

Background: Successful development of new treatments for rare diseases (RDs) and their sustainable patient access require overcoming a series of challenges related to research and health technology assessment (HTA). These impediments, which may be unique to RDs or also apply to common diseases but are particularly pertinent in RDs, are diverse and interrelated. **Objective:** To develop for the first time a catalog of primary impediments to RD research and HTA, and to describe the cause and effect of individual challenges. **Methods:** Challenges were identified by an international 22-person expert working group and qualitative outreach to colleagues with relevant expertise. A broad range of stakeholder perspectives is represented. Draft results were presented at annual European and North American International Society for Pharmacoeconomics and Outcomes Research (ISPOR) congresses, and written comments were received by the 385-strong ISPOR Rare Disease Review Group from two rounds of review. Findings were refined and confirmed via targeted literature search. **Results:** Research-related challenges linked to the low prevalence of RDs were categorized into those pertaining to disease recognition and diagnosis, evaluation of treatment effect, and patient recruitment for clinical research. HTA-related challenges were classified into issues relating to the lack of a tailored HTA method for RD treatments and uncertainty for HTA agencies and health care payers. **Conclusions:** Identifying and highlighting diverse, but interrelated, key challenges in RD research and HTA is an essential first step toward developing implementable and sustainable solutions. A collaborative multistakeholder effort is required to enable faster and less costly development of safe, efficacious, and appropriate new RD therapies that offer value for money.

Keywords: cost-effectiveness, health policy, health technology assessment, orphan designation, rare diseases.

Background to the Rare Disease Working Group

In 2013, two working groups were established under the auspices of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Rare Disease Special Interest Group. The first working group undertook a review of rare disease [RD] terms and definitions, motivated by recognition of the lack of a universal definition of rare diseases or health technologies for their treatment and the existing diversity of definitions applied to rare diseases. The output of this research was the article "Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group," published in 2015 in *Value in Health* [1].

The second working group, Challenges in Research and Health Technology Assessment of Rare Disease Technologies, identified and reviewed challenges faced by those engaged in research and health technology assessment (HTA) in RDs and their treatments. The goal of the working group was to evaluate these challenges and disseminate the findings via publication and presentations. An outline was initially developed by working group members representing different

The authors represent the ISPOR Rare Disease Special Interest Group's Challenges in Research and Health Technology Assessment of Rare Disease Technologies Working Group.The authors declare that they followed the ISPOR Code of Ethics publication guidelines. The authors declare that they have no competing interests.

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stakeholder perspectives from Europe and the United States, and sequential drafts were reviewed and modified during monthly teleconferences among the coauthors. Further feedback was obtained during work-to-date presentations given at annual ISPOR European congresses in Dublin, Amsterdam, Milan, and Glasgow, and annual ISPOR international meetings in Montreal and Boston. The final version of this article represents the outcome of these discussions, conference feedback, and written comments received by members of the ISPOR Rare Disease Special Interest Group from two rounds of review.

Introduction

Approximately 60 million people in the United States and European Union are affected by an RD [2]. Although RD research and clinical development of technologies for the treatment of RDs are rapidly expanding areas, there is still no universally accepted terminology or definition as to what constitutes an RD. Typically, RDs are characterized by low frequency, where frequency is expressed in terms of prevalence or incidence within a specific country or geographical region. A global review of RD terminology found that 58% of definitions included a prevalence threshold with an average global threshold of 40 cases/100,000 people [1].

According to the European Organisation for Rare Diseases (EURORDIS), an alliance of more than 700 RD patient organizations in 65 countries, more than 6000 distinct RDs exist, of which approximately 80% are of genetic origin [3]. On average, five new RDs are described every week in the medical literature [3]. RDs represent a broad assortment of disorders and constellations of clinical signs and symptoms but the vast majority of RDs affect children and are chronic and life threatening [4]. No cure exists for the substantial majority of RDs, and only a few RD treatments with proven efficacy are currently available [5].

Consequently, countries throughout the world have recognized the need to enact laws and regulations to provide incentives for the development of new and innovative technologies for the treatment of RDs [6–10]. Advancements in molecular genetics, understanding of disease pathogenesis, and medical technology have led to enhanced identification of RDs and pathways for improving RD diagnosis, prognosis, and treatment, as well as more accurate subclassification of common diseases into collections of RDs with distinct phenotypes [11–13].

However, the development of new RD therapies faces significant obstacles with respect to research and HTA. These challenges had not previously been evaluated comprehensively and, consequently, this ISPOR Rare Disease working group developed a multistakeholder catalog of the principal difficulties faced in RD research, during evidence generation for HTA, and HTA of RD treatments. Although identification of the obstacles is an important first step toward providing efficient and practical solutions, the working group anticipates the generation of another detailed report providing recommendations to address the challenges identified here. Challenges related to pricing of health technologies for RDs, their adoption, and patient access were not within the remit of this project.

Methods

Impediments to RD research and HTA were identified by a working group comprising 22 members with relevant expertise, as well as through qualitative outreach to colleagues specializing in RDs in contract research, the life sciences industry, and academia. The preliminary list of challenges underwent three rounds of review by the working group for comprehensiveness, refinement, and merger of duplicates. The challenges identified were analyzed for interrelationships and classified into categories. Findings were underpinned by a targeted literature search. Written comments were received by the 385-person ISPOR Rare Disease Review Group from two rounds of review and further verified when draft reports were presented at ISPOR annual international congresses in North America and Europe. A broad range of stakeholder perspectives from researchers, clinicians, industry, regulatory and HTA agencies, patients, payers, and market access specialists are represented in this report.

Results

The following sections describe the cause and effect of individual challenges and their relevance in RDs. Results are grouped into challenges relating to RD research and HTA of RD treatments, respectively, and subcategorized. It should be noted that, although the identified impediments are diverse, they are interrelated. Furthermore, some of the identified issues are unique to RDs, whereas others also apply to common diseases but are especially relevant or burdensome in RDs.

Challenges in Research

Research-related challenges linked to the low prevalence of RDs were grouped into three categories, as illustrated in Figure 1.

Disease recognition and diagnosis

Several interrelated challenges pertain to the recognition and diagnosis of RDs, all of which impinge on the quality of epidemiologic and clinical studies and complicate the characterization of unmet patient needs, potential efficacy, safety, effectiveness, and value of treatments for RDs.

Lack of familiarity with RDs. Insufficient awareness and knowledge of RDs can increase the likelihood of misdiagnosis and delayed accurate diagnosis [14–21]. Patients unfamiliar with pertinent signs and symptoms may not seek medical advice when appropriate. Similarly, clinicians may fail to recognize the disease [14,15] or may incorrectly attribute symptoms to common diseases with which they are more familiar. This is reflected in the average delay of 7.6 years in the United States and 5.6 years in the United Kingdom before a patient with an RD receives the correct diagnosis [22]. In a survey-based outcome study of symptomatic patients with α-1 antitrypsin deficiency, an underrecognized rare genetic condition that increases the risk of lung emphysema and liver disease, the average diagnostic delay was 8.3 ± 6.9 years after onset of symptoms [23].

Disease heterogeneity. Incomplete understanding of a disease and its etiology may severely limit the comparability of findings from epidemiologic and clinical studies. Heterogeneity in pathogenesis, symptom presentation, natural history, disease severity, and progression can greatly impede efforts to characterize an RD in clinical research and to identify it in routine clinical practice, often resulting in misdiagnosis and an underestimation of true disease frequency.

The heterogeneous clinical presentation of many RDs hampers identification of affected patients, as seen across the broad spectrum of phenotypes in Gaucher's disease, ranging from lethal disease in neonates to asymptomatic older adults [24]. It is not uncommon for patients with RDs, such as Behçet's disease or late-onset Pompe disease, to exhibit a long initial asymptomatic phase during which their condition may not be identified [25,26]. In many RDs, no genotype–phenotype correlations have yet been established [24]. In addition, RD patients may not seek medical advice until symptoms become burdensome. These factors further complicate efforts to fully understand the presentation, etiology, and natural history of an RD, thereby making it particularly difficult to provide individual patients with prognostic