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Health Policy Analysis

Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group

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ABSTRACT

Background: At present, there is no universal definition of rare disease. **Objective:** To provide an overview of rare disease definitions currently used globally. **Methods:** We systematically searched for definitions related to rare disease from organizations in 32 international jurisdictions. Descriptive statistics of definitions were generated and prevalence thresholds were calculated. **Results:** We identified 296 definitions from 1109 organizations. The terms "rare disease(s)" and "orphan drug(s)" were used most frequently (38% and 27% of the definitions, respectively). Qualitative descriptors such as "life-threatening" were used infrequently. A prevalence threshold was specified in at least one definition in 88% of the jurisdictions. The average prevalence threshold across organizations within individual jurisdictions ranged from 5 to 76 cases/100,000 people. Most jurisdictions (66%) had an average prevalence threshold between 40 and 50 cases/100,000 people, with a global average of 40 cases/100,000 people. Prevalence thresholds used by different organizations within individual jurisdictions varied substantially. Across jurisdictions, umbrella patient organizations had the highest (most liberal) average prevalence threshold (47 cases/100,000 people), whereas private payers had the lowest threshold (18 cases/100,000 people). **Conclusions:** Despite variation in the terminology and prevalence thresholds used to define rare diseases among different jurisdictions and organizations, the terms "rare disease" and "orphan drug" are used most widely and the average prevalence threshold is between 40 and 50 cases/100,000 people. These findings highlight the existing diversity among definitions of rare diseases, but suggest that any attempts to harmonize rare disease definitions should focus on standardizing objective criteria such as prevalence thresholds and avoid qualitative descriptors.

Keywords: orphan drugs, prevalence, rare disease, terminology.

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Background to the Rare Disease Working Group

In June 2013, the Rare Disease Terminology & Definitions Used in Outcomes Research Working Group was established under the auspices of the ISPOR Rare Disease Special Interest Group. Members developed the concept because of the lack of a universal definition of rare diseases or the technologies used in their treatments and the existing diversity in the use of different definitions used to describe rare diseases and the underlying connotations associated with them.

The leadership group represents a diverse range of perspectives. They work in regulatory agencies, research organizations, academia, and the pharmaceutical industry. In addition, the group was international, comprising ISPOR members from the United Kingdom, Germany, Serbia, Belgium, Canada, Italy, The Netherlands, Switzerland, and the United States. In addition, local researchers in Latin America and Asia Pacific contributed to the findings in those parts of the world.

The leadership group met approximately every 5 weeks by teleconference to develop an outline and methodology, enlist volunteer researchers through ISPOR's regional chapters as well as discuss the literature review, findings, analysis, translations, and issues that arose during the course of manuscript development. In addition, members met in person at the ISPOR Annual European congresses in Dublin and Amsterdam and the ISPOR International Meeting in Montreal.

Preliminary findings were presented in a forum presentation at the 2013 ISPOR Annual Meeting in Dublin, and a first draft was presented at the ISPOR Annual International Meeting in Montreal. Oral comments were received during the presentations. Written

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comments were received during two rounds of review with the 200+ person ISPOR Rare Disease Review Group.

All comments were considered, and most were substantive and constructive. Comments were addressed as appropriate in subsequent versions of the report.

Introduction

Increased focus on rare diseases over the last several decades has been spurred mainly by legislation intended to facilitate patient access to effective treatments by incentivizing pharmaceutical and biotechnology companies to develop new medicines that would otherwise not be profitable [1]. As an indication of the success of the 1983 Orphan Drug Act in the United States, more than 420 orphan drugs and biologic products for rare diseases have been approved by the Food and Drug Administration (FDA), compared with fewer than 10 such products in the decade before the Act [2,3]. Similarly, since 2000, when the European Union (EU) established procedures for orphan drug application and incentives for development in their EU Regulation on Orphan Medicines (EC/141/2000) to address rare conditions, 84 orphan drugs have received market authorization by the EU Commission, 2 of which were subsequently withdrawn [4]. Increased attention on rare diseases has also resulted from an improved genetic, molecular, and biochemical understanding resulting from recent scientific and technological advances [5].

A rare disease is a health condition that affects a small number of people compared with other prevalent diseases in the general population. To date, between 5000 and 8000 distinct rare diseases have been documented [4], and new rare diseases are reported regularly in the medical literature [5,6]. Social awareness uptake and global connectedness in the area of rare diseases is noticeable. For example, when the first Rare Disease Day began in 2008, only 18 jurisdictions participated compared with 84 in 2014 [4]. The total number of patients affected is large (e.g., 27–36 million people in the EU and 25 million in the United States [5]), posing important challenges to health care providers, particularly in the context of escalating costs [6,7].

It is important that the terminology related to definitions of rare diseases is understood by different stakeholder groups. Understanding is complicated by the definitions themselves, which differ according to the context in which they are used (such as rare disease advocacy groups vs. private payers) and applied (e.g., for regulatory approval vs. reimbursement).

Most definitions appear to at least consider disease prevalence, but other criteria sometimes also apply, including disease severity, whether the disease is life-threatening, whether there are alternative treatment options available, and whether it is heritable [8,9]. The use of diverse terminology and the use of inconsistent definitions can result in confusion and inconsistencies in access to treatment. The absence of agreed definitions for rare disease terminology has also aided the increased colloquial use of some terms for rare diseases, such as “ultraorphan” or “neglected,” in a way that might not always correspond to the formal definitions of these terms. In addition, some terms may be implicitly associated with emotional connotations (e.g., “life-threatening,” “orphan,” and “neglected”) that may differ depending on the type of organization making reference to the term.

Despite progress in a wide range of collaborative regulatory and patient-related activities internationally, there is no global consensus definition of rare disease and related health care interventions. Moreover, the extent of global variation in definitions related to rare disease is unclear.

This article presents a review of the terminology used in definitions for rare disease and associated health technologies identified from a systematic Web search of documentation from 32 relevant national and international organizations from six geographic regions. Our review provides a comprehensive overview of the commonalities and differences that exist in definitions used across the relevant types of organization and multiple jurisdictions globally.

Methods

Search Process

Members of the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) who volunteered to participate actively in this research were invited to join the leadership group. They represented a diverse range of stakeholders, including regulatory, academic, pharmaceutical industry, and patient organizations. Reflecting ISPOR membership demographic characteristics, they were predominantly from Europe and North America.

The systematic search process was developed in three steps. First, the leadership group identified English-language terms used in the context of defining rare disease and associated health technologies (Table 1). The search terms were created with the aim of capturing all relevant definitions to generate a comprehensive audit of definitions currently in use, and were not restricted or categorized to reflect potential subcategories of definitions, such as “very rare” or “ultrarare” disease.

Second, the leadership group identified the types of agencies and organizations that were likely relevant, and classified them as health technology assessment (HTA) agency, private payer, public payer, regulator, research center, umbrella patient organization, or other (including pharmaceutical trade organizations and nonregulatory government agencies), as presented in Table 2. To make the review more manageable, we included only those patient organizations that were not disease-specific, that is, umbrella patient organizations and advocacy groups (Table 2). Umbrella organizations were included if they were jurisdiction-specific. Variations in the mix of national organizations included in the analysis were permitted across jurisdictions, expecting that some jurisdictions would not have all the agencies or organizations specified.

The leadership group finally selected jurisdictions that represented each of the six geographic regions of the world (North America, South America, Asia, Europe, Africa, and Oceania). These are listed in Table 3. Jurisdictions were included only if there was a positive response to the solicitation to participate and if there was information publicly available. For example, Liberia could not be included because there was no relevant information available on any Web sites that were searched.

Table 1 – Search terms used to identify definitions.

Highly specialized technology
Neglected disease
Orphan disease
Orphan drug
Orphan medicinal product
Orphan product
Orphan subset
Rare and neglected disease
Rare condition
Rare disease
Rare disorder
Syndrome without a name
Ultraorphan disease
Ultraorphan drug
Ultrarare disease
Undiagnosed disease
Very rare disease

Table 2 – Organization types included in the search.

Organization	Definition	Example
Health technology assessment agency	Agencies with a primary mandate to carry out health technology assessments, including governmental, quasi-governmental, and nongovernmental organizations	National Institute for Health and Care Excellence (NICE) in the United Kingdom
Private payer	Organizations such as private health insurance providers	Aetna in the United States
Public payer	Public health insurance providers	Ontario Drug Benefit Program in Canada
Regulator	Regional and national government agencies that regulate pharmaceuticals and medical devices	Food and Drug Administration (FDA) in the United States
Research center	Includes any research-focused organizations, not restricted to those with a special interest in rare diseases	National Center for Advancing Translational Sciences in the United States
Umbrella patient organization	Includes advocacy (patient) groups, policy groups, and organizations that provide resources for patients with rare diseases	National Organization for Rare Disorders (NORD)
Other	Any organization that could not be classified into one category was categorized as "Other," including pharmaceutical trade organizations and nonregulatory government agencies	The Ignite Project in Canada

Table 3 – List of jurisdictions included in the search.

Region	Jurisdiction	Data verified
Africa	South Africa	
Asia	China	x
	India	x
	Japan	x
	Korea	
	Russia	
	Taiwan	
	Turkey	x
Europe	Czech Republic	x
	Denmark	x
	England	x
	European Union	x
	France	
	Germany	
	Ireland	
	Italy	x
	The Netherlands	x
	Poland	x
	Scotland	x
	Slovakia	x
	Spain	
	Sweden	x
	United Kingdom	x
	Wales	x
North America	Canada	x
	Mexico	
	United States	
Oceania	Australia	x
South America	Argentina	
	Brazil	x
	Chile	x
	Colombia	

A working group was assembled that included researchers who spoke the native language for the jurisdiction in which they were asked to search for information according to the methods described below.

Data Collection

Data collection comprised a systematic Internet-based search that was carried out between December 2, 2013, and April 17, 2014. Each member of the working group searched for each of the 17 terms in Web sites relevant to each organization and any documentation contained therein. The researchers had discretion in determining equivalent terms in other languages, recognizing that terms might not translate directly. Researchers applied their local knowledge to identify relevant agencies and organizations.

If a term was found in documentation available for a given organization, the full definition that included the search term (in the native language), as well as the source (a complete list of the sources of definitions identified is available from the corresponding author on request) (valid reference hyperlink), was recorded on a jurisdiction-specific data extraction table. A standardized template for data recording was used for all local searches to ensure consistency of search terms and data format. Definitions in a language other than English were transcribed and recorded in both the original language and English. If more than one definition was found on the same Web site, both definitions were recorded. If a term was not found, a null finding was recorded in the database. If another term was found that was not among the predefined search terms, it was added to the spreadsheet with the requisite definition and source information.

A central data management process, overseen by the ISPOR Rare Disease Special Interest Group liaison, ensured that the database was verified as having been completed appropriately, and data recorded correctly. Specifically, a single individual collected and collated all local search results into a single electronic master database. Collation and data entry were then

verified by at least one other researcher to ensure accuracy. Data that were incomplete or improperly recorded were returned to the researcher with directions on how to satisfy the requirements for adequate reporting.

If a researcher was unable to complete the task as per protocol, or if local language fluency was an issue, a volunteer researcher located in the target jurisdiction was identified to assist in the completion and verification of the task/content. These in-country researchers were identified through the ISPOR regional chapters, the ISPOR Regional Consortia, or the ISPOR member database. In most cases, the original spreadsheet was sent to the verifier to check the original researcher's findings. If any of the original researcher's findings were deemed incorrect or missing, the verifier added that information through another search.

Data Analysis

Data from each jurisdiction, including the United Kingdom and the EU, were combined into a master database for analysis. We calculated the frequency with which each search term (e.g., "rare disease") and individual descriptors (e.g., "rare") were used within the definitions that were identified. Identified definitions were reviewed to determine how frequently the following qualitative descriptors were used: "life-threatening" (or "life threatening"), "debilitating," "not available," "unavailable," "not possible," "severe," "intractable," "no treatment," "no alternative," "no cure," "incurable," "fatal." We also calculated the frequency with which the terms "genetic," "hereditary," or "heritable" were used. We also examined the distribution of definitions per jurisdiction and organization type.

Prevalence thresholds used in each definition were converted to absolute frequency and number of cases per 100,000 people [10,11]; an average value was used if a range of thresholds was presented within a single definition. Where prevalence was not specified but was implied in the definition, for example, if there was a specification of the patient population size, we calculated the implied prevalence using the size of the population (as of 2014) in the jurisdiction of interest. Prevalence thresholds used in definitions were examined for individual jurisdictions, geographic regions, and organization type.

Jurisdiction-specific thresholds were estimated by calculating the average value from all organizations within that jurisdiction. We calculated the coefficient of variation, defined as the ratio of the SD to the mean of the distribution of prevalence thresholds for individual jurisdictions.

Results

Terminology Used in Definitions

A total of 1109 agencies or organizations were searched from 32 jurisdictions, resulting in the identification of 296 definitions. In addition to the 17 search terms, researchers identified 6 additional terms that were used as search terms (see Table 4). Only those terms that were used in at least one definition (N = 23; see Table 4) were included in the analysis.

With 112 definitions, the most frequently defined term was "rare disease(s)." This term accounted for 38% of all definitions and was defined more frequently than "orphan disease(s)" (18 definitions; 6%) (Table 4). Seventy-nine definitions of "orphan drug(s)" were identified.

Among the descriptors used to refer to a type (i.e., adjectives), "rare" was used most frequently (used in 151 definitions), although "orphan" was also used frequently (127 definitions). Both these terms were used much more often than other related descriptors such as "neglected" (6 definitions) and "specialized" (9 definitions) (Table 5). Among adjectives used as descriptors in definitions, "rare" was the most frequent (52% of the definitions).

Among the descriptors used to refer to rarity (modifiers), "ultra" (used in 16 definitions) was used more frequently than "very" (4 definitions), although both descriptors were seldom used (Table 5).

Among the descriptors used to refer to a condition (i.e., nouns), "disease" (used in 153 definitions) was used most frequently and was used more often than "condition" (9 definitions), "disability" (2 definitions), and "syndrome" (1 definition) (Table 5).

Few definitions used qualitative descriptors of the severity of the disease; indeed, most definitions (N = 208; 70%) did not use such terms. When a descriptor(s) was used, the most prevalent was the use of two terms (19%) followed by 9% with one descriptor. No definitions used more than three such terms. The qualitative descriptors that were used most frequently were "life-threatening" (15%), followed by "debilitating" (10%), "severe" (3%), and "intractable" (1%). Terms related to genetics were used very infrequently in definitions: only 10 (3.4%) definitions used the term "genetic," whereas only 1 definition used the term "hereditary" and no definitions used the term "heritable."

When the number of definitions identified was stratified according to the type of organization, the umbrella patient organizations and research centers had a relatively higher proportion of definitions of rare disease than did other types of organizations (Table 6). We identified at least one definition in

Table 4 – Frequency of terms used across all 296 definitions identified.

Search term	Number of definitions	Proportion of total (%)
Rare disease*	112	38
Orphan drug	79	27
Orphan disease	18	6
Orphan medicinal product	16	5
Rare disorder	11	4
Ultrarare disease	10	3
Highly specialized technologies	9	3
Rare condition	9	3
Neglected disease	5	2
Ultraorphan drug	4	1
Orphan product	4	1
Very rare disease	4	1
Orphan indication†	2	1
Low-frequency disease†	2	1
Pharmacological therapies of high complexity†	2	1
Rare disability†	2	1
Ultraorphan disease	2	1
Priority review drugs†	1	<1
Orphan pharmaceutical product†	1	<1
Syndrome without a name	1	<1
Rare and neglected disease	1	<1
Extremely rare disease†	1	<1
Orphan subset†	1	<1
Rare medicinal technology†	1	<1

* Includes definitions that use qualifiers in addition to "rare disease" such as "intractable," for example, in definitions used in Japan and Korea.

† Terms included by local researchers for use during searches but not included in the original list of search terms.

Table 5 – Frequency of use of individual descriptors* of interest in definitions.

Term	N	Proportion (%)
Type descriptor (adjective)		
Rare	151	51.6
Orphan	127	43.5
Specialized	9	3.2
Neglected	6	1.6
Rarity descriptor (modifier)		
Ultra	16	75.0
Very	4	25.0
Condition descriptor (noun)		
Disease	153	92.7
Condition	9	5.5
Disability	2	1.2
Syndrome	1	0.6

* Descriptors have been grouped as adjectives, verbs (modifiers), and nouns.

almost half the research centers and umbrella patient organizations that were searched (Table 6). In contrast, definitions were identified in only 27% of regulatory agencies, 25% of HTA agencies, 17% of public payers, and 8% of private payers (Table 6).

Prevalence Thresholds

Most definitions explicitly or implicitly included a prevalence threshold (172 of 296 definitions [58%] definitions). When stratified by geography, 28 of 32 (88%) jurisdictions included a prevalence threshold in at least one definition of rare disease. Scotland, Mexico, Wales, and Turkey specified prevalence in all (100%) definitions for rare disease we identified in these countries. Only the United States, Australia, and Japan did not specify prevalence explicitly in any definition. We identified only one instance in which incidence was specified in a definition of rare disease (an umbrella patient organization in China). Therefore, it appears that prevalence is the universally preferred epidemiology metric used in definitions of rare disease.

Where prevalence was specified explicitly, various forms of expression were used, including being expressed as a fraction (e.g., 0.00040), as a percentage, or as the number of cases/10,000 or 100,000 people. Prevalence thresholds ranged from 1 case/1,000,000 people, which was used to define ultrarare disease by an HTA agency in Italy (*Unità di Valutazione dell'Efficacia del Farmaco*: www.uvef.it), to 150 cases per 100,000 people, which was used in a definition by an umbrella patient organization in China (CHINA-DOLLS Center for Rare Disorders: http://chinadolls.org.cn/page/4365).

The geographic distribution of prevalence thresholds for individual jurisdictions (averaged across all definitions for each jurisdiction) is presented in Figure 1, and the corresponding average prevalence values are presented in Table 7. The average prevalence thresholds ranged from 5 cases/100,000 for Korea to 76 cases/100,000 people for China.

Note that the range for the average prevalence is presented to illustrate that different prevalence thresholds are used within individual jurisdictions across all definitions identified. For example, the average value of 40 cases/100,000 people for the EU includes definitions from nonregulatory organizations, which specify lower prevalence thresholds than the 50 cases/100,000 used in the European Medicines Agency definition. When averaged across jurisdictions, the global average prevalence was 40 cases/100,000 people, which was equal to the global median prevalence of 40 cases/100,000 people. More than half the jurisdictions in our sample (21 of 32, or 66%) had an average prevalence threshold that was between 40 and 50 cases/100,000 people. The coefficient of variation for the average prevalence thresholds for individual jurisdictions was 0.44.

Examination of the distribution of prevalence per organization type (Table 8), irrespective of geographic location, revealed that umbrella patient organizations had the highest average prevalence threshold among organization types (46 cases/100,000 people; range <1–150), whereas private payers had the lowest values (28 cases/100,000 people; range 1–64). Regulators, HTA agencies, and public payers were intermediate (30–41 cases/100,000 people; range <1–65).

When the range in prevalence thresholds for definitions used by different types of organization was examined within individual jurisdictions, there was substantial variability (data not shown).

Discussion

We identified definitions pertaining to rare diseases and associated concepts and health technologies in all jurisdictions searched, and definitions were identified in a diverse range of organizations within individual jurisdictions. The broad representation of jurisdictions and organizations that we found to have defined rare disease and/or associated technologies suggests that there is a universal desire to distinguish "rare diseases" from "common diseases" in a formal manner. This reflects a growing international trend to establish specific health policies

Table 6 – Number of organizations for which definitions were identified.

Organization type	Number of definitions identified (A)	Number of organizations searched (B)	Proportion of total (A/B) (%)
Private payer	10	125	8
Public payer	48	290	17
Health technology assessment agency	40	158	25
Regulator	78	289	27
Umbrella patient organization	89	186	48
Other*	22	44	50
Research center	9	17	53
Total	296	1109	

* Includes any organization that could not be classified into a category, including pharmaceutical trade organizations and nonregulatory government agencies.

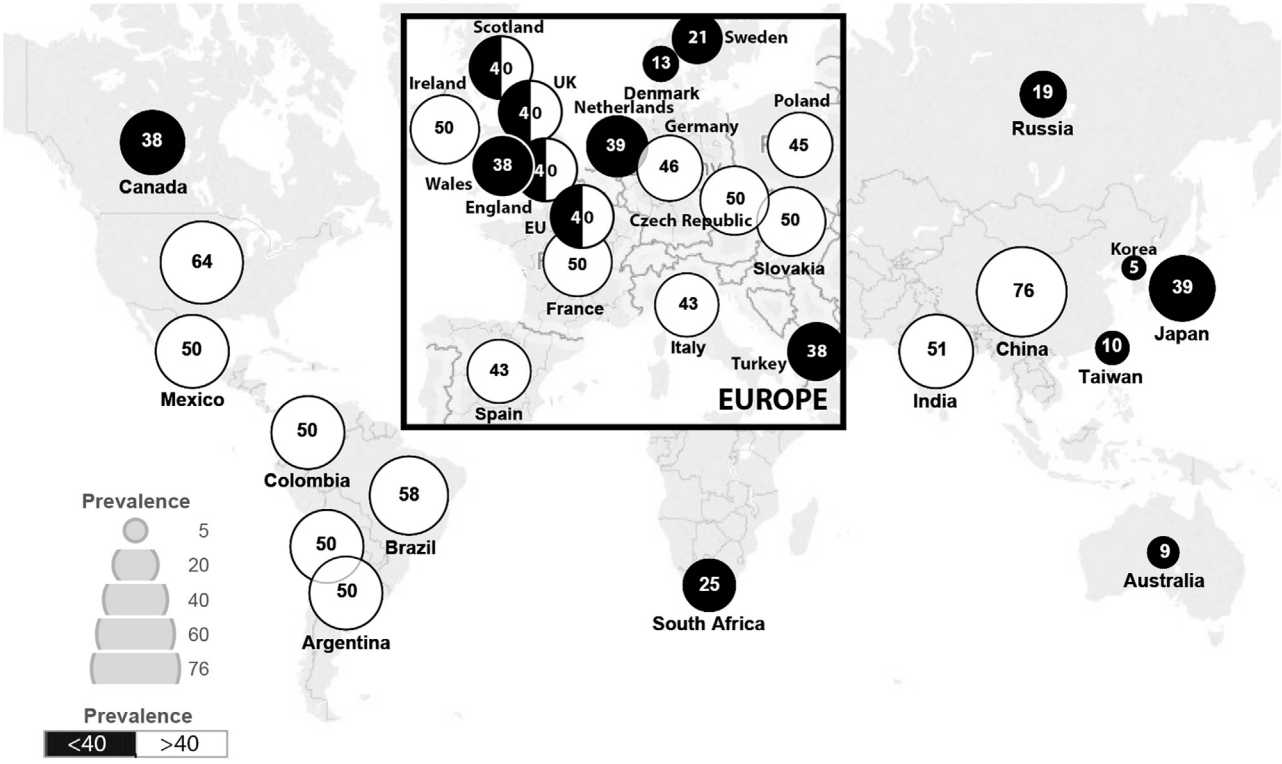

Fig. 1 – Regional distribution of prevalence thresholds for jurisdictions included in the present study. The size of the circles corresponds to the average prevalence threshold (number of cases per 100,000 people) for all organizations within a jurisdiction. Black and white circles correspond to jurisdictions in which the average prevalence in definitions of rare disease is lower or higher, respectively, than the average across all jurisdictions in this study of 40 cases/100,000 people.

for rare diseases. It is important to note that our study has focused on the terminology used to define rare disease; clarification of the concept of what constitutes a rare disease represents an important area for further research.

Our finding that more than six times as many definitions used the term "rare disease" rather than "orphan disease" suggests that "rare disease" is the preferred terminology. The observation that the term "orphan drug" was used in many definitions suggests that "orphan" is predominantly used in the context of defining the technologies associated with the treatment of rare diseases. Most definitions that we identified were relatively rigorous and were based on objective, or measurable, criteria. Although few definitions used terminology that was qualitative and less objective, such as "life-threatening," including terms that could be emotionally loaded, such as "debilitating," a prevalence threshold was used either explicitly or implicitly in most (58%) of the definitions that we identified. In addition, we found that at least one definition of rare disease in every jurisdiction searched included a prevalence threshold. These findings suggest that disease prevalence is the preferred epidemiology metric used in definitions of rare disease. Indeed, prevalence rather than incidence is the most appropriate metric because this reflects how widespread a disease is (as opposed to reflecting the rate of occurrence) and is amenable to use for specific subpopulations. More importantly, the use of prevalence facilitates international comparison.

A notable distinction between the definitions of rare disease in the context of orphan medicinal products provided by the main regulatory authorities in the United States, the EU, and Japan (Table 9) is the absence of an explicit prevalence threshold in the US and Japanese definitions of a rare disease [3,12–14]. Although prevalence is not specified explicitly in the FDA definition, a disease prevalence of 64 cases/100,000 people is implied [3], based on current estimates of the size of the population of the United States (as of 2014).

The global average prevalence threshold across all organizations within the jurisdictions in which we identified definitions was 40 cases/100,000 people. There is variability among individual jurisdictions with regard to the prevalence threshold cited in publicly available definitions of rare disease [1,15,16]. Our results indicate that the average prevalence thresholds used in different jurisdictions range from 5 to 76 cases/100,000 people, with even more variability among different organizations within individual jurisdictions. Although this represents a 15-fold relative difference in the average prevalence thresholds used to define rare diseases in different jurisdictions, most jurisdictions (N = 21 or 66%) had an average prevalence threshold of between 40 and 50 cases per 100,000 people, that is, an absolute difference of 15 cases/100,000 people.

Despite (or perhaps because of) such variation, recent developments in the EU are moving toward a harmonized definition of rare disease, at least in the political arena. Specifically, the European Council Recommendation on an action in the field of rare diseases required all EU member states to recommended adoption of national plans and policies for rare disease by the end of 2013, and the "adequate definition" of rare diseases is endorsed specifically [12]. Most EU member states have since published their national rare disease plans, and it is noteworthy that most governments have adopted the EU definition of a rare disease (affecting no more than 5/10,000 persons) as a definition of rare disease in their national strategies [17], suggesting a marked shift in Europe toward harmonization of a prevalence threshold for the rare disease on a political level.

Table 7 – Average prevalence used in definitions per jurisdiction.

Jurisdiction	Cases per 100,000 people	Range	
		Min.	Max.
Korea	5	5	5
Australia	9	9	9
Taiwan	10	10	10
Denmark	13	1	20
Russia	19	7	50
Sweden	21	10	50
South Africa	25	25	25
Turkey	38	1	50
Canada	38	1	50
Wales	38	2	50
The Netherlands	39	1	50
Japan	39	39	39
European Union	40	2	50
United Kingdom	40	1	50
England	40	1	50
Scotland	40	2	50
Spain	43	2	50
Italy	43	<1	50
Poland	45	2	60
Germany	46	12	50
Czech Republic	50	50	50
Argentina	50	50	50
Colombia	50	50	50
Mexico	50	50	50
Slovakia	50	50	50
France	50	50	50
Chile	50	50	50
Ireland	50	50	50
India	51	2	100
Brazil	58	50	65
United States	64	64	64
China	76	<1	150
Global average	40		

If these developments in Europe are indicative of a growing appetite for international standardization of definitions for rare disease, our findings suggest that one component of such a harmonized definition could be the use of a prevalence threshold of between 40 and 50 cases/100,000 people. In addition, our findings suggest that using terminology such as "rare disease" would be preferential in a universal definition of rare disease because this would conform to the most widely used terminology in current use. Terms such as "orphan drug" should be reserved for use in definitions related to the technologies associated with the treatment of rare diseases.

Similarly, very few definitions made reference to genetics, as illustrated by our finding that the term "genetic" was used in only 10 definitions. This might reflect the fact that not all rare diseases result from genetic defects and the causes of many rare diseases remain unknown. It should be noted that although terms such as "neglected disease" and "ultrarare disease" were included as search terms, this does not imply that these terms describe conditions that should be viewed as similar to rare diseases in general. Indeed, we did not subgroup the search terms a priori to differentiate between the high and low end of the prevalence range, but our findings suggest that definitions used for "very

Table 8 – Average prevalence thresholds used in definitions per organization type.

Organization type	Cases per 100,000 people	Range	
		Min.	Max.
Private payer	28	1	64
Health technology assessment agency	30	<1	60
Public payer	31	<1	65
Regulator	41	1	64
Other	44	1	64
Umbrella patient organization	46	<1	150

Table 9 – Definitions of "rare disease" from prominent regulatory agencies.

Jurisdiction	Organization	Definition of rare disease
United States	Food and Drug Administration	The term "rare disease or condition" means any disease or condition that (A) affects <200,000 persons in the United States, or (B) affects >200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.
European Union (EU)	European Medicines Agency	Rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU.
Japan*	Ministry of Health, Labour and Welfare (MHLW)	The number of patients who may use the drug or medical device should be <50,000 in Japan.

* Note that the data analysis was based on the Japanese MHLW definition issued before the update released on May 23, 2014.

rare" and "ultrarare" diseases and conditions could be viewed as a distinct subcategory within rare diseases. When definitions for "very rare" and "ultrarare" disease were excluded from the analysis of prevalence thresholds, the global average prevalence threshold increased from 40 to 44 cases/100,000 people, reflecting the lower prevalence thresholds used in such definitions.

Adopting a standardized prevalence threshold for defining rare disease internationally would be challenging, and might not be desirable given region-specific demographic, political, and financial (and other) considerations. Indeed, we observed a wide range in prevalence thresholds used by different types of organization within individual jurisdictions, which likely reflects the differences in mandates and remits of the various organizations. When it comes to defining rare disease, the primary interests of payers, which are heavily weighted to account for health care utilization costs, may not be aligned with the primary goals of patient groups, which are focused on access to effective treatments, or those of policymakers, whose priority may lie primarily in improving efficiency in the delivery of health care. Indeed, the growing number of high-cost treatments for rare diseases is likely to have an impact on pharmaceutical expenditure.

Because health care policy is usually controlled at national and regional levels, differences in definitions (e.g., different prevalence thresholds) across different organizations *within* a jurisdiction could pose a much greater challenge for policymakers than differences across jurisdictions, particularly with respect to the potential consequences of different national prevalence thresholds to access and equality of access to health care technologies for the treatment of rare diseases. This challenge is illustrated by our finding that not only have private and public payers produced relatively few definitions compared with other types of organization, but the definitions that have been published by payer organizations tend also to be more stringent than those published by other organizations.

Despite the aforementioned challenges, we suggest that future development of definitions of rare disease should focus on objective, quantitative metrics such as prevalence and avoid the use of qualitative descriptors. The use of nonobjective descriptors could still be accommodated in conceptual definitions of rare disease, whereas operational definitions require the rigor and objectivity imparted by the use of specific prevalence thresholds.

Study Limitations

Our study has several limitations that should be highlighted. First, not all data from all jurisdictions were verified independently. Therefore, data for unverified jurisdictions may be more likely than data for verified jurisdictions to contain errors. We note, however, that minimal changes were made to data as a result of verification, and in addition, the consolidated database was quality checked independently.

Second, several geographic regions (notably Oceania and Africa) had relatively few representative jurisdictions that were included in the search. Therefore, there may be sampling bias in terms of geographic representation and consequently a bias in the definitions that were discovered. The representation of regions and jurisdictions in our sample, however, is an accurate reflection of the global distribution of resources applied to clinical research, and includes all the major markets within which rare diseases have emerged as an issue.

Third, it was sometimes difficult to adequately translate terminology from some non-English languages into English. The result is that the frequency of terms used in definitions from non-English sources may not precisely reflect the use of such terminology in the local context. For example, in Italy, the terms "rare disease," "orphan disease," and "rare condition" appear to be used synonymously. It is not clear how this might have biased the results, although we note that we accepted each translator at face value to avoid introducing a bias into which terms were used in the English translations.

Conclusions

Our systematic review of definitions of rare disease revealed that despite variation in the particular terminology and prevalence thresholds used to define rare diseases among different jurisdictions and types of organization, both within and among jurisdictions, there is some global consistency in using the terms "rare disease" and "orphan drug" preferentially in defining a rare disease and the technologies associated with rare diseases, respectively.

Relatively few definitions (<30%) included qualifiers relating to disease severity and/or a lack of existing treatments, whereas many definitions (58%) included a prevalence threshold. The average prevalence thresholds used to define rare diseases ranged among different jurisdictions from 5 to 76 cases/100,000 people, with a global average prevalence threshold of 40 cases/100,000 people. Few definitions also included qualifiers relating to disease severity and the lack of existing treatments.

Our results highlight the need for further research to better understand both the extent and roots of the existing diversity of definitions for rare diseases and to examine the scope for the possible harmonization of the definition of rare disease within

individual jurisdictions and perhaps globally by focusing on standardizing objective criteria such as prevalence thresholds and avoiding less rigorous qualitative descriptors. Based on our results, the terminology "rare disease," coupled with a prevalence threshold in the range of 40 to 50 cases/100,000, could present a realistic starting point for a harmonized definition of rare diseases.

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