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Complete List of Authors:	Abozaid, Ghada; Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences, Pharmacy Practice; Princess Nourah bint Abdulrahman University, Pharmacy Practice Kerr, Katie; Queen's University Belfast, Centre of Public Health Alomary, Hiba; Princess Nourah bint Abdulrahman University, Department of Applied Linguistics Al-Omar, Hussain A.; King Saud Univ, Clinical Pharmacy McKnight, Amy; Queen's University Belfast, Centre for Public Health
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Global Insight into Rare Disease and Orphan Drug Definitions: A Systematic Literature Review

Ghada Mohammed Abozaid[1,2]*, Katie Kerr[1], Hiba Alomary[3], Hussain Abdulrahman Al-Omar[4,5,6], Amy Jayne McKnight[1]

*Corresponding author: gabozaid01@Qub.ac.uk.

Abstract:

Background: Cumulatively, rare diseases (RDs) affect more than 450 million people worldwide; there is no universal agreement on what defines an RD. Medications used to prevent, diagnose, treat, or cure RDs are often referred to as orphan drugs (ODs); similarly, there is no consensus on the definition of ODs. These definitions are crucial for identifying, treating, and tracking RDs, as well as for considering drug evaluations for approval, pricing, reimbursement, patient access, enhancing health care policy, and promoting research. This study sheds light on the available global definitions, classifications and criteria used for RDs, ultrarare diseases (URDs), ODs, and ultra-orphan drugs (UODs), and provides insights into the rationale behind these definitions.

Methods: A systematic literature review was conducted using the Medline, EMBASE, Scopus, and Web of Science databases to search for definitions and underlying criteria used to define RDs, ODs, and their subtypes. A narrative synthesis and content and descriptive analyses were performed.

Results: Online searches identified 2,712 published articles spanning from 1985 to 2021. Only 93 articles met the inclusion criteria, with 209 distinct definitions extracted. Specifically, 93 of these articles pertained to 119 RDs, 11 URDs, 67 ODs, and 12 UODs.

Conclusions: Solely prevalence-based criteria are challenging because more diseases are identified at different frequencies in individual countries. Establishing a country-specific definition would enhance comprehension; facilitate intercountry evaluations; enhance health care efficiency, availability, and accessibility to ODs; strengthen the principles of equity and equality in health care; improve research and development; and support improved outcomes for patients with complex and rare medical conditions.

Keywords: rare disease, ultra-rare, orphan drug, ultra-orphan drugs, qualitative, quantitative, healthcare, criteria.

Strengths and limitations

- This systematic literature review, based on PROSPERO International Prospective Register of Systematic Reviews (CRD42021252701) and PRISMA-P, explores criteria for determining RDS and ODs without publication design, year, or regional restrictions.
- Unlike other reviews, this study explored different criteria for defining RDs and ODs issued by different agencies and entities to fulfil their mandates in relation to RDs and ODs.
- The searched articles showed inconsistent terminology, and despite seeking library specialist feedback, some relevant studies might have been missed.
- The results might be subject to biases in publication selection, language, and database.

Background

Rare diseases (RDs) represent a major public health concern requiring more effective interventions to alleviate the burden on patients, carers, health, and social care systems. RDs, sometimes known as 'orphan diseases' and affect a minority of people, are typically medical conditions that are individually identified with low prevalence within a particular population [(1)]. Globally, RDs affect more than 450 million individuals [(2)], the majority of whom are disproportionately disadvantaged and lack effective treatment. No multipurpose and universally agreed upon definition of an RD [(3)] exists, making optimal care difficult; definitions implemented internationally each depend on the context and perspectives of various stakeholders, some of which employ qualitative and/or quantitative criteria.[(4)]

The qualitative criteria used to define RDs are primarily subjective and include terms such as "life-threatening", "alternative treatment options", "severity of disease", and "neglected". Some of these criteria have major emotional impacts, such as on the severity of the illness, its potential fatality, heritability, or the lack of effective therapies [(5)]. On the other hand, quantitative criteria to define RDs are objective and measurable in nature and include disease incidence [(6)] and prevalence [(7)], which are key indicators for understanding the frequency of disease occurrence within a population. Certain diseases can be labelled rare in one nation but not in another owing to population genetic variations, environmental or societal influences, or disparities in survival rates across different regions [(8)]. A lack of sufficient data on which diseases are categorised as rare creates an obstacle in understanding these conditions and proportions and disease coding; ensuring accurate diagnoses; and encouraging pharmaceutical companies [(9)] to invest in the research and development of medications for these diseases and manufacture orphan drugs (ODs), which, consequently, constitute a considerable challenge in making treatments available and accessible.

Overall, effective therapies are available for fewer than 5% of individuals diagnosed with RDs. The definition of RD is used to determine the eligibility of a medication for a regulatory designation as an OD. This is a status granted to pharmaceutical products that are developed to treat RDs and incentivized by governments and regulatory bodies to encourage product development and production. For instance, pricing preferences, market exclusivity, financial incentives, protocol assistance, grants and research funding, and extended patent protection are different forms of incentives offered to industry.

OD definitions extend across international borders and are frequently linked to RD definitions that are based on epidemiological data for the target disease and economic data for the drug market [3]. Some countries set priorities for RD expenditures and resource allocation to address OD accessibility and help policymakers enhance the efficiency and delivery of ODs [6]. Adopting a universal definition can be challenging due to regional variations in terms of demographic, economic, survival, and sociocultural factors [10]. For example, in Saudi Arabia (SA), there is no multipurpose national definition for RD or OD, which could impact diagnoses, treatment strategies, and resource allocation, highlighting the need for a localized and country-specific definition. Approximately 80% of RDs have a genetic cause, which increases the risk of inherited autosomal conditions in offspring from consanguineous marriages [11]; in SA, 70% of total marriages are consanguineous, which may increase the prevalence of some genetic diseases [12].

There are considerable challenges associated with the context and practical use of RDs, ODs, and subtype definitions employed by various stakeholders. This systematic literature review (SLR) delves into the diverse definitions and criteria used by countries to define RDs, ODs, and their subtypes, providing deeper insight into different factors, encouraging the establishment of robust criteria, and supporting policy deliberations.

Methods

Systematic literature review protocol

The protocol for this SLR [9] was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42021252701) and follows the PRISMA-P [13, 14] guidelines. The PROSPERO template ensures transparency and accountability for SLRs, while the PRISMA-P provides a flowchart for the identification, screening, eligibility, and inclusion phases of the review process.

Search strategy

The PubMed/Medline, EMBASE, Scopus, and Web of Science (Science and Social Sciences Citation Index) databases were queried to answer the research question "What are the criteria for defining RDs, URDs, ODs, and UODs globally?". The search strategies and terms used were identified based on specific inclusion and exclusion criteria. The inclusion criteria included rare disease patients receiving treatment with an OD. The publication year, country, and jurisdiction were not restricted. Studies that were published in English and provided data for the general human population were included. The exclusion criteria included rare cancers, infectious diseases, poisonings, studies focused on specific RDs or ODs, non-English language studies and nonhuman studies. The identified articles subsequently underwent both forward and reverse citation screening.

Study selection and data extraction

After searching the different databases, studies were selected, and duplicates were removed. To determine the initial eligibility of the studies based on the inclusion and exclusion criteria [9], two rounds of abstract and title screening were performed by two reviewers (GMA and KK) independently. A third reviewer (AM) arbitrated any disputes between GMA and KK, and all decisions were recorded in a Microsoft Excel® spreadsheet. Likewise, for full-text screening, if there were instances of missing or unreported data or if further details were necessary, GMA reached out to the study author(s) to request missing data. The timeframe for a response before excluding the article due to insufficient information was set at 3 weeks.

The extracted data encompassed various elements, including author names, publication information, journal title, study design, organization, country, quality assessment, and reference definitions of RDs and ODs. Additionally, these data encompassed qualitative and/or quantitative criteria used to define RDs, ODs, and their subtypes. The qualitative criteria considered disease features, intended drug use, patient group, therapeutic impact, and regulatory support, offering a comprehensive view beyond numerical values. The quantitative criteria considered numerical thresholds pivotal for regulation, science, and policies, providing precise metrics based on disease prevalence and target demographics. Moreover, the extracted data involved the underlying reasoning for each definition, the status of the definition, and whether the RD and OD definitions were considered by reviewers independently using the Covidence® platform, a web-based platform for conducting SLRs [15, 16].

Quality assessment

The study quality was assessed by GA and KK using the Joanna Briggs Institute (JBI) critical appraisal tools [17, 18] to evaluate the trustworthiness, relevance, and outcomes of published studies conducted independently using a Microsoft Excel® spreadsheet.

Data analysis

A narrative synthesis summarizing the data from the included studies was performed. The preliminary synthesis involved content analysis of the qualitative data, with coding employed to explore themes. Descriptive statistics were performed and included frequencies and percentages to report and summarize the quantitative criteria from the included studies. This process was intended to illustrate the key themes and numerical information presented in these definitions by using two independent coders (GMA and HiA) with different backgrounds; conflicts were resolved through collaborative discussion. The analyses aimed to identify key elements defining RDs, URDs, ODs, and UODs qualitatively and quantitatively.

Findings

PRISMA and quality assessment

The initial search yielded 2,712 studies identified from different databases. The published articles spanned from 1985 to 2021. A total of 2019 articles were duplicates and were removed; for example, title and abstract screening excluded 466 studies, and 235 studies were recorded as not relevant to the SLR research questions due to a lack of abstracts (n=27) or were not in English (n=3); instead, they focused on nonhuman (n=2), cancer related RDs (n=19), specific RDs (n=173), or infections (n=5) or poisonings (n=227). The final review included 93 studies whose full texts were retrieved (Figure 1)

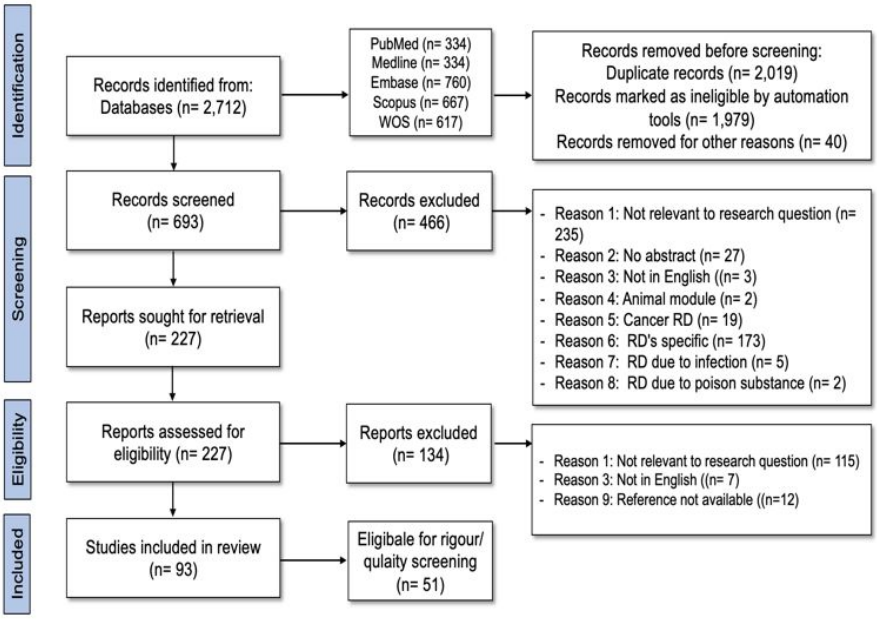

Figure 1. PRISMA flow chart of the study identification and screening process.

A total of 93 articles met the inclusion criteria, and 209 distinct definitions were extracted. Specifically, 93 of these articles mentioned RDs, 11 URDs, 67 ODs, and 12 UODs. Fifty-one studies were considered in the final quality assessment. A full list of included studies is provided in (**Supplementary Table 1**). Likewise, the critical appraisal results for systematic reviews and research syntheses, economic evaluations, text opinion studies, analytical cross-sectional studies, qualitative research, prevalence studies, and cohort studies were outlined and provided in (**Supplementary Table 2**).

Geographical overview of the definitions

A total of 209 definitions were identified in the 93 included articles; these were for RDs (n=119, 56.93%); URDS (n=11, 5.26%); ODs (n=67, 32.06%); and UODs (n=12, 5.75%) (Figure 2).

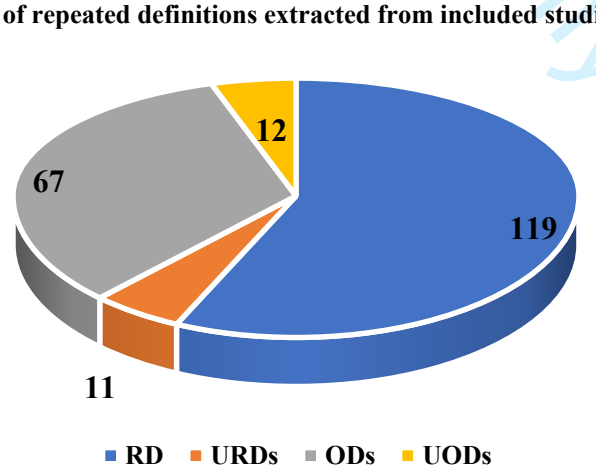

Figure 2. Repeated definitions included in the studies.

RD and OD definitions were often linked. Nonetheless, the most frequent definition employed for RDs, and ODs was the European Union (EU) definition, accounting for approximately 40% and 24%, respectively, of the cases. EU nations employ both qualitative and quantitative criteria to define RDs as "*diseases that are life-threatening or chronically debilitating illnesses with extremely low prevalence (less than 5 per 10,000)*" [19, 20]. Similarly, the United States of America (USA) Food and Drug Administration (FDA) defines RDs as *"any ailment or condition that impacts fewer than 200,000 individuals in the USA or that affects over 200,000 people in the USA, with no foreseeable likelihood of recuperating the expenses associated with developing and providing a drug for such a disease or condition through sales of the drug in the USA"* [21, 22]. An OD in the EU is typically defined as *"a pharmaceutical product for diagnosing, preventing, or treating a rare disease"* [23].

The geographical analysis presented in this SLR examined the global distribution of RD (**Supplementary Table 3**), OD (**Supplementary Table 4**), URD (**Supplementary Table 5**), and UOD (**Supplementary Table 6**) criteria used to define them across different geographic regions.

Rare disease definitions

In Europe, 48 studies discussed RD definitions. Specifically, the EU (36), the United Kingdom (UK) (3), Germany (1), Latvia (1), the Netherlands (1), Poland (2), Romania (1), France (2), and Ukraine (1) had studies that defined RDs as diseases with a prevalence of 5 or fewer cases per 10,000 individuals. The UK defines RDs based on a prevalence threshold of fewer than 1 in 2,000 people. In Eastern Europe and Northern Asia, Russia had one article; in Southeast Europe,

Southwestern Europe and Asia, Turkey had an article discussing RD definitions, both showcasing differences in prevalence thresholds compared to the EU definition.

In North America, 28 studies were identified, 24 from the USA and 2 from Canada. The USA defines RDs based on a prevalence of less than 200,000 individuals living with an RD. In addition, the Rare Disease Act (RDA) defines RDs based on qualitative criteria indicating that it occurs so infrequently in the USA that there is no reasonable expectation for the cost of developing and making a drug available in the USA for such a disease or condition to be recuperated from its sales. However, the Canadian Organization for Rare Disorders (CORD) suggested that 1 in 12 Canadians, approximately 2.8 million individuals, might be living with an RD. South America contributed 2 studies—one from Chile and one from Peru—where RDs were defined by disease severity, categorizing them as "life-threatening" and "severely or chronically debilitating" (**Supplementary Table 3**).

Oceania had differing prevalence thresholds according to RD definitions: Australia (10) and New Zealand (1) used a disease prevalence of 1.1 per 10,000 individuals. Australia has established a prevalence rate of 1.16 per 100,000 individuals for an RD. The prevalence threshold for orphan disease designation is 0.9 in 10,000 individuals. The estimated incidence rate is 1 in 10,000 individuals in Australia.

Asian countries (Japan, Taiwan, China, South Korea, Singapore, India, Armenia, and the Philippines) each defined RDs based on varying criteria such as prevalence rates, genetic disorders, disease severity, and incidence thresholds (**Supplementary Table 3**).

In Africa, Egypt and Kenya were the only countries to mention and discuss RD definitions based on specific conditions and disease severity.

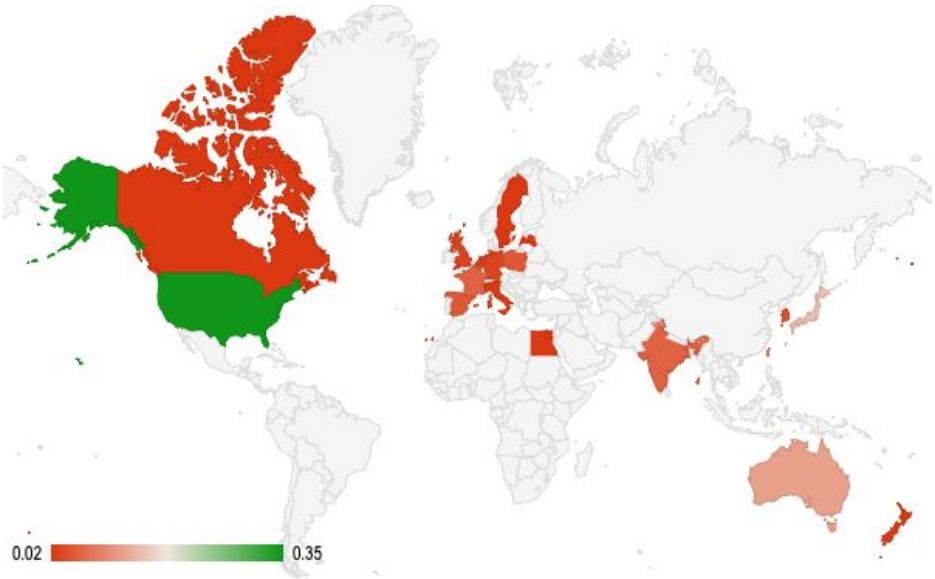

Figure 3. Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence)

The majority of the definitions extracted were from Europe [EU (43%), the UK (22%), France (6%), Poland (5%), Spain (5%), Belgium (4%), Germany (3%), the Netherlands (3%), England (3%), Scotland (3%), Lativa (2%), Italy (2%), and Sweden (2%)], followed by North America [US (35%) and Canada (2%)] and Asia and Oceania [Japan (15%), Australia (12%), Taiwan (9%), India (6%), South Korea (4%), New Zealand (2%) and Singapore (2%)]. Global perspectives on RD definitions from the World Health Organization (WHO) and Orphanet revealed further variations in prevalence thresholds and disease severity criteria (Figure 3).

Ultrarare disease definitions

The definitions of URDs primarily originated from the European continent, encompassing the UK, Poland, and North America, and including, e.g., Alberta and Ontario; URDs typically affect ≤1 in

50,000 or fewer individuals within a population. Additional criteria for classifying URDs varied by region and authority. The Advisory Group for National Specialized Services stipulates that in England, the prevalence should be less than 500 individuals affected (~2500/100,000 of the population). The National Institute for Health and Care Excellence (NICE) further narrows this definition, classifying URDs as those with a prevalence of ≤1:50,000 people. Ontario employs a criterion of fewer than 1 in 150,000 live births or new diagnoses per year, while the definition in Poland aligns with the EU definition, designating URDs as affecting fewer than 1 in 50,000 people. URDs may also be termed "singular cases" or "individual cases," given their exceptionally low prevalence (**Supplementary Table S5**).

Orphan drug definitions

Nineteen studies described OD definitions within Europe, with one from Italy and another from Germany both adopting the European Medicines Agency (EMA) definition, indicating that a drug can be defined as an OD if it is intended for the diagnosis, prevention, or treatment of life-threatening or chronically serious debilitating conditions affecting no more than 5 in 10,000 individuals. Similarly, one study from Italy followed the Italian Medicines Agency (AIFA) criteria, focusing on three aspects: unmet medical needs, clinical added value, and quality of evidence. Moreover, 1 study from Germany suggested that specific health technology assessment (HTA) criteria be used for the definition of ODs; these criteria are associated with higher *p* values when sample sizes are limited, when surrogate endpoints are utilized, when therapeutic benefit is added, and when the annual budget impact for a given indication is less than €50 million.

In North America, there were nine studies, all of which aligned with the USA FDA regulations, indicating that an OD represents a condition affecting fewer than 200,000 persons in the USA or meets the cost recovery provisions.

In Asia, six studies described ODs, one from Singapore, one from Vietnam, and two from China, all of which contributed to the body of evidence on orphan drugs. It was also reported in two studies that the OD Centre in Korea provides medications for diseases affecting fewer than 1 in 20,000 individuals. These encompass illnesses lacking adequate treatments or drugs or drugs that notably enhance safety or efficacy compared to existing alternatives. In contrast, in China, ODs are characterized by their availability as pharmaceutical products or active ingredients that are not developed, imported, or registered due to low commercial returns and unfavourable marketing conditions. These drugs are designated for diseases affecting fewer than 1 in 10,000 individuals. Similarly, ODs in Vietnam are described by their availability as pharmaceutical products or active ingredients not developed, imported, or registered due to low commercial returns and unfavourable marketing conditions (**Supplementary Table S4**).

Ultra-orphan drug definitions

One study from the UK defined UODs as drugs for diseases with an extremely low prevalence, often less than 0.18 per 10,000 individuals. Three studies introduced the NICE definition for "ultra-orphan" drugs as those targeting conditions with less than 1 case per 50,000 persons. These drugs are typically granted approval for the treatment of diseases that affect fewer than 1,000 patients, underscoring their exceptional rarity. In England, the Highly Specialised Technologies (HST) Programme has implemented cost-effectiveness thresholds for UODs, while the WHO provides specific recommendations for cost thresholds. Scotland has introduced a distinct definition that

places emphasis on conditions affecting fewer than 1 in 50,000 individuals. Furthermore, Scotland has also redefined its criteria for UODs to facilitate early access programs and streamline reimbursement processes, with a particular focus on conditions impacting approximately 100 individuals.

Qualitative criteria

The review identified 35 qualitative criteria for RDs, 37 for ODs, 7 for URDs, and 11 for UODs. The identified qualitative criteria were categorized into 7 themes related to RDs, URDs, ODs, and UODs: nature, aetiology, disease nature affecting the patients, disease nature affecting the patient's society, population characteristics, benefits from taking the treatment, and indications (**Supplementary Table S7**).

The most frequent qualitative criteria used in defining RDs and URDs were "disease" 148 times and 13 times, respectively, and "condition" 30 times and 3 times, respectively. For ODs and UODs, the most frequent qualitative criteria were "drugs" 83 times and 8 times, respectively, and "medical products" 36 times and 2 times, respectively. In terms of aetiology, the term "genetic" was used 7 times for RDs and once for ODs. Interestingly, "hereditary" was exclusively reported for ODs. The qualitative criterion "life-threatening" was found 23 times and "debilitating" 21 times for RDs, while for ODs, these qualitative criteria appeared 20 and 10 times, respectively. Some qualitative criteria were used to assess the extent of the impact on society, whether the disease was rare or common. The subtheme "low prevalence" appeared 12 times in definitions related to RDs, similarly describing "low-occurrence criteria", "infrequent population affliction", and a "small number of patients with RDs". However, no data pertaining to URDs, ODs, or UODs were identified. Notably, the theme "benefits from taking the treatment" was found to be associated only

with ODs. In the indications theme, the qualitative criteria "treatment and prevention" were used repeatedly (55 and 23 for ODs and 7 and 1 for RDs, respectively) (**Supplementary Table 8**).

Quantitative criteria

These quantitative criteria yielded 10 criteria for RDs, five criteria for ODs, four for URDs and three for UODs (**Supplementary Table S7**).

In the context of defining RDs, ODs, and their subtypes, quantitative criteria were less common than qualitative criteria. The most popular metric was "prevalence", rather than "incidence", "incidence rate", "number of cases", "threshold", "estimated measures", "range", "percentage", or "frequency". Quantitative criteria such as "cost-effective threshold" and "annual budget impact for a particular indication", as well as "willingness-to-pay", were exclusively recorded for ODs (**Supplementary Table S9**).

Discussion

This review sheds light on various definitions and criteria used by different countries by different stakeholders, provides deeper insights into different elements, promotes the development of strong criteria, and facilitates policy dialogue. The present analyses revealed inconsistency in definitions; regional disparities in RD occurrence ranging from approximately 5,000 to 8,000 [24]; and various terminologies and criteria used to define RDs, ODs and their subtypes.

Some definitions rely on qualitative criteria, such as disease severity, life-threatening or hereditary nature, or the presence of alternative treatment options [5, 25]. The subjective criteria lack substantial evidence and vary based on the specific organization that uses the term. However, the UK [26]

adopts similar criteria to those used by the EMA to define RDs. This finding suggested a degree of alignment in the RD classification between Europe and the UK. The European Organisation for Rare Diseases (EURORDIS) definition has a broader scope because it includes both RDs and neglected diseases within the classification of ODs [27]. This is an acknowledgement of diseases that are neglected even if they are not rare.

There was controversy surrounding the term "orphan" in the context of ODs and variation in the interpretations of it in different countries. This term was initially used in the early 1960s to describe a class of drugs used to treat RDs. Drugs for RDs were considered ODs due to a lack of profitability and financial and other incentives, which became profitable by the beginning of the 1990s [28]. In the UK, the use of the term "orphan" has been criticized, particularly by Rosalind Hurley of the European Medicines Agency (EMA), who expressed regret over its usage [28]. Despite this criticism, Richter [10] argues that the term is consistent in referring to technologies for RDs. In Australia, ODs refer to medicines, vaccines or in vivo diagnostic agents used to treat, prevent or diagnose or not available to treat, prevent or diagnose another disease [29]. This provides a broader understanding of the term and its application in different regions.

Disease severity is considered a critical criterion in evaluating the impact of ODs on health-related outcomes in patients, considering that diseases can substantially affect both health and health-related quality of life [41]. Haendal et al. [39] recommended that a multitude of overlapping terminologies, models, and metadata exist for the identification and classification of RDs. Failure to do so can have substantial consequences, affecting drug approvals, market entry prices, and reimbursement recommendations and ultimately impeding patient access to ODs.

Additionally, some definitions depend on quantitative criteria, such as the disease prevalence threshold, which constitutes the favoured epidemiological element utilized in 58% of RD definitions [5]. However, establishing a prevalence threshold poses challenges due to diverse information sources. This challenge is exacerbated by the absence of firmly established diagnostic criteria or coding systems necessary to gather these data [30]. As a result, certain diseases could be deemed rare in one country but not in another owing to genetic population diversity, environmental or societal pressures, and variations in survival challenges across different regions [8].

One study [10] presented a comprehensive overview of RD definitions worldwide, collating 296 definitions from 1109 organizations across 32 international jurisdictions. The findings indicated the common use of terms such as "RDs" and "ODs," while descriptive qualifiers such as "life-threatening" were less prevalent. Moreover, 88% of the investigations specified prevalence thresholds ranging from 5 to 76 cases per 100,000 people, with 66% of jurisdictions adopting thresholds between 40 and 50 cases per 100,000 individuals. The study [10] underscored the substantial diversity in defining RDs across various jurisdictions and organizational structures. This highlights the necessity for standardization, particularly in objective criteria such as prevalence thresholds, while recommending the avoidance of subjective qualifiers to achieve a harmonized definition of rare diseases. Despite the widespread use of terms such as "RDs" and "ODs", the study emphasized the importance of focusing on standardized metrics to ensure clarity and consistency in identifying RDs globally.

This SLR emphasizes the importance of developing a local definition for each country, regardless of which criteria will apply. Subjective qualifiers could occasionally provide additional context or complexity to the description of RDs, ODs, and their subtypes. On the other hand, depending too

much on subjective standards may result in inconsistent results and implementation challenges. For comprehensive definitions of RDs, ODs, and their subtypes, it is better to combine qualitative and quantitative criteria to be reviewed and updated periodically.

In summary, an exploration of the worldwide definitions of RDs, ODs, and their subtypes provides a comprehensive understanding of their complex nature. The diversity in criteria among nations and institutions accentuates the problem of defining them, influenced by genetic variations, societal factors, and regional disparities. This important fact illuminates the critical challenges and factors required to address these conditions and advance the development of treatments for individuals affected by RDs globally.

Recommendations for future use

This study highlights the importance of establishing a country-specific consensus on the definition of the distinctive combination of genetic, phenotypic, and environmental characteristics as well as sociocultural and economic factors. RDs should be linked toto individuals to steer the research and enhance the diagnosis and care of patients with RDs and the availability of treatments [38] based on scientific principles. Qualitative and quantitative criteria and subthemes should be included in the definition. Therefore, understanding the economic and ethical principles of and health care burdens associated with RDs, ODs, and their subtypes is essential for policymakers to shape policies, especially in underdeveloped policy areas. Moreover, there is a need for international collaboration and data exchange to improve the global understanding and treatment of RDs, which in turn can affect pricing, reimbursement, and patient access to ODs. Additionally, more robust evidence is needed to effectively implement the United Nations (UN) 2030 Agenda principles and Sustainable

Development Goals of '*leaving no one behind'*, '*reducing inequalities'*, and '*addressing the needs of those furthest behind first'* to support the RD community.

Conclusion

A comprehensive study on RD, OD and subtype definitions across countries is lacking. In particular, these definitions are considered outdated, with no scientific grounding. There is a need to address problems associated with diseases that impact only a small percentage of the population. These definitions are meant to provide a framework for identifying and supporting the development of ODs. Therefore, local evaluations of qualitative and/or quantitative criteria are needed to shift therapeutic outcomes from treatment to transformative and curative treatment, to gather comprehensive patient data, to accurately determine disease prevalence, and to ensure equity and equality in accessing appropriate treatments. It is imperative for each country to develop a local definition or reporting system or establish a national registration program. This approach would not only facilitate the collection of vital health information but also foster a more effective health care ecosystem that addresses the needs of individuals affected by these conditions.

Author affiliations

[1]Centre for Public Health, Institute of Clinical Sciences B, Royal Victoria Hospital, Queen's University Belfast School of Medicine, Dentistry and Biomedical Sciences, Belfast, UK. https://orcid.org/0000-0002-8469-8885; https://orcid.org/0000-0002-7482-709X

[2]Pharmacy Practice Department, College of Pharmacy, Princess Nourah bint Abdulrahman University, PO Box 84428, Riyadh, Zip Code: 11451, Saudi Arabia. https://orcid.org/0000-0002-4523-0577 ; email: gaabozeed@pnu.edu.sa

[3]Department of Applied Linguistics, College of Languages, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. https://orcid.org/my-orcid?orcid=0000-0001-7476-0561

[4]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia. https://orcid.org/0000-0002-0765-0466

[5]Health Technology Assessment Unit, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia.

[6]Center of Health Technology Assessment, Ministry of Health, Riyadh, Saudi Arabia.

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Competing interests None declared

Patient and public involvement The research's design, methodology, reporting, or distribution strategies did not involve patients or public.

Patient consent for publication Not required

Provenance and peer review External peer review; not commissioned.

Data sharing statement All of the study's data were fully accessible to the author(s), who also bear responsibility for the data's accuracy and integrity. This study has no more unpublished data. There are no more statistics available.

Abbreviations AGNSS= Advisory Group for National Specialised Services; AM= Amy Jayne McKnight; CM= Consanguineous Marriage; CMS= Congenital Myasthenic Syndrome; DOH = Department of Health; EMA= European Medicines Agency; EU= European Union; FDA= Food and Drug Administration, GMA = Ghada Mohammed Abozaid; HiA= Hiba Alomary; HAA= Hussain Abdulrahman Al-Omar; HST= Highly Specialised Technology Programme; JBI= Joanna Briggs Institute; KK = Katie Kerr; NICE= National Institute for Health and Care Excellence; OD= orphan drugs; ORDI = Organization For Rare Diseases India; PNU= Princess Nourah Bint Abdulrahman University; PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RD = Rare Diseases; RDTWG = Rare Diseases Technical Working Group; SA= Saudi Arabia; SLR= Systematic Literature Review; TFRD = The Taiwan Foundation for Rare Disorders; UOD= Ultra- Orphan Drug; UK= United Kingdom; URD= Ultra- Rare disease; US= United States; WHO = World Health Organization; WTP= Willingness To Pay.

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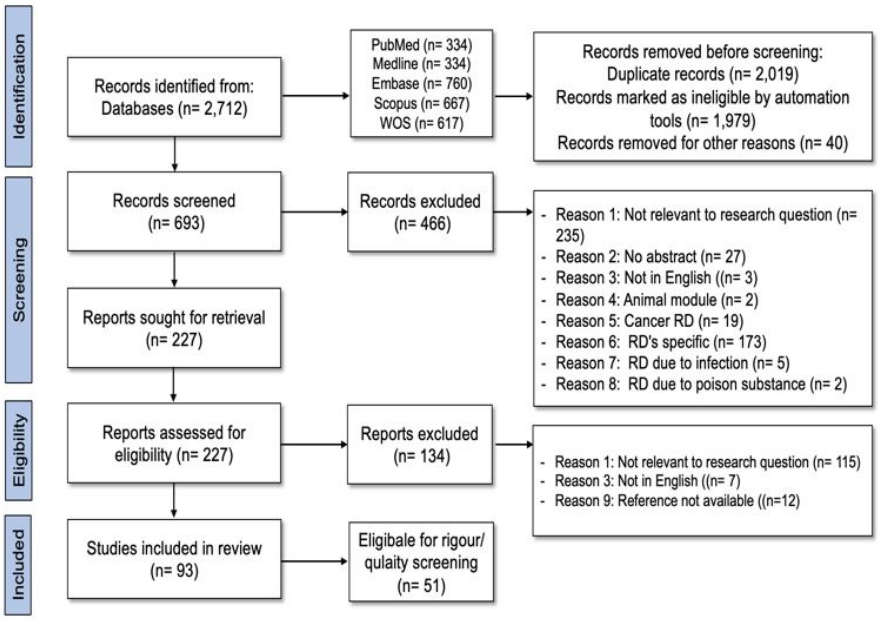

Figure 1. PRISMA flow chart of the study identification and screening process.

Supplementary Table S1: List of included studies

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
1992[18]	USFAD/ Orphan Drug Act, P.L. 97-414, 1983.	Review	This paper examines some of the special problems that are associated with the design and implementation of studies to evaluate the safety and efficacy of orphan drugs.	The legal definition of a rare disease or condition is one that "either (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation than 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.	Orphan drug and biological products are Pharmaceuticals that are generally not considered to be attractive for commercial development. Generally, orphan drug products are used in treating or preventing rare diseases		
2002[19]	United States	Book - Chapter	The information presented is directed both at the fortunate individuals al-ready involved in drug development and at those adventuresome sorts who are considering entering the field. We hope this book will provide readers with in-sights into this exciting arena and begin to explain the complicated process of developing a promising new drug		Orphan products are used to treat rare diseases or conditions that by definition, affect fewer than 200,000 people (or up to 1 in 1300) in the United States.		
2003[20]	United States; Paris, France/ European Medicinal Evaluation Agency	Review	To analyse the American and European experience on the Orphan Medicinal Products.		A medical product can receive the designation as an orphan medical product if it can be established that it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating disease affecting not more than 5 in 10 thousand persons in the EU. American definition of OD not clear		
2004[21]	United States; India, Japan, Australia/ US FDA	Review	This article reviews the bias for classification of orphan drugs, the discovery of orphan drugs, and attempts by pharmaceutical industries, academician (scientist) and practicing physician, with their respective perspectives, advantages and disadvantages in discovery and development of orphan drugs and some historical aspects.	Rare disease or condition is any disease or condition which affects less than two hundred thousand persons in the United States or affects more than two hundred thousand persons in the United States, but for which there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in US.	- Orphan Drugs have been defined in USA as those drugs intended to treat either a rare disease or more common disease where the sponsor cannot make any profit. - As per the definition US FDA, Orphan drugs are those drugs used in diseases or circumstances which occur so infrequently in USA, that there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in the USA. - The availability of orphan drugs to patients before being granted a Marketing Authorization is possible. US FDA designated orphan drug with t-IND (treatment Investigational New Drug) in some cases such as when the drug is intended for the treatment of a serious or life-threatening disease, when no alternative drug or treatment is available, and thirdly, the product is in the process of clinical trials and in an active phase of Marketing Authorization application		
2005[22]	UK, United States, Japan, Australia	Education and debate	We examine the justifications for special status for rare diseases and ask whether the cost effectiveness of drugs for rare or very rare diseases should be treated differently from that of other drugs and intervention.	Definitions of orphan disease: United States diseases with a prevalence of 7.5/10 000; Japan diseases with a prevalence of 4.0/10 000; Australia diseases with a prevalence of 1.1/10 000; and EU diseases with a prevalence of 5.0/10 000.			The UK defines Ultra Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or less
2006[23]	European Union Regulation (EC) No 141/2000	Book - Chapter		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. As a guide, low prevalence is taken as prevalence of less than 5 per 10,000 persons in the European Union [1]"	-The lack of drug development for products intended for the prevention, treatment or diagnosis of rare diseases has made necessary the creation of a number of incentives to stimulate the development of such products. These drugs are known as orphan drugs. - In the EU a medicinal product to treat rare diseases is designated as an orphan medicinal product based on either a demonstrated insufficient return on investment or the rarity of the condition and, the absence of satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorized, or if such method exists, the assumption that the product		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
					will be of significant benefit to those affected by the condition. -Criteria for orphan designation are the following. Firstly, a criterion is based on the low prevalence ("rarity") of the condition, i.e., condition affecting not more than 5 in 10,000 persons in the European Union. Alternatively the sponsor can apply for more frequent conditions if it can be shown that the development would not be justified by sufficient financial return, i.e., if without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the investment by the sponsor. Second it is necessary for designation that the life-threatening or debilitating nature of the condition is justified. The sponsor is invited to provide any scientific and medical references that may support the life-threatening or seriously debilitating nature of the condition. Finally the sponsors are also required to demonstrate that either there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question or, if such methods exist, that the medicinal product will be of significant benefit to those affected by that condition.		
2006[24]	USA Orphan Drug Act, European	Policy And Practice	In this paper we propose selection criteria for an Orphan Medicines Model List that could form a departure point for future work towards an extensive WHO Orphan Medicines Programme.	In the USA Orphan Drug Act, the definition relates to an absolute number (<200 000 patients in the USA), while the European regulation uses a relative measure (<5 cases per 10 000 inhabitants) and requires disorders to be life threatening and/or chronically debilitating.			
2008[25]	United States	Book - Chapter		The legislative definition for a rare disease in the United States is one with a prevalence of less than 200,000 persons or, if over 200,000 persons, one for which there is no reasonable expectation of recovering drug development costs within seven years of market approval			
2009[26]	United States of America, Japan, EU, Australia, and Taiwan	Review		A rare disease is defined as a disease or condition affecting fewer than 200,000 persons in the United States of America, <50,000 patients in Japan, The EU defines rare diseases as life threatening or chronically debilitating diseases which are of such low prevalence in 2,000) that special combined efforts are needed to address them. Australia: < 2000 individuals. Taiwan: < 1 in 10,000 people.			
2010[27]	United States/ Orphan Drug Act of 1983	Book	- To provide a convenient repository for the substantial work that has been accomplished by individual investigators treating rare genetic disorders with simple molecules. - To provide a handbook that will enable potential clinician/ scientists and others to rapidly survey the field, thus ascertaining what has been done and what can yet be done.	In that legislation, an orphan disease was defined as a condition that affects fewer than 200,000 Americans." Serious, life-threatening disorders across the age span.	Serious, life-threatening disorders across the age span.		
2010[28]	United States/ Orphan Drug Act	Review			The Act initially defined an orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease or condition of interest in the United States as a surrogate for the lack of profitability.		
2010[29]	United States/ the Office of Rare Diseases Research (ORDR)	Book-Chapter	This chapter will focus on many of the activities of the ORDR and include other significant activities related to rare diseases research and orphan products development	The disorders and conditions in the rare diseases category are defined by the prevalence figure of fewer than 200,000 people in the United States with the specific disease. An estimated 25			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
				million to 30 million people in the United States have a rare disease or condition."			
2010[30]	UK; EU, World Health Organisation, Australia, Japan and the United States	Book-Chapter		-Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual, quality of life or socio-economic potential. -According to the World Health Organisation, a rare disease affects at most 6.5 out of every 10,000 individuals. -Australia, Japan, and the United States have set prevalence's of 1.16, 4.07 and 6.68 per 100,000 individuals respectively for a given rare disease."		
2010[31]	United States/ The Orphan Drug Act	Review			The Orphan Drug Act defined an ,orphan product' as a drug that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA. There are over 6000 conditions that meet the definition of a rare disease		
2011[32]	UK, WHO, US FDA, EU, Japan, Australia:	General review	This article aims to provide a description of principal aspects of policy and practice associated with orphan drugs and treatments of rare diseases and give perspectives for 2011 on new and emerging approaches for addressing patient access." "This article summarizes the current state of international orphan drug patient access and describes developments up to 2011. Emerging policies and practices that will affect patient access in 2011 and beyond are also explored."	-WHO: Frequency of 6.5-10/ 10,000 inhabitants US FDA: Affecting, <7 patients/10,000 residents (estimated to affect about 200,000 patients/year -EU: Affecting ≤ 5 patients/10,000 residents (estimated to affect about 30 million EU citizens) -Japan: Affecting <40/100,000 of the population. -Australia: Affecting <11/100,000 inhabitants or ≤2000Australians	Drugs used in the treatment of rare diseases or conditions, or significant unmet medical needs and are referred to as orphan drugs because, as described by EU Regulation (2011c) , the pharmaceutical industry has little incentive under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	Ultra-orphan diseases, in the UK, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population	
2011[33]	Spain	Abstract	We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU.		In the European Union (EU), orphan drugs are used for the diagnosis, prevention, or treatment of life-threatening or serious conditions that affect5 in 10,000 people (NOTE THE OVERLAP BETWEEN ORPHAN DRUG AND RARE DISEASE DEFINITION)		
2011[34]	Canada	Abstract	The scope of this study is to describe the ODs regulations in Canada, evidence requirements by the national regulatory agency, national and regional funding criteria, market access challenges associated with ODs, and approaches to obtain access to ODs in Canada.	The Canadian Organization of Rare Diseases (CORD) defines a rare disease as one that afflicts less that 1 person in 200 000.			
2012[35]	Middle East (Egypt, Iran, Turkey, Iraq, Saudi Arabia, Yemen, Syria, United Arab Emirates or UAE, Israel, Jordan, Lebanon, Oman, Kuwait, Qatar, Bahrain, and Cyprus) plus the Palestinian territories of the West Bank and the Gaza Strip	Policy Forum			An orphan drug is a drug developed specifically to treat a rare medical condition		
2012[36]	United States	Editorial		-The terms, orphan diseases, and, rare diseases, are commonly used interchangeably worldwide and have been defined as ,any disease or condition that affects a small percentage of the population. -The US Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, as does Japan.			

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Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
				-The European Commission on Public Health defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. -The definition of ,low prevalence, varies between countries but usually ranges from 1/1,000 to 1/200,000 -The alternative term, orphan disease, is used in reference to a combination of the paucity of treatment availability, lack of resources, and severity of disease.			
2012[37]	United States	Review	- In this article we present the findings of this analysis, which, consistent with the IOM recommendation, are intended to identify factors correlating with rare disease product approvals that could inform future development programs, and to identify areas where additional resources might be directed. - In this work we provide an up-to date analysis of drug, target interactions for approved and clinical trial drugs and examine the major developments and trends in pharmaceutical development - For the purpose of supporting rare disease product development, we undertook an evaluation of CDER, rare disease marketing application history, focusing on a recent five-year period (2006 - 2010).	Rare diseases, which are disorders affecting less than 200,000 persons in the USA, also have considerable unmet medical needs.			
2012[38]	European Union countries	Review	The aim of this study was to quantify both the sales and volume uptake of orphan drugs in Europe and to assess whether a country, gross domestic product (GDP) and/or health technology assessment (HTA) influences the orphan drugs, market uptake.	In the European Union, a rare disease is defined as a life-threatening or chronically debilitating disease with the prevalence among 50 per 100 000 people or less	Orphan drugs are drugs intended for the treatment of rare diseases.		
2012[39]	Singapore, Taiwan, Korea, and China	Meeting Abstract		-Since 1991, Singapore, Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. -The Taiwan Foundation for Rare Disorders helped secure the Rare Disease and Orphan Drugs Act in 2000. Diseases affecting fewer than 1 in 10,000 that are officially recognized are eligible for medical coverage. -In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000. -In China, in 2011, medical professionals called for legislation to support healthcare, research, orphan drug development, and epidemiological studies for diseases affecting fewer than 1 in 10,000	-Since 1991, Singapore, Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. -In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000.		
2013[40]	Middle East	Critical Review	We provide a critical review of the literature on the availability of orphan drugs in the Middle East.		An orphan drug is a drug developed specifically to treat a rare medical condition.		
2013[41]	United States; UK; and EU	Review	We examined the characteristics of orphan drug (OD) designations and approvals by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2000 and 2011.		Criteria for Orphan designation is generally based on the number of patients affected by the disease (<200,000 US patients and <5 in 10,000 EU patients). The EU also requires that a satisfactory alternative treatment is not available or that the new drug is significantly better than drugs currently marketed.		
2013[42]	UK	Conference	- The presentation provides a brief review of all supportive incentives in the field of orphan medicinal products as: the European orphan medicinal product (OMP) regulation, Guideline on Clinical Trials in Small Populations and Commission Regulation (EC) No 2049/2005 / support of small and medium enterprises (SMEs)." - It also introduces the concept of Clinical added value of orphan medicinal products, as one of the key instruments to increase the availability of orphan medicinal products in the member states."		- The orphan drug intended for diagnosis, prevention or treatment of a life threatening or chronic debilitating condition. - The prevalence of the condition, for which the OMP (orphan medicinal product) is intended, must be less than 5 in 10,000" - OMP has to fulfil following criteria: 1. Seriousness of the condition the investigated drug must be intended for diagnosis, prevention, or treatment of a life-threatening or chronic debilitating condition.		

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Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
					2. Low prevalence/irretrievable investment: the prevalence of the condition, for which the OMP is intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to generate sufficient return to justify the investment. In some situations, the condition is defined as a subset of another frequent condition. To accept this subset it is needed to prove that the subset is medically recognizable and the investigated OMP is only effective only in this subset and not in the condition per se. 3. Medical need No other treatment authorised in EU for this condition or if there is one, the designated OMP must provide a significant benefit over the existing method. The significant benefit is given on the basis of/upon clinically relevant advantage or major contribution to patient care EC/847/200		
2013[43]	Taiwan, and Republic of China	Registry data analysis	- This paper aims to describe the prevalence of RDs over time from 2002 to 2011 based on the national RDs registry data in Taiwan". - To describe a general demographic picture of patients with rare diseases in Taiwan and particularly focuses on the prevalence of rare diseases over time, age, and gender distributions.	- Rare disease as a disease whose prevalence is less than 1 in 10,000 in Taiwan. - Taiwan officially included RDs as one type of disability and initiated the RDs disability registry in the social welfare system in 2002 (the Physically and Mentally Disabled Citizens Protection Act, 2001)			
2013[3]	China	Review	In this article, the primary tasks faced by China have been proposed: to call on the government to legislate as soon as possible; to establish information platform of rare diseases and orphan drugs for sharing the global rare diseases resources; to establish Rare Disease Outpatient Service (RDOPS)for improving the level of diagnosis and treatment; to carry out tertiary prevention of the rare diseases; to establish the rare diseases epidemiological surveillance system in our country	- World Health Organization (WHO) defines a rare disease as affecting 65/100 000~100/100 000 persons. A disease is considered as rare when it affects 1 person per 2,000 in Europe, <200 000 people in the United States, <50 000 people (1 person per 2500) in Japan and 1 person per 10 000 in Taiwan. In China, the Chinese Society of Genetic Medicine defines rare disease as 'diseases affect less than one over 500 000 and genetic disorders affect with less than one over 50 000 of the incidences in new-born babies. - Rare diseases are serious chronic diseases, difficulties in obtaining timely, accurate diagnoses and are often life-threatening	Orphan drugs are those intended to diagnose, prevent, or treat rare diseases or pathologies that are serious or life-threatening, and whose development costs are superior to the expected return on investment		
2013[44]	Seven European countries, Belgium	Review	This study aimed to identify, describe, and classify MEAs applied to orphan medicinal products (OMPs) by national payers and to analyse their practice in Europe. The present study, focusing on seven European countries, had three main objectives, namely to: (i) examine the processes through which MEAs are implemented by national healthcare payers, (ii) identify, describe, and classify MEAs applied to OMPs by national healthcare payers, and (iii) analyse and compare identified MEAs related to OMPs within and between countries.	Life-threatening or chronically debilitating diseases with a prevalence of 5 out of 10,000 or less			
2013[45]	United States/ Orphan Drug Act (ODA)	Book - Chapter		- Rare diseases, also referred to as orphan diseases, are defined in the United States (US) by the Orphan Drug Act (ODA) as diseases or conditions that affect fewer than 200,000 persons in the US. - Most rare diseases are serious, life-limiting, or life-threatening conditions	Orphan designated drugs are those that are: intended to treat, prevent, or diagnose diseases or conditions affecting fewer than 200,000 persons in the US; and have shown promise, based on supporting evidence, in the treatment of the disease or condition.		
2013[46]	Netherlands	Research Article	In the Netherlands, we decided to build a registry for patients with metabolic disorders and also to optimize the codes for national use in medical and clinical genetics. With these purposes in mind, we developed, with a dedicated group of clinical specialists, a clinically oriented annotation system for metabolic disorders based on two existing national coding systems.	Rare diseases are life threatening or chronically debilitating diseases with a prevalence of up to five per 10,000 inhabitants in the European Union (EU)			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
2013[47]	China, WHO, United States, Japan, and Australia	Commentary		- A rare disease is referred to as any disease that affects an extremely small percentage of the population. - The World Health Organization (WHO) defines a disease as a rare disease when its incidence ranges approximately from 0.65-1% in the whole population. - Rare disease is identified in the United States (US), Japan, and Australia when it afflicts less than 200,000 (approx. 0.75% of the population), 50,000 (approx. 0.4% of the population), and 2,000 (approx. 0.1% of the population) people, respectively. - Expert consensus indicates that a rare disease could be identified in China when the incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.		
2014[48]	Poland	Abstract	The aim of this study was to identify the cost-effectiveness threshold for an orphan designation in Poland.		- According to criteria specified by the European Medicines Agency (EMA) a medicine must meet 3 criteria to qualify for orphan designation, i.e. that the treatment, prevention or diagnosis of a disease is life-threatening or chronically debilitating; the prevalence level in the European Union (EU) of no more than 5 cases in 10,000 patients is necessary; no satisfactory method of disease diagnosis, prevention or treatment or if such method exists, the drug must deliver significant benefits to patients. - In Poland there is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.		
2014[49]	UK, US	Review	We aim to highlight how the emergence of omics technologies and the development of integrated , systems medicine, approaches might offer ways to overcome research challenges in rare disease and allow patients to ultimately reap the benefits of better scientific understanding of their condition.	Rare diseases are defined in the European Union as those with a prevalence of < 5 in 10,000 and in the US as diseases that affect fewer than 200,000 US citizens			
2014[50]	Latvia	Conferences	This study aims to determine the trends in reimbursement of ODs in Latvia within the framework of individual reimbursement system in 2008, 2011.	Rare diseases, also related to as orphan diseases, are life-threatening or chronically debilitating conditions of different origin. Disease is considered as rare if it affects not more than 5 in 10 000 people in the EU.	- Orphan drugs (ODs) are medicinal products intended for diagnosis, prevention, or treatment of life-threatening or very serious diseases affecting less than 5 in 10 000 people in the European Union (EU). - These drugs are called ‚orphans, because the pharmaceutical industry has little interest, under normal market conditions, in developing and marketing such products intended for only a small number of patients suffering from very rare conditions		
2014[51]	National Institute for Health and Care Excellence (NICE)	Abstract	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000. Medicines for these indications are difficult to develop in part due to challenges associated with recruiting for clinical trials from a small patient population. Within this context, global payer bodies have assessed these therapies with modified evidence requirements and opportunity for very high prices. We performed a health technology assessment (HTA) review of two ultra-orphan products – eculizumab/Soliris and iduronate-2-sulfatase (IDS)/Elaprase – to gain insight into the evolving HTA evidence requirements for ultra-orphan medicines and comparatively evaluate key decision drivers across geographies.			Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000.	
2014[52]	Belgium	Qualitative research	The aim of this study is to use a combination of qualitative research methods to examine which official and non-official factors influence reimbursement decisions for orphan drugs in Belgium.	In Europe, rare diseases are defined as life-threatening or chronically debilitating diseases with a prevalence of 50 out of 100000 individuals or less.			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
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2014[53]	India, US, Europe, and Japan	Review	An attempt has been made to put forward the challenges faced by rare disease drug development and the current scenario of orphan drug legislations in India. The objective of this review is to look into Indian orphan drug regulations and an emphasis has been laid on Orphan Drugs Act (ODA) of US and orphan drug policies of other developed countries such as Europe, Japan, and Australia, thus showing the requirement of adopting ODA like legislation in India.	- In United States (US), the Orphan Drugs Act (ODA) is a federal law concerning rare diseases that affect fewer than 200,000 people or are of low prevalence (<7.5/10,000 in the community) - A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000) - Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan, definition of rare disease."			
2014[54]	USA, EU, Japan, Australia, Taiwan, South Korea, Alberta, and Ontario	Perspective-workshop	The present paper sets out to explain the rationale underlying a recent expert consensus, recommending a more rigorous assessment of the clinical effectiveness of ultra-rare disorders (URDs,) applying established standards of evidence-based medicine.	- Definitions for, orphan disorders, typically include a criterion of prevalence or incidence and differ somewhat between jurisdictions. - In the USA, these are disorders with a prevalence of less than 200,000 affected persons (according to the Orphan Drug Act of 1983, and Orphan Drug Regulation of 1993) - In the EU, prevalence must be less than 1 per 2000 (or less than 0.05%) of the population (according to EU Regulation CE No. 141/2000 of 2000) - Strict criteria have also been set in Japan (fewer than 4 per 10,000, according to Orphan Drug Regulation of 1993) - Australia (less than 1.1 per 10,000, according to Orphan Drug Policy of 1997) - In Taiwan and South Korea, prevalence thresholds have been set at less than 1 per 10,000 and 1 per 20,000, respectively		- URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE, Alberta). The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~1 in 100,000 of the English population). An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario - No official definition of ‚ultra-orphan disorders, has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE) conditions with a prevalence of less than 1 per 50,000 persons"	National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"
2014[55]	United States	Position Statement	This article examines the trends in public discussion of high-cost drugs and the potential consequences for orphan drug development.	Prevalence of under 200,000 people in the United States	Drugs to treat conditions defined as rare, that is with a prevalence of under 200,000 people in the United States		
2015[56]	United States	Abstract	We assessed trends in approvals of new drugs with orphan indications in the US and in the prevalence of orphan drugs approved by the FDA from 1983 to 2014 compared to non-orphan drug approvals in the same time frame		Orphan drugs are indicated for rare diseases and conditions.		Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e.: ultra-orphan drugs)
2015[57]	Egypt, U.S.	Chapter	We introduce in this study a system that classifies the orphan drugs according to their probability of structural similarity		- Orphan drugs are a treatment for rare diseases. - Orphan drug legislation by the U.S. Food and Drug Administration (FDA) is motivating drug companies to develop drugs that have low development costs in order to treat rare diseases."		
2015[58]	United States (US) and European Union (EU),	Poster/Abstract only	The objective of this research is to identify the number of medicines that have been granted orphan designation in the United States (US) and European Union (EU) and analyse the approval trends over a ten-year time horizon with a specific focus on the number of ODs with an oncology indication.		- OD may be defined as a pharmaceutical product aimed at treating rare diseases or disorders. - OD tend to consider the prevalence of the disease and the estimation of the population affected by the disease. - In the USA a rare disease is defined as: <200,000 patients (<6.37 in 10,000, based on US population of 314m) - In Europe a rare disease is defined as: <5 in 10,000 (<250,000 patients, based on EU population of 506m).		
2016[59]	EU, Germany	Forum	Here we examine the factors that account for these failures and describe a variety of possible remedies. This analysis focuses on the EU perspective, though many findings are relevant toother global markets.		An orphan designation is granted to a product when the prevalence of the treated condition in the EU is not more than 5 in 10,000 or it is unlikely that marketing of the product would generate sufficient returns to justify the investment needed for its development.		
2016[60]	Italy	Review		Rare diseases (RDs), including those of genetic origin, are defined by the European Union (EU) as life-threatening or chronically			

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				debilitating conditions whose prevalence is so low (less than 5 per 10,000)			
2016[61]	UK; (EU15 plus Nordics and Poland)	Abstract	To review HTA requirements currently in place for treatments for rare diseases in selected European countries (EU15 plus Nordics and Poland), to identify and evaluate differences between country requirements.	Definitions of orphan (prevalence ≤5:10,000)			Ultra-orphan drug (prevalence ≤1:50,000)
2016[62]	France	Poster/Abstract only	This study aims to analyse their impact on reassessment with a specific focus on orphan medicines.		Orphan designation is a status assigned to a drug intended to treat a rare condition.		
2016[63]	Japan and Europe	Model	This study focused on the difference of rare disease prevalence between Japan and Europe, classified the rare diseases comprehensively using cluster analysis and analysed the influence of prevalence on research activity and drug development.	Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment	Designated intractable diseases over 50,000 patients were targeted for orphan drug designation in April 2015. They were excluded due to the short implementation time. The prevalence was calculated as the rate per 100,000 population using the number of patients with the latest disease provided by the MHLW website		
2016[64]	Asia-Pacific, Australia, Japan, Singapore, South Korea, and Taiwan	Poster/Abstract only	To evaluate the impact of national orphan drug policy and existing reimbursement mechanisms over the implementation of managed entry agreements (MEAs) for orphan drugs in the context of five Asia-Pacific countries.		- Australia: Prevalence threshold for orphan disease designation: 0.9 in 10,000 - Japan: Prevalence threshold for orphan disease designation: <3.9 in 10,000 - Singapore: Prevalence threshold: 37.7 in 10,000 - South Korea: Prevalence threshold: <4.0 in 10,000 - Taiwan: Prevalence threshold for orphan disease designation: <1 in 10,000"		
2017[65]	Spain	Abstract	Identify if the official criteria of Spanish P&R process are related with P&R approval for ODs.			Ultra-orphan diseases affecting <1/50000 inhabitants	
2017[66]	China	Commentary	The current authors proffered 300,000 to 500,000 cases as a reference threshold with which to define rare diseases in China. This proposal linked the concept of rare diseases with orphan drugs, so it is highly useful in terms of Chinese policymaking on rare diseases	- Disorders with a prevalence less than 1/500,000 or with an incidence less than 1/10,000 among new-borns - More recent - 300,000 to 500,000 cases as a reference threshold with which to define rare diseases in China			
2017[67]	Bulgarian	Text and opinion	- To highlight the possible trends in the further development of requirements for orphan medicines entering the Bulgarian market on the basis of the global situation and trends." - The goals of the current study are to determine the access of orphan medicines to the Bulgarian pharmaceutical market considering the currently available legislation on Health Technology Assessment (HTA) and reimbursement strategies for orphan medicines, the current number of orphan medicines included in the PDL and their total financial burden"		Orphan medicinal products (OMPs) are used to severely life-threatening diseases with no or limited available therapeutic options		
2017[68]	Sweden	Editorial Commentary	Processes related to drug pricing, reimbursement, and thereby availability, vary between countries, thus having implications on patient care. These processes are discussed, with specific focus on three drugs used in paediatric nephrology: a galsidase beta (for Fabry disease), eculizumab (for atypical haemolytic uremic syndrome), and cysteamine bitartrate (for cystinosis).	Rare diseases are severe, chronic, debilitating, and/or life-threatening conditions that are often hereditary and, by definition, affect less than 1 in 2000 individuals in the European Union, or fewer than 200,000 individuals in the USA, at any given time		Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe (EU regulation 536/2014).	
2017[69]	French	Poster/Abstract only	- To explore French stakeholders, policy, implicit or explicit, toward orphan drugs on both Transparency Committee (TC) assessment and pricing decisions - To compare authorities, decisions between two periods of time (2006-2010 and 2011-2016) in order to describe variations on assessment and price lifecycle."	In Europe orphan disease is defined by a prevalence of less than 5 in 10 000 inhabitants which represent a maximum target population of 30 000 patients in France.	An orphan drug is a pharmaceutical agent that is been developed specifically to treat a rare disease, itself referred to as an orphan disease. Often severe and disabling, affecting a limited number of people (the threshold admitted for the prevalence is 1 in 2000 in Europe).		
2017[70]	Europe	Book - Chapter	Is to bring together the necessary elements for an efficient overall strategy, hence the adoption of Commission Communication COMM (2008) 679 final on 11 November 2008 1. Making rare diseases more visible 2. Encouraging Member States to develop national rare diseases plans in their health policies. 3. Providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared	Rare diseases, are defined by the European Union as life-threatening or chronically debilitating diseases with low prevalence (less than 5 per 10,000).			

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2017[71]	UK, England, and Wales	Poster/Abstract only	The objective of this study was to evaluate National Institute for Health and Care Excellence Highly Specialised Technology (NICE HST) programme evaluations in the context of the changes and assess the potential impact they may have on patient access to ultra-orphan treatments in England and Wales			Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)	
2017[72]	Europe	Research article	Our multidisciplinary working group discussed the most relevant clinical and economic issues that are perceived to complicate the cost-effectiveness evaluation of orphan diseases and orphan medicinal products and to drive the high ICERs. Subsequently potential policy approaches are presented.	Orphan disease is defined in the EU Orphan Regulation 141/2000 (10) as: 1. A disease that is Life-threatening or chronically debilitating. 2. Prevalence of the condition in the EU of less than 5 in 10,000 or unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and 3. No satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorized in the EU, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.			
2017[73]	UK	Research	The aims of this study were to apply the MCDA framework that was proposed by Hughes-Wilson et al. (Orphanet J Rare Dis 7:74, 2012) to a range of orphan drugs in different diseases, with a view to testing the relationship between drug price and aggregated MCDA scores for each product.	Disease with a prevalence of 1 per 2,000 or less			
2018[74]	Sweden	Review	In this work we provide an up-to date analysis of drug target interactions for approved and clinical trial drugs and examine the major developments and trends in pharmaceutical development	Rare diseases are defined in the US as a disease or condition affecting less than one in 200 000 people.	Orphan drugs encompass pharmaceuticals that are intended to treat these types of diseases		
2018[75]	Poland, Netherlands, and Russia	Review	The goal of this article is to provide an in-depth review of rare disease policies and the reimbursement of ODs in 3 European countries, two EU members (Poland, the Netherlands) and a non-EU one (Russia).	Poland uses the EU definition of rare disorders, which considers a disease as rare if it affects less than 1 in 2000 people (< 5 in 10000 people)		Ultra-rare being <1 in 50000 people'	
2018[76]	Poland	Systematic review	The goal of this article is to provide an overview of the current state of knowledge and latest developments in the field of MCDA in HTA for orphan drugs, to review existing models, their design characteristics, as well as to identify opportunities for further model improvement.		The disease prevalence threshold in the EU for an orphan drug designation is well-defined at ≤ 5 per 10.000		
2018[77]	China	Research	The primary objectives are to establish standardization for registration platform, to build biobanks of genomic data, and to create partnerships for data sharing and research collaboration	The United States defines rare diseases as disorders affecting fewer than 200,000 individuals while the European definition is diseases with a prevalence of lower than 5/10,000.	In 2010, at a seminar conducted by the Genetics Society of the Chinese Medical Association, experts mainly in the field of medical genetics proposed that (any diseases of prevalence lower than 1/500,000 in the overall population or 1/10,000 among new-born's should be considered as a rare disease).		
2018[78]	UK, Scotland	Review	This review identified special HTA, and reimbursement considerations introduced for assessment of orphan drugs and implications for manufacturers.		- According to the European Medicines Agency definition, orphan drugs are intended for diagnosis, prevention, or treatment of rare diseases whose conditions affect no more than 5 in 10,000 persons. - OD proven at marketing authorization if the annual budget impact is less than €30 million per year for a particular indication. - Certain special HTA criteria are applied to orphan drugs: 1. Higher P values for small sample sizes 2. Use of surrogate endpoints 3. Additional benefit is considered proven if the budget impact is less than €50 million per year for a particular indication. - Higher therapeutic benefit is automatically recognized for orphan drugs because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorization procedure.		- Currently, no official definition of "ultra-orphan disorders" has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons. - In October 2018, a process will be introduced to allow faster access to ultra-orphan drugs: •The Scottish government will introduce a new definition of ultra-orphan medicines that can treat very

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							rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland
2018[79]	Taiwan, United States, EU, and Japan	Research article	- The objectives of this study were to examine 2003,2014 longitudinal trends in the prevalence and expenditure of rare diseases in Taiwan. We also analysed these trends for two specific rare diseases, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), because ALS is the main targeted rare disease in the ice bucket challenge activity, and MS is another rare disease with similar symptoms to those of ALS. - This study examined the national trends in the prevalence of rare diseases and their health-related economic burden (including medication costs) in Taiwan.	- The general definition of a rare disease in Taiwan is <1/10,000 persons. - In the United States and Japan, a rare disease is one with a prevalence of fewer than 200,000 persons and 50,000, respectively. The EU defines rare diseases as fewer than 5 per 10,000 persons			
2018[80]	UK, England	Poster/Abstract only	This research aims to identify, compare, and evaluate willingness to pay (WTP) thresholds across countries		WHO recommends a WTP of <3 times GDP per capita/QALY		HST for ultra-orphan indications Euro113,900-341,700/QALY in England
2018[81]	Germany	Review	- The valid guidelines and the regulations of the German health system are discussed in this article. - The criteria for indication and monitoring of off-label use are shown, especially focused on the problem of refractory myasthenia gravis.	- Since 2000, diseases with a prevalence of < 5 out of every 10,000 people in the EU have been defined as "rare diseases." - According to a statement by Orphanet regarding **myasthenia gravis** in Europe, this amounts to a prevalence of 1–9/100,000 population.		Rare diseases are "singular cases" or "individual cases", which are considered "ultra-rare diseases" (prevalence: <1:10,000), including, for example MuSK-positive myasthenia gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS)	
2018[82]	United States	Abstract	To estimate the pharmacy budget impact (per member per month [PMPM]) of five orphan drugs with single chronic indications.	There are up to 7,000 rare diseases, defined as a condition affecting fewer than 200,000 people.			
2018[83]	Canada, Scotland, Australia, and New Zealand	Research	The objective of the present study was to analyse the basis for Common Drug Review (CDR) orphan drug recommendations and to compare recommendations to those in other jurisdictions. In the current study we have reviewed CDR recommendations for orphan drugs, defined the parameters involved in decision making, and compared recommendations with those made in Scotland, Australia, and New Zealand.	- (Canada) proposed definition of a rare or orphan disease as one that affects < 1in 2000 persons, a definition aligned to that used in the European Union - Approximately 7000 such diseases have been identified and it is estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease			
2018[84]	Spain	Meeting Abstract	This presentation will review these forces and the multiple business models for pursuing orphan indications that they offer and discuss some of the unique scientific and business aspects that make the orphan space unique, including the crucial central role of rare disease patient organizations.	Rare diseases, which are those affecting <5 in 10,000 people in Europe.			
2018[85]	France	Poster/Abstract only	The aim of this analysis was to discuss ICERs of orphan drugs and their characterizations issued by the CEESP		Orphan drugs according to the Transparency Committee's opinions and designations are typically indicated in conditions that have a prevalence of below 5 in 10,000		
2018[86]	Japan	Symposium	Overview the designation and supporting systems for development of orphan drugs in Japan and foreign country, and introduce our experience of promoting the orphan drug in neuromuscular fields	- Rare diseases are any diseases that affected the relatively small number of patients, and generally chronically debilitating, life threatening. - Rare disease is definitely in the space of unmet medical needs.	Orphan drugs, which are the drugs for rare diseases		
2018[87]	United States	Review	The purpose of this study was to compare published ICER estimates, as a measure of relative value, across several orphan drugs which are indicated to treat rare diseases in paediatrics and adults.	A rare disease was defined as a condition with a prevalence of ≤620/million persons.		Ultra-rare diseases (affecting <20/million persons)"	
2019[88]	United States, WHO, and Europe	Book - chapter		- WHO, orphan disease refers to a disease with a low prevalence of less than 6.5–10 cases in 10,000 people. - USA, orphan disease is defined as one that affects less than 200,000 individuals. - Europe, disease with prevalence of less than 5 in 10,000 people	- Orphan drugs are defined as the drugs used for the diagnosis, prevention, or treatment of orphan disease. - Orphan drugs are those drugs having both orphan and non-orphan indications		
2019[89]	UK	Model	- Our study tested the criteria preferences and possibilities for implementation of the EVIDEM MCDA framework for orphan drugs with a diverse group of 140 stakeholders in Kazakhstan,	Diseases that are life-threatening or chronically debilitating are qualified as rare diseases (RD) in the EU if their prevalence is <5 per 10.000			

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			Netherlands, Poland, Romania, Russia, Turkey, and Ukraine (KZ, NL, PL, RO, RU, TR, UA). - The purpose of the study was to perform a weight elicitation for the EVIDEM rare disease model (v3.0) in a wider region in Eurasia with a sizeable group of experts (100-200), in order to identify key differences between countries and types of stakeholders as well as to compare weighting results from other studies. A secondary goal was to test the usefulness of a questionnaire tool designed for this purpose.				
2019[90]	UK	Abstract			- For a drug to be appraised via the HST process, it must meet seven criteria, based on: a small and defined distinct patient population, a limited number of specialist treatment centres for the indication in question, treatment price, and severity of the condition. - The current NICE appraisal system means orphan drugs that do not meet HST criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of ¬£30 k/QALY, or £50 k/QALY when end-of-life criteria are met		
2019[91]	UK	Poster/Abstract only	This research compares NICE Highly Specialised Technologies (HST) appraisal outcomes with corresponding guidance by other European HTA bodies, stratified by payer archetype: cost-effectiveness versus clinical effectiveness			Ultra-orphan disease (prevalence: <1:50,000)	
2019[92]	Italy	Meeting Abstracts	This paper aims to give some insights into the Italian Pricing & Reimbursement (P&R) Policies on Orphan Medical Products (OMPs) highlighting the strengths and weaknesses of the system.		- OMPs are drugs intended for the treatment of conditions affecting less than 5 in 10,000 people in the EU. - AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmet medical needs, clinical added value, and quality of evidence.		
2019[93]	UK (England and Scotland)	Review/ Poster	This research reviewed recent assessments of orphan and ultra-orphan drugs by NICE and the SMC, and disparities in availability for NHS patients between England and Scotland.		Treatments for diseases with a prevalence of <5 in 10,000 in the EU, which are life-threatening or severely disabling and have no satisfactory treatment available, are granted orphan designation by the European Medicines Agency (EMA)		The NICE Highly Specialised Technology Programme (HSTP) and the SMC consider ultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "
2019[94]	UK	Review	This review provides an overview of NIBSC, work in rare diseases and highlights the positive impact of the work of standardization institutions in this field	Rare diseases are defined as conditions not affecting more than 5 in 10,000 people in Europe			
2019[95]	Spain	Review	The present study aims to develop a reflective MCDA framework, based on EVIDEM methodology, with relevant criteria that allows the evaluation and positioning of OD to aid decision-making at the national level in Spain.		Orphan Drugs (ODs) are intended for the diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 (rare diseases) in the European Union (EU).		
2020[96]	India, Organization for Rare Diseases India (ORDI), WHO, EU, US, Japan, and Australia	Review	This review provides a brief account on RDs and their prevalence, followed by a discussion on the major RDs-associated challenges in general, an account on the methods that can be adopted for conducting fruitful molecular genetic studies of monogenic diseases, and the experiences of genetic research in Indian context with a special reference to a genetically vulnerable and low resource region like J&K - India.	- Organization for Rare Diseases India (ORDI) has suggested a threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals in India. - The base prevalence rate of RDs set by the World Health Organization (WHO) is approximately 1 in 2,000 people. - A genetic disorder prevalent in the European Union (EU) is considered rare only if it affects 5 or less per 10,000 cases, whereas the incidence rate for RDs in the United States is 7 or less per 10,000 individuals. These numbers translate to nearly 30 million Europeans and 25 million North Americans (approximately 1 in every 10) affected by any of the known RDs. - The incidence rate is estimated to be ≤2.5 cases in 10,000 and 1 in 10,000 individuals for Japan and Australia, respectively			
2020[97]	Belgium	Position Statement	The current paper aims to set a further step and translate the findings and recommendations from the many existing initiatives into a pragmatic and realistic methodology. The proposed tool will provide guidance to inform multi-stakeholder discussions and		Many of the treatments developed for rare diseases will have an Orphan Medicinal Product (OMP) designation, indicating that they are likely to deliver benefit in an area		

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			reimbursement decision making about specialised treatments for rare diseases." "Additionally, the paper provides guidance on the potential of Real-World Evidence (RWE) ,i.e., data collected outside the context of RCTs to help address such uncertainties.		of high unmet need. Their approval may be based on a small or uncontrolled trial		
2020[98]	Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom.	Systematic Review	This study aimed to create a comprehensive and in-depth overview of rare diseases policies and reimbursement of OMPs in a selection of 12 countries in the Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom. the aim of this article is to bridge the identified gaps by presenting an overview and comparison of current rare disease policies, HTA and reimbursement processes for orphan drugs in a broader range of Eurasian countries.	- The EU has officially defined rare diseases as being rare when they affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) and in most of the selected countries this definition is used [FR, DE, LV, NL, PL, RO, UK, and UA - In Russia the maximum prevalence for a rare disease is defined as 1 in 10,000 - Some countries use additional definitions in situations where a condition is not officially defined as rare, such as in the UK, where the National Health Service (NHS) classifies all conditions that require specialized medical care also as rare if they occur in <500 citizens yearly. - Turkey defines a rare disease when they affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition. - There is no specific definition for ,rare disease, in Armenian legislation, only ,levels of disability, which define whether the patient will receive the necessary medicines for free or not	The Netherlands defines the classification ,orphan drug' as either having an official EU orphan designation or one that targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no registered medicine exists.		Effective from October 2018, Scotland has introduced a new definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes
2020[99]	France	Review	To detect among the drugs approved for limited populations any impact of the orphan status on the assessment outcome of medical benefit (SMR) or improvement in medical benefit (ASMR) carried out by the French authority for health (HAS)	Prevalence of rare disease < 5/10 000 as per EMA"	An orphan designation is granted by EMA for a medicinal drug intended to treat a life-threatening or chronically debilitating disease, provided a maximum prevalence in the Europe of 5/10,000 and when no satisfactory authorised method can be authorised, or, if such a method exists, the medicine must be of significant benefit to patients.		
2020[100]	UK	Commentary	This paper explores the successes and limitation of both the regulation and its implementation mechanisms in the current regulatory context, and suggests some improvements that could maximise its benefits and boost rare disease research even further	- Rare diseases are categorized as ,orphan diseases, because their occurrence in a small number of patients means that, despite apparent high unmet medical need, there is limited scientific understanding, making it difficult to justify the development risk and investment to develop new treatments. - The European Union defines a rare (or ,orphan,) disease as a life-threatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union.		Prevalence can be much lower, leading to the concept of the, ultra-orphan disease, for diseases with an estimated prevalence of <1 in 50,000 people	
2020[101]	India	Abstract	The purpose of this paper is to identify the hurdles in the field of orphan drugs in India and suggest solutions to address the same.	An orphan disease is defined as a condition that affects fewer than200,000 people nationwide	Orphan Drug is used to treat such a condition.		
2020[102]	India	Review	To understand orphan drugs and national policy on treatments of rare diseases. To overview the condition for pricing of orphan drugs in India and government schemes which are helping out for patient needs. To highlight the need of regulations on orphan drugs for sale and manufacture of orphan drugs in India.	A rare disease is a health disorder of low occurrence that affects a limited number of people in the general population as opposed to other prevalent diseases.	Orphan drugs are the drugs and natural products used in the treatment, diagnosis, or prevention of rare disease.		
2020[103]	194 World Health Organization member countries and other areas (Hong Kong, Kosovo, Macau, Palestine, Sahrawi, Republic, Philippines and Taiwan)"	Health Policy Analysis	This study aims to provide an up-to-date global overview of ODP (Orphan drug policies) in the era of innovative medicine and to reflect associated changes in drug regulation policy. This review provides an overview of global policies that optimize development, licensing, pricing, and reimbursement of orphan drugs.	- Rare diseases are typically defined as conditions with limited treatment alternatives, with an average prevalence of fewer than 40 to 50 cases per 100 000 population or that affect a small number of patients compared with the total population. - When defining rare diseases, most countries/ areas adhered to the European Union definition of low prevalence (0.05%), whereas others followed the number of prevalent cases, such as Australia (< 2000), South Korea (<20 000), and the United States (<200 000). Countries/areas such as Chile, Kenya, Peru, and Singapore required the disease severity to be, life threatening, and severely- or chronically-,debilitating. - Rare disease or condition, means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 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	- Orphan drugs are often defined as drugs intended for the treatment, diagnosis, prophylaxis, or rehabilitation of rare diseases. - Orphan drugs are also defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions. Countries/areas such as China and Vietnam acknowledged orphan drug designation from reference competent authorities. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the community when the application is made, or that it is intended for the		

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				condition will be recovered from sales in the United States of such drug (United States) - Designation of rare diseases: The DOH, upon recommendation of the RDTWG, shall have the authority to designate any disease that is recognized to rarely afflict the population of the country as a rare disease. (The Philippines)	diagnosis, prevention or treatment of life-threatening, seriously debilitating or serious and chronic condition in the community and that without incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment, and (b) that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the Community or, if such a method exists, that the medicinal product will be of significant benefit to those affected by that condition. - In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor must submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorization is made. (European Union		
2020[104]	Santiago de Chile	Book - Chapter		- Rare diseases (RDs) or orphan diseases, by definition, are conditions that affect a small number of individuals most RDs are chronic and debilitating and are a substantial cause for disability and early death. - Based on Orphanet, disease inventory, it is evident that the majority of RDs are of genetic etiology, and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers." - RDs are a highly heterogeneous group of disorder		
2020[105]	China, Australia, Japan, South Korea, and Taiwan	Poster/Abstract only	We sought to identify the regulations and policies related to market access for orphan drugs in five major markets from the APAC Region, with the aim of providing an overview of the factors designed to support sponsors of orphan medicinal products. Specifically, we focused on policies in Australia, China, Japan, South Korea, and Taiwan	- "China: Rare disease defined as that affecting less than 1 per 500,000 population. - South Korea: Rare disease defined as that affecting: Less than 20,000 people in Korea (i.e., <4 per 10,000 population) - Japan: Rare disease defined as that affecting: Less than 50,000 people in Japan (i.e., <4 per 10,000 population). - Taiwan: Rare disease defined as that affecting less than 1 per 10,000 population. - Australia: Rare disease defined as that affecting less than 5 per 10,000 population"			
2021[106]	South Korea	Expert Opinion	This paper reviews key factors that should be considered in the process of development, regulation, and market access of orphan drugs in South Korea with a particular focus on the pricing and reimbursement review process.		In South Korea, the Korea Ministry of Food and Drug Safety formulates ODs, which should satisfy two conditions related to the number of patients and the existence of alternatives. In other words, drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments or drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD.		
2021[107]	UK	Review	This review provides an overview of the strengths and limitations of value assessment frameworks (VAFs) for the reimbursement of orphan drugs in Europe and may serve as a guide for decision-makers.	- Rare diseases are a group of diverse diseases, each characterized with low prevalence: occurring in less than one in 2,000 people in Europe. - They are defined as life-threatening or chronically debilitating, and are mostly caused by a genetic predisposition	The, Orphan Medicinal Product Regulation defines OMPs as products for the ,diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union		
2021[108]	Spain	Research	This study aimed to determine the most relevant criteria for the reimbursement of OMPs in Spain, from a multi-stakeholder perspective, and using multi-criteria decision analysis (MCDA). The objective of this study was twofold: first, to review, discuss, and reach a consensus on the most relevant criteria for decision-making about pricing and financing OMPs in Spain; and second, to prioritize them according to their relative importance based on	- Rare diseases are diseases of low prevalence and high complexity that can lead to death or chronic disability. - In Europe, rare diseases are defended as those pathologies that affect less than 5 people per 10,000 inhabitants.	Orphan medicinal products (OMPs), which are intended to diagnose, prevent, or treat rare diseases, have a shared community procedure for being designated as such in the European Union, and this community approach provides opportunities for research, development, and marketing	Ultra-rare, affecting less than 1 person per 50,000 inhabitants."	

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
			the preferences stated by different stakeholders, following the MCDA methodology.				
2021[109]	New Zealand	Online survey	The objectives of this study were to measure the relative societal importance of values of New Zealanders in informing drug funding decisions and to determine how New Zealanders trade of funding in various scenarios between common and rare diseases.	A rare disorder is defined by PHARMAC (the Pharmaceutical Management Agency) as affecting less than 1:50,000 people in the New Zealand population, which is a considerably lower prevalence threshold than other nations that are from 5 to 76 per 100,000 people			

Supplementary Table S2: Critical Appraisal Result

Critical Appraisal Result for Systemic Reviews and Research Syntheses studies

Studies	Q1) Is the review question clearly and explicitly stated?	Q2) Were the inclusion criteria appropriate for the review question?	Q3) Was the search strategy appropriate?	Q4) Were the sources and resources used to search for studies adequate?	Q5) Were the criteria for appraising studies appropriate?	Q6) Was critical appraisal conducted by two or more reviewers independently?	Q7) Were there methods to minimize errors in data extraction?	Q8) Were the methods used to combine studies appropriate?	Q9) Was the likelihood of publication bias assessed?	Q10) Were recommendations for policy and/or practice supported by the reported data?	Q11) Were the specific directives for new research appropriate?
1. 2018 [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. 2020 [84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. 2021 [110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1. Critical Appraisal Result for Text Opinion studies

Studies	Q1) Is the source of the opinion clearly identified?	Q2) Does the source of opinion have standing in the field of expertise?	Q3) Are the interests of the relevant population the central focus of the opinion?	Q4) Is the stated position the result of an analytical process, and is there logic in the opinion expressed?	Q5) Is there reference to the extant literature?	Q6) Is any incongruence with the literature/sources logically defended?
1.2003 [3]	Yes	Yes	Yes	Yes	Yes	Yes
2.2005 [5]	Yes	Yes	Not applicable	No	Yes	Yes
3.2006 [7]	Yes	Yes	Yes	Not applicable	Yes	No
4.2009 [9]	Yes	Yes	Yes	Not applicable	Yes	Not applicable
5.2010 [11]	Yes	Yes	Yes	Yes	Yes	No
6.2010 [12]	Yes	Yes	Unclear	No	Yes	No
7.2014 [33]	Yes	Yes	Yes	Yes	Yes	Yes
8.2017 [51]	Yes	Yes	Yes	Yes	Yes	Yes
9.2017 [111]	Yes	Yes	Yes	Yes	Unclear	NO
10. 2019 [78]	Yes	Yes	Yes	NO	Yes	Yes
11. 1992 [1]	Yes	No	Yes	NO	Yes	Not applicable
12. 2004	Yes	Yes	Yes	Yes	Yes	Not applicable
13. 2008 [8]	Yes	Yes	Yes	Yes	Yes	NO
14. 2010 [13]	Yes	Yes	NO	NO	Yes	Not applicable

15. 2011 [15]	Yes	Yes	Yes	Yes	Yes	NO
16. 2013 [25]	Yes	Yes	Yes	Yes	Yes	NO
17. 2013 [28]	Yes	Yes	Yes	Yes	Yes	NO
18. 2014 [37]	Yes	Yes	Yes	Yes	Yes	NO
19. 2016 [44]	Yes	Yes	NO	Yes	Yes	NO
20. 2018 [55]	Yes	Yes	Yes	Yes	Yes	Yes
21. 2018 [59]	Yes	Yes	Yes	Yes	Yes	NO
22. 2018 [65]	Yes	Yes	NO	Yes	Yes	NO
23. 2020 [80]	Yes	Yes	Yes	Yes	Yes	NO
24. 2020 [86]	Yes	Yes	Yes	Yes	Yes	NO
25. 2020 [112]	Yes	Yes	Yes	Yes	Yes	NO
26. 2020 [88]	Yes	Yes	Yes	Yes	Yes	NO
27. 2021 [91]	Yes	Yes	Yes	Yes	Yes	Yes
28. 2010 [14]	Yes	Yes	NO	Yes	Yes	No applicable
29. 2018 [61]	Yes	Yes	Yes	Yes	Yes	NO
30. 2021 [91]	Yes	Yes	Yes	Yes	Yes	NO

2. Critical Appraisal Result for Economic Evaluations studies

Studies	Q1) Is there a well-defined question?	Q2) Is there comprehensive description of alternatives?	Q3) Are all important and relevant costs and outcomes for each alternative identified?	Q4) Has clinical effectiveness been established?	Q5) Are costs and outcomes measured accurately?	Q6) Are costs and outcomes valued credibly?	Q7) Are costs and outcomes adjusted for differential timing?	Q8) Is there an incremental analysis of costs and consequences?	Q9) Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Q10) Do study results include all issues of concern to users?	Q11) Are the results generalizable to the setting of interest in the review?
1.2012 [21]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Yes
2.2014 [34]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes
3.2014 [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.2018 [63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.2018 [67]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Yes	No	Yes	Yes
6.2017 [57]	Yes	Yes	Yes	Yes	Yes	Unclear	NO	NO	NO	Yes	Yes

3. Critical Appraisal Result for Analytical Cross-Sectional Studies

Studies	Q1) Were the criteria for inclusion in the sample clearly defined?	Q2) Were the study subjects and the setting described in detail?	Q3) Was the exposure measured in a valid and reliable way?	Q4) Were objective, standard criteria used for measurement of the condition?	Q5) Were confounding factors identified?	Q6) Were strategies to deal with confounding factors stated?	Q7) Were the outcomes measured in a valid and reliable way?	Q8) Was appropriate statistical analysis used?

2012 [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2015 [41]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Unclear

4. Critical Appraisal Result for Qualitative Research studies

Studies	Q1) Is there congruity between the stated philosophical perspective and the research methodology?	Q2) Is there congruity between the research methodology and the research question or objectives?	Q3) Is there congruity between the research methodology and the methods used to collect data?	Q4) Is there congruity between the research methodology and the representation and analysis of data?	Q5) Is there congruity between the research methodology and the interpretation of results?	Q6) Is there a statement locating the researcher culturally or theoretically?	Q7) Is the influence of the researcher on the research, and vice- versa, addressed?	Q8) Are participants, their voices adequately represented?	Q9) Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Q10) Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?
1. 2014 [36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. 2021 [92]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
3. 2021 [93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
4. 2013 [30]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Yes
5. 2019 [59]	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	Yes

5. Critical Appraisal Result for Prevalence Studies

Studies	Q1) Was the sample frame appropriate to address the target population?	Q2) Were study participants sampled in an appropriate way?	Q3) Was the sample size adequate?	Q4) Were the study subjects and the setting described in detail?	Q5) Was the data analysis conducted with sufficient coverage of the identified sample?	Q6) Were valid methods used for the identification of the condition?	Q7) Was the condition measured in a standard, reliable way for all participants?	Q8) Was there appropriate statistical analysis?	Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?
1. 2016 [47]	Yes	Yes	NO	Yes	Yes	Yes	Yes	Yes	Yes
2. 2013 [26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Not applicable

6. Critical Appraisal Result for Cohort Studies

Studies	Q1) Were the two groups similar and	Q2) Were the exposures measured	Q3) Was the exposure	Q4) Were confounding	Q5) Were strategies to deal with	Q6) Were the groups/participants free of the	Q7) Were the outcomes	Q8) Was the follow up time reported and	Q9) Was follow up complete, and if not, were	Q10) Were strategies to address	Q11) Was appropriate

	recruited from the same population?	similarly to assign people to both exposed and unexposed groups?	measured in a valid and reliable way?	factors identified?	confounding factors stated?	outcome at the start of the study (or at the moment of exposure)?	measured in a valid and reliable way?	sufficient to be long enough for outcomes to occur?	the reasons to loss to follow up described and explored?	incomplete follow up utilized?	statistical analysis used?
1. 2018 [61]	Not applicable	Yes	Yes	NO	NO	Yes	Unclear	NO	NO	Yes	Not applicable

Supplementary Table S3: RDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
North America	US (25)	24 (26%)	Orphan Drug Regulation	Defines RD according to prevalence: ‘‘rare disease’ means any disease or condition that affects less than 200000 persons in the USA’.	1993	developed
			RDA		2002	
			ODA	Defined RDs based on qualitative descriptors as follows: ‘the term ‘rare disease or condition’ means any disease or condition which occurs so infrequently in the USA that there is no reasonable expectation that the cost of developing and making a drug for use in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug’.	1983	
			FDA	Define RD as ‘any disease or condition that affects less than 200000 people in the USA or affects >200000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug’		
	Canada (3)	2 (2%)	CORD	Rare disease as one that afflicts less than 1 person in 200 000.		Aligned to EU
				Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease		
South America	Chile (1)	1 (1%)		Required the disease severity to be ‚life threatening, and severely- or chronically debilitating.		
	Peru (1)					
Europe	UK (3)	2 (2%)	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in 2000 people. (i.e., a prevalence of 5 or less per 10,000)	2021	
			NHS	Some countries use additional definitions in situations where a condition is not officially defined as rare. classifies all conditions that require specialized medical care as rare if they occur in <500 citizens yearly		
	EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000 persons in the European Union) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential.		
			European Commission on Public Health	Defines rare diseases as ‚life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them		
			Orphan Drug Regulation	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare	141/2000	
			EMA	prevalence of rare disease < 5/10 000		
	Germany (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Latvia (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Netherlands (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Poland (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
	Romania (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	France (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Ukraine (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
Oceania	Australia (10)	10 (11%)		Diseases with a prevalence of 1.1/10 000		
				Diseases with a prevalence < 2000 individuals.		
				Australia have set prevalence's of 1.16 per 100,000 individuals for a given disease.		
				Affecting <11/100,000 inhabitants or ,≤2000 Australians		
				Prevalence threshold for orphan disease designation: 0.9 in 10,000		
				The incidence rate is estimated to be 1 in 10,000 individuals for Australia		
	New Zealand (1)	1 (1%)	PHARMAC	Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold than other nations that are from 5 to 76 per 100,000 people		
Asia	Japan (13)	13 (14%)		Japan diseases with a prevalence of 4.0/10,000		
				<50,000 patients in Japan		
				Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment		
				The incidence rate is estimated to be ≤2.5 cases in 10,000 for Japan		
	Taiwan (7)	7 (8%)	Taiwan Foundation for Rare Disorders	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical coverage.	2000	
			Physically and Mentally Disabled Citizens Protection Act	RD is one type of disability	2001	
	China (5)	5 (5%)	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences in Newborn babies.		
				Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.		
	South Korea (4)	5 (5%)		Prevalence thresholds have been set at less than 1 per 20,000		
				Prevalence threshold: <4.0 in 10,000		
				< 20,000 people in Korea (i.e., <4 per 10,000 population)		
	Singapore (2)	2 (2%)		Required the disease severity to be life threatening, and severely- or chronically debilitating.		
				Prevalence threshold: 37.7 in 10,000		
	India (1)	1 (1%)	ORDI	Threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals		
	Armenian legislation (1)	1 (1%)		There is no specific definition for rare disease only levels of disability which define whether the patient will receive the necessary medicines for free or not		
	Philippines		The DOH, upon recommendation of the RDTWG,			
Africa	Kenya			Required the disease severity to be ,life threatening, and severely- or chronically ,debilitating.		

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
Eastern Europe & Northern Asia.	Russia (1)	1 (1%)		Maximum prevalence for a rare disease is defined as 1 in 10,000		
South-eastern Europe & Southwestern Asia	Turkey (1)	1 (1%)		Affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition.		
	WHO (5)	5 (5%)		Rare disease affects at most 6.5 out of every 10,000 individuals.		
				Frequency of 6.5-10/ 10,000 inhabitants		
				Incidence ranges approximately from 0.65-1% in the whole population.		
				Rare disease as affecting 65/100 000~100/100 000 persons.		
	Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic etiology and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers."		

*The Rare Diseases Act (RDA; the Orphan Drug Act (ODA; the Food and Drug Administration (FDA); The Canadian Organization of Rare Diseases (CORD); National Health Service (NHS); - PHARMAC (the Pharmaceutical Management Agency)**;** Organization for Rare Diseases India (ORDI)*

Supplementary Table S4: ODs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
Europe	EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically and seriously debilitating condition affecting not more than 5 in 10 000 EU people or that it is unlikely that marketing the drug in the EU would generate sufficient benefit for the affected people and for the drug manufacturer to justify the investment		
			NICE	The current NICE appraisal system means orphan drugs that do not meet HST criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of¬£30 k/QALY, or¬£50 k/QALY when end-of-life criteria are met		
			EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs and are referred to as orphan drugs because, the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	(2011 c)	

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
			The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union		
			The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered medicine exists		
			Poland	There is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2024 is approximately € 26 800.		
	Italian (1)	1 (1%)	Medicines Agency (AIFA)	AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmet medical needs, clinical added value and quality of evidence.		
	German (1)	1 (1%)		Certain special HTA criteria are applied to orphan drugs: Higher P values for small sample sizes; Use of surrogate endpoints, Higher therapeutic benefit is automatically recognised for orphan drugs because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorisation procedure. budget impact is less than €50 million per year for a particular indication		
North America	US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200, 000 persons in the USA' (which equates to approximately 6 cases per 10,000 population) 'or meets cost recovery provisions of the act'		
			Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease. condition of interest in the United States as a surrogate for the lack of profitability."		
				Orphan product, as one that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA		
Asia	Singapore (1)	1(1%)	Orphan Drugs Policy	Allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner.	1991	
	Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.		
			the Korea Ministry of Food and Drug Safety formulates ODs	Drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments or drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD		
	China (2)	2 (2%)		Orphan drugs are defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions		
				Drug used for diseases affecting fewer than 1 in 10,000		
	Vietnam (1)	1(1%)		Orphan drugs are defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions		

Supplementary Table S5: URDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
Europe	UK			Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 1/50,000 of the population (Hugheset al., 2005)		
			NICE	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1 in 50,000		
	Alberta		NICE	URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE, A-15ur-a).		
	England		Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~1 in 100,000 of the English population)		
	Ontario			An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario		
				ultra-orphan diseases affecting <1/50000 inhabitants		
			(EU regulation 536/2014)	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe		
	England and Wales		NICE	"Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)"		
	Poland			Poland uses the EU definition of 'Ultra-rare being <1 in 50000 people'		Adopted EU definition
				rare disease there are “singular cases” or “individual cases”, which are considered ultra-rare diseases” (prevalence: <1:10,000), including, for example MuSK-positive myasthenia gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS)		
				ultra-rare diseases (affecting <20/million persons)"		
				the prevalence can be much lower, leading to the concept of the ‚ultra-orphan disease, for diseases with an estimated prevalence of <1 in 50,000 people "		
				Ultra-rare, affecting less than 1 person per 50,000 inhabitants."		

Continent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
				ultra-orphan (prevalence: <1:50,000)		
			NICE Highly Specialised Technology Programme (HSTP) and the SMC	The NICE Highly Specialised Technology Programme (HSTP) and the SMC consider ultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "		

Supplementary Table S6: UODs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopted / developed
				Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or less		
				NICE: applied it to drugs with indications for conditions with a prevalence of less than [illegible] per 50,000 persons"		
				Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e. ultra-orphan drugs)		
				Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence ≤1:50,000) were consistent in most countries.		
	Scotland		The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland		
	England			HST for ultra-orphan indications Euro113,900-341,700/QALY in England		
			WHO	WHO recommends a WTP of <3 times GDP per capita/QALY		
	Scotland			New definition for ultra-orphan drugs: ‚medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes	Effective from October 2018	
			NICE	No official definition of ‚ultra-orphan disorders, has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence;		

36/bmjopen-2024-086527 on 25 January 2025. Downloaded from

Continent	Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopted / developed
				NICE), who applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"		
			NICE	Currently, no official definition of “ultra-orphan disorders” has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons.		

Supplementary Table S7: Qualitative and Quantitative descriptors and themes

RDs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Theme	Qualitative Descriptors
Nature	1. Disease	Disease nature affecting the pt.	17. Rare
	2. Condition		18. Disable
	3. Disorder		19. Life-Limiting condition
	4. Pathologies		20. Life-threatening
	5. Status		21. Substantial cause for early death
	6. Severe		22. Long-Term Treatment
	7. Chronic		23. Debilitating
	8. Serious	Disease nature affecting the pt.'s Society	24. Considerable reduction in an individual's quality of life
	9. Intractable		25. Considerable reduction in socio-economic potential
	10. High Complexity		26. Unmet medical needs
	11. Medic* (medical, Medicinal, Medically, & Medicine)	Population characteristics	27. Low Prevalence
	12. Drugs		28. Small number of patients
	13. Heterogeneous Group		29. Low Occurrence
Etiology	14. Unknown Etiology		30. Rarely afflict the population
	15. Genetic		31. Population
	16. Hereditary		32. People
Quantitative Descriptors			33. Inhabitant* (s)
Measures	1. Prevalence	Indication	34. Treat* (Treatment)
	2. Absolute # of patients		35. Prevent* (Prevention)
	3. Incidence		
	4. Incidence rate		
	5. Frequency		
	6. Number of case references		
	7. Threshold		
	8. Range		
	9. Percentage		
	10. Estimated measure		

ODs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Themes	Qualitative Descriptors
Nature of Product	1. Medical Product	Unmet Need	21. No alternative treatment
	2. Agent		22. Treatment Price
	3. Biological Products		23. Lack profit

ct	4. Product		24. Lack of drug development
	5. Pharmaceutical Product		25. Little interest
	6. Active Ingredients not developed, imported, or registered		26. No/limited available therapy
			27. Attractive for commercial development
	7. Drug		
Disease nature affecting the pt.'s Society.	8. Rare Diseases	Benefits from taking the treatments	28. Clinical added value
	9. Life-Threatening Condition		29. Improve safety or efficacy
	10. Debilitating Disease		30. Product will be of significant benefit
	11. Disease with a limited number of specialist treatment centers		31. New drug is significantly better than drugs currently marketed
	12. Serious Condition	Indication	32. Indications
	13. Rare medical condition		33. Diagnosis
	14. Interactable diseases		34. Treatment
	15. Unmet medical needs		35. Prevention
	16. Common disease where the sponsor cannot make any profit		36. Prophylaxis
			37. Rehabilitation
Population Characteristics	17. Low prevalence		
	18. Small number of patients		
	19. Population		
	20. People		
Quantitative Descriptors			
Measures	1. Prevalence		
	2. Cost-effectiveness threshold		
	3. Annual budget impact for a particular indication		
	4. Number of cases reference		
	5. Willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY		

URDs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Quantitative
Nature	1. Disease	**Measurements**	1. Prevalence
	2. Chronic		2. Incidence
Population Characteristics	Very small patient		3. Incidence rate
	Population		4. Estimated measure
	People		
	Persons		
	Inhabitants		

UODs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Qualitative
Nature	1. Very rare conditions	Indication	1. Indications
	2. Medicines		2. Treat
	3. Drug		3. Approved for use
	4. Disease	Population Characteristics	1. Patients
	5. Condition		2. Persons
Theme	Quantitative		3. People
Measurements	1. Prevalence		
	2. Willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY.		

Supplementary Table S8: Qualitative criteria frequently used for RDs, ODs, URDs, and ODs in the definition.

Theme	Qualitative Descriptor	RD	URD	OD	UODs
Nature	1. Disease	148	13	60	2
	2. Condition	30	3	52	4
	3. Disorder	18	1	2	1
	4. Pathologies	1	-	1	-
	5. Status	1	-	2	-
	6. Sever*	5	-	5	-
	7. Chronic	22	1	7	-
	8. Serious	3	-	12	-
	9. Intractable	1	-	1	-
	10. High Complexity	1	-	-	-
	11. Heterogeneous	1	-	-	-
	12. Product	-	-	35	-
	13. Medic* (medical, Medicinal, Medically, & Medicine)	5	-	36	2
	14. Agent	-	-	1	-
	15. Biological Products	-	-	1	-
	16. Pharmaceutical Product	-	-	2	-
	17. Active Ingredient not developed, imported, or registered	-	-	1	-
	18. Drugs	8	-	83	8
Etiology	19. Unknown Etiology	1	-	-	-
	20. Genetic	7	-	1	-
	21. Hereditary	1	-	-	-
Disease nature	22. Rare Diseases	40	4	16	-
	23. Disab* (Disability & Disabling)	5	-	2	-
	24. Life -Limiting	1	-	0	-

Theme	Qualitative Descriptor	RD	URD	OD	UODs
affecting the pt.	25. Life-threatening	23	-	20	-
	26. Substantial cause for early death	1	-	0	-
	27. Long-Term Treatment	1	-	0	-
	28. Debilitating	21	-	10	-
Disease nature affecting the pt.'s Society	29. Considerable reduction in an individual's quality of life	1	-	0	-
	30. Considerable reduction in socio- economic potential	2	-	0	-
	31. Unmet medical needs	3	-	3	-
	32. Disease with limited number of specialist treatment centers	-	-	1	-
	33. Common disease where the sponsor cannot make any profit	-	-	1	-
Population Characteristics	34. Low Prevalence	12	-	2	-
	35. Low Occurrence	2	-	-	-
	36. Rarely afflict the population	1	-	-	-
	37. Small number of patients	3	-	1	-
	38. Very small patient Population	-	1	-	-
	39. Population	20	3	7	-
	40. People	29	2	8	2
	41. Inhabitant* (s)	6	2	-	-
Benefits from taking the treatment	42. Clinical added value	-	-	1	-
	43. Improve safety or efficacy	-	-	1	-
	44. Product will be of significant benefit	-	-	2	-
	45. New drug is significantly better than drugs currently marketed	-	-	1	-
Indication	46. Indications	-	-	4	4
	47. Diagnosis	-	-	23	-
	48. Treat* (Treatment)	7	-	55	2
	49. Prevent* (Prevention)	1	-	23	-
	50. Rehabilitation	-	-	1	-
	51. Prophylaxis	-	-	1	-

Supplementary Table S9: Quantitative criteria frequency used of RDs, ODs, URDs, and ODs in the definition.

Theme	Quantitative Descriptor	RD	URD	OD	UOD
Measurements	1. Prevalence	51	10	22	6
	2. Absolute # of patients	1	-	-	-
	3. Incidence	7	1	-	-
	4. Incidence rate	2	1	-	-
	5. Frequency	1	-	-	-
	6. Number of* (cases reference, patients, people, prevalent cases, and individuals)	6	-	5	-

	7. Threshold	3	-	-	-
	8. Estimated measure	5	1	-	-
	9. Range	2	-	-	-
	10. Percentage	3	-	-	-
	11. Cost-effectiveness threshold	-	-	2	-
	12. Annual budget impact for a particular indication	-	-	1	-
	13. willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY	-	-	1	1

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Global Insight into Rare Disease and Orphan Drug Definitions: A Systematic Literature Review

Ghada Mohammed Abozaid[1,2]*, Katie Kerr[1], Hiba Alomary[3], Hussain Abdulrahman Al-Omar[4,5,6], Amy Jayne McKnight[1]

*Corresponding author: gabozaid01@Qub.ac.uk.

Abstract:

Objectives This study sheds light on the available global definitions, classifications and criteria used for rare diseases (RDs), ultrarare diseases (URDs), orphan drugs (ODs), and ultra-orphan drugs (UODs), and provides insights into the rationale behind these definitions.

Design A systematic literature review was conducted to identify existing definitions and the criteria used to define RDs, ODs, and their subtypes.

Data Sources: Searches were performed in the PubMed/Medline, EMBASE, Scopus, and Web of Science (Science and Social Sciences Citation Index) databases covering articles published from 1985 to 2021.

Eligibility Criteria for selecting studies: English-language studies on the general human population were included if they provided definitions or criteria for RDs, ODs, and /or their subtypes without restrictions on publication year, country, or jurisdiction.

Data extraction and synthesis Two independent reviewers conducted the search, screening, and data extraction. Narrative synthesis, content analysis, and descriptive analyses were conducted to

extract and categorize definitions and criteria from these sources. Study quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools.

Results Online searches identified 2,712 published articles. Only 93 articles met the inclusion criteria, with 209 distinct definitions extracted. Specifically, 93 of these articles pertained to 119 RDs, 11 URDs, 67 ODs, and 12 UODs.These definitions varied in their reliance on prevalence-based and other contextual criteria.

Conclusion Prevalence-based criteria alone pose challenges, as disease frequencies differ by country. Establishing country-specific definitions can enhance understanding, support intercountry evaluations, improve healthcare efficiency and access to ODs, and strengthen equity and equality in healthcare. Such efforts would also promote research and development and support better outcomes for patients with complex and rare conditions.

PROSPERO registration number CRD42021252701.

Keywords: rare disease, ultra-rare, orphan drug, ultra-orphan drugs, qualitative, quantitative, healthcare, criteria.

Strengths and limitations

- This systematic literature review, based on PROSPERO International Prospective Register of Systematic Reviews (CRD42021252701) and PRISMA-P, explores criteria for determining RDs and ODs without publication design, year, or regional restrictions.
- Unlike other reviews, this study explored different criteria for defining RDs and ODs issued by different agencies and entities to fulfil their mandates in relation to RDs and ODs.

- The searched articles showed inconsistent terminology, and despite seeking library specialist feedback, some relevant studies might have been missed.
- The results might be subject to biases in publication selection, language, and database.

Background

Rare diseases (RDs) represent a major public health concern requiring more effective interventions to alleviate the burden on patients, carers, health, and social care systems. RDs, sometimes known as 'orphan diseases'[1, 2] and affect a minority of people, are typically medical conditions that are individually identified with low prevalence within a particular population [3]. Globally, RDs affect more than 450 million individuals [4], the majority of whom are disproportionately disadvantaged and lack effective treatment. No multipurpose and universally agreed upon definition of an RD [5] exists, making optimal care difficult; definitions implemented internationally each depend on the context and perspectives of various stakeholders, some of which employ qualitative and/or quantitative criteria.[6]

The qualitative criteria used to define RDs are primarily subjective and include terms such as "life-threatening", "alternative treatment options", "severity of disease", and "neglected". Some of these criteria have major emotional impacts, such as on the severity of the illness, its potential fatality, heritability, or the lack of effective therapies [7]. On the other hand, quantitative criteria to define RDs are objective and measurable in nature and include disease incidence [8] and prevalence [9], which are key indicators for understanding the frequency of disease occurrence within a population. Certain diseases can be labelled rare in one nation but not in another owing to population genetic variations, environmental or societal influences, or disparities in survival rates across different regions [10]. A lack of sufficient data on which diseases are categorised as rare creates an obstacle in understanding these conditions and proportions and disease coding; ensuring

accurate diagnoses; and encouraging pharmaceutical companies [11] to invest in the research and development of medications for these diseases and manufacture orphan drugs (ODs), which, consequently, constitute a considerable challenge in making treatments available and accessible.

Overall, effective therapies are available for fewer than 5% of individuals diagnosed with RDs. The definition of RD is used to determine the eligibility of a medication for a regulatory designation as an OD. This is a status granted to pharmaceutical products that are developed to treat RDs and incentivized by governments and regulatory bodies to encourage product development and production. For instance, pricing preferences, market exclusivity, financial incentives, protocol assistance, grants and research funding, and extended patent protection are different forms of incentives offered to industry.

OD definitions extend across international borders and are frequently linked to RD definitions that are based on epidemiological data for the target disease and economic data for the drug market [5]. Some countries set priorities for RD expenditures and resource allocation to address OD accessibility and help policymakers enhance the efficiency and delivery of ODs [6]. Adopting a universal definition can be challenging due to regional variations in terms of demographic, economic, survival, and sociocultural factors [12]. For example, in Saudi Arabia (SA), there is no multipurpose national definition for RD or OD, which could impact diagnoses, treatment strategies, and resource allocation, highlighting the need for a localized and country-specific definition. Approximately 80% of RDs have a genetic cause, which increases the risk of inherited autosomal conditions in offspring from consanguineous marriages [13]; in SA, 70% of total marriages are consanguineous, which may increase the prevalence of some genetic diseases [14].

There are considerable challenges associated with the context and practical use of RDs, ODs, and subtype definitions employed by various stakeholders. One significant challenge is the

inconsistency in definitions across regions and regulatory agencies. For example, the EU and the US use different prevalence thresholds to define RDs, complicating regulatory frameworks and market access for ODs. This variation also affects clinical trials and research, as the lack of harmonized definitions can hinder data comparability and international collaboration. Moreover, pharmaceutical companies face additional regulatory and pricing barriers due to these differences, which can delay drug approval and patient access. From a patient care perspective, disparities in definitions may lead to inequities in diagnosis, treatment, and access to therapies. OD treatments may not be available to patients in other regions with the same condition, fragmenting advocacy efforts. Finally, economic and ethical considerations, such as cost-effectiveness criteria and the financial burden on healthcare systems, further complicate the practical use of the RD and OD definitions, highlighting the need for harmonization to ensure equitable and efficient healthcare delivery globally for RD patients.

This systematic literature review (SLR) delves into the diverse definitions and criteria used by countries to define RDs, ODs, and their subtypes, providing deeper insight into different factors, encouraging the establishment of robust criteria, and supporting policy deliberations.

Methods

Systematic literature review protocol

The protocol for this SLR [11] was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42021252701) and follows the PRISMA-P [15, 16] guidelines. The PROSPERO template ensures transparency and accountability for SLRs, while the PRISMA-P provides a flowchart for the identification, screening, eligibility, and inclusion phases of the review process.

Search strategy

The PubMed/Medline, EMBASE, Scopus, and Web of Science (Science and Social Sciences Citation Index) databases were queried to answer the research question "What are the criteria for defining RDs, URDs, ODs, and UODs globally?" as in (**Supplementary Table 1**). The search strategies and terms used were identified based on specific inclusion and exclusion criteria. The inclusion criteria included rare disease patients receiving treatment with an OD. The publication year, country, and jurisdiction were not restricted. Studies that were published in English and provided data for the general human population were included. The exclusion criteria included rare cancers, infectious diseases, poisonings [11], studies focused on specific RDs or ODs, non-English language studies and nonhuman studies. The identified articles subsequently underwent both forward and reverse citation screening. The initial search was conducted in 2021, and two updates were performed: one on 31st December 2022, and the second on 31st December 2023. We carried out these updates to incorporate the latest and pertinent studies.

Study selection and data extraction

After searching the different databases, studies were selected, and duplicates were removed. To determine the initial eligibility of the studies based on the inclusion and exclusion criteria [11], two rounds of abstract and title screening were performed by two reviewers (GMA and KK) independently. A third reviewer (AM) arbitrated any disputes between GMA and KK, and all decisions were recorded in a Microsoft Excel® spreadsheet. Likewise, for full-text screening, if there were instances of missing or unreported data or if further details were necessary, GMA reached out to the study author(s) to request missing data. The timeframe for a response before excluding the article due to insufficient information was set at 3 weeks.

The extracted data encompassed various elements, including author names, publication information, journal title, study design, organization, country, quality assessment, and reference definitions of RDs and ODs. Additionally, these data encompassed qualitative and/or quantitative criteria used to define RDs, ODs, and their subtypes. The qualitative criteria considered disease features, intended drug use, patient group, therapeutic impact, and regulatory support, offering a comprehensive view beyond numerical values. The quantitative criteria considered numerical thresholds pivotal for regulation, science, and policies, providing precise metrics based on disease prevalence and target demographics. Moreover, the extracted data involved the underlying reasoning for each definition, the status of the definition, and whether the RD and OD definitions were considered by reviewers independently using the Covidence® platform, a web-based platform for conducting SLRs [17, 18].

Quality assessment

The study quality was assessed by GA and KK using the Joanna Briggs Institute (JBI) critical appraisal tools [19, 20] to evaluate the trustworthiness, relevance, and outcomes of published studies conducted independently using a Microsoft Excel® spreadsheet.

Data analysis

A narrative synthesis summarizing the data from the included studies was performed. The preliminary synthesis involved content analysis of the qualitative data, with coding employed to explore themes. Descriptive statistics were performed and included frequencies and percentages to report and summarize the quantitative criteria from the included studies. This process was intended to illustrate the key themes and numerical information presented in these definitions by using two independent coders (GMA and HiA) with different backgrounds; conflicts were resolved through collaborative discussion. The analyses aimed to identify key elements defining RDs, URDs, ODs, and UODs qualitatively and quantitatively.

Findings

PRISMA and quality assessment

The initial search yielded 2,712 studies identified from different databases. The published articles spanned from 1985 to 2021. A total of 2019 articles were duplicates and were removed; for example, title and abstract screening excluded 466 studies, and 235 studies were recorded as not relevant to the SLR research questions due to a lack of abstracts (n=27) or were not in English (n=3); instead, they focused on nonhuman (n=2), cancer related RDs (n=19), specific RDs (n=173), or infections (n=5) or poisonings (n=227) (**Supplementary Table 2**). The final review included 93 studies whose full texts were retrieved (**Figure 1**)

A total of 93 articles met the inclusion criteria, and 209 distinct definitions were extracted. Specifically, 93 of these articles mentioned RDs, 11 URDs, 67 ODs, and 12 UODs. Fifty-one studies were considered in the final quality assessment. A full list of included studies is provided in (**Supplementary Table 3**). Likewise, the critical appraisal results for systematic reviews and research syntheses, economic evaluations, text opinion studies, analytical cross-sectional studies, qualitative research, prevalence studies, and cohort studies were outlined and provided in (**Supplementary Table 4**).

Geographical overview of the definitions

A total of 209 definitions were identified in the 93 included articles; these were for RDs (n=119, 56.93%); URDS (n=11, 5.26%); ODs (n=67, 32.06%); and UODs (n=12, 5.75%) (**Figure 2**).

RD and OD definitions were often linked. Nonetheless, the most frequent definition employed for RDs, and ODs was the European Union (EU) definition, accounting for approximately 40% and 24%, respectively, of the cases. EU nations employ both qualitative and quantitative criteria to define RDs as "*diseases that are life-threatening or chronically debilitating illnesses with extremely low prevalence (less than 5 per 10,000)*" [21, 22]. Similarly, the United States of America (USA) Food and Drug Administration (FDA) defines RDs as *"any ailment or condition that impacts fewer than 200,000 individuals in the USA or that affects over 200,000 people in the USA, with no foreseeable likelihood of recuperating the expenses associated with developing and providing a drug for such a disease or condition through sales of the drug in the USA"* [23, 24]. An OD in the EU is typically defined as *"a pharmaceutical product for diagnosing, preventing, or treating a rare disease"* [25].

The geographical analysis presented in this SLR examined the global distribution of RD (**Supplementary Table 5**), OD (**Supplementary Table 6**), URD (**Supplementary Table 7**), and UOD (**Supplementary Table 8**) criteria used to define them across different geographic regions.

Rare disease definitions

In Europe, 48 studies discussed RD definitions. Specifically, the EU (36), the United Kingdom (UK) (3), Germany (1), Latvia (1), the Netherlands (1), Poland (2), Romania (1), France (2), and Ukraine (1) had studies that defined RDs as diseases with a prevalence of 5 or fewer cases per 10,000 individuals. The UK defines RDs based on a prevalence threshold of fewer than 1 in 2,000 people. In Eastern Europe and Northern Asia, Russia had one article; in Southeast Europe, Southwestern Europe and Asia, Turkey had an article discussing RD definitions, both showcasing differences in prevalence thresholds compared to the EU definition.

In North America, 28 studies were identified, 24 from the USA and 2 from Canada. The USA defines RDs based on a prevalence of less than 200,000 individuals living with an RD. In addition, the Rare Disease Act (RDA) defines RDs based on qualitative criteria indicating that it occurs so infrequently in the USA that there is no reasonable expectation for the cost of developing and making a drug available in the USA for such a disease or condition to be recuperated from its sales. However, the Canadian Organization for Rare Disorders (CORD) suggested that 1 in 12 Canadians, approximately 2.8 million individuals, might be living with an RD. South America contributed 2 studies—one from Chile and one from Peru—where RDs were defined by disease severity, categorizing them as “life-threatening” and “severely or chronically debilitating” (**Supplementary Table 5**).

Oceania had differing prevalence thresholds according to RD definitions: Australia (10) and New Zealand (1) used a disease prevalence of 1.1 per 10,000 individuals. Australia has established a prevalence rate of 1.16 per 100,000 individuals for an RD. The prevalence threshold for orphan disease designation is 0.9 in 10,000 individuals. The estimated incidence rate is 1 in 10,000 individuals in Australia.

Asian countries (Japan, Taiwan, China, South Korea, Singapore, India, Armenia, and the Philippines) each defined RDs based on varying criteria such as prevalence rates, genetic disorders, disease severity, and incidence thresholds (**Supplementary Table 5**).

In Africa, Egypt and Kenya were the only countries to mention and discuss RD definitions based on specific conditions and disease severity.

The majority of the definitions extracted were from Europe [EU (43%), the UK (22%), France (6%), Poland (5%), Spain (5%), Belgium (4%), Germany (3%), the Netherlands (3%), England (3%), Scotland (3%), Lativa (2%), Italy (2%), and Sweden (2%)], followed by North America [US (35%) and Canada (2%)] and Asia and Oceania [Japan (15%), Australia (12%), Taiwan (9%), India (6%), South Korea (4%), New Zealand (2%) and Singapore (2%)]. Global perspectives on RD definitions from the World Health Organization (WHO) and Orphanet revealed further variations in prevalence thresholds and disease severity criteria (**Figure 3**). **A summary of RDs definitions is provided based on the country provided in *Table 1***

223 **Table 1: A summary of RDs definitions is provided based on the country**

Country, frequency	# of articles; (%)		(RD) definition	Date
US (25)	24 (26%)	Orphan Drug Regulation	Defines RD according to prevalence: ‘‘rare disease’ means any disease or condition that affects less than 200000 persons in the USA’.	1993
		RDA		2002
		ODA	Defined RDs based on qualitative descriptors as follows: ‘the term ‘rare disease or condition’ means any disease or condition which occurs so infrequently in the USA that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug’.	1983
		FDA	Define RD as ‘any disease or condition that affects less than 200000 people in the USA or affects >200000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug’	
Canada (3)	2 (2%)	CORD	Rare disease as one that afflicts less than 1 person in 200 000.	
			Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease	
UK (3)	2 (2%)	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in 2000 people. (i.e., a prevalence of 5 or less per 10,000)	2021
		NHS	Some countries use additional definitions in situations where a condition is not officially defined as rare. classifies all conditions that require specialized medical care as rare if they occur in <500 citizens yearly	
EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000persons in the European Union) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential.	
		European Commission on Public Health	Defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them.	
		Orphan Drug Regulation	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare	141/2000

Country, frequency	# of articles; (%)		(RD) definition	Date
		EMA	prevalence of rare disease < 5/10 000	
France (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)	
Japan (13)	13 (14%)		Japan diseases with a prevalence of 4.0/10,000	
			<50,000 patients in Japan	
			Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment	
			The incidence rate is estimated to be ≤2.5 cases in 10,000 for Japan	
Taiwan (7)	7 (8%)	Taiwan Foundation for Rare Disorders	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical coverage.	2000
		Physically and Mentally Disabled Citizens Protection Act	RD is one type of disability	2001
China (5)	5 (5%)	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences in Newborn babies.	
			Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.	
South Korea (4)	5 (5%)		Prevalence thresholds have been set at less than 1 per 20,000	
			Prevalence threshold: <4.0 in 10,000	
			< 20,000 people in Korea (i.e., <4 per 10,000 population)	
WHO (5)	5 (5%)		Rare disease affects at most 6.5 out of every 10,000 individuals.	
			Frequency of 6.5-10/ 10,000 inhabitants	
			Incidence ranges approximately from 0.65-1% in the whole population.	
			Rare disease as affecting 65/100 000~100/100 000 persons.	
Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic etiology, and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers."	

The Rare Diseases Act (RDA; the Orphan Drug Act (ODA; the Food and Drug Administration (FDA); The Canadian Organization of Rare Diseases (CORD); National Health Service (NHS).

Ultrarare disease definitions

The definitions of URDs primarily originated from the European continent, encompassing the UK, Poland, and North America, and including, e.g., Alberta and Ontario; URDs typically affect ≤1 in 50,000 or fewer individuals within a population. Additional criteria for classifying URDs varied by region and authority. The Advisory Group for National Specialized Services stipulates that in England, the prevalence should be less than 500 individuals affected (~2500/100,000 of the population). The National Institute for Health and Care Excellence (NICE) further narrows this definition, classifying URDs as those with a prevalence of ≤1:50,000 people. Ontario employs a criterion of fewer than 1 in 150,000 live births or new diagnoses per year, while the definition in Poland aligns with the EU definition, designating URDs as affecting fewer than 1 in 50,000 people. URDs may also be termed "singular cases" or "individual cases," given their exceptionally low prevalence (**Supplementary Table 7**). **Based on the country asummary of URDs definitions is provided in *Table 2***

238 **Table 2: A summary of URDs definitions is provided based on the country.**

Country, frequency		(URD) definition
UK		Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population (Hugheset al., 2005)
	NICE	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000
England	Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~ less than 1/100,000 of the English population)
Ontario		An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario
England and Wales	NICE	"Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)"

Orphan drug definitions

Nineteen studies described OD definitions within Europe, with one from Italy and another from Germany both adopting the European Medicines Agency (EMA) definition, indicating that a drug can be defined as an OD if it is intended for the diagnosis, prevention, or treatment of life-threatening or chronically serious debilitating conditions affecting no more than 5 in 10,000 individuals. Similarly, one study from Italy followed the Italian Medicines Agency (AIFA) criteria, focusing on three aspects: unmet medical needs, clinical added value, and quality of evidence. Moreover, 1 study from Germany suggested that specific health technology assessment (HTA) criteria be used for the definition of ODs; these criteria are associated with higher *p* values when sample sizes are limited, when surrogate endpoints are utilized, when therapeutic benefit is added, and when the annual budget impact for a given indication is less than €50 million.

In North America, there were nine studies, all of which aligned with the USA FDA regulations, indicating that an OD represents a condition affecting fewer than 200,000 persons in the USA or meets the cost recovery provisions.

In Asia, six studies described ODs, one from Singapore, one from Vietnam, and two from China, all of which contributed to the body of evidence on orphan drugs. It was also reported in two studies that the OD Centre in Korea provides medications for diseases affecting fewer than 1 in 20,000 individuals. These encompass illnesses lacking adequate treatments or drugs or drugs that notably enhance safety or efficacy compared to existing alternatives. In contrast, in China, ODs are characterized by their availability as pharmaceutical products or active ingredients that are not developed, imported, or registered due to low commercial returns and unfavourable marketing conditions. These drugs are designated for diseases affecting fewer than 1 in 10,000 individuals.

Similarly, ODs in Vietnam are described by their availability as pharmaceutical products or active ingredients not developed, imported, or registered due to low commercial returns and unfavourable marketing conditions (**Supplementary Table 6**). **A summary of ODs definitions is provided based on the country in *Table 3***

266 **Table 3: A summary of ODs definitions is provided based on the country.**

Country, frequency	# of articles; (%)		(RD) definition	Date
EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically and seriously debilitating condition affecting not more than 5 in 10 000 EU people or that it is unlikely that marketing the drug in the EU would generate sufficient benefits for the affected people and for the drug manufacturer to justify the investment	
		NICE	The current NICE appraisal system means orphan drugs that do not meet HTA criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of ¬£30 k/QALY, or ¬£50 k/QALY when end-of-life criteria are met	
		EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs and are referred to as orphan drugs because, the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	(2011c)
		The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union	
		The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered medicine exists	
		Poland	There is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.	
US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200, 000 persons in the USA' (which equates to approximately 6 cases per 10,000 population) 'or meets cost recovery provisions of the act'	
		Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons	

Country, frequency	# of articles; (%)		(RD) definition	Date
			affected by the disease. condition of interest in the United States as a surrogate for the lack of profitability."	
			Orphan product, as one that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA	
Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.	
		the Korea Ministry of Food and Drug Safety formulates ODs	Drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments or drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD	
China (2)	2 (2%)		Orphan drugs are defined by their availability as pharmaceutical products of active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions.	

Ultra-orphan drug definitions

One study from the UK defined UODs as drugs for diseases with an extremely low prevalence, often less than 0.18 per 10,000 individuals. Three studies introduced the NICE definition for "ultra-orphan" drugs as those targeting conditions with less than 1 case per 50,000 persons. These drugs are typically granted approval for the treatment of diseases that affect fewer than 1,000 patients, underscoring their exceptional rarity. In England, the Highly Specialised Technologies (HST) Programme has implemented cost-effectiveness thresholds for UODs, while the WHO provides specific recommendations for cost thresholds. Scotland has introduced a distinct definition that places emphasis on conditions affecting fewer than 1 in 50,000 individuals. Furthermore, Scotland has also redefined its criteria for UODs to facilitate early access programs and streamline reimbursement processes, with a particular focus on conditions impacting approximately 100 individuals. ***Table 4*** **provide a summary of UODs definitions based on the country**

279 **Table 4: A summary of UODs definitions is provided based on the country.**

Country, frequency		(UOD) definition	Date
UK	NICE	Drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"	
Scotland	The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people – approximately 100 people or fewer in Scotland	
England		HST for ultra-orphan indications Euro113,900-341,700/QALY in England	
	WHO	WHO recommends a WTP of <3 times GDP per capita/QALY	
Scotland		New definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes	Effective from October 2018

Qualitative criteria

The review identified 35 qualitative criteria for RDs, 37 for ODs, 7 for URDs, and 11 for UODs. The identified qualitative criteria were categorized into 7 themes related to RDs, URDs, ODs, and UODs: nature, aetiology, disease nature affecting the patients, disease nature affecting the patient's society, population characteristics, benefits from taking the treatment, and indications (**Supplementary Table 9**).

The most frequent qualitative criteria used in defining RDs and URDs were "disease" 148 times and 13 times, respectively, and "condition" 30 times and 3 times, respectively. For ODs and UODs, the most frequent qualitative criteria were "drugs" 83 times and 8 times, respectively, and "medical products" 36 times and 2 times, respectively. In terms of aetiology, the term "genetic" was used 7 times for RDs and once for ODs. Interestingly, "hereditary" was exclusively reported for ODs. The qualitative criterion "life-threatening" was found 23 times and "debilitating" 21 times for RDs, while for ODs, these qualitative criteria appeared 20 and 10 times, respectively. Some qualitative criteria were used to assess the extent of the impact on society, whether the disease was rare or common. The subtheme "low prevalence" appeared 12 times in definitions related to RDs, similarly describing "low-occurrence criteria", "infrequent population affliction", and a "small number of patients with RDs". However, no data pertaining to URDs, ODs, or UODs were identified. Notably, the theme "benefits from taking the treatment" was found to be associated only with ODs. In the indications theme, the qualitative criteria "treatment and prevention" were used repeatedly (55 and 23 for ODs and 7 and 1 for RDs, respectively) (**Supplementary Table 10**).

Quantitative criteria

These quantitative criteria yielded 10 criteria for RDs, five criteria for ODs, four for URDs and three for UODs (**Supplementary Table 9**).

In the context of defining RDs, ODs, and their subtypes, quantitative criteria were less common than qualitative criteria. The most popular metric was "prevalence", rather than "incidence", "incidence rate", "number of cases", "threshold", "estimated measures", "range", "percentage", or "frequency". Quantitative criteria such as "cost-effective threshold" and "annual budget impact for a particular indication", as well as "willingness-to-pay", were exclusively recorded for ODs (**Supplementary Table 11**).

Discussion

This review sheds light on various definitions and criteria used by different countries and stakeholders, provides deeper insights into different elements, promoting the development of strong criteria, and facilitates policy dialogue. The present analyses revealed inconsistency in definitions; regional disparities in RD occurrence range from approximately 5,000 to 8,000 [26]; and various terminologies and criteria used to define RDs, ODs and their subtypes.

Some definitions rely on qualitative criteria, such as disease severity, life-threatening or hereditary nature, or the presence of alternative treatment options [7, 27]. These subjective criteria lack substantial evidence and vary based on the specific organization that uses the term. However, the UK [28] adopts similar criteria to those used by the EMA to define RDs, suggesting a degree of alignment in the RD classification between Europe and the UK. The European Organisation for Rare Diseases (EURORDIS) definition has a broader scope because it includes both RDs and neglected diseases within the

classification of ODs [29]. This inclusion acknowledges diseases that may be neglected even if they are not strictly rare.

Additionally, we observe that historical differences in definitions have had tangible consequences on healthcare outcomes and drug development priorities over recent decades. For instance, the variation in prevalence thresholds between the USA (fewer than 200,000 individuals) and the EU (fewer than 1 in 2,000) has influenced patient eligibility for support and access to treatments, with different thresholds potentially limiting access in regions with more restrictive definitions. These discrepancies have also shaped pharmaceutical investment strategies, as varying definitions impact the perceived market size and economic feasibility of developing treatments for rare diseases in different regions.

There has been controversy surrounding the term "orphan" in the context of ODs, reflecting differences in interpretations across countries. Initially coined in the early 1960s to describe a class of drugs for RDs, the term highlighted the economic disincentives for developing treatments due to limited profitability. However, by the 1990s, government incentives made RD drug development more viable [30]. In the UK, the use of the term "orphan" has been criticized, particularly by Rosalind Hurley of the European Medicines Agency (EMA), who expressed regret over its usage [30]. Despite this criticism, Richter [12] argues that the term is consistent in referring to technologies for RDs. In Australia, ODs refer to medicines, vaccines or in vivo diagnostic agents used to treat, prevent or diagnose or not available to treat, prevent or diagnose another disease [31]. This provides a broader understanding of the term and its application in different regions.

Disease severity is considered a critical criterion in evaluating the impact of ODs on health-related outcomes in patients, considering that diseases can substantially affect both health and health-related quality of life [41]. Haendal et al. [39] recommended that a multitude of overlapping terminologies,

models, and metadata exist for the identification and classification of RDs. Failure to do so can have substantial consequences, affecting drug approvals, market entry prices, and reimbursement recommendations and ultimately impeding patient access to ODs.

Additionally, some definitions depend on quantitative criteria, such as the disease prevalence threshold, which constitutes the favoured epidemiological element utilized in 58% of RD definitions [7]. However, establishing a prevalence threshold poses challenges due to diverse information sources. This challenge is exacerbated by the absence of firmly established diagnostic criteria or coding systems necessary to gather these data [32]. As a result, certain diseases could be deemed rare in one country but not in another owing to genetic population diversity, environmental or societal pressures, and variations in survival challenges across different regions [10].

One study [12] presented a comprehensive overview of RD definitions worldwide, collating 296 definitions from 1109 organizations across 32 international jurisdictions. The findings indicated the common use of terms such as "RDs" and "ODs," while descriptive qualifiers such as "life-threatening" were less prevalent. Moreover, 88% of the investigations specified prevalence thresholds ranging from 5 to 76 cases per 100,000 people, with 66% of jurisdictions adopting thresholds between 40 and 50 cases per 100,000 individuals. The study [12] underscored the substantial diversity in defining RDs across various jurisdictions and organizational structures. This highlights the necessity for standardization, particularly in objective criteria such as prevalence thresholds, while recommending the avoidance of subjective qualifiers to achieve a harmonized definition of rare diseases. Despite the widespread use of terms such as "RDs" and "ODs", the study emphasized the importance of focusing on standardized metrics to ensure clarity and consistency in identifying RDs globally.

This SLR emphasizes the importance of developing a local definition for each country, regardless of the criteria applied. Subjective qualifiers can occasionally provide additional context or complexity to the description of RDs, ODs, and their subtypes. However, relying too heavily on subjective standards may lead to inconsistent results and implementation challenges. For comprehensive definitions of RDs, ODs, and their subtypes, it is better to combine qualitative and quantitative criteria, which should be reviewed and updated periodically.

Additionally, differences in disease classification across regions can lead to significant disparities in patient care, research funding, and access to treatments. For instance, cystic fibrosis [33] is classified as rare in Europe and North America, where it benefits from orphan drug designations, incentivizing pharmaceutical companies to develop treatments. However, in regions where it is less common, the lack of this classification can limit research initiatives and access to specialized care [34]. Similarly, sickle cell anemia is considered rare in the US [35] and UK [35] but is more common in parts of Africa [36], the Middle East [36], eastern and southwestern regions of Saudi Arabia [35], where healthcare systems are better equipped to handle it. In contrast, in countries where sickle cell is classified as rare, patients may face limited treatment options and fewer specialists [37]. These examples highlight how the classification of a disease as rare in one country and common in another can lead to inconsistencies in care, treatment availability, and research focus, underscoring the importance of harmonizing definitions across regions.

In summary, an exploration of the worldwide definitions of RDs, ODs, and their subtypes provides a comprehensive understanding of their complex nature. The diversity in criteria among nations and institutions accentuates the problem of defining them, influenced by genetic variations, societal factors, and regional disparities. This important fact illuminates the critical challenges and factors required to address these conditions and advance the development of treatments for individuals affected by RDs globally.

Recommendations for future use

This study highlights the importance of establishing a country-specific consensus on the definition of the distinctive combination of genetic, phenotypic, and environmental characteristics as well as sociocultural and economic factors. RDs should be linked toto individuals to steer the research and enhance the diagnosis and care of patients with RDs and the availability of treatments [38] based on scientific principles. Qualitative and quantitative criteria and subthemes should be included in the definition. Therefore, understanding the economic and ethical principles of and health care burdens associated with RDs, ODs, and their subtypes is essential for policymakers to shape policies, especially in underdeveloped policy areas. Moreover, there is a need for international collaboration and data exchange to improve the global understanding and treatment of RDs, which in turn can affect pricing, reimbursement, and patient access to ODs. Additionally, more robust evidence is needed to effectively implement the United Nations (UN) 2030 Agenda principles and Sustainable Development Goals of '*leaving no one behind'*, '*reducing inequalities'*, and '*addressing the needs of those furthest behind first'* to support the RD community.

Conclusion

A comprehensive study on RD, OD and subtype definitions across countries is lacking. In particular, these definitions are considered outdated, with no scientific grounding. There is a need to address problems associated with diseases that impact only a small percentage of the population. These definitions are meant to provide a framework for identifying and supporting the development of ODs. Therefore, local evaluations of qualitative and/or quantitative criteria are needed to shift therapeutic outcomes from treatment to transformative and curative treatment, to gather comprehensive patient data, to accurately determine disease prevalence, and to ensure equity and equality in accessing appropriate

treatments. It is imperative for each country to develop a local definition or reporting system or establish a national registration program. This approach would not only facilitate the collection of vital health information but also foster a more effective health care ecosystem that addresses the needs of individuals affected by these conditions.

Author affiliations

[1]Centre for Public Health, Institute of Clinical Sciences B, Royal Victoria Hospital, Queen's University Belfast School of Medicine, Dentistry and Biomedical Sciences, Belfast, UK. https://orcid.org/0000-0002-8469-8885; https://orcid.org/0000-0002-7482-709X

[2]Pharmacy Practice Department, College of Pharmacy, Princess Nourah bint Abdulrahman University, PO Box 84428, Riyadh, Zip Code: 11451, Saudi Arabia. https://orcid.org/0000-0002-4523-0577 ; email: gaabozeed@pnu.edu.sa

[3]Department of Applied Linguistics, College of Languages, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. https://orcid.org/my-orcid?orcid=0000-0001-7476-0561

[4]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia. https://orcid.org/0000-0002-0765-0466

[5]Health Technology Assessment Unit, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia.

[6]Center of Health Technology Assessment, Ministry of Health, Riyadh, Saudi Arabia.

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Competing interests None declared

Patient and public involvement The research's design, methodology, reporting, or distribution strategies did not involve patients or public.

Patient consent for publication Not required

Provenance and peer review External peer review; not commissioned.

Data sharing statement All of the study's data were fully accessible to the author(s), who also bear responsibility for the data's accuracy and integrity. This study has no more unpublished data. There are no more statistics available.

Abbreviations AGNSS= Advisory Group for National Specialised Services; AM= Amy Jayne McKnight; CM= Consanguineous Marriage; CMS= Congenital Myasthenic Syndrome; DOH = Department of Health; EMA= European Medicines Agency; EU= European Union; FDA= Food and Drug Administration, GMA = Ghada Mohammed Abozaid; HiA= Hiba Alomary; HAA= Hussain Abdulrahman Al-Omar; HST= Highly Specialised Technology Programme; JBI= Joanna Briggs Institute; KK = Katie Kerr; NICE= National Institute for Health and Care Excellence; OD= orphan drugs; ORDI = Organization For Rare Diseases India; PNU= Princess Nourah Bint Abdulrahman University; PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RD = Rare Diseases; RDTWG = Rare Diseases Technical Working Group; SA= Saudi Arabia; SLR= Systematic Literature Review; TFRD = The Taiwan Foundation for Rare Disorders; UOD= Ultra- Orphan Drug; UK= United Kingdom; URD= Ultra- Rare disease; US= United States; WHO = World Health Organization; WTP= Willingness To Pay.

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Figure Legends

Figure 1: Description of PRISMA flow chart in **Figure 1**.

Figure 2: Description of of Repeated definitions included in the studies in **Figure 2**

Figure 3: Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence) in **Figure 3**

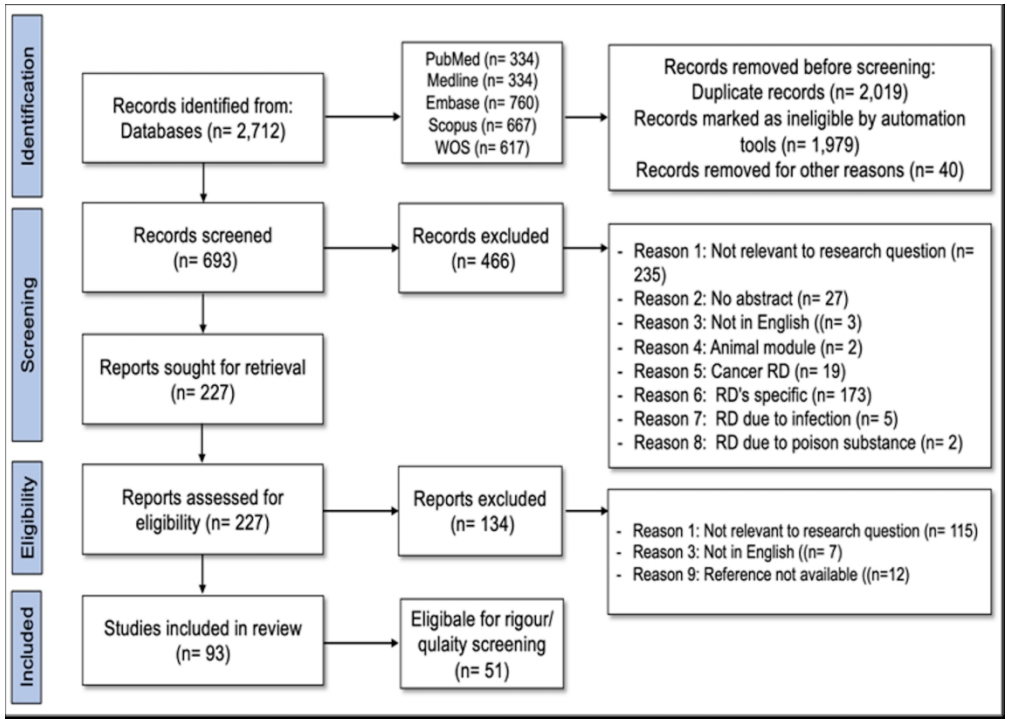

Figure 1. PRISMA flow chart of the study identification and screening process.

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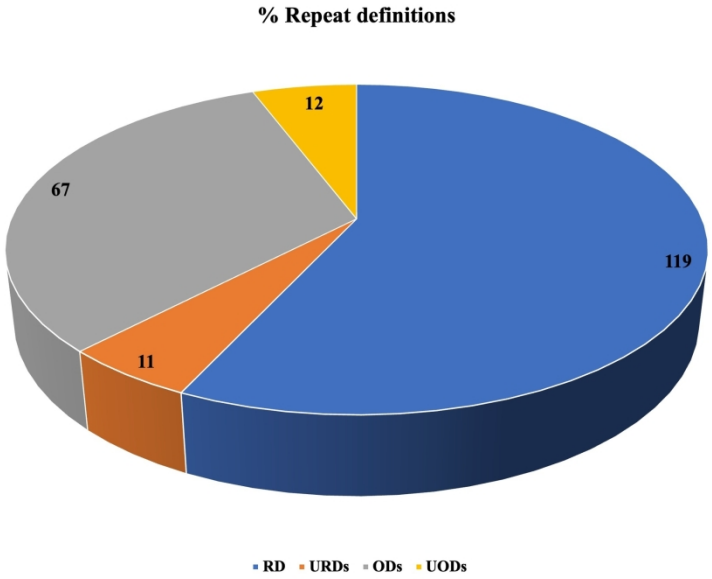


Figure 2. Repeated definitions included in the studies.

224x134mm (300 x 300 DPI)

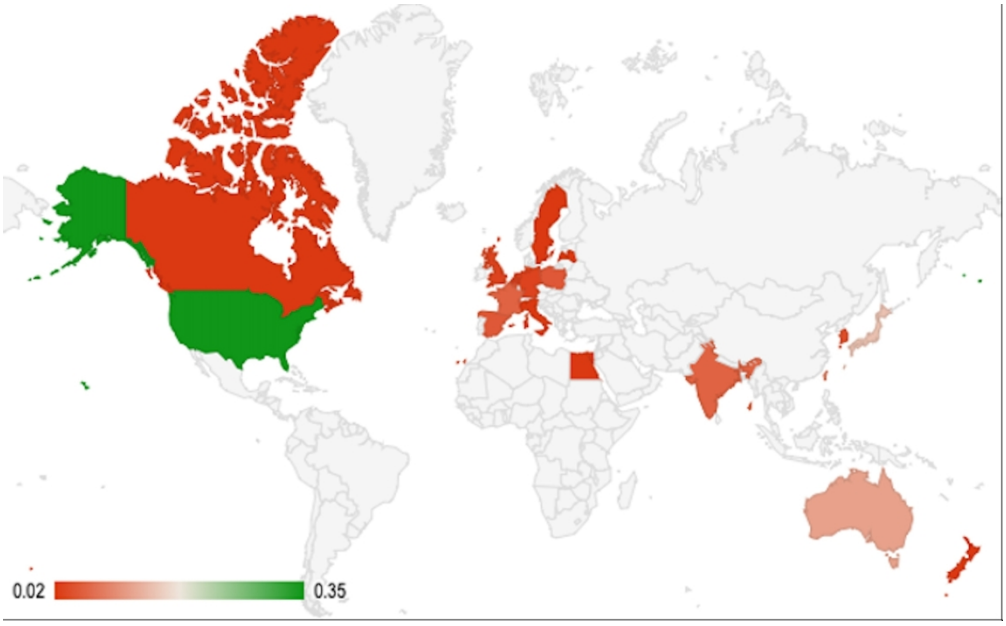


Figure 3. Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence)

117x72mm (600 x 600 DPI)

Supplementary Table 1: Research question: What are the criteria to define Rare Diseases and Orphan Drugs globally?

Concept 1: Criteria / Concept 2: Define/ Concept 3: Rare Disease(s)/ Concept 4: Orphan Drug(s)

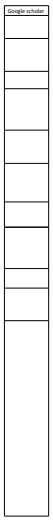
	Concept 1	Concept 2	Concept 3	Concept 4	Total	limit to english & human
PubMed	Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]	Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields]	"Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields]	"Orphan Drug Production"[Mesh] OR "Orphan medicinal product*"[All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields]	((((Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]) OR (Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields])) AND ("Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields])) AND ("Orphan Drug Production"[Mesh] OR "Orphan medicinal product*" [All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields])	
	11,155,322	14,855,618	78,992	2,409	435	334
Medline	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1 OR 2 And 3 and 4	
	10,653,511	7,966,623	98,302	2,236	510	334
Embase	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, heading word, drug	1 OR 2 And 3 and 4	

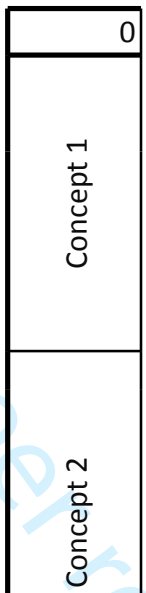
	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	name, keyword, floating subheading word, candidate term word]	Disease*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]		
	13,859,313	10,574,947	160,442	4828	1,010	760
Scopus	TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)	TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)	TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")	TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*")	(TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)) OR (TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)) AND (TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")) AND (TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*"))
	29,871,274	21,496,075	134,422	4,160	782	667
WOS	ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI., CPCI-S, CPCI-SSH, ESCI.	ALL FIELDS: (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	ALL FIELDS: ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	ALL FIELDS: ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	#7 AND #6 AND #5 Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. ...Less	
	20,665,577	18,096,480	90,196	3,462	646	617
					Total	2,712

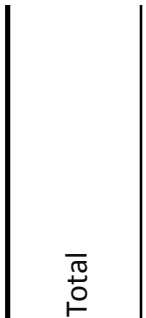
Research question:
What are the criteria to define Rare Diseases and Orphan Drugs globally?

Concept 1: Criteria / Concept 2: Define/ Concept 3: Rare Disease(s)/ Concept 4: Orphan Drug(s)/ Concept 5: globally

		PubMed	Medline	Embase	Scopus	WOS	clinicla trail	Grey litreture
Concept 1	Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]	11,135,352	[Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*].mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier,	10,637,027	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13,803,059	TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)	29,831,800	ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	20,619,793		
Concept 2	Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields]	14,829,899	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7,953,349	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	10,551,266	TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)	21,465,803	ALL FIELDS: (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	18,057,982		
Concept3	"Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "Intractable disease*"[All Fields]	78,766	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	98,080	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	158,897	TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "Intractable disease*" OR "Rare Disease*")	134,136	ALL FIELDS: ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "Intractable disease*" OR "Rare Disease*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	89,916		
Concept 4	"Orphan Drug Production"[Mesh] OR "Orphan medicinal product*" [All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields]	1,431	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug Production*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,401	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug Production*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	730	TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*")	1,498	ALL FIELDS: ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	595		
Concept 5	Global*[All Fields] OR international [All Fields] OR worldwide [All Fields] OR universal [All Fields] OR intercontinental [All Fields] OR world[All Fields]	1,973,372	(Global* or international or worldwide or universal or intercontinental or world).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,466,424	(Global* or international or worldwide or universal or intercontinental or world).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2,120,598	TITLE-ABS-KEY (global* OR international OR worldwide OR universal OR intercontinental OR world)	5,674,342	ALL FIELDS: (global* OR international OR worldwide OR universal OR intercontinental OR world) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	13,115,361		
Total	((((Criteria[All Fields] OR Standard*[All Fields] OR classification[All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]) AND (Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields])) AND (Global*[All Fields] OR international [All Fields] OR worldwide [All Fields] OR universal [All Fields] OR intercontinental [All Fields] OR world[All Fields])) AND ("Orphan Drug Production"[Mesh] OR "Orphan medicinal product*"[All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields])) AND ("Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "Intractable disease*"[All Fields])	40	1 and 2 and 3 and 4 and 5	28	1 and 2 and 3 and 4 and 5	24	(TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)) AND (TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)) AND (TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "Intractable disease*" OR "Rare Disease*")) AND (TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*")) AND (TITLE-ABS-KEY (global* OR international OR worldwide OR universal OR intercontinental OR world))	35	ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) AND ALL FIELDS: (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify) AND ALL FIELDS: ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "Intractable disease*" OR "Rare Disease*") AND ALL FIELDS: ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*") AND ALL FIELDS: (global* OR international OR worldwide OR universal OR intercontinental OR world) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	13		







Research ques
What are the criteria to define Rare Disea

29/04

	PubMed
Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]	11,155,322
Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields]	14,855,618
"Rare Diseases"[Mesh] OR “Orphan disease*”[All Fields] OR “Rare condition*”[All Fields] OR “Rare disorder*”[All Fields] OR “Rare disability*”[All Fields] OR “Neglected disease*”[All Fields] OR “Undiagnosed disease*”[All Fields] OR “Low-frequency disease*”[All Fields] OR “life-threatening disease*”[All Fields] OR “debilitating disease*”[All Fields] OR “severe disease*”[All Fields] OR “intractable disease*”[All Fields]	78,992
"Orphan Drug Production"[Mesh] OR “Orphan medicinal product*” [All Fields] OR “Orphan product*”[All Fields] OR “Orphan subset*”[All Fields] OR “Orphan indication*”[All Fields] OR “Highly specialized technolog*”[All Fields] OR “Priority review drug*”[All Fields] OR "Orphan Drug*"[All Fields]	2,409
(((Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR	

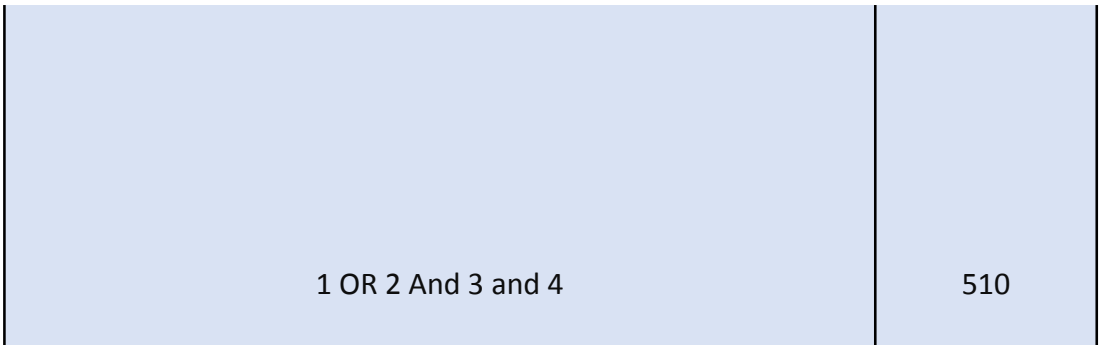
Norm*[All Fields]) OR (Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields])) AND ("Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields])) AND ("Orphan Drug Production"[Mesh] OR "Orphan medicinal product*" [All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields])	435
limit to english and human	334

334
334
760
667
617
2,712

stion:
ases and Orphan Drugs globally?

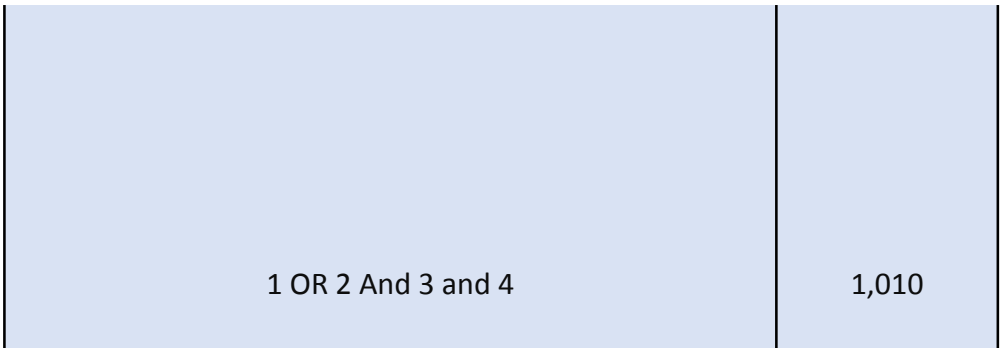
27/04

	Medline
(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	10,653,511
(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7,966,623
(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	98,302
(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2,236



Cc

	Embase
(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13,859,313
(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	10,574,947
(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	160,442
(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4828



oncept 1: Criteria / Concept 2: Define/ Concept 3: Rare Disease(s)/ Concept 4: Orpha

	Scopus
TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)	29,871,274
TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)	21,496,075
TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")	134,422
TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*")	4,160
(TITLE-ABS-KEY (criteria OR standard* OR classification OR	

measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)) OR (TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)) AND (TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")) AND (TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*"))	782
limited to english	667

ın Drug(s)

	WOS
ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	20,665,577
ALL FIELDS: (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	18,096,480
ALL FIELDS: ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	90,196
ALL FIELDS: ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	3,462

#7 AND #6 AND #5 Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. ...Less	646
limited to english	617

https://www.crd.york.ac.uk/prospero/#searchadvanced

rare disease
orphan disease
orphan drug

435	510	1,010	392	646	2,993

total	2174
Duplication	1656

2714
1989
879

4th May	
2714	
1990	32 manual
701	

247	0
3	0
5	

	17/06	3-Jun	27-May	20-May	6-May
WOS	4	2	4	2	2

Search Results		Auto-duplicate removal
MEDLINE	173	173
EMBASE	630	498
PubMed	17	13
Google Scholar	206	182
Web of Science	721	721
Scopus	23	19
Total	**1770**	1606

After auto-duplicate removal: 1606

Manually identified duplicates: 208 = 1398 articles for title/abstract screeni

After title / abstract screening: 92 for full text screening *19 articles identified from other sourc

Full text screening exclusion reasons

4 excluded as they were review articles
4 excluded as they were conference abstracts with full texts available
9 excluded as they were not primary studies of multiomics and rare dis
2 excluded as they did not specify what rare cancers were analysed (cc
26 excluded as they were single omic analysis
45

TOTAL INCLUDED = 66

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sease
onference abstracts)

	2005	Towards an Optimal Orphan Medicinal Products (OMI	Biotechnol	Review	Scopus
	2009	Orphan-Drug Applications	Guidebook	Scopus	
	2010	Preface	Small Mole	Editorial	Scopus
Abdallah, K	2021	Methodological Quality Assessment of Budget Impact	Frontiers in Pharmacology		
Abou-El-En	2016	Overcoming Challenges Facing Advanced Therapies in	Cell Stem C	Note	Scopus
Abrahamya	2011	Survival distributions impact the power of randomize	J Clin Epidemiol		
Abrahamya	2014	Using value-of-information methods when the disease	J Gen Intern Med		
Acaster, S.	2017	Patient-Reported Outcome and Observer-Reported O	Value Heal	Editorial	Scopus
Acharya Va	2015	Expensive therapies: Legal and ethical analyses	Paediatrics and Child Health (Can		
Achour, L.,	2018	Psy59 - Orphan Drugs Prices Comparison in Middle Ea	Value in Health		
Adjibi, Yola	2010	Orphandev, french clinical trials network dedicated to	Orphanet Journal of Rare Disease		
Aggarwal, S	2018	Trends in HTA submissions for rare diseases: Insights f	Value in Health		
Akesson, A	2017	At the Cross Section of Thrombotic Microangiopathy a	Ther Apher Dial		
Akyoney, S	2020	Gene defining by whole exome reanalysis	Gazi Medical Journal		
Al Mahmas	2020	Acquired hemophilia A: when an overlooked autoimm	Expert Opinion on Orphan Drugs		
Alberighi, C	2013	PW02-027 - CAPS and cost-effectiveness analysis proj	Pediatric Rheumatology		
Albinana, V	2011	Hereditary haemorrhagic telangiectasia (Rendu-Osler-	Haemophilia		
Alghamdi, A	2014	APhA2014 abstracts of contributed papers	Journal of the American Pharmac		
Alhawwash	2015	Trends in approvals of new drugs with orphan designa	Value in Health		
Ali, Ahmad	2014	An overview of current and future therapeutic strateg	Expert Opinion on Orphan Drugs		
Allen, G., H	2017	Do EU5 Countries with Favourable Healthcare Expend	Value in Health		
Almalki, Z.,	2013	The challenge of accessing orphan drugs in the Middle	Value in Health		
Almalki, Z.	2012	Access to orphan drugs in the Middle East: Challenge	Intractable Article		
Almutairi, F	2013	Analysis of orphan drug designations and approvals in	Value in Health		
Alonso, Ver	2014	National rare diseases registry in Spain: Pilot study of	Orphanet Journal of Rare Disease		
Alonso-Veg	2019	The senseless orphanage of Chagas disease	Expert Opinion on Orphan Drugs		
Álvarez-Ro	2019	Determining the value contribution of emicizumab (H	Global & Regional Health Technol		
Anand, G.	2005	Why Genzyme can charge so much for Cerezyme	Wall St J (East Ed)		
Anandabas	2019	Orphan Diseases and Drugs	Introductio	Scopus	
Anastasaki,	2017	Orphan Drug Reimbursement In Europe: Do Less Strin	Value in Health		
Andersen, T	2012	The political empowerment of rare disease patient ad	Orphanet Journal of Rare Disease		
Angural, A.	2020	Review: Understanding Rare Genetic Diseases in Low	Front Genet		
Annemans,	2020	TRUST4RD: tool for reducing uncertainties in the evid	Orphanet J	Article	
Annunziata	2017	Galactosialidosis: historic aspects and overview of inv	Expert Opin Orphan Drugs		
Anonymou	1996	Gaucher disease. Current issues in diagnosis and treat	JAMA		
Anonymou	2008	New medicines in 2007: Regulatory agencies and poli	Prescrire International		
Anonymou	2010	The needs of the few	Nature		
Anonymou	2014	7th European Conference on Rare Diseases and Orpha	Orphanet Journal of Rare Disease		
Anonymou	2016	8th European Conference on Rare Diseases & Orphan	Orphanet Journal of Rare Disease		
Antoniu, Sa	2013	Fresh from the designation pipeline: orphan drugs rec	Expert Opi	Article	Scopus
Antoniu, Sa	2015	Fresh from the designation pipeline: orphan drugs rec	Expert Opi	Article	Scopus
Armstrong,	2013	Is scorpion antivenom cost-effective as marketed in th	Toxicon		
Arnould, B.	2018	Role of patient-reported outcome evaluation in the a	Value in Health		
Arnould, Be	2019	26th Annual Conference of the International Society f	Qual Life Res		
Arnould, B.	2019	Pro147 Mapping Proqolid to Rare Diseases: A on-Goin	Value in Health		
Arsic, J., Kr	2014	Sources of Information and Pharmacists' Knowledge F	Value Health		
Asbury, C. I	1991	THE ORPHAN DRUG-ACT - THE 1ST 7 YEARS	Jama-Journal of the American Me		
Asbury, C. I	1992	Evolution and current status of the Orphan Drug Act	Int J Techn	Article	Scopus
Attwood, M	2018	Orphan Drugs and Their Impact on Pharmaceutical De	Trends Pha	Erratum	Scopus
Aulois-Grio	2018	Psy135 - Access to Orphan Drugs – Regulation within t	Value in Health		

Ayme, S.	2011 Poster Presentations	FEBS Journal	
Ayme, Segc	2012 State of the art of rare disease activities in Europe: A I	Orphanet Journal of Rare Disease	
Ayme, S.	2017 Focused Workshop	European Journal of Neurology	
Azaiez, C.,	2016 Orphan drug shortage in the United States: A long last	Value in Health	
Azie, N. and	2012 Rare diseases: the bane of modern society and the qu	Clin Pharmacol Ther	
Babar, Z. U	2014 Identifying priority medicines policy issues for New Ze	BMJ Open	
Badia, X., G	2017 Are P&R Official Criteria Related With Real P&R Apprc	Value in Health	
Badia, X., V	2020 Impact of the therapeutic positioning report in the P&	Orphanet J Rare Dis	
Badyal, D.	2006 Orphan diseases and drugs	Indian Jour Letter	Scopus
Bai, J. P., Ba	2013 Strategic biomarkers for drug development in treating	AAPS J	
Baiardi, Pac	2010 Clinical trial design and management	Pharmacet Short Surve	Scopus
Bakker, Em	2017 Current and prospective pharmacotherapies for the tr	Expert Opinion on Orphan Drugs	
Baldovino,	2016 Rare Diseases in Europe: from a Wide to a Local Persp	Isr Med Assoc J	
Balik, Ismai	2018 Biotechnological drugs and the society of national dru	Gazi Medical Journal	
Ballot, C., K	2012 Abstracts	Fundamental & Clinical Pharmacc	
Balmukhan	2019 Fp830the Clinical and Genetic Feautres of Vitamin D-I	Nephrology Dialysis Transplantati	
Bang, J. S. a	2021 The national drug formulary listing process for orphar	Expert Opinion on Orphan Drugs	
Barak, Adai	2011 Orphan drugs: pricing, reimbursement and patient acc	Internatior Review	Scopus
Baran, Alek	2018 Bridging East with West of Europe – a comparison of (	Acta Polon Article	Scopus
Baran-Kooi	2019 Applicability of the EVIDEM multi-criteria decision ana	Acta Polon Article	Scopus
Baran-Kooi	2018 Multi-Criteria Decision Analysis (MCDA) Models in He	Front Public Health	
Baran-Kooi	2019 Overview of Regulatory Initiatives in the European Un	Acta Polon Review	
Barbieri, M	2014 Ambrisentan for the treatment of pulmonary arterial	Expert Opinion on Orphan Drugs	
Barkovich,	2016 Brain biomarkers and neuroimaging to diagnose urea	Expert Opinion on Orphan Drugs	
Barman-Ak	2019 Patient empowerment and access to medicines: Insigl	Medicine Access @ Point of Care	
Barrera, L.	2010 Ethical Aspects on Rare Diseases	Rare Diseases Epidemiology	
Bavisetty, S	2013 Emergence of pediatric rare diseases: Review of prese	Rare Dis	
Belgaied, W	2018 Comparison of Orphan Drugs Prices Between Europe a	Value in Health	
Bell, S. A. a	2014 A comparison of interventional clinical trials in rare ve	Orphanet J Rare Dis	
Berdunov,	2019 Pns150 Conditional Marketing Authorisation for Nove	Value in Health	
Bernard, L.	2012 PHP30 The Bittersweet Success of Orphan Drugs	Value in Health	
Bernardini,	2014 Are we ready? What is missing and what is needed? A	Orphanet Journal of Rare Disease	
Bernstein, .	2018 Human plasma-derived C1 esterase inhibitor for on-d	Expert Opinion on Orphan Drugs	
Bewicke-Cc	2019 Pro156 Approaches to the Collection of Utility Values	Value in Health	
Bhalla, Ash	2007 Patents on therapeutics in developing countries: the c	Expert Opinion on Therapeutic Pa	
Bhat, Pooja	2016 Antibodies in autoimmune retinopathy	Expert Opinion on Orphan Drugs	
Bhattaram,	2017 Clinical drug development for rare disease in neurolo	Neurology	
Bin Sawad,	2020 Nd3 Orphan Drug Market Access Challenges in Europe	Value in Health	
Black, J., Pr	2016 Identifying precedent device-reliant generic erosion d	Value in Health	
Blankart, C	2010 Availability of and access to orphan drugs: An internat	Value in Health	
Blin, O., Let	2020 Orphan drug clinical development	Therapie	
Bloechl-Dai	2006 Special situations, market fragmentation I: Orphan dr	Clinical Pha Scopus	
Blonda, A.,	2021 How to Value Orphan Drugs? A Review of European V	Frontiers ir Review	
Bloom, Bru	2015 Recent successes and future predictions on drug repu	Expert Opinion on Orphan Drugs	
Boelaert, M	2017 Miltefosine: A case study of a product development p	Tropical Medicine and Internatior	
Boncheva,	2020 PRO74 Is IT Possible to Accelerate the Access of Patie	Value in Health	
Bonner, N.,	2016 Challenges and solutions associated with patient-cent	Value in Health	
Boon, W., M	2015 Governance of conditional reimbursement practices i	Health Policy	
Boon, W. a	2008 Exploring emerging technologies using metaphors--a s	Soc Sci Med	
Bosone, En	2017 Timely Access to Priority Medicines in Europe	Medicine Access @ Point of Care	

Boyce, M.	2012	Abstracts of the 9th Annual ENETS (European Neuroe	Neuroendocrinology		
Boyer, L. V.	2013	Effectiveness of Centruroides scorpion antivenom cor	Toxicon		
Braamskan	2014	The role of rosuvastatin in the treatment of pediatric	Expert Opinion on Orphan Drugs		
Brabers, A.	2011	Does market exclusivity hinder the development of Fc	Orphanet Journal of Rare Disease		
Breckenrid	2004	Pharmacogenetics: ethical problems and solutions	Nat Rev Ge	Review	Scopus
Brennan, K	2015	New and emerging treatments of Charcot–Marie–Too	Expert Opinion on Orphan Drugs		
Briggs, M. I	2015	New therapeutic targets in rare genetic skeletal disea	Expert Opin Orphan Drugs		
Brown, R. J	2019	Pro105 a Review of Six Years of the Nice Highly Specia	Value in Health		
Bruyaka, O	2012	Strategic Corporate Social Responsibility and Orphan	Journal of I	Article	Scopus
Bubela, T.,	2015	Bringing regenerative medicines to the clinic: The futu	Regenerati	Review	Scopus
Burdett, E.,	2010	Engineering tumors: a tissue engineering perspective	Tissue Eng Part B Rev		
Burton, A.,	2021	Drug Discovery and Development in Rare Diseases: Ta	Drug Design Development and Th		
Cabrera-Lo	2012	Assessing the effectiveness of rapamycin on angiomy	Orphanet J Rare Dis		
Caetano, R	2020	The case of eculizumab: litigation and purchases by th	Rev Saude Publica		
Cap, M., Ki	2011	Abstracts of the 2011 Joint Annual Meeting of the Ger	Br J Clin Pharmacol		
Carr, D. R. a	2016	An early assessment of nice highly specialised technol	Value in Health		
Carr, D. R. a	2016	Gene therapies: the challenge of super-high-cost trea	Regen Med		
Casini, S., V	2017	Human iPSC-Derived Cardiomyocytes for Investigatior	Cardiovasc Drugs Ther		
Catalá-Lópe	2011	PHP7 Orphan Drugs for Rare Diseases in the Europear	Value in Health		
Cato, A., W	2002	Orphan drug development: David and goliath	Clinical Dru	Scopus	
Chan, Adrie	2019	Orphan drugs-access and unmet needs in 194 countri	The Lancet		
Charco, J. M	2021	Prion Diseases: History, Diversity, and Socioeconomic	Araucaria-Revista Iberoamericana		
Chaves Res	2018	Psy185 - Alternative Methodologies Implemented by	Value in Health		
Chaves Res	2018	Psy183 - Scope Review of Orphan Drug Public Policies	Value in Health		
Chen, C., D	2014	Orphan drugs and rare diseases: A scientometric revie	Expert Opi	Review	Scopus
Cheng, C. Y	2019	Pro82 Reimbursement and Pricing of Orphan Drugs in	Value in Health		
Cheng, H. H	2021	Orphan drugs in different countries and development	Intractable & Rare Diseases Resea		
Child, A.	2019	Pns216 Nice Highly Specialised Technology Assessmer	Value in Health		
Chirveches	2016	Systematic review of international models of care on	Value in Health		
Chisolm, St	2014	Partnering in medical education: rare disease organiza	Expert Opinion on Orphan Drugs		
Choudhury	2019	The role of patient organizations in the rare disease e	Orphanet J Rare Dis		
Chow, Shei	2019	Statistical considerations for rare diseases drug devel	Journal of Biopharmaceutical Stat		
Church, L. I	2008	Long term management of patients with cryopyrin-as	Biologics	Review	Scopus
Ciafaloni, E	2019	Efficacy and Safety of Dichlorphenamide for Primary P	Pediatr Neurol		
Clarke, Joe	2010	The Price of Care Versus the Cost of Caring	Fabry Disea	Scopus	
Colasante,	2020	PRO66 Trends in Withdrawal of Orphan Designation fo	Value in Health		
Contesse, M	2019	The Case for the Use of Patient and Caregiver Percept	Adv Ther		
Conti, C. C.	2015	The trends in orphan drug authorisation and approval	Value in Health		
Cornu, C., H	2013	Abstracts of the 17th Annual Meeting of French Socie	Fundam Clin Pharmacol		
Cornu, C., M	2017	Focused Workshop	European Journal of Neurology		
Costabel, U	2005	Pulmonary alveolar proteinosis: a new autoimmune d	Sarcoidosis Vasc Diffuse Lung Dis		
Coyle, D., C	2014	Opportunity cost of funding drugs for rare diseases: th	Med Decis Making		
Coyle, D., D	2020	HTA methodology and value frameworks for evaluatic	Eur J Health Econ		
Coyle, S., M	2020	PRO81 Is EU Orphan Medicine Status Working? a Retr	Value in Health		
Crausaz, S.	2015	Competing for public funding of medicines to treat ra	Bull World Health Organ		
Crossnohe	2019	Pro51 Responsiveness and Acceptability of the Eq-5d	Value in Health		
Csimma, C.	2015	Translating research into drug development-the TACT	Neuromuscular Disorders		
Cui, Y. and	2017	Defining rare diseases in China	Intractable Rare Dis Res		
Curry, A., D	2019	Pro49 a Comparison of the Nice Hst Program with Hea	Value in Health		
Cutillo, C. M	2017	A Global Approach to Rare Diseases Research and Orp	Rare Diseases Epidemiology: Upd		

Czech, M.,	2020	A Review of Rare Disease Policies and Orphan Drug Re	Frontiers in Public Health		
Czech, M.,	2018	BRIDGING EAST WITH WEST OF EUROPE - A COMPARI	Acta Poloniae Pharmaceutica		
Dabbous, C	2019	Ro2 Assessing the Relationship between Lifelong Valu	Value in Health		
Dalsania, R	2014	Payer Management And Pricing Dynamics For Non-Or	Value in Health		
Darrow, J. J	2018	The FDA Breakthrough-Drug Designation - Four Years	N Engl J Me	Article	Scopus
Dasenbroo	2012	Symposium Summaries	Pediatric Pulmonology		
Davies, D. I	1983	Orphan drugs	Lancet		
Dawkins, H	2018	Progress in Rare Diseases Research 2010-2016: An IR	Clin Transl	Review	Scopus
de Andres-	2021	A multi-stakeholder multicriteria decision analysis for	Orphanet Journal of Rare Disease		
de Andrés-	2020	PRO96 A Multi-Stakeholder Multicriteria Decision Ana	Value in Health		
de Blieck, E	2013	Methodology of clinical research in rare diseases: dev	Contemp Clin Trials		
De Boeck, C	2019	Symposium Summaries	Pediatr Pulmonol		
De Chalenc	2014	Rare diseases and disabilities: Improving the informat	Orphanet Journal of Rare Disease		
De Joannis,	2019	Pns137 Orphan Drugs: What Factors Impact the Price	Value in Health		
De Ridder,	2012	National plans: Case study Belgium	Orphanet Journal of Rare Disease		
de Ruijter,	2018	Psy176 - Significant Benefit and Relative Effectiveness	Value in Health		
de Sola-Mc	2019	Funding orphan medicinal products beyond price: sus	Eur J Health Econ		
DeBarber, A	2014	A US perspective on newborn screening: a powerful t	Expert Opinion on Orphan Drugs		
Della Casa A	2015	The RaDiCEA project: Cost of illness (COI) analysis app	Pediatric Rheumatology		
DeRidder, H	2012	Mechanism of coordinated access to orphan drugs	Orphanet Journal of Rare Disease		
Desser, A. a	2010	Orphan drugs: Does society value rarity?	Value in Health		
Dhombres,	2011	OntoOrpha: An ontology to support the editing and a	CEUR Workshop Proce	Scopus	
Di Minno, C	2021	Cost-effectiveness analysis of caplacizumab in the nev	Global & R	Article	
Diab, D., de	2020	PRO87 Limited Target Population: IMPACT on Medica	Value in Health		
Diop, A. G.	2015	Advocacy in resource limited world	Journal of the Neurological Scienc		
Divino, V., I	2015	The budget impact of orphan drugs in the us and Can	Value in Health		
Divino, Vict	2014	The budget impact of orphan drugs in the U.S.: A 200	Blood		
Djambazov	2020	PNS135 A Comparative Analysis on Application of Ma	Value in Health		
Djambazov	2020	PNS187 Differences and Similarities in the LEVEL of Ev	Value in Health		
Djambazov	2020	PNS168 Differences and Similarities in the LEVEL of Ev	Value in Health		
Djambazov	2020	PNS148 Differences and Similarities in the LEVEL of Ev	Value in Health		
Dodman, S	2020	PRO67 Does Society Support The Prioritisation Of Higl	Value in Health		
Donadieu, J	2020	How Many Patients Have Congenital Neutropenia? a I	Blood		
Donadieu, J	2016	Abstracts From the 32nd Annual Meeting of the Histic	Pediatr Blood Cancer		
Dooms, Ma	2014	Understanding off-label use and the new challenges	Orphanet Journal of Rare Disease		
Doux, J.	2015	Barriers and Opportunities: A View across the Develo	J Invest De	Editorial	Scopus
Dusza, M.,	2019	Pro98 Ultra-Orphan Medicinal Products Assessment: (	Value in Health		
Dusza, M.,	2019	Pro108 Analysis of Nice and Us Icer Hta Outcomes for	Value in Health		
E. Haffner,	2010	The U.S. Food and Drug Administration and the regula	Small Mole	Scopus	
Edfjall, Cata	2012	Leveraging existing opportunities for improved Orpha	Orphanet Journal of Rare Disease		
Efthymiadc	2018	Differentiation of Health-Related Quality of Life Outcc	Int J Technol Assess Health Care		
Ekins, S., Pu	2020	Repurposing the Dihydropyridine Calcium Channel Inh	Pharm Res		
Ensor, Chri	2012	Abstracts and Index of Authors	Pharmacotherapy: The Journal of		
Ethgen, O.,	2012	PHP102 From Value to Price: What Should Be the Pat	Value in Health		
Faduola, Pa	2013	Monoclonal biologics in Acute Myeloid Leukemia (AM	Translational Biomedicine		
Faeh, Andr	2012	A Just Distribution of Health Care in the Case of Orpha	European J	Article	Scopus
Falk, K., Bro	2015	Similarities and differences in orphan drug reimburse	Value in Health		
Fecarotta, S	2011	The videofluoroscopic swallowing study shows a susta	Am J Med Genet A		
Feldman, N	2011	Sodium oxybate for the treatment of excessive sleepi	Sleepiness	Scopus	
Feng, S., Liu	2018	National Rare Diseases Registry System of China and F	Human Ge	Editorial Material	

Ferizovic, N	2018	Php244 - Bridging the Gap: Ensuring Fair Assessment	Value in Health	
Fernandez-	2013	Speaker Abstracts	Basic & Clinical Pharmacology & T	
Fernández-	2016	Design of Biomedical Robots for the Analysis of Cance	Man–Machine Interactions 4	
Field, M. J.,	2011	Rare Diseases and Orphan Products: Accelerating Res	Scopus	
Fiorentino,	2012	Non-Speaker Abstracts	Haemophilia	
Foltánová,	2012	Orphan drugs used for treatment in pediatric patients	Acta Facult Article	Scopus
Foltánová,	2013	Orphan Dugs in EU / Lieky na zriedkavé choroby v EÚ	Acta Facult Review	Scopus
Foltanova,	2012	ESCP 40th International Symposium on Clinical Pharm	International Journal of Clinical Pl	
Fontana, D	2014	Non-available medicines (NAMs): A challenge for pub	Latin Amer Article	Scopus
Fontanet, N	2018	Psy49 - Budgetary Impact of Orphan Drugs in the Cata	Value in Health	
Fralick, Mic	2018	Off-label use of drugs for rare diseases: A population-	Journal of General Internal Medic	
Franceschi	2020	PRO99 Real-World Application of Multiple Criteria De	Value in Health	
Freiberg, M	2020	PRO126 Patient Support in Orphan Indication - Persist	Value in Health	
Gabreels, F	2010	Building centres of expertise according to the Dutch n	Orphanet Journal of Rare Disease	
Gallagher, .	2015	A cost-effective enhanced retrospective observationa	Value in Health	
Galuppi, Eli	2016	Hypertrophic osteoarthropathy: classification, diagno	Expert Opinion on Orphan Drugs	
Garcia San	2016	Review of the recommendations made by the nationa	Value in Health	
Garcia San	2016	Review of health technology assessment (HTA) requir	Value in Health	
Gardiner, R	2014	Innovation May Drive Streamlined Access to New Biop	Value Health	
Gea, E., Gil	2013	41st ESCP symposium on clinical pharmacy: personalise	International Journal of Clinical Pharmacy	
Giannuzzi,	2018	9th European Conference on Rare Diseases & Orphan	Orphanet Journal of Rare Disease	
Gilabert-Pe	2016	Development of a multi-criteria decision analysis (MC	Value in Health	
Girn, S., Ca	2020	PRO84 Assessment of National Institute for Health an	Value in Health	
Godman, B	2015	Are new models needed to optimize the utilization of	Expert Rev Clin Pharmacol	
Gombocz, I	2020	Public spending on orphan medicines: a review of the	J Pharm Po Article	Scopus
Gordon, Au	2014	The Progeria Research Foundation: its remarkable jou	Expert Opinion on Orphan Drugs	
Goshua, Ge	2020	Cost Effectiveness of Caplacizumab in Acquired Thron	Blood	
Gottwald, S	2013	Personalisierte Medizin als Orphanisierung: rechtliche	Ethik in der Article	Scopus
Grabowski,	2005	Increasing R&D Incentives for Neglected Diseases: Les	Internatior Scopus	
Grabowski,	2015	The roles of patents and research and development ir	Health Aff (Millwood)	
Gras, J.	2016	LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k	Drugs of the Future	
Gras, J.	2021	Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat	Drugs of the Future	
Griffin, Jan	2020	TAFAMIDIS: THE COST TO OUR PATIENTS	Journal of the American College o	
Grimm, S. E	2021	Building a trusted framework for uncertainty assessm	Orphanet J Rare Dis	
Groft, S. C.	1985	Orphan drug development in the United States	CPJ Article	Scopus
Groft, S. C.	2009	Collaborative research efforts and related activities of	Italian Jour Article	Scopus
Groft, Step	2010	The Office of Rare Diseases Research: Serving a coord	Small Mole Scopus	
Grosse, Scc	2018	Symposium Summaries	Pediatric Pulmonology	
Grosvenor,	2011	Orphan drugs face tougher scrutiny in securing favora	Value in Health	
Gruppen, N	2011	Poster Session	Pediatric Nephrology	
Grzywacz, I	2014	The Cost-Effectiveness Threshold For Orphan Designa	Value Health	
Gungor, D.,	2011	Survival and associated factors in 268 adults with Pon	Orphanet J Rare Dis	
Guo, D., Jin	2018	The International Society for Biological and Environme	Biopreserv Biobank	
Haffner, M	1997	Support for orphan drug development: legislation in the United States, Japan and Europ		
Haffner, M	1992	Evaluation of orphan products by the U.S. Food and D	Int J Techn Article	Scopus
Hajimiri, S.	2019	Pro92 an Analysis of Orphan Medicines Expenditure ir	Value in Health	
Haley, C. J.	2006	The Minor Use and Minor Species Animal Health Act:	Food and D Review	Scopus
Hall, Aimee	2019	Original Abstracts from the 2019 European Meeting o	Current Medical Research and Op	
Hamstra, M	2020	Recruitment, retention, and adherence in a clinical tri	Clin Trials	

Hanna, E.,	2016	Comparison of the trends of orphan drugs designatior	Value in Health	
Hanson, K.	2014	Novel approaches to patient recruitment and data int	Value in Health	
Harvey, Mi	2017	Challenges and opportunities for biotech companies c	Journal of Pharmacy and Pharma	
Hassan, Ma	2014	Comparative effectiveness research and the rise of or	Internatior Article	Scopus
Hauk, M., S	2019	M043 Two Day 20-Step Desensitization for Galsulfase	Annals of Allergy, Asthma & Immı	
Hendrich, J	2019	Pro14 Is the Reimbursement of Orphan Medical Prodı	Value in Health	
Hennicke, J	2018	Abstracts from the 25th European Society for Animal	BMC Proceedings	
Hensen, M	2010	Early access: Analysis of the French ATU system	Value in Health	
Heyes, A. E	2018	Psy184 - Hta and Reimbursement Considerations for F	Value in Health	
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Hoffman, D	2014	Four-year placebo-controlled trial of docosahexaenoi	JAMA Ophthalmol	
Horgan, D.,	2020	Time for Change? The Why, What and How of Promot	Biomed Hub	
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Hsu, Jason	2016	Abstracts of the 32nd International Conference on Ph	Pharmacoepidemiol Drug Saf	
Hsu, J. C., V	2018	Disease and economic burden for rare diseases in Tai	PLoS One	
Huckle, R.	2015	Challenges in benefit–risk assessment of orphan drug	Regulatory Article	Scopus
Huckle, Ric	2019	The need for speed - Enhancing treatment access for	Regulatory Rapporteur	
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Hutchings,	2012	PHP100 Defining Elements of Value for Rare Disease T	Value in Health	
Hutchings,	2013	Payer Assessment and Reimbursement Policy for Rare	Value in Health	
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Hyde, R. an	2010	Orphan drug pricing and payer management in the Ur	American H Review	Scopus
Hyry, H. I.,	2013	The legal imperative for treating rare disorders	Orphanet J Rare Dis	
Inmaculada	2020	Sodium benzoate suspension in non-ketotic hyperglyc	European Journal of Hospital Pha	
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Iskrov, G. G	2013	Insight into reimbursement decision-making criteria ir	Folia Med (Article	Scopus
Ismail, A. a	2013	Orphan Drug Access: Risk/Reward Analysis of Local Cl	Value in Health	
Ismailoglu,	2017	Divergence of Evaluation of Orphan Drugs Between R	Value in Health	
Ivanova, H.	2018	Prm38 - How Much Is Your Life Worth? Defining What	Value in Health	
Jain, Sanjay	2016	Utilising Nanotechnology and Nanosystems for Treatr	Pharmaceu Review	Scopus
Jain, S., Edv	2016	Advances and challenges in the development of drug	Regulatory Article	Scopus
Jaiswal, H.,	2020	PCN87 Key Clinical and Economic Rationales for Onco	Value in Health Regional Issues	
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Jobard, M.,	2011	39th ESCP European symposium on clinical pharmacy	International Journal of Clinical Pl	
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Johnson, S.	2010	The ERS guidelines for LAM: trying a rationale approa	Respir Med	
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Jones, C. A.	2018	Market access for advanced therapy medicinal produ	Value in Health	
Jones, K. ar	2020	Expanded access and commercial packaging for niche	Manufactu Article	Scopus
Jonker, C. J	2020	Inhibitor development in previously untreated patient	Haemophilia	
Joshi, M. a	2020	Pns14 Value Assessment of Orphan Drugs	Value in Health	

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Jyothi, M. S	2020	Regulatory Overview on Rare Diseases and Orphan Dr	International Journal of Pharmace		
Kager, L., P	2010	Review of mifamurtide in the treatment of patients w	Ther Clin Risk Manag		
Kamusheva	2017	Orphan medicinal products' access to the Bulgarian pl	Expert Opinion on Orphan Drugs		
Kamusheva	2020	Clinical and economic assessment of nusinersen: the I	Expert Opinion on Orphan Drugs		
Kang, D., Cl	2019	Pdg54 International Comparison of Orphan Drug Polic	Value in Health		
Kanters, T.	2014	Cost-effectiveness of enzyme replacement therapy wi	Orphanet J Rare Dis		
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Kapur, A. K	2012	PHP15 The Impact of Orphan Drug Incentives on Inno	Value in Health		
Karpman, D	2017	Orphan drug policies and use in pediatric nephrology	Pediatr Nephrol		
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Khan, N., K	2011	NI3 Economic Evaluation in Niche Markets: The Role c	Value in Health		
Kido, A., Ta	2020	Nationwide incidence of central retinal artery occlusic	BMJ Open		
Kiernan, Fic	2016	The future of pharmacoeconomic policy - does value-	Journal of I	Article	Scopus
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Klepacki, R	2015	APhA2015 abstracts of contributed papers	Journal of the American Pharmac		
Klimes, J., D	2012	PCN134 Expenditures and Availability of Orphan Drug	Value in Health		
Klug, B., Ce	2012	Regulatory structures for gene therapy medicinal proc	Methods Enzymol		
Kockaya, G	2019	Pro75 Patient Access to Orphan Medicines in Turkey	Value in Health		
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Koromina, M., Fanaras		Ethics and equity in rare disease research and healthc	Personalize	Review; Early Access	
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Li, T.	2016	Compare policies and research situation of rare disea	Value in Health		

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Ma, N., Nie	2013	Current status and countermeasure of the research oı	Life Science	Article	Scopus
Ma, Y., Guo	2019	Moyamoya disease: A retrospective study of 198 case	Med Clin (Barc)	
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Macaulay,	2018	Psy134 - Has the Nice Hst Process Been a Success? Co	Value in Health	
Macaulay,	2019	Pro112 the Hst Test: Good, Better, Best?	Value in Health	
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Magliano, G	2016	Cost effectiveness of icatibant for hereditary angioede	Value in Health	
Malinowsk	2015	Evaluation of United States schools and colleges of ph	Molecular Genetics and Metaboli	
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Montserrat	2012	Abstracts of the XXX International Congress of the Wc	Haemophilia
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Morel, T., A	2013	Reconciling uncertainty of costs and outcomes with th	Orphanet J Rare Dis
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Mueller-La	2014	DeSScipher, a jump in the future	Clinical and Experimental Rheuma
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Mumford, A	2020	PNS185 Solutions to the Comparator Question in the A	Value in Health
Muscolo, L	2014	Managed entry agreements	Orphanet Journal of Rare Disease
Muscolo, L	2012	PHP39 The "Weight" of Orphan Drugs in the Europear	Value in Health
Musumeci,	2016	Increasing management of orphan drugs	Journal of Managed Care and Spe
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Nacar, S., A	2018	Php162 - Licenced Orphan Medicines Expenditure in T	Value in Health
Nakamura,	2018	Promotion and challenges of Development for Orphar	Annals of Oncology
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Nelson, L.,	2019	Pmu87 Review of Orphan Treatments Assessed by Nic	Value in Health
Nessa, Aziz	2015	Molecular mechanisms of congenital hyperinsulinism	Expert Opinion on Orphan Drugs
Nestler-Par	2018	Challenges in Research and Health Technology Assess	Value Health
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Nicod, E., K	2016	Dealing with uncertainty and accounting for social val	Value in Health

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Norman, P	2014	Pulmonary arterial hypertension: a rare disease that e	Expert Opinion on Orphan Drugs	
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O'Connor,	2019	Commonly setting biological standards in rare disease	Expert Opinion on Orphan Drugs	
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Olry, Annie	2020	10th European Conference on Rare Diseases & Orpha	Orphanet J Rare Dis	
Olsen, Bjor	2015	Translational Medical Research	Research ir	Scopus
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Shelley, W.	1988	The orphan patient	N Engl J Me	Letter Scopus
Sherwin, G	2014	Pricing and Market Access of Orphan Drugs in Asia: a	Value Health	
Sherwin, G	2016	Pricing and market access of orphan drugs in China: A	Value in Health	
Shih, D. Y. a	2014	Orphan Drug Policy: Approaches To Market Access In	Value Health	
Shih, Shaw	2018	Advances in genetic understanding of gorlin syndrom	Expert Opinion on Orphan Drugs	

Simoens, S	2012	Market access of orphan drugs and the role of multi-c	Orphanet Journal of Rare Disease	
Simoens, S.	2011	How much is the life of a cancer patient worth? A pha	J Clin Pharm Ther	
Simoens, S.	2013	Cost-effectiveness assessment of orphan drugs: a scie	Appl Health Econ Health Policy	
Sindelar, A.	1988	Orphan products: An intriguing opportunity		Scopus
Siracusano,	2017	Selected Abstracts From XXXIV National Congress of t	High Blood Press Cardiovasc Prev	
Sireau, Nic	2017	Introduction	Rare Disea	Scopus
Sireau, Nic	2017	Rare Diseases	Scopus	
Skeldon, G.	2020	PRO95 Patient Engagement Process in Rare Disease: F	Value in Health	
Sladecek, S	2016	Relationship between orphan disease prevalence, diff	Value in Health	
Smid, Bouv	2014	A systematic review on effectiveness and safety of eli	Expert Opinion on Orphan Drugs	
Smith, T. J.	2019	Challenges in Orphan Drug Development: Identificatic	Annual Review of Pharmacology a	
Soliani, Ma	2017	Canakinumab for the treatment of TNF-receptor asso	Expert Opinion on Orphan Drugs	
Sollie, A., S	2013	A new coding system for metabolic disorders demons	Hum Mutat	
Song, Peipe	2013	Rare disease patients in China anticipate the sunlight	Drug Discoveries & Therapeutics	
Song, Peipe	2019	Policy measures taken in Japan to improve the quality	Expert Opinion on Orphan Drugs	
Spagnolo, F	2013	Clinical trials of idiopathic pulmonary fibrosis: choosin	Clinical Investigation	
Spilker, Ber	2007	Orphan Drugs	Principles a	Scopus
Spino, C., Ja	2016	Changing the Paradigm for the Treatment and Develo	Front Pediatr	
Spoors, J. a	2014	Orphan and Rare Diseases - the Payer Perspective	Value Health	
Stacpoole,	2011	Program for SIMD Annual Meeting February 27–Marc	Molecular Genetics and Metaboli	
Stacpoole,	2018	Development of a novel observer reported outcome t	Mitochondrion	
Statland, J.	2012	Mexiletine for symptoms and signs of myotonia in no	JAMA	
Steagall, W	2005	Clinical and molecular insights into lymphangioleiomy	Sarcoidosis Vasculitis and Diffuse	
Stella, P. ar	2014	Pharmaceutical pricing, cost containment and new tre	Orphanet J Rare Dis	
Stolk, Piete	2006	Rare essentials: drugs for rare diseases as essential m	Bulletin of the World Health Orga	
Struik, Mar	2015	The importance of biobank and nationwide registry fc	Expert Opinion on Orphan Drugs	
Suárez-Rive	2018	Therapy with coenzyme Q10	Coenzyme	Scopus
Sugarbaker	2018	Pseudomyxoma peritonei and appendiceal carcinoma	Expert Opinion on Orphan Drugs	
Sumanth, M	2004	Orphan drugs	Indian Jour	Review Scopus
Suppiah, R.	2011	A model to predict cardiovascular events in patients v	Arthritis Care Res (Hoboken)	
Surralles, J.	2014	RE(ACT)2014Rare Diseases. 2nd International Congres	Molecular Syndromology	
Swiderski, I	2015	Therapeutic potential of orphan drugs for the rare ske	Expert Opinion on Orphan Drugs	
Synodinos,	2018	Abstracts from Plenary and Keynote Speakers	Public Health Genomics	
Tambuyzer	2000	The European orphan medicinal products regulation	Journal of I	Review Scopus
Tan, S., Dur	2012	PHP76 Evidence Requirements for Pricing and Reimbu	Value in Health	
Tanaudomi	2020	Combined adult and pediatric trials in orphan drugs a	Clinical Pharmacology and Therap	
Taneja, A.,	2020	Rare diseases in India: time for cure-driven policy initi	Current Science	
Tanimoto, T	2014	Concerns about unapproved meningococcal vaccinati	Orphanet J Rare Dis	
Tankovic, C	2013	Designing robust clinical trials for orphan drugs	Orphan Dri	Scopus
Taylor, Fior	2014	Pharmacotherapy of placental site and epithelioid tro	Expert Opinion on Orphan Drugs	
Teagarden,	2014	Breaking through for breakthroughs: the problem of r	Expert Opinion on Orphan Drugs	
Templin, C.	2017	Transition From Orphan Disease To Full Assessment Ir	Value in Health	
Templin, C.	2019	Pbi68 Added Benefit Assessment of Atmps in German	Value in Health	
Thamer, M	1998	A cross-national comparison of orphan drug policies: I	Journal of Health Politics Policy ar	
Thomas, S.	2019	Incentivizing Therapies for Rare Diseases-Reply	JAMA	Letter Scopus
Thorat, C.,	2012	What the Orphan Drug Act has done lately for childre	Pediatrics	
Thumar, R.	2016	Analysis of the ultra-orphan drugs approved by the FI	Value in Health	
Thurtle, Ele	2018	Original Abstracts from the 2018 European Meeting o	Curr Med Res Opin	
Tilson, Hug	2011	Abstracts of the 27th International Conference on Pha	Pharmacoepidemiol Drug Saf	
Tinelli, C., I	2005	The Italian register for diffuse infiltrative lung disorde	Sarcoidosis Vasc Diffuse Lung Dis	

Tingley, K.,	2018	Using a meta-narrative literature review and focus gr	Orphanet J Rare Dis		
Tomasson,	2012	Assessment of health-related quality of life as an outc	Arthritis Care Res (Hoboken)		
Tomeo, F., Mariz, S., B		Haemophilia, state of the art and new therapeutic op	British Journal of Clinical Pharmac		
Tomeo, F.,	2021	Haemophilia, state of the art and new therapeutic op	Br J Clin Ph Review		Scopus
Tomita, N.,	2010	Accessibility to orphan drugs in Japan-Has the orphan	Value in Health		
Torrent-Fa	2001	The EU challenges on the designation of orphan medi	Pharmaceu	Article	Scopus
Torres, Ros	2019	Current understanding of Lesch-Nyhan disease and pc	Expert Opinion on Orphan Drugs		
Toumi, M.,	2014	Impact Of Advanced Therapy Medicinal Products Cost	Value in Health		
Trad, M., B	2017	Advancing drug development in neuro-orphan indicat	Journal of the Neurological Scienc		
Trieste, L.,	2015	Cost-effectiveness analysis and prevention effects of	Pediatric Rheumatology		
Trip, A. M.,	2014	Multi-Criteria Decision Analysis for Reimbursing Orph	Value Health		
Tsiantou, V	2014	Access To Orphan Drugs In Greece During Economic C	Value Health		
Tuchmann-	2020	Administration of gamma-hydroxybutyrate instead of	JIMD Rep		
Tumiene, B	2019	Talks	FEBS Open Bio		
Tumiene, B	2019	Abstracts from the 52nd European Society of Human	European Journal of Human Gene		
Tzouma, V.	2017	Value assessment criteria for orphan drugs across eig	Value in Health		
Uitto, J., Jia	2014	Pseudoxanthoma Elasticum: Diagnostic Features, Clas	Expert Opin Orphan Drugs		
Ulrich, Lind	2010	Efforts to develop orphan drugs: The FDA experience	Pharmaceu	Short Surve	Scopus
Utz, Jeanin	2012	Program for SIMD annual meeting	Molecular Genetics and Metaboli		
van der Bee	2012	Clinical features and predictors for disease natural pr	Orphanet J Rare Dis		
van Dusser	2014	Cost-effectiveness of enzyme replacement therapy fo	Orphanet J Rare Dis		
van Rijswijl	2013	Changes in disease activity, lung function and quality	Expert Opinion on Orphan Drugs		
van Sonder	2014	Treatment options for Lambert–Eaton myasthenic syr	Expert Opinion on Orphan Drugs		
Van Tendel	2018	Php220 - Old Drugs Turned New for Ultra Orphan Dise	Value in Health		
Vandevelde	2021	Belgian rare diseases plan in clinical pathology: identi	Orphanet J Rare Dis		
Vandewalle	2018	Php243 - Do Disease Severity and/or Quality of Clinica	Value in Health		
Viriato, D.,	2020	An Economic Evaluation of Voretigene Neparvovec fo	Adv Ther	Article	Scopus
Vokinger, K	2020	1586MO Pivotal trial endpoints of drugs for rare and r	Annals of Oncology		
Wagner, M	2016	Can the EVIDEM Framework Tackle Issues Raised by E	Pharmacoeconomics		
Wagner, M	2019	Moving Towards Accountability for Reasonableness -	Int J Health Policy Manag		
Walker, A.	2016	Challenges in Using MCDA for Reimbursement Decisic	Value Heal	Editorial	Scopus
Walker, Ch	2010	Designation, plausibility, protocol assistance, clinical t	Pharmaceu	Short Surve	Scopus
Walker, S.,	2019	Pro101 Orphan Drug Reimbursement in England and I	Value in Health		
Wallraven,	2013	Abstracts of the American Society of Gene & Cell Ther	Mol Ther		
Walsh, M.,	2013	Plasma exchange and glucocorticoid dosing in the tre	Trials		
Walshe, J. I	2005	The management of rare diseases	Clin Med (L	Letter	Scopus
Walzer, S. a	2013	Would a New Therapy for Children Be Refused in the	Value in Health		
Wang, Geo	2019	Orphan black box: Explanatory principles	International Journal of Technolo		
Wang, G., M	2020	Pro61 Evidence of Very Low Utilization of Medicines F	Value in Health		
Wang, G. D	2018	Orphan legislation - Leave no one behind?	Value in Health		
Wang, Yun	2017	Message Passing on Factor Graph: A Novel Approach	Advances in Data Mining. Applica		
Warnants,	2020	PRO86 Approaches to the Collection of Utility Values f	Value in Health		
Watson, Al	2020	10th European Conference on Rare Diseases & Orpha	Orphanet J Rare Dis		
Weinreich,	2012	Public support for neonatal screening for Pompe dise	Orphanet J Rare Dis		
Weinstein,	2017	Orphan Drugs In The Uk, Do They Meet The Nice High	Value in Health		
Wellman-L	2010	The US Orphan Drug Act: rare disease research stimul	Health Policy		
Wells, D., H	2015	The TREAT-NMD Advisory Committee for Therapeutic	Neuromuscular Disorders		
Westermar	2010	The COMP perspective	Pharmaceu	Short Surve	Scopus
Westermar	2011	Invited Lectures	Basic & Clinical Pharmacology & T		
White, R. S	2015	Pharmaceutical and Medical Devices: FDA Oversight	Issue Brief	Article	Scopus

Whittal, A.,	2021	Examining the impact of different country processes f	Internatior	Article	
Wickliffe, J.	2011	CYP1A2*1F and GSTM1 alleles are associated with sus	Mol Med		
Wilson, Chi	2013	Market access procedures for orphan drugs	Orphan Dri	Scopus	
Wilson, Cai	2013	Pharmacotherapy of gestational trophoblastic neopla	Expert Opinion on Orphan Drugs		
Wilson, L.	2020	PRO1 The Market Access Landscape for Orphan Drugs	Value in Health Regional Issues		
Wise, Jacqu	2018	US drugs were granted breakthrough approval on wea	Bmj	Note	Scopus
Wolf, Sarah	2019	Inpatient drug reimbursement: Approaches for a dem	International Journal of Technolo		
Wonder, M	2015	FDA breakthrough medicines; have they caused break	Value in Health		
Wong-Rieg	2012	State of the art of rare disease activities around the w	Orphanet Journal of Rare Disease		
Wong-Rieg	2017	Orphan disease overview: Status of rare disease and c	Journal of Pharmacy and Pharma		
Wong-Rieg	2018	OP100 How Health Technology Assessment Is Adaptir	International Journal of Technolo		
Wood, J., S	2013	Multifaceted roles of ultra-rare and rare disease patie	Drug Discov Today		
Wu, Jasmai	2018	Abstract	Pharmacoepidemiology and Drug		
Yamoah, L.	2021	Evaluating New Zealanders' Values for Drug Coverage	Pharmacoeconomics		
Yi, Baxian,	2014	Rare Disease Drug Policy and Inheritance and Innovat	Asian Socia	Article	Scopus
Yoneyama,	2018	A Pharmacometric Approach to Substitute for a Conve	Clin Pharmacokinet		
You, Shuo,	2019	A Phase II Trial of Topical Sodium Nitrite in Patients w	Blood		
Youssefian,	2016	Kindler syndrome, an orphan disease of cell/matrix ac	Expert Opinion on Orphan Drugs		
Zaby, Andr	2011	Orphan drugs: ten years of experience with the EU fra	Internatior	Review	Scopus
Zacherle, E	2018	Psy121 - Relative Value Assessment of Treatments for	Value in Health		
Zamora, B.	2019	Comparing access to orphan medicinal products in Eu	Orphanet J Rare Dis		
Zanon, Pao	2010	Orphan drugs in haematology	Pharmacet	Short Surve	Scopus
Zelei, T., M	2020	Pro63 Systematic Literature Review of Traditional and	Value in Health		
Zelei, T., Mendola, N.		Criteria and Scoring Functions Used in Multi-criteria D	Pharmacoeconomics-Open		
Zelei, T., M	2021	Criteria and Scoring Functions Used in Multi-criteria D	Pharmacoecon Open		
Zhang, A., \	2016	Health technology assessment (HTA) for orphan drugs	Value in Health		
Zhang, Nicc	2019	Estimating the Global Epidemiology of Amyloid Light-(	Clinical Lymphoma Myeloma and		
Zhang, Xiar	2021	A comprehensive analysis of rare diseases in China thi	Molecular Genetics and Metaboli		
Zhang, Yan	2011	Abstracts of the 27th International Conference on Pha	Pharmacoepidemiol Drug Saf		
Zhao, M. ai	2018	Rare Diseases: Drug Discovery and Informatics Resour	Interdiscip Sci		
Zuluaga Sai	2019	Pro14 Improved Quality of Life and Life-Years in Patie	Value in Health		

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Supplementary Table 3: List of included studies

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
1992[18]	USFAD/ Orphan Drug Act, P.L. 97-414, 1983.	Review	This paper examines some of the special problems that are associated with the design and implementation of studies to evaluate the safety and efficacy of orphan drugs.	The legal definition of a rare disease or condition is one that "either (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation than 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.	Orphan drug and biological products are Pharmaceuticals that are generally not considered to be attractive for commercial development. Generally, orphan drug products are used in treating or preventing rare diseases		
2002[19]	United States	Book - Chapter	The information presented is directed both at the fortunate individuals al-ready involved in drug development and at those adventuresome sorts who are considering entering the field. We hope this book will provide readers with in-sights into this exciting arena and begin to explain the complicated process of developing a promising new drug		Orphan products are used to treat rare diseases or conditions that by definition, affect fewer than 200,000 people (or up to 1 in 1300) in the United States.		
2003[20]	United States; Paris, France/ European Medicinal Evaluation Agency	Review	To analyse the American and European experience on the Orphan Medicinal Products.		A medical product can receive the designation of an orphan medical product if it can be established that it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 thousand persons in the EU. American definition of OD not clear		
2004[21]	United States; India, Japan, Australia/ US FDA	Review	This article reviews the bias for classification of orphan drugs, the discovery of orphan drugs, and attempts by pharmaceutical industries, academician (scientist) and practicing physician, with their respective perspectives, advantages and disadvantages in discovery and development of orphan drugs and some historical aspects.	Rare disease or condition is any disease or condition which affects less than two hundred thousand persons in the United States or affects more than two hundred thousand persons in the United States, but for which there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in US.	- Orphan Drugs have been defined in USA as those drugs intended to treat either a rare disease or more common disease where the sponsor cannot make any profit. - As per the definition US FDA, Orphan drugs are those drugs used in diseases or circumstances which occur so infrequently in USA, that there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in the USA. - The availability of orphan drugs to patients before being granted a Marketing Authorization is possible. USFDA designated orphan drug with t-IND (treatment Investigational New Drug) in some cases such as when the drug is intended for the treatment of a serious or life-threatening disease, when no alternative drug or treatment is available, and thirdly, the product is in the process of clinical trials and in an active phase of Marketing Authorization application		
2005[22]	UK, United States, Japan, Australia	Education and debate	We examine the justifications for special status for rare diseases and ask whether the cost effectiveness of drugs for rare or very rare diseases should be treated differently from that of other drugs and intervention.	Definitions of orphan disease: United States diseases with a prevalence of 7.5/10 000; Japan diseases with a prevalence of 4.0/10 000; Australia diseases with a prevalence of 1.1/10 000; and EU diseases with a prevalence of 5.0/10 000.			The UK defines Ultra Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or less
2006[23]	European Union Regulation (EC) No 141/2000	Book - Chapter		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. As a guide, low prevalence is taken as prevalence of less than 5 per 10,000 persons in the European Union [1]"	-The lack of drug development for products intended for the prevention, treatment or diagnosis of rare diseases has made necessary the creation of a number of incentives to stimulate the development of such products. These drugs are known as orphan drugs. - In the EU a medicinal product to treat rare diseases is designated as an orphan medicinal product based on either a demonstrated insufficient return on investment or the rarity of the condition and, the absence of satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorized, or if such method exists, the assumption that the product		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
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					will be of significant benefit to those affected by the condition. -Criteria for orphan designation are the following. Firstly, a criterion is based on the low prevalence ("rarity") of the condition, i.e., condition affecting not more than 5 in 10,000 persons in the European Union. Alternatively, the sponsor can apply for more frequent conditions if it can be shown that the development would not be justified by sufficient financial return, i.e., if without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the investment by the sponsor. Secondly, it is necessary for designation that the life-threatening or debilitating nature of the condition is justified. The sponsor is invited to provide any scientific and other medical references that may support the life-threatening or seriously debilitating nature of the condition. Finally, the sponsors are also required to demonstrate that either there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question or that if such methods exist, that the medicinal product will be of significant benefit to those affected by that condition.		
2006[24]	USA Orphan Drug Act, European	Policy And Practice	In this paper we propose selection criteria for an Orphan Medicines Model List that could form a departure point for future work towards an extensive WHO Orphan Medicines Programme.	In the USA Orphan Drug Act, the definition relates to an absolute number (<200 000 patients in the USA), while the European regulation uses a relative measure (<5 cases per 10 000 inhabitants) and requires disorders to be life threatening and/or chronically debilitating.			
2008[25]	United States	Book - Chapter		The legislative definition for a rare disease in the United States is one with a prevalence of less than 200,000 persons or, if over 200,000 persons, one for which there is no reasonable expectation of recovering drug development costs within seven years of market approval			
2009[26]	United States of America, Japan, EU, Australia, and Taiwan	Review		A rare disease is defined as a disease or condition affecting fewer than 200,000 persons in the United States of America. <50,000 patients in Japan, The EU defines rare diseases as life threatening or chronically debilitating diseases which are of such low prevalence in 2,000) that special combined efforts are needed to address them. Australia: < 2000 individuals. Taiwan: < 1 in 10,000 people.			
2010[27]	United States/ Orphan Drug Act of 1983	Book	- To provide a convenient repository for the substantial work that has been accomplished by individual investigators treating rare genetic disorders with simple molecules. - To provide a handbook that will enable potential clinician/ scientists and others to rapidly survey the field, thus ascertaining what has been done and what can yet be done.	In that legislation, an orphan disease was defined as a condition that affects fewer than 200,000 Americans." Serious, life-threatening disorders across the age span.	Serious, life-threatening disorders across the age span.		
2010[28]	United States/ Orphan Drug Act	Review			The Act initially defined an orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease or condition of interest in the United States as a surrogate for the lack of profitability.		
2010[29]	United States/ the Office of Rare Diseases Research (ORDR)	Book-Chapter	This chapter will focus on many of the activities of the ORDR and include other significant activities related to rare diseases research and orphan products development	The disorders and conditions in the rare diseases category are defined by the prevalence figure of fewer than 200,000 people in the United States with the specific disease. An estimated 25			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
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				million to 30 million people in the United States have a rare disease or condition."			
2010[30]	UK; EU, World Health Organisation, Australia, Japan and the United States	Book-Chapter		-Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual, quality of life or socio-economic potential. -According to the World Health Organisation, a rare disease affects at most 6.5 out of every 10,000 individuals. -Australia, Japan, and the United States have set prevalence's of 1.16, 4.07 and 6.68 per 100,000 individuals respectively for a given rare disease."		
2010[31]	United States/ The Orphan Drug Act	Review			The Orphan Drug Act defined an ,orphan product' as a drug that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA. There are over 6000 conditions that meet the definition of a rare disease		
2011[32]	UK, WHO, US FDA, EU, Japan, Australia:	General review	This article aims to provide a description of principal aspects of policy and practice associated with orphan drugs and treatments of rare diseases and give perspectives for 2011 on new and emerging approaches for addressing patient access." "This article summarizes the current state of international orphan drug patient access and describes developments up to 2011. Emerging policies and practices that will affect patient access in 2011 and beyond are also explored."	-WHO: Frequency of 6.5-10/ 10,000 inhabitants US FDA: Affecting, <7 patients/10,000 residents (estimated to affect about 200,000 patients/year -EU: Affecting ≤ 5 patients/10,000 residents (estimated to affect about 30 million EU citizens) -Japan: Affecting <40/100,000 of the population. -Australia: Affecting <11/100,000 inhabitants or ≤2000Australians	Drugs used in the treatment of rare diseases or disorders with significant unmet medical needs and are referred to as orphan drugs because, as described by EURORDIS (2011c) , the pharmaceutical industry has little incentive under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	Ultra-orphan diseases, in the UK, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population	
2011[33]	Spain	Abstract	We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU.		In the European Union (EU), orphan drugs are used for the diagnosis, prevention, or treatment of life-threatening or serious conditions that affect5 in 10,000 people (NOTE THE OVERLAP BETWEEN ORPHAN DRUG AND RARE DISEASE DEFINITION)		
2011[34]	Canada	Abstract	The scope of this study is to describe the ODs regulations in Canada, evidence requirements by the national regulatory agency, national and regional funding criteria, market access challenges associated with ODs, and approaches to obtain access to ODs in Canada.	The Canadian Organization of Rare Diseases (CORD) defines a rare disease as one that afflicts less that 1 person in 200 000.			
2012[35]	Middle East (Egypt, Iran, Turkey, Iraq, Saudi Arabia, Yemen, Syria, United Arab Emirates or UAE, Israel, Jordan, Lebanon, Oman, Kuwait, Qatar, Bahrain, and Cyprus) plus the Palestinian territories of the West Bank and the Gaza Strip	Policy Forum			An orphan drug is a drug developed specifically to treat a rare medical condition		
2012[36]	United States	Editorial		-The terms, orphan diseases, and, rare diseases, are commonly used interchangeably worldwide and have been defined as ,any disease or condition that affects a small percentage of the population. -The US Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, as does Japan.			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
				-The European Commission on Public Health defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. -The definition of ,low prevalence, varies between countries but usually ranges from 1/1,000 to 1/200,000 -The alternative term, orphan disease, is used in reference to a combination of the paucity of treatment availability, lack of resources, and severity of disease.			
2012[37]	United States	Review	- In this article we present the findings of this analysis, which, consistent with the IOM recommendation, are intended to identify factors correlating with rare disease product approvals that could inform future development programs, and to identify areas where additional resources might be directed. - In this work we provide an up-to date analysis of drug, target interactions for approved and clinical trial drugs and examine the major developments and trends in pharmaceutical development - For the purpose of supporting rare disease product development, we undertook an evaluation of CDER, rare disease marketing application history, focusing on a recent five-year period (2006 - 2010).	Rare diseases, which are disorders affecting less than 200,000 persons in the USA, also have considerable unmet medical needs.			
2012[38]	European Union countries	Review	The aim of this study was to quantify both the sales and volume uptake of orphan drugs in Europe and to assess whether a country, gross domestic product (GDP) and/or health technology assessment (HTA) influences the orphan drugs, market uptake.	In the European Union, a rare disease is defined as a life-threatening or chronically debilitating disease with the prevalence among 50 per 100 000 people or less	Orphan drugs are drugs intended for the treatment of rare diseases.		
2012[39]	Singapore, Taiwan, Korea, and China	Meeting Abstract		-Since 1991, Singapore, Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. -The Taiwan Foundation for Rare Disorders helped secure the Rare Disease and Orphan Drugs Act in 2000. Diseases affecting fewer than 1 in 10,000 that are officially recognized are eligible for medical coverage. -In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000. -In China, in 2011, medical professionals called for legislation to support healthcare, research, orphan drug development, and epidemiological studies for diseases affecting fewer than 1 in 10,000	-Since 1991, Singapore, Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. -In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000.		
2013[40]	Middle East	Critical Review	We provide a critical review of the literature on the availability of orphan drugs in the Middle East.		An orphan drug is a drug developed specifically to treat a rare medical condition.		
2013[41]	United States; UK; and EU	Review	We examined the characteristics of orphan drug (OD) designations and approvals by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2000 and 2011.		Criteria for Orphan designation is generally based on the number of patients affected by the disease (<200,000 US patients and <5 in 10,000 EU patients). The EU also requires that a satisfactory alternative treatment is not available or that the new drug is significantly better than drugs currently marketed.		
2013[42]	UK	Conference	- The presentation provides a brief review of all supportive incentives in the field of orphan medicinal products as: the European orphan medicinal product (OMP) regulation, Guideline on Clinical Trials in Small Populations and Commission Regulation (EC) No 2049/2005 / support of small and medium enterprises (SMEs)." - It also introduces the concept of Clinical added value of orphan medicinal products, as one of the key instruments to increase the availability of orphan medicinal products in the member states."		- The orphan drug intended for diagnosis, prevention or treatment of a life threatening or chronic debilitating condition. - The prevalence of the condition, for which the OMP (orphan medicinal product) is intended, must be less than 5 in 10,000" - OMP has to fulfil following criteria: 1. Seriousness of the condition the investigated drug must be intended for diagnosis, prevention, or treatment of a life-threatening or chronic debilitating condition.		

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					2. Low prevalence/irretrievable investment: at the prevalence of the condition, for which the OMP is intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to generate sufficient return to justify the investment. In some situations, the condition is defined as a subset of another frequent condition. To accept this subset it is needed to prove that the subset is medically recognizable and the investigated OMP is clearly effective only in this subset and not in the condition per se. 3. Medical need No other treatment authorised in EU for this condition or if there is one, the designated OMP must provide a significant benefit over the existing method. The significant benefit is given on the basis of/upon clinically relevant advantage or major contribution to patient EC/847/200		
2013[43]	Taiwan, and Republic of China	Registry data analysis	- This paper aims to describe the prevalence of RDs over time from 2002 to 2011 based on the national RDs registry data in Taiwan". - To describe a general demographic picture of patients with rare diseases in Taiwan and particularly focuses on the prevalence of rare diseases over time, age, and gender distributions.	- Rare disease as a disease whose prevalence is less than 1 in 10,000 in Taiwan. - Taiwan officially included RDs as one type of disability and initiated the RDs disability registry in the social welfare system in 2002 (the Physically and Mentally Disabled Citizens Protection Act, 2001)			
2013[3]	China	Review	In this article, the primary tasks faced by China have been proposed: to call on the government to legislate as soon as possible; to establish information platform of rare diseases and orphan drugs for sharing the global rare diseases resources; to establish Rare Disease Outpatient Service (RDOPS)for improving the level of diagnosis and treatment; to carry out tertiary prevention of the rare diseases; to establish the rare diseases epidemiological surveillance system in our country	- World Health Organization (WHO) defines a rare disease as affecting 65/100 000~100/100 000 persons. A disease is considered as rare when it affects 1 person per 2,000 in Europe, <200 000 people in the United States, <50 000 people (1 person per 2500) in Japan and 1 person per 10 000 in Taiwan. In China, the Chinese Society of Genetic Medicine defines rare disease as 'diseases affect less than one over 500 000 and genetic disorders affect with less than one over 50 000 of the incidences in new-born babies. - Rare diseases are serious chronic diseases, difficulties in obtaining timely, accurate diagnoses and are often life-threatening	Orphan drugs are those intended to diagnose, prevent, or treat rare diseases or pathologies that are serious or life-threatening, and whose development costs are superior to the expected return on investment		
2013[44]	Seven European countries, Belgium	Review	This study aimed to identify, describe, and classify MEAs applied to orphan medicinal products (OMPs) by national payers and to analyse their practice in Europe. The present study, focusing on seven European countries, had three main objectives, namely to: (i) examine the processes through which MEAs are implemented by national healthcare payers, (ii) identify, describe, and classify MEAs applied to OMPs by national healthcare payers, and (iii) analyse and compare identified MEAs related to OMPs within and between countries.	Life-threatening or chronically debilitating diseases with a prevalence of 5 out of 10,000 or less			
2013[45]	United States/ Orphan Drug Act (ODA)	Book - Chapter		- Rare diseases, also referred to as orphan diseases, are defined in the United States (US) by the Orphan Drug Act (ODA) as diseases or conditions that affect fewer than 200,000 persons in the US. - Most rare diseases are serious, life-limiting, or life-threatening conditions	Orphan designated drugs are those that are: intended to treat, prevent, or diagnose diseases or conditions affecting fewer than 200,000 persons in the US; and have shown promise, based on supporting evidence, in the treatment of the disease or condition.		
2013[46]	Netherlands	Research Article	In the Netherlands, we decided to build a registry for patients with metabolic disorders and also to optimize the codes for national use in medical and clinical genetics. With these purposes in mind, we developed, with a dedicated group of clinical specialists, a clinically oriented annotation system for metabolic disorders based on two existing national coding systems.	Rare diseases are life threatening or chronically debilitating diseases with a prevalence of up to five per 10,000 inhabitants in the European Union (EU)			

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2013[47]	China, WHO, United States, Japan, and Australia	Commentary		- A rare disease is referred to as any disease that affects an extremely small percentage of the population. - The World Health Organization (WHO) defines a disease as a rare disease when its incidence ranges approximately from 0.65-1% in the whole population. - Rare disease is identified in the United States (US), Japan, and Australia when it afflicts less than 200,000 (approx. 0.75% of the population), 50,000 (approx. 0.4% of the population), and 2,000 (approx. 0.1% of the population) people, respectively. - Expert consensus indicates that a rare disease could be identified in China when the incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.			
2014[48]	Poland	Abstract	The aim of this study was to identify the cost-effectiveness threshold for an orphan designation in Poland.		- According to criteria specified by the European Medicines Agency (EMA) a medicine must meet 3 criteria to qualify for orphan designation, i.e.: for treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence level in the European Union (EU) of no more than 5 cases in 10,000 patients is necessary; no satisfactory method of disease diagnosis, prevention or treatment or if such method exists, the drug must still deliver significant benefits to patients. - In Poland there is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.		
2014[49]	UK, US	Review	We aim to highlight how the emergence of omics technologies and the development of integrated , systems medicine, approaches might offer ways to overcome research challenges in rare disease and allow patients to ultimately reap the benefits of better scientific understanding of their condition.	Rare diseases are defined in the European Union as those with a prevalence of < 5 in 10,000 and in the US as diseases that affect fewer than 200,000 US citizens			
2014[50]	Latvia	Conferences	This study aims to determine the trends in reimbursement of ODs in Latvia within the framework of individual reimbursement system in 2008, 2011.	Rare diseases, also related to as orphan diseases, are life-threatening or chronically debilitating conditions of different origin. Disease is considered as rare if it affects not more than 5 in 10 000 people in the EU.	- Orphan drugs (ODs) are medicinal products intended for diagnosis, prevention, or treatment of life-threatening or very serious diseases affecting less than 5 in 10 000 people in the European Union (EU). - These drugs are called ‚orphans, because the pharmaceutical industry has little interest, under normal market conditions, in developing and marketing products intended for only a small number of patients suffering from very rare conditions		
2014[51]	National Institute for Health and Care Excellence (NICE)	Abstract	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000. Medicines for these indications are difficult to develop in part due to challenges associated with recruiting for clinical trials from a small patient population. Within this context, global payer bodies have assessed these therapies with modified evidence requirements and opportunity for very high prices. We performed a health technology assessment (HTA) review of two ultra-orphan products – eculizumab/Soliris and iduronate-2-sulfatase (IDS)/Elaprase – to gain insight into the evolving HTA evidence requirements for ultra-orphan medicines and comparatively evaluate key decision drivers across geographies.			Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000.	
2014[52]	Belgium	Qualitative research	The aim of this study is to use a combination of qualitative research methods to examine which official and non-official factors influence reimbursement decisions for orphan drugs in Belgium.	In Europe, rare diseases are defined as life-threatening or chronically debilitating diseases with a prevalence of 50 out of 100000 individuals or less.			

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2014[53]	India, US, Europe, and Japan	Review	An attempt has been made to put forward the challenges faced by rare disease drug development and the current scenario of orphan drug legislations in India. The objective of this review is to look into Indian orphan drug regulations and an emphasis has been laid on Orphan Drugs Act (ODA) of US and orphan drug policies of other developed countries such as Europe, Japan, and Australia, thus showing the requirement of adopting ODA like legislation in India.	- In United States (US), the Orphan Drugs Act (ODA) is a federal law concerning rare diseases that affect fewer than 200,000 people or are of low prevalence (<7.5/10,000 in the community) - A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000) - Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan, definition of rare disease."			
2014[54]	USA, EU, Japan, Australia, Taiwan, South Korea, Alberta, and Ontario	Perspective-workshop	The present paper sets out to explain the rationale underlying a recent expert consensus, recommending a more rigorous assessment of the clinical effectiveness of ultra-rare disorders (URDs,) applying established standards of evidence-based medicine.	- Definitions for, orphan disorders, typically include a criterion of prevalence or incidence and differ somewhat between jurisdictions. - In the USA, these are disorders with a prevalence of less than 200,000 affected persons (according to the Orphan Drug Act of 1983, and Orphan Drug Regulation of 1993) - In the EU, prevalence must be less than 1 per 2000 (or less than 0.05%) of the population (according to EU Regulation CE No. 141/2000 of 2000) - Strict criteria have also been set in Japan (fewer than 4 per 10,000, according to Orphan Drug Regulation of 1993) - Australia (less than 1.1 per 10,000, according to Orphan Drug Policy of 1997) - In Taiwan and South Korea, prevalence thresholds have been set at less than 1 per 10,000 and 1 per 20,000, respectively		- URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE, Alberta). The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~1 in 100,000 of the English population). An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario - No official definition of ‚ultra-orphan disorders, has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE) conditions with a prevalence of less than 1 per 50,000 persons"	National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"
2014[55]	United States	Position Statement	This article examines the trends in public discussion of high-cost drugs and the potential consequences for orphan drug development.	Prevalence of under 200,000 people in the United States	Drugs to treat conditions defined as rare, that with a prevalence of under 200,000 people in the United States		
2015[56]	United States	Abstract	We assessed trends in approvals of new drugs with orphan indications in the US and in the prevalence of orphan drugs approved by the FDA from 1983 to 2014 compared to non-orphan drug approvals in the same time frame		Orphan drugs are indicated for rare diseases and conditions.		Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e.: ultra-orphan drugs)
2015[57]	Egypt, U.S.	Chapter	We introduce in this study a system that classifies the orphan drugs according to their probability of structural similarity		- Orphan drugs are a treatment for rare diseases. - Orphan drug legislation by the U.S. Food and Drug Administration (FDA) is motivating drug companies to develop drugs that have low development costs in order to treat rare diseases."		
2015[58]	United States (US) and European Union (EU),	Poster/Abstract only	The objective of this research is to identify the number of medicines that have been granted orphan designation in the United States (US) and European Union (EU) and analyse the approval trends over a ten-year time horizon with a specific focus on the number of ODs with an oncology indication.		- OD may be defined as a pharmaceutical product aimed at treating rare diseases or disorders. - OD tend to consider the prevalence of the disease and the estimation of the population affected by the disease. - In the USA a rare disease is defined as: <200,000 patients (<6.37 in 10,000, based on US population of 314m) - In Europe a rare disease is defined as: <5 in 10,000 (<250,000 patients, based on EU population of 506m).		
2016[59]	EU, Germany	Forum	Here we examine the factors that account for these failures and describe a variety of possible remedies. This analysis focuses on the EU perspective, though many findings are relevant toother global markets.		An orphan designation is granted to a product when the prevalence of the treated condition in the EU is not more than 5 in 10,000 or it is unlikely that marketing of the product would generate sufficient returns to justify the investment needed for its development.		
2016[60]	Italy	Review		Rare diseases (RDs), including those of genetic origin, are defined by the European Union (EU) as life-threatening or chronically			

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				debilitating conditions whose prevalence is so low (less than 5 per 10,000)			
2016[61]	UK; (EU15 plus Nordics and Poland)	Abstract	To review HTA requirements currently in place for treatments for rare diseases in selected European countries (EU15 plus Nordics and Poland), to identify and evaluate differences between country requirements.	Definitions of orphan (prevalence ≤5:10,000)			Ultra-orphan drug (prevalence ≤1:50,000)
2016[62]	France	Poster/Abstract only	This study aims to analyse their impact on reassessment with a specific focus on orphan medicines.		Orphan designation is a status assigned to a drug intended to treat a rare condition.		
2016[63]	Japan and Europe	Model	This study focused on the difference of rare disease prevalence between Japan and Europe, classified the rare diseases comprehensively using cluster analysis and analysed the influence of prevalence on research activity and drug development.	Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment	Designated intractable diseases over 50,000 patients are targeted for orphan drug designation in April ,2015 were excluded due to the short implementation. The prevalence was calculated as the rate per 100,000 population using the number of patients with the target disease provided by the MHLW website		
2016[64]	Asia-Pacific, Australia, Japan, Singapore, South Korea, and Taiwan	Poster/Abstract only	To evaluate the impact of national orphan drug policy and existing reimbursement mechanisms over the implementation of managed entry agreements (MEAs) for orphan drugs in the context of five Asia-Pacific countries.		- Australia: Prevalence threshold for orphan disease designation: 0.9 in 10,000 - Japan: Prevalence threshold for orphan disease designation: <3.9 in 10,000 - Singapore: Prevalence threshold: 37.7 in 10,000 - South Korea: Prevalence threshold: <4.0 in 10,000 - Taiwan: Prevalence threshold for orphan disease designation: <1 in 10,000"		
2017[65]	Spain	Abstract	Identify if the official criteria of Spanish P&R process are related with P&R approval for ODs.			Ultra-orphan diseases affecting <1/50000 inhabitants	
2017[66]	China	Commentary	The current authors proffered 300,000 to 500,000 cases as a reference threshold with which to define rare diseases in China. This proposal linked the concept of rare diseases with orphan drugs, so it is highly useful in terms of Chinese policymaking on rare diseases	- Disorders with a prevalence less than 1/500,000 or with an incidence less than 1/10,000 among new-borns - More recent - 300,000 to 500,000 cases as a reference threshold with which to define rare diseases in China			
2017[67]	Bulgarian	Text and opinion	- To highlight the possible trends in the further development of requirements for orphan medicines entering the Bulgarian market on the basis of the global situation and trends." - The goals of the current study are to determine the access of orphan medicines to the Bulgarian pharmaceutical market considering the currently available legislation on Health Technology Assessment (HTA) and reimbursement strategies for orphan medicines, the current number of orphan medicines included in the PDL and their total financial burden"		Orphan medicinal products (OMPs) are used in severe life-threatening diseases with no or limited available therapeutic options		
2017[68]	Sweden	Editorial Commentary	Processes related to drug pricing, reimbursement, and thereby availability, vary between countries, thus having implications on patient care. These processes are discussed, with specific focus on three drugs used in paediatric nephrology: a galsidase beta (for Fabry disease), eculizumab (for atypical haemolytic uremic syndrome), and cysteamine bitartrate (for cystinosis).	Rare diseases are severe, chronic, debilitating, and/or life-threatening conditions that are often hereditary and, by definition, affect less than 1 in 2000 individuals in the European Union, or fewer than 200,000 individuals in the USA, at any given time		Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe (EU regulation 536/2014).	
2017[69]	French	Poster/Abstract only	- To explore French stakeholders, policy, implicit or explicit, toward orphan drugs on both Transparency Committee (TC) assessment and pricing decisions - To compare authorities, decisions between two periods of time (2006-2010 and 2011-2016) in order to describe variations on assessment and price lifecycle."	In Europe orphan disease is defined by a prevalence of less than 5 in 10 000 inhabitants which represent a maximum target population of 30 000 patients in France.	An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare disease, itself referred to as an orphan disease. Often severe and disabling, affecting a limited number of people (the threshold admitted for the prevalence is 1 in 2000 in Europe).		
2017[70]	Europe	Book - Chapter	Is to bring together the necessary elements for an efficient overall strategy, hence the adoption of Commission Communication COMM (2008) 679 final on 11 November 2008 1. Making rare diseases more visible 2. Encouraging Member States to develop national rare diseases plans in their health policies. 3. Providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared	Rare diseases, are defined by the European Union as life-threatening or chronically debilitating diseases with low prevalence (less than 5 per 10,000).			

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2017[71]	UK, England, and Wales	Poster/Abstract only	The objective of this study was to evaluate National Institute for Health and Care Excellence Highly Specialised Technology (NICE HST) programme evaluations in the context of the changes and assess the potential impact they may have on patient access to ultra-orphan treatments in England and Wales			Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)	
2017[72]	Europe	Research article	Our multidisciplinary working group discussed the most relevant clinical and economic issues that are perceived to complicate the cost-effectiveness evaluation of orphan diseases and orphan medicinal products and to drive the high ICERs. Subsequently potential policy approaches are presented.	Orphan disease is defined in the EU Orphan Regulation 141/2000 (10) as: 1. A disease that is Life-threatening or chronically debilitating. 2. Prevalence of the condition in the EU of less than 5 in 10,000 or unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and 3. No satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorized in the EU, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.			
2017[73]	UK	Research	The aims of this study were to apply the MCDA framework that was proposed by Hughes-Wilson et al. (Orphanet J Rare Dis 7:74, 2012) to a range of orphan drugs in different diseases, with a view to testing the relationship between drug price and aggregated MCDA scores for each product.	Disease with a prevalence of 1 per 2,000 or less			
2018[74]	Sweden	Review	In this work we provide an up-to date analysis of drug target interactions for approved and clinical trial drugs and examine the major developments and trends in pharmaceutical development	Rare diseases are defined in the US as a disease or condition affecting less than one in 200 000 people.	Orphan drugs encompass pharmaceuticals that are intended to treat these types of diseases		
2018[75]	Poland, Netherlands, and Russia	Review	The goal of this article is to provide an in-depth review of rare disease policies and the reimbursement of ODs in 3 European countries, two EU members (Poland, the Netherlands) and a non-EU one (Russia).	Poland uses the EU definition of rare disorders, which considers a disease as rare if it affects less than 1 in 2000 people (< 5 in 10000 people)		Ultra-rare being <1 in 50000 people'	
2018[76]	Poland	Systematic review	The goal of this article is to provide an overview of the current state of knowledge and latest developments in the field of MCDA in HTA for orphan drugs, to review existing models, their design characteristics, as well as to identify opportunities for further model improvement.		The disease prevalence threshold in the EU for an orphan drug designation is well-defined at ≤ 5 per 10.000		
2018[77]	China	Research	The primary objectives are to establish standardization for registration platform, to build biobanks of genomic data, and to create partnerships for data sharing and research collaboration	The United States defines rare diseases as disorders affecting fewer than 200,000 individuals while the European definition is diseases with a prevalence of lower than 5/10,000.	In 2010, at a seminar conducted by the Genetics Society of the Chinese Medical Association, experts mainly in the field of medical genetics proposed that (any diseases of prevalence lower than 1/500,000 in the overall population or 1/10,000 among new-born's should be considered as a rare disease).		
2018[78]	UK, Scotland	Review	This review identified special HTA, and reimbursement considerations introduced for assessment of orphan drugs and implications for manufacturers.		- According to the European Medicines Agency definition, orphan drugs are intended for diagnosis, prevention, or treatment of rare diseases, whose conditions affect no more than 5 in 10,000 persons. - OD proven at marketing authorization if the annual budget impact is less than €30 million per year for particular indication. - Certain special HTA criteria are applied to orphan drugs: 1. Higher P values for small sample sizes 2. Use of surrogate endpoints 3. Additional benefit is considered proven if the budget impact is less than €50 million per year for particular indication. - Higher therapeutic benefit is automatically recognized for orphan drugs because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorization procedure.		- Currently, no official definition of "ultra-orphan disorders" has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons. - In October 2018, a process will be introduced to allow faster access to ultra-orphan drugs: •The Scottish government will introduce a new definition of ultra-orphan medicines that can treat very

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				RD	OD	URD	UOD
							rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland
2018[79]	Taiwan, United States, EU, and Japan	Research article	- The objectives of this study were to examine 2003,2014 longitudinal trends in the prevalence and expenditure of rare diseases in Taiwan. We also analysed these trends for two specific rare diseases, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), because ALS is the main targeted rare disease in the ice bucket challenge activity, and MS is another rare disease with similar symptoms to those of ALS. - This study examined the national trends in the prevalence of rare diseases and their health-related economic burden (including medication costs) in Taiwan.	- The general definition of a rare disease in Taiwan is <1/10,000 persons. - In the United States and Japan, a rare disease is one with a prevalence of fewer than 200,000 persons and 50,000, respectively. The EU defines rare diseases as fewer than 5 per 10,000 persons			
2018[80]	UK, England	Poster/Abstract only	This research aims to identify, compare, and evaluate willingness to pay (WTP) thresholds across countries		WHO recommends a WTP of <3 times GDP per capita/QALY		HST for ultra-orphan indications Euro113,900-341,700/QALY in England
2018[81]	Germany	Review	- The valid guidelines and the regulations of the German health system are discussed in this article. - The criteria for indication and monitoring of off-label use are shown, especially focused on the problem of refractory myasthenia gravis.	- Since 2000, diseases with a prevalence of < 5 out of every 10,000 people in the EU have been defined as "rare diseases." - According to a statement by Orphanet regarding **myasthenia gravis** in Europe, this amounts to a prevalence of 1–9/100,000 population.		Rare diseases are "singular cases" or "individual cases", which are considered "ultra-rare diseases" (prevalence: <1:10,000), including, for example MuSK-positive myasthenia gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS)	
2018[82]	United States	Abstract	To estimate the pharmacy budget impact (per member per month [PMPM]) of five orphan drugs with single chronic indications.	There are up to 7,000 rare diseases, defined as a condition affecting fewer than 200,000 people.			
2018[83]	Canada, Scotland, Australia, and New Zealand	Research	The objective of the present study was to analyse the basis for Common Drug Review (CDR) orphan drug recommendations and to compare recommendations to those in other jurisdictions. In the current study we have reviewed CDR recommendations for orphan drugs, defined the parameters involved in decision making, and compared recommendations with those made in Scotland, Australia, and New Zealand.	- (Canada) proposed definition of a rare or orphan disease as one that affects < 1in 2000 persons, a definition aligned to that used in the European Union - Approximately 7000 such diseases have been identified and it is estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease			
2018[84]	Spain	Meeting Abstract	This presentation will review these forces and the multiple business models for pursuing orphan indications that they offer and discuss some of the unique scientific and business aspects that make the orphan space unique, including the crucial central role of rare disease patient organizations.	Rare diseases, which are those affecting <5 in 10,000 people in Europe.			
2018[85]	France	Poster/Abstract only	The aim of this analysis was to discuss ICERs of orphan drugs and their characterizations issued by the CEESP		Orphan drugs according to the Transparency Committee's opinions and designations are typically indicated in conditions that have a prevalence of below 5 in 10,000		
2018[86]	Japan	Symposium	Overview the designation and supporting systems for development of orphan drugs in Japan and foreign country, and introduce our experience of promoting the orphan drug in neuromuscular fields	- Rare diseases are any diseases that affected the relatively small number of patients, and generally chronically debilitating, life threatening. - Rare disease is definitely in the space of unmet medical needs.	Orphan drugs, which are the drugs for rare diseases		
2018[87]	United States	Review	The purpose of this study was to compare published ICER estimates, as a measure of relative value, across several orphan drugs which are indicated to treat rare diseases in paediatrics and adults.	A rare disease was defined as a condition with a prevalence of ≤620/million persons.		Ultra-rare diseases (affecting <20/million persons)"	
2019[88]	United States, WHO, and Europe	Book - chapter		- WHO, orphan disease refers to a disease with a low prevalence of less than 6.5–10 cases in 10,000 people. - USA, orphan disease is defined as one that affects less than 200,000 individuals. - Europe, disease with prevalence of less than 5 in 10,000 people	- Orphan drugs are defined as the drugs used for the diagnosis, prevention, or treatment of orphan disease. - Orphan drugs are those drugs having both orphan and non-orphan indications		
2019[89]	UK	Model	- Our study tested the criteria preferences and possibilities for implementation of the EVIDEM MCDA framework for orphan drugs with a diverse group of 140 stakeholders in Kazakhstan,	Diseases that are life-threatening or chronically debilitating are qualified as rare diseases (RD) in the EU if their prevalence is <5 per 10.000			

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			Netherlands, Poland, Romania, Russia, Turkey, and Ukraine (KZ, NL, PL, RO, RU, TR, UA). - The purpose of the study was to perform a weight elicitation for the EVIDEM rare disease model (v3.0) in a wider region in Eurasia with a sizeable group of experts (100-200), in order to identify key differences between countries and types of stakeholders as well as to compare weighting results from other studies. A secondary goal was to test the usefulness of a questionnaire tool designed for this purpose.				
2019[90]	UK	Abstract			- For a drug to be appraised via the HST process, it must meet seven criteria, based on: a small and defined distinct patient population, a limited number of specialist treatment centres for the indication in question, treatment price, and severity of the condition. - The current NICE appraisal system means orphan drugs that do not meet HST criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of¬£30 k/QALY, rising to £50 k/QALY when end-of-life criteria are met		
2019[91]	UK	Poster/Abstract only	This research compares NICE Highly Specialised Technologies (HST) appraisal outcomes with corresponding guidance by other European HTA bodies, stratified by payer archetype: cost-effectiveness versus clinical effectiveness			Ultra-orphan disease (prevalence: <1:50,000)	
2019[92]	Italy	Meeting Abstracts	This paper aims to give some insights into the Italian Pricing & Reimbursement (P&R) Policies on Orphan Medical Products (OMPs) highlighting the strengths and weaknesses of the system.		- OMPs are drugs intended for the treatment of seriously conditions affecting less than 5 in 10,000 people in the EU. - AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmet medical needs, clinical added value, and quality of evidence.		
2019[93]	UK (England and Scotland)	Review/ Poster	This research reviewed recent assessments of orphan and ultra-orphan drugs by NICE and the SMC, and disparities in availability for NHS patients between England and Scotland.		Treatments for diseases with a prevalence of <5 in 10,000 in the EU, which are life-threatening or severely disabling and have no satisfactory treatment available, are granted orphan designation by the European Medicines Agency (EMA)		The NICE Highly Specialised Technology Programme (HSTP) and the SMC consider ultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "
2019[94]	UK	Review	This review provides an overview of NIBSC, work in rare diseases and highlights the positive impact of the work of standardization institutions in this field	Rare diseases are defined as conditions not affecting more than 5 in 10,000 people in Europe			
2019[95]	Spain	Review	The present study aims to develop a reflective MCDA framework, based on EVIDEM methodology, with relevant criteria that allows the evaluation and positioning of OD to aid decision-making at the national level in Spain.		Orphan Drugs (ODs) are intended for the diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 (rare diseases) in the European Union (EU).		
2020[96]	India, Organization for Rare Diseases India (ORDI), WHO, EU, US, Japan, and Australia	Review	This review provides a brief account on RDs and their prevalence, followed by a discussion on the major RDs-associated challenges in general, an account on the methods that can be adopted for conducting fruitful molecular genetic studies of monogenic diseases, and the experiences of genetic research in Indian context with a special reference to a genetically vulnerable and low resource region like J&K - India.	- Organization for Rare Diseases India (ORDI) has suggested a threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals in India. - The base prevalence rate of RDs set by the World Health Organization (WHO) is approximately 1 in 2,000 people. - A genetic disorder prevalent in the European Union (EU) is considered rare only if it affects 5 or less per 10,000 cases, whereas the incidence rate for RDs in the United States is 7 or less per 10,000 individuals. These numbers translate to nearly 30 million Europeans and 25 million North Americans (approximately 1 in every 10) affected by any of the known RDs. - The incidence rate is estimated to be ≤2.5 cases in 10,000 and 1 in 10,000 individuals for Japan and Australia, respectively			
2020[97]	Belgium	Position Statement	The current paper aims to set a further step and translate the findings and recommendations from the many existing initiatives into a pragmatic and realistic methodology. The proposed tool will provide guidance to inform multi-stakeholder discussions and		Many of the treatments developed for rare diseases will have an Orphan Medicinal Product (OMP) designation, indicating that they are likely to deliver benefit in an area		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
			reimbursement decision making about specialised treatments for rare diseases." "Additionally, the paper provides guidance on the potential of Real-World Evidence (RWE) ,i.e., data collected outside the context of RCTs to help address such uncertainties.		of high unmet need. Their approval may be based on a small or uncontrolled trial		
2020[98]	Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom.	Systematic Review	This study aimed to create a comprehensive and in-depth overview of rare diseases policies and reimbursement of OMPs in a selection of 12 countries in the Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom. the aim of this article is to bridge the identified gaps by presenting an overview and comparison of current rare disease policies, HTA and reimbursement processes for orphan drugs in a broader range of Eurasian countries.	- The EU has officially defined rare diseases as being rare when they affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) and in most of the selected countries this definition is used [FR, DE, LV, NL, PL, RO, UK, and UA - In Russia the maximum prevalence for a rare disease is defined as 1 in 10,000 - Some countries use additional definitions in situations where a condition is not officially defined as rare, such as in the UK, where the National Health Service (NHS) classifies all conditions that require specialized medical care also as rare if they occur in <500 citizens yearly. - Turkey defines a rare disease when they affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition. - There is no specific definition for ,rare disease, in Armenian legislation, only ,levels of disability, which define whether the patient will receive the necessary medicines for free or not	The Netherlands defines the classification ,orphan drug, as either having an official EU orphan designation or one that targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no registered medicine exists.		Effective from October 2018, Scotland has introduced a new definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes
2020[99]	France	Review	To detect among the drugs approved for limited populations any impact of the orphan status on the assessment outcome of medical benefit (SMR) or improvement in medical benefit (ASMR) carried out by the French authority for health (HAS)	Prevalence of rare disease < 5/10 000 as per EMA"	An orphan designation is granted by EMA for all medicinal drug intended to treat a life-threatening or chronically debilitating disease, provided a maximum prevalence in the Europe of 5/10,000 and when no satisfactory authorised method can be authorised, or, if such a method exists, the medicine must be of significant benefit to patients.		
2020[100]	UK	Commentary	This paper explores the successes and limitation of both the regulation and its implementation mechanisms in the current regulatory context, and suggests some improvements that could maximise its benefits and boost rare disease research even further	- Rare diseases are categorized as ,orphan diseases, because their occurrence in a small number of patients means that, despite apparent high unmet medical need, there is limited scientific understanding, making it difficult to justify the development risk and investment to develop new treatments. - The European Union defines a rare (or ,orphan,) disease as a life-threatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union.		Prevalence can be much lower, leading to the concept of the, ultra-orphan disease, for diseases with an estimated prevalence of <1 in 50,000 people	
2020[101]	India	Abstract	The purpose of this paper is to identify the hurdles in the field of orphan drugs in India and suggest solutions to address the same.	An orphan disease is defined as a condition that affects fewer than200,000 people nationwide	Orphan Drug is used to treat such a condition.		
2020[102]	India	Review	To understand orphan drugs and national policy on treatments of rare diseases. To overview the condition for pricing of orphan drugs in India and government schemes which are helping out for patient needs. To highlight the need of regulations on orphan drugs for sale and manufacture of orphan drugs in India.	A rare disease is a health disorder of low occurrence that affects a limited number of people in the general population as opposed to other prevalent diseases.	Orphan drugs are the drugs and natural products used in treatment, diagnosis, or prevention of rare diseases.		
2020[103]	194 World Health Organization member countries and other areas (Hong Kong, Kosovo, Macau, Palestine, Sahrawi, Republic, Philippines and Taiwan)"	Health Policy Analysis	This study aims to provide an up-to-date global overview of ODP (Orphan drug policies) in the era of innovative medicine and to reflect associated changes in drug regulation policy. This review provides an overview of global policies that optimize development, licensing, pricing, and reimbursement of orphan drugs.	- Rare diseases are typically defined as conditions with limited treatment alternatives, with an average prevalence of fewer than 40 to 50 cases per 100 000 population or that affect a small number of patients compared with the total population. - When defining rare diseases, most countries/ areas adhered to the European Union definition of low prevalence (0.05%), whereas others followed the number of prevalent cases, such as Australia (< 2000), South Korea (<20 000), and the United States (<200 000). Countries/areas such as Chile, Kenya, Peru, and Singapore required the disease severity to be, life threatening, and severely- or chronically-,debilitating. - Rare disease or condition, means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 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	- Orphan drugs are often defined as drugs intended for the treatment, diagnosis, prophylaxis, or rehabilitation of rare diseases. - Orphan drugs are also defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions. Countries/areas such as China and Vietnam acknowledged orphan drug designation from reference competent authorities. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the community when the application is made, or that it is intended for the		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
				condition will be recovered from sales in the United States of such drug (United States) - Designation of rare diseases: The DOH, upon recommendation of the RDTWG, shall have the authority to designate any disease that is recognized to rarely afflict the population of the country as a rare disease. (The Philippines)	diagnosis, prevention or treatment of life-threatening, seriously debilitating or serious and chronic condition in the community and that without incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment, and (b) that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in the EU that has been authorized in the Community or, if such a method exists, that the medicinal product will be of significant benefit to those affected by that condition. - In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorization in the European Union		
2020[104]	Santiago de Chile	Book - Chapter		- Rare diseases (RDs) or orphan diseases, by definition, are conditions that affect a small number of individuals most RDs are chronic and debilitating and are a substantial cause for disability and early death. - Based on Orphanet, disease inventory, it is evident that the majority of RDs are of genetic etiology, and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers." - RDs are a highly heterogeneous group of disorder			
2020[105]	China, Australia, Japan, South Korea, and Taiwan	Poster/Abstract only	We sought to identify the regulations and policies related to market access for orphan drugs in five major markets from the APAC Region, with the aim of providing an overview of the factors designed to support sponsors of orphan medicinal products. Specifically, we focused on policies in Australia, China, Japan, South Korea, and Taiwan	- "China: Rare disease defined as that affecting less than 1 per 500,000 population. - South Korea: Rare disease defined as that affecting: Less than 20,000 people in Korea (i.e., <4 per 10,000 population) - Japan: Rare disease defined as that affecting: Less than 50,000 people in Japan (i.e., <4 per 10,000 population). - Taiwan: Rare disease defined as that affecting less than 1 per 10,000 population. - Australia: Rare disease defined as that affecting less than 5 per 10,000 population"			
2021[106]	South Korea	Expert Opinion	This paper reviews key factors that should be considered in the process of development, regulation, and market access of orphan drugs in South Korea with a particular focus on the pricing and reimbursement review process.		In South Korea, the Korea Ministry of Food and Drug Safety formulates ODs, which should satisfy two conditions related to the number of patients and the existence of alternatives. In other words, drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments of drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD.		
2021[107]	UK	Review	This review provides an overview of the strengths and limitations of value assessment frameworks (VAFs) for the reimbursement of orphan drugs in Europe and may serve as a guide for decision-makers.	- Rare diseases are a group of diverse diseases, each characterized with low prevalence: occurring in less than one in 2,000 people in Europe. - They are defined as life-threatening or chronically debilitating, and are mostly caused by a genetic predisposition	The, Orphan Medicinal Product Regulation defines OMPs as products for the ,diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union		
2021[108]	Spain	Research	This study aimed to determine the most relevant criteria for the reimbursement of OMPs in Spain, from a multi-stakeholder perspective, and using multi-criteria decision analysis (MCDA). The objective of this study was twofold: first, to review, discuss, and reach a consensus on the most relevant criteria for decision-making about pricing and financing OMPs in Spain; and second, to prioritize them according to their relative importance based on	- Rare diseases are diseases of low prevalence and high complexity that can lead to death or chronic disability. - In Europe, rare diseases are defended as those pathologies that affect less than 5 people per 10,000 inhabitants.	Orphan medicinal products (OMPs), which are intended to diagnose, prevent, or treat rare diseases, have a shared community procedure for being designated as such in the European Union, and this community approach provides opportunities for research, development, and marketing	Ultra-rare, affecting less than 1 person per 50,000 inhabitants."	

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
			the preferences stated by different stakeholders, following the MCDA methodology.				
2021[109]	New Zealand	Online survey	The objectives of this study were to measure the relative societal importance of values of New Zealanders in informing drug funding decisions and to determine how New Zealanders trade of funding in various scenarios between common and rare diseases.	A rare disorder is defined by PHARMAC (the Pharmaceutical Management Agency) as affecting less than 1:50,000 people in the New Zealand population, which is a considerably lower prevalence threshold than other nations that are from 5 to 76 per 100,000 people			

Supplementary Table 4: Critical Appraisal Result

Critical Appraisal Result for Systemic Reviews and Research Syntheses studies

Studies	Q1) Is the review question clearly and explicitly stated?	Q2) Were the inclusion criteria appropriate for the review question?	Q3) Was the search strategy appropriate?	Q4) Were the sources and resources used to search for studies adequate?	Q5) Were the criteria for appraising studies appropriate?	Q6) Was critical appraisal conducted by two or more reviewers independently?	Q7) Were there methods to minimize errors in data extraction?	Q8) Were the methods used to combine studies appropriate?	Q9) Was the likelihood [illegible]atio [illegible]s [illegible]ed?	Q10) Were recommendations for policy and/or practice supported by the reported data?	Q11) Were the specific directives for new research appropriate?
1. 2018 [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. 2020 [84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. 2021 [110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1. Critical Appraisal Result for Text Opinion studies

Studies	Q1) Is the source of the opinion clearly identified?	Q2) Does the source of opinion have standing in the field of expertise?	Q3) Are the interests of the relevant population the central focus of the opinion?	Q4) Is the stated position the result of an analytical process, and is there logic in the opinion expressed?	Q5) Is there reference to the extant literature?	Q6) Is any incongruence with the literature/sources logically defended?
1.2003 [3]	Yes	Yes	Yes	Yes	Yes	Yes
2.2005 [5]	Yes	Yes	Not applicable	No	Yes	Yes
3.2006 [7]	Yes	Yes	Yes	Not applicable	Yes	No
4.2009 [9]	Yes	Yes	Yes	Not applicable	Yes	Not applicable
5.2010 [11]	Yes	Yes	Yes	Yes	Yes	No
6.2010 [12]	Yes	Yes	Unclear	No	Yes	No
7.2014 [33]	Yes	Yes	Yes	Yes	Yes	Yes
8.2017 [51]	Yes	Yes	Yes	Yes	Yes	Yes
9.2017 [111]	Yes	Yes	Yes	Yes	Unclear	NO
10. 2019 [78]	Yes	Yes	Yes	NO	Yes	Yes
11. 1992 [1]	Yes	No	Yes	NO	Yes	Not applicable
12. 2004	Yes	Yes	Yes	Yes	Yes	Not applicable
13. 2008 [8]	Yes	Yes	Yes	Yes	Yes	NO
14. 2010 [13]	Yes	Yes	NO	NO	Yes	Not applicable

15. 2011 [15]	Yes	Yes	Yes	Yes	Yes	NO
16. 2013 [25]	Yes	Yes	Yes	Yes	Yes	NO
17. 2013 [28]	Yes	Yes	Yes	Yes	Yes	NO
18. 2014 [37]	Yes	Yes	Yes	Yes	Yes	NO
19. 2016 [44]	Yes	Yes	NO	Yes	Yes	NO
20. 2018 [55]	Yes	Yes	Yes	Yes	Yes	Yes
21. 2018 [59]	Yes	Yes	Yes	Yes	Yes	NO
22. 2018 [65]	Yes	Yes	NO	Yes	Yes	NO
23. 2020 [80]	Yes	Yes	Yes	Yes	Yes	NO
24. 2020 [86]	Yes	Yes	Yes	Yes	Yes	NO
25. 2020 [112]	Yes	Yes	Yes	Yes	Yes	NO
26. 2020 [88]	Yes	Yes	Yes	Yes	Yes	NO
27. 2021 [91]	Yes	Yes	Yes	Yes	Yes	Yes
28. 2010 [14]	Yes	Yes	NO	Yes	Yes	No applicable
29. 2018 [61]	Yes	Yes	Yes	Yes	Yes	NO
30. 2021 [91]	Yes	Yes	Yes	Yes	Yes	NO

2. Critical Appraisal Result for Economic Evaluations studies

Studies	Q1) Is there a well-defined question?	Q2) Is there comprehensive description of alternatives?	Q3) Are all important and relevant costs and outcomes for each alternative identified?	Q4) Has clinical effectiveness been established?	Q5) Are costs and outcomes measured accurately?	Q6) Are costs and outcomes valued credibly?	Q7) Are costs and outcomes adjusted for differential timing?	Q8) Is there an incremental analysis of costs and consequences?	Q9) Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Q10) Do study results include all issues of concern to users?	Q11) Are the results generalizable to the setting of interest in the review?
1.2012 [21]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Yes
2.2014 [34]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes
3.2014 [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.2018 [63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.2018 [67]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Yes	No	Yes	Yes
6.2017 [57]	Yes	Yes	Yes	Yes	Yes	Unclear	NO	NO	NO	Yes	Yes

3. Critical Appraisal Result for Analytical Cross-Sectional Studies

Studies	Q1) Were the criteria for inclusion in the sample clearly defined?	Q2) Were the study subjects and the setting described in detail?	Q3) Was the exposure measured in a valid and reliable way?	Q4) Were objective, standard criteria used for measurement of the condition?	Q5) Were confounding factors identified?	Q6) Were strategies to deal with confounding factors stated?	Q7) Were the outcomes measured in a valid and reliable way?	Q8) Was appropriate statistical analysis used?

. 2012 [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
. 2015 [41]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Unclear

4. Critical Appraisal Result for Qualitative Research studies

Studies	Q1) Is there congruity between the stated philosophical perspective and the research methodology?	Q2) Is there congruity between the research methodology and the research question or objectives?	Q3) Is there congruity between the research methodology and the methods used to collect data?	Q4) Is there congruity between the research methodology and the representation and analysis of data?	Q5) Is there congruity between the research methodology and the interpretation of results?	Q6) Is there a statement locating the researcher culturally or theoretically?	Q7) Is the influence of the researcher on the research, and vice- versa, addressed?	Q8) Are participants, their voices adequately represented?	Q9) Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Q10) Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?
1. 2014 [36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. 2021 [92]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
3. 2021 [93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
4. 2013 [30]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Yes
5. 2019 [59]	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	Yes

5. Critical Appraisal Result for Prevalence Studies

Studies	Q1) Was the sample frame appropriate to address the target population?	Q2) Were study participants sampled in an appropriate way?	Q3) Was the sample size adequate?	Q4) Were the study subjects and the setting described in detail?	Q5) Was the data analysis conducted with sufficient coverage of the identified sample?	Q6) Were valid methods used for the identification of the condition?	Q7) Was the condition measured in a standard, reliable way for all participants?	Q8) Was there appropriate statistical analysis?	Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?
1. 2016 [47]	Yes	Yes	NO	Yes	Yes	Yes	Yes	Yes	Yes
2. 2013 [26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Not applicable

6. Critical Appraisal Result for Cohort Studies

Studies	Q1) Were the two groups similar and	Q2) Were the exposures measured	Q3) Was the exposure	Q4) Were confounding	Q5) Were strategies to deal with	Q6) Were the groups/participants free of the	Q7) Were the outcomes	Q8) Was the follow up time reported and	Q9) Was follow up complete, and if not, were	Q10) Were strategies to address	Q11) Was appropriate

	recruited from the same population?	similarly to assign people to both exposed and unexposed groups?	measured in a valid and reliable way?	factors identified?	confounding factors stated?	outcome at the start of the study (or at the moment of exposure)?	measured in a valid and reliable way?	sufficient to be long enough for outcomes to occur?	the reasons to loss to follow up described and explored?	incomplete follow up utilized?	statistical analysis used?
1. 2018 [61]	Not applicable	Yes	Yes	NO	NO	Yes	Unclear	NO	NO	Yes	Not applicable

Supplementary Table 5: RDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
North America	US (25)	24 (26%)	Orphan Drug Regulation	Defines RD according to prevalence: "rare disease' means any disease or condition that affects less than 200000 persons in the USA'.	1993	developed
			RDA		2002	
			ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare disease or condition' means any disease or condition which occurs so infrequently in the USA that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug'.	1983	
			FDA	Define RD as 'any disease or condition that affects less than 200000 people in the USA or affects >200000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug'		
	Canada (3)	2 (2%)	CORD	Rare disease as one that afflicts less than 1 person in 200 000.		Aligned to EU
				Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease		
South America	Chile (1)	1 (1%)		Required the disease severity to be ,life threatening, and severely- or chronically-, debilitating.		
	Peru (1)					
Europe	UK (3)	2 (2%)	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in 2000 people. (i.e., a prevalence of 5 or less per 10,000)	2021	
			NHS	Some countries use additional definitions in situations where a condition is not officially defined as rare. classifies all conditions that require specialized medical care as rare if they occur in <500 citizens yearly		
	EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10 000 persons in the European Union) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential.		
			European Commission on Public Health	Defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them.		
			Orphan Drug Regulation	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare	141/2000	
			EMA	prevalence of rare disease < 5/10 000		
	Germany (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Latvia (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Netherlands (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Poland (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
	Romania (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	France (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Ukraine (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
Oceania	Australia (10)	10 (11%)		Diseases with a prevalence of 1.1/10 000		
				Diseases with a prevalence < 2000 individuals.		
				Australia have set prevalence's of 1.16 per 100,000 individuals for a given rare disease.		
				Affecting <11/100,000 inhabitants or ,≤2000 Australians		
				Prevalence threshold for orphan disease designation: 0.9 in 10,000		
				The incidence rate is estimated to be 1 in 10,000 individuals for Australia		
	New Zealand (1)	1 (1%)	PHARMAC	Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold than other nations that are from 5 to 76 per 100,000 people		
Asia	Japan (13)	13 (14%)		Japan diseases with a prevalence of 4.0/10,000		
				<50,000 patients in Japan		
				Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment		
				The incidence rate is estimated to be ≤2.5 cases in 10,000 for Japan		
	Taiwan (7)	7 (8%)	Taiwan Foundation for Rare Disorders	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical coverage.	2000	
			Physically and Mentally Disabled Citizens Protection Act	RD is one type of disability	2001	
	China (5)	5 (5%)	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences in Newborn babies.		
				Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.		
	South Korea (4)	5 (5%)		Prevalence thresholds have been set at less than 1 per 20,000		
				Prevalence threshold: <4.0 in 10,000		
				< 20,000 people in Korea (i.e., <4 per 10,000 population)		
	Singapore (2)	2 (2%)		Required the disease severity to be life threatening, and severely- or chronically-, debilitating.		
				Prevalence threshold: 37.7 in 10,000		
	India (1)	1 (1%)	ORDI	Threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals.		
	Armenian legislation (1)	1 (1%)		There is no specific definition for rare disease only levels of disability which define whether the patient will receive the necessary medicines for free or not		
	Philippines		The DOH, upon recommendation of the RDTWG,			
Africa	Kenya			Required the disease severity to be ,life threatening, and severely- or chronically- ,debilitating.		

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
Eastern Europe & Northern Asia.	Russia (1)	1 (1%)		Maximum prevalence for a rare disease is defined as 1 in 10,000		
South-eastern Europe & Southwestern Asia	Turkey (1)	1 (1%)		Affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition.		
	WHO (5)	5 (5%)		Rare disease affects at most 6.5 out of every 10,000 individuals.		
				Frequency of 6.5-10/ 10,000 inhabitants		
				Incidence ranges approximately from 0.65-1% in the whole population.		
				Rare disease as affecting 65/100 000~100/100 000 persons.		
	Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic etiology and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers."		

The Rare Diseases Act (RDA; the Orphan Drug Act (ODA; the Food and Drug Administration (FDA); The Canadian Organization of Rare Diseases (CORD); National Health Service (NHS); - PHARMAC (the Pharmaceutical Management Agency); Organization for Rare Diseases India (ORDI)

Supplementary Table 6: ODs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
Europe	EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically and seriously debilitating condition affecting not more than 5 in 10 000 EU people or that it is unlikely that marketing the drug in the EU would generate sufficient benefit for the affected people and for the drug manufacturer to justify the investment		
			NICE	The current NICE appraisal system means orphan drugs that do not meet HST criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of £30 k/QALY, or £50 k/QALY when end-of-life criteria are met		
			EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs and are referred to as orphan drugs because, the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	(2011 c)	

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
			The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union		
			The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered medicine exists		
			Poland	There is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.		
	Italian (1)	1 (1%)	Medicines Agency (AIFA)	AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmet medical needs, clinical added value and quality of evidence.		
	German (1)	1 (1%)		Certain special HTA criteria are applied to orphan drugs: Higher P values for small sample sizes; Use of surrogate endpoints, Higher therapeutic benefit is automatically recognised for orphan drugs because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorisation procedure. budget impact is less than €50 million per year for a particular indication		
North America	US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200, 000 persons in the USA' (which equates to approximately 7.5 cases per 10,000 population) 'or meets cost recovery provisions of the act'		
			Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1985 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease. condition of interest in the United States as a surrogate for the lack of profitability."		
				Orphan product, as one that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA		
Asia	Singapore (1)	1(1%)	Orphan Drugs Policy	Allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner.	1991	
	Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.		
			the Korea Ministry of Food and Drug Safety formulates ODs	Drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments or drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD		
	China (2)	2 (2%)		Orphan drugs are defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions.		
				Drug used for diseases affecting fewer than 1 in 10,000		
	Vietnam (1)	1(1%)		Orphan drugs are defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions		

Supplementary Table 7: URDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
Europe	UK			Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population (Hugheset al., 2005)		
			NICE	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1/50,000		
	Alberta		NICE	URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE Alberta).		
	England		Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~1 in 100,000 of the English population)		
	Ontario			An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario		
				ultra-orphan diseases affecting <1/50000 inhabitants		
			(EU regulation 536/2014)	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe		
	England and Wales		NICE	"Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)"		
	Poland			Poland uses the EU definition of 'Ultra-rare being <1 in 50000 people'		Adopted EU definition
				rare disease there are “singular cases” or “individual cases”, which are considered “ultra-rare diseases” (prevalence: <1:10,000), including, for example MuSK-positive myasthenia gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS) "		
				ultra-rare diseases (affecting <20/million persons)"		
				the prevalence can be much lower, leading to the concept of the ,ultra-orphan disease, for diseases with an estimated prevalence of <1 in 50,000 people "		
				Ultra-rare, affecting less than 1 person per 50,000 inhabitants."		

Continent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
				ultra-orphan (prevalence: <1:50,000)		
			NICE Highly Specialised Technology Programme (HSTP) and the SMC	The NICE Highly Specialised Technology Programme (HSTP) and the SMC consider ultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "		

Supplementary Table 8: UODs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopted / developed
				Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or less		
				NICE: applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"		
				Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e.: ultra-orphan drugs)		
				Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence ≤1:50,000) were consistent in most countries.		
	Scotland		The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland		
	England			HST for ultra-orphan indications Euro113,900-341,700/QALY in England		
			WHO	WHO recommends a WTP of <3 times GDP per capita/QALY		
	Scotland			New definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes	Effective from October 2018	
			NICE	No official definition of ,ultra-orphan disorders, has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), who applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"		

Continent	Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopted / developed
			NICE	Currently, no official definition of “ultra-orphan disorders” has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons.		

Supplementary Table 9: Qualitative and Quantitative descriptors and themes

RDs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Theme	Qualitative Descriptors
Nature	1. Disease	Disease nature affecting the pt.	17. Rare
	2. Condition		18. Disable
	3. Disorder		19. Life-Limiting condition
	4. Pathologies		20. Life-threatening
	5. Status		
	6. Severe		21. Substantial cause for early death
	7. Chronic		22. Long-Term Treatment
	8. Serious		23. Debilitating
	9. Intractable	Disease nature affecting the pt.'s Society	24. Considerable reduction in an individual's quality of life
	10. High Complexity		
	11. Medic* (medical, Medicinal, Medically, & Medicine)		
	12. Drugs		
	13. Heterogeneous Group		
Etiology	14. Unknown Etiology		25. Considerable reduction in socio-economic potential
	15. Genetic		
	16. Hereditary		
Quantitative Descriptors			26. Unmet medical needs
Measures	1. Prevalence	Population characteristics	27. Low Prevalence
	2. Absolute # of patients		28. Small number of patients
	3. Incidence		29. Low Occurrence
	4. Incidence rate		30. Rarely afflict the population
	5. Frequency		31. Population
	6. Number of case references		32. People
	7. Threshold		33. Inhabitant* (s)
	8. Range	Indication	34. Treat* (Treatment)
	9. Percentage		35. Prevent* (Prevention)
	10. Estimated measure		

ODs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Themes	Qualitative Descriptors
Nature of Product	1. Medical Product	Unmet Need	21. No alternative treatment
	2. Agent		22. Treatment Price
	3. Biological Products		23. Lack profit

	4. Product		24. Lack of drug development
	5. Pharmaceutical Product		25. Little interest
	6. Active Ingredients not developed, imported, or registered		26. No/limited available therapy
			27. Attractive for commercial development
	7. Drug		
Disease nature affecting the pt.'s Society.	8. Rare Diseases	Benefits from taking the treatments	28. Clinical added value
	9. Life-Threatening Condition		29. Improve safety or efficacy
	10. Debilitating Disease		30. Product will be of significant benefit
	11. Disease with a limited number of specialist treatment centers		31. New drug is significantly better than drugs currently marketed
	12. Serious Condition	Indication	32. Indications
	13. Rare medical condition		33. Diagnosis
	14. Interactable diseases		34. Treatment
	15. Unmet medical needs		35. Prevention
	16. Common disease where the sponsor cannot make any profit		36. Prophylaxis
			37. Rehabilitation
Population Characteristics	17. Low prevalence		
	18. Small number of patients		
	19. Population		
	20. People		
Quantitative Descriptors			
Measures	1. Prevalence		
	2. Cost-effectiveness threshold		
	3. Annual budget impact for a particular indication		
	4. Number of cases reference		
	5. Willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY		

URDs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Quantitative
Nature	1. Disease	**Measurements**	1. Prevalence
	2. Chronic		2. Incidence
Population Characteristics	Very small patient		3. Incidence rate
	Population		4. Estimated measure
	People		
	Persons		
	Inhabitants		

UODs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Qualitative
Nature	1.Very rare conditions	Indication	1. Indications
	2.Medicines		2. Treat
	3.Drug		3. Approved for use
	4.Disease	Population Characteristics	1. Patients
	5.Condition		2. Persons
Theme	Quantitative		3. People
Measurements	1.Prevalence		
	2.Willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY.		

Supplementary Table 10: Qualitative criteria frequently used for RDs, ODs, URDs, and ODs in the definition.

Theme	Qualitative Descriptor	RD	URD	OD	UODs
Nature	1. Disease	148	13	60	2
	2. Condition	30	3	52	4
	3. Disorder	18	1	2	1
	4. Pathologies	1	-	1	-
	5. Status	1	-	2	-
	6. Sever*	5	-	5	-
	7. Chronic	22	1	7	-
	8. Serious	3	-	12	-
	9. Intractable	1	-	1	-
	10. High Complexity	1	-	-	-
	11. Heterogeneous	1	-	-	-
	12. Product	-	-	35	-
	13. Medic* (medical, Medicinal, Medically, & Medicine)	5	-	36	2
	14. Agent	-	-	1	-
	15. Biological Products	-	-	1	-
	16. Pharmaceutical Product	-	-	2	-
	17. Active Ingredient not developed, imported, or registered	-	-	1	-
	18. Drugs	8	-	83	8
Etiology	19. Unknown Etiology	1	-	-	-
	20. Genetic	7	-	1	-
	21. Hereditary	1	-	-	-
Disease nature affecti	22. Rare Diseases	40	4	16	-
	23. Disab* (Disability & Disabling)	5	-	2	-
	24. Life -Limiting	1	-	0	-

Theme	Qualitative Descriptor	RD	URD	OD	UODs
	25. Life-threatening	23	-	20	-
	26. Substantial cause for early death	1	-	0	-
	27. Long-Term Treatment	1	-	0	-
	28. Debilitating	21	-	10	-
Disease nature affecting the pt.'s Society	29. Considerable reduction in an individual's quality of life	1	-	0	-
	30. Considerable reduction in socio- economic potential	2	-	0	-
	31. Unmet medical needs	3	-	3	-
	32. Disease with limited number of specialist treatment centers	-	-	1	-
	33. Common disease where the sponsor cannot make any profit	-	-	1	-
Population Characteristics	34. Low Prevalence	12	-	2	-
	35. Low Occurrence	2	-	-	-
	36. Rarely afflict the population	1	-	-	-
	37. Small number of patients	3	-	1	-
	38. Very small patient Population	-	1	-	-
	39. Population	20	3	7	-
	40. People	29	2	8	2
	41. Inhabitant* (s)	6	2	-	-
Benefits from taking the treatment	42. Clinical added value	-	-	1	-
	43. Improve safety or efficacy	-	-	1	-
	44. Product will be of significant benefit	-	-	2	-
	45. New drug is significantly better than drugs currently marketed	-	-	1	-
Indication	46. Indications	-	-	4	4
	47. Diagnosis	-	-	23	-
	48. Treat* (Treatment)	7	-	55	2
	49. Prevent* (Prevention)	1	-	23	-
	50. Rehabilitation	-	-	1	-
	51. Prophylaxis	-	-	1	-

Supplementary Table 11: Quantitative criteria frequency used of RDs, ODs, URDs, and ODs in the definition.

Theme	Quantitative Descriptor	RD	URD	OD	UOD
Measurements	1. Prevalence	51	10	22	6
	2. Absolute # of patients	1	-	-	-
	3. Incidence	7	1	-	-
	4. Incidence rate	2	1	-	-
	5. Frequency	1	-	-	-
	6. Number of* (cases reference, patients, people, prevalent cases, and individuals)	6	-	5	-

	7. Threshold	3	-	-	-
	8. Estimated measure	5	1	-	-
	9. Range	2	-	-	-
	10. Percentage	3	-	-	-
	11. Cost-effectiveness threshold	-	-	2	-
	12. Annual budget impact for a particular indication	-	-	1	-
	13. willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY	-	-	1	1

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Global Insight into Rare Disease and Orphan Drug Definitions: A Systematic Literature Review

Ghada Mohammed Abozaid[1,2]*, Katie Kerr[1], Hiba Alomary[3], Hussain Abdulrahman Al-Omar[4,5,6], Amy Jayne McKnight[1]

*Corresponding author: gabozaid01@Qub.ac.uk.

Abstract:

Objectives This study sheds light on the available global definitions, classifications and criteria used for rare diseases (RDs), ultrarare diseases (URDs), orphan drugs (ODs), and ultra-orphan drugs (UODs), and provides insights into the rationale behind these definitions.

Design A systematic literature review was conducted to identify existing definitions and the criteria used to define RDs, ODs, and their subtypes.

Data Sources: Searches were performed in the PubMed/Medline, EMBASE, Scopus, and Web of Science (Science and Social Sciences Citation Index) databases covering articles published from 1985 to 2021.

Eligibility Criteria for selecting studies: English-language studies on the general human population were included if they provided definitions or criteria for RDs, ODs, and /or their subtypes without restrictions on publication year, country, or jurisdiction.

Data extraction and synthesis Two independent reviewers conducted the search, screening, and data extraction. Narrative synthesis, content analysis, and descriptive analyses were conducted to

extract and categorize definitions and criteria from these sources. Study quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools.

Results Online searches identified 2,712 published articles. Only 93 articles met the inclusion criteria, with 209 distinct definitions extracted. Specifically, 93 of these articles pertained to 119 RDs, 11 URDs, 67 ODs, and 12 UODs.These definitions varied in their reliance on prevalence-based and other contextual criteria.

Conclusion Prevalence-based criteria alone pose challenges, as disease frequencies differ by country. Establishing country-specific definitions can enhance understanding, support intercountry evaluations, improve healthcare efficiency and access to ODs, and strengthen equity and equality in healthcare. Such efforts would also promote research and development and support better outcomes for patients with complex and rare conditions.

PROSPERO registration number CRD42021252701.

Keywords: rare disease, ultra-rare, orphan drug, ultra-orphan drugs, qualitative, quantitative, healthcare, criteria.

Strengths and limitations

- This systematic literature review, based on PROSPERO International Prospective Register of Systematic Reviews (CRD42021252701) and PRISMA-P, explores criteria for determining RDs and ODs without publication design, year, or regional restrictions.
- Unlike other reviews, this study explored different criteria for defining RDs and ODs issued by different agencies and entities to fulfil their mandates in relation to RDs and ODs.

- The searched articles showed inconsistent terminology, and despite seeking library specialist feedback, some relevant studies might have been missed.
- The results might be subject to biases in publication selection, language, and database.
- A limitation of this study is that it relies only on literature-based definitions, which may not fully capture the regulatory definitions officially adopted by agencies, despite these being the ones directly applicable in in real-world situations.

Background

Rare diseases (RDs) represent a major public health concern requiring more effective interventions to alleviate the burden on patients, carers, health, and social care systems. RDs, sometimes known as 'orphan diseases' [1, 2] and affect a minority of people, are typically medical conditions that are individually identified with low prevalence within a particular population [3]. Globally, RDs affect more than 450 million individuals [4], the majority of whom are disproportionately disadvantaged and lack effective treatment. No multipurpose and universally agreed upon definition of an RD [5] exists, making optimal care difficult; definitions implemented internationally each depend on the context and perspectives of various stakeholders, some of which employ qualitative and/or quantitative criteria. [6]

The qualitative criteria used to define RDs are primarily subjective and include terms such as "life-threatening", "alternative treatment options", "severity of disease", and "neglected". Some of these criteria have major emotional impacts, such as on the severity of the illness, its potential fatality, heritability, or the lack of effective therapies [7]. On the other hand, quantitative criteria to define RDs are objective and measurable in nature and include disease incidence [8] and prevalence [9], which are key indicators for understanding the frequency of disease occurrence within a population. Certain diseases can be labelled rare in one nation but not in another owing to

population genetic variations, environmental or societal influences, or disparities in survival rates across different regions [10]. A lack of sufficient data on which diseases are categorised as rare creates an obstacle in understanding these conditions and proportions and disease coding; ensuring accurate diagnoses; and encouraging pharmaceutical companies [11] to invest in the research and development of medications for these diseases and manufacture orphan drugs (ODs), which, consequently, constitute a considerable challenge in making treatments available and accessible.

Overall, effective therapies are available for fewer than 5% of individuals diagnosed with RDs. The definition of RD is used to determine the eligibility of a medication for a regulatory designation as an OD. This is a status granted to pharmaceutical products that are developed to treat RDs and incentivized by governments and regulatory bodies to encourage product development and production. For instance, pricing preferences, market exclusivity, financial incentives, protocol assistance, grants and research funding, and extended patent protection are different forms of incentives offered to industry.

OD definitions extend across international borders and are frequently linked to RD definitions that are based on epidemiological data for the target disease and economic data for the drug market [5]. Some countries set priorities for RD expenditures and resource allocation to address OD accessibility and help policymakers enhance the efficiency and delivery of ODs [6]. Adopting a universal definition can be challenging due to regional variations in terms of demographic, economic, survival, and sociocultural factors [12]. For example, in Saudi Arabia (SA), there is no multipurpose national definition for RD or OD, which could impact diagnoses, treatment strategies, and resource allocation, highlighting the need for a localized and country-specific definition. Approximately 80% of RDs have a genetic cause, which increases the risk of inherited

autosomal conditions in offspring from consanguineous marriages [13]; in SA, 70% of total marriages are consanguineous, which may increase the prevalence of some genetic diseases [14].

There are considerable challenges associated with the context and practical use of RDs, ODs, and subtype definitions employed by various stakeholders. One significant challenge is the inconsistency in definitions across regions and regulatory agencies. For example, the EU and the US use different prevalence thresholds to define RDs, complicating regulatory frameworks and market access for ODs. This variation also affects clinical trials and research, as the lack of harmonized definitions can hinder data comparability and international collaboration. Moreover, pharmaceutical companies face additional regulatory and pricing barriers due to these differences, which can delay drug approval and patient access. From a patient care perspective, disparities in definitions may lead to inequities in diagnosis, treatment, and access to therapies. OD treatments may not be available to patients in other regions with the same condition, fragmenting advocacy efforts. Finally, economic and ethical considerations, such as cost-effectiveness criteria and the financial burden on healthcare systems, further complicate the practical use of the RD and OD definitions, highlighting the need for harmonization to ensure equitable and efficient healthcare delivery globally for RD patients.

This systematic literature review (SLR) delves into the diverse definitions and criteria used by countries to define RDs, ODs, and their subtypes, providing deeper insight into different factors, encouraging the establishment of robust criteria, and supporting policy deliberations.

Methods

Systematic literature review protocol

The protocol for this SLR [11] was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42021252701) and follows the PRISMA-P [15, 16] guidelines. The PROSPERO template ensures transparency and accountability for SLRs, while the PRISMA-P provides a flowchart for the identification, screening, eligibility, and inclusion phases of the review process.

Search strategy

The PubMed/Medline, EMBASE, Scopus, and Web of Science (Science and Social Sciences Citation Index) databases were queried to answer the research question "What are the criteria for defining RDs, URDs, ODs, and UODs globally?" as in (**Supplementary Table 1**). The search strategies and terms used were identified based on specific inclusion and exclusion criteria. The inclusion criteria included rare disease patients receiving treatment with an OD. The publication year, country, and jurisdiction were not restricted. Studies that were published in English and provided data for the general human population were included.

The exclusion criteria included rare cancers, infectious diseases, poisonings [11], studies focused on specific RDs or ODs, non-English language studies and nonhuman studies. The decision to restrict the search to English-language studies was based on several considerations. First, the majority of high-impact journals publish in English, which is the primary language for scientific communication worldwide. Limiting the search to English ensures that we capture the most relevant and widely recognized studies. Second, the scarcity of resources for translating non-English articles, coupled with the potential for errors when utilizing automatic translation tools, could potentially compromise the reliability and accuracy of data extraction and synthesis processes. Furthermore, language constraints in systematic reviews generally have little effect on the overall conclusions, especially in fields where English-language publications dominate the

literature. For RDs and ODs in particular, the concentration of research and policy discussions in English-speaking or international journals is significant. Restricting the search to English enables a practical, targeted evaluation while maintaining scientific rigor.

Rare cancers were excluded from this review to maintain a focused scope and ensure that the analysis remained manageable and relevant to the broader definitions of RDs and ODs. Rare cancers often follow distinct clinical, regulatory, and research frameworks compared to non-cancerous RDs. These include oncology-specific diagnostic criteria, treatment pathways, and regulatory incentives such as OD designation. Including rare cancers would have introduced complexity, potentially detracting from the broader analysis of non-cancerous RDs and ODs. Additionally, rare cancers are frequently treated as a separate category in both regulatory contexts and the literature. Their exclusion aligns with the rationale detailed in the published protocol [11].

The identified articles subsequently underwent both forward and reverse citation screening. The initial search was conducted in 2021. To ensure the review included the most recent and pertinent studies, updated searches were performed on 31st December 2022 and 31st December 2023. These updates represent a methodological refinement to the original protocol and were undertaken to capture contemporary studies published after the initial search period. This approach reflects our commitment to ensuring comprehensive coverage of relevant literature and providing the most up-to-date evidence in the analysis.

Patient and public involvement

Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Study selection and data extraction

After searching the different databases, studies were selected, and duplicates were removed. To determine the initial eligibility of the studies based on the inclusion and exclusion criteria [11], two rounds of abstract and title screening were performed by two reviewers (GMA and KK) independently. A third reviewer (AM) arbitrated any disputes between GMA and KK, and all decisions were recorded in a Microsoft Excel® spreadsheet. Likewise, for full-text screening, if there were instances of missing or unreported data or if further details were necessary, GMA reached out to the study author(s) to request missing data. The timeframe for a response before excluding the article due to insufficient information was set at 3 weeks.

The extracted data encompassed various elements, including author names, publication information, journal title, study design, organization, country, quality assessment, and reference definitions of RDs and ODs. Additionally, these data encompassed qualitative and/or quantitative criteria used to define RDs, ODs, and their subtypes. The qualitative criteria considered disease features, intended drug use, patient group, therapeutic impact, and regulatory support, offering a comprehensive view beyond numerical values. The quantitative criteria considered numerical thresholds pivotal for regulation, science, and policies, providing precise metrics based on disease prevalence and target demographics. Moreover, the extracted data involved the underlying reasoning for each definition, the status of the definition, and whether the RD and OD definitions were considered by reviewers independently using the Covidence® platform, a web-based platform for conducting SLRs [17, 18].

Quality assessment

The study quality was assessed by GA and KK using the Joanna Briggs Institute (JBI) critical appraisal tools [19, 20] to evaluate the trustworthiness, relevance, and outcomes of published studies conducted independently using a Microsoft Excel® spreadsheet.

Data analysis

A narrative synthesis summarizing the data from the included studies was performed. The preliminary synthesis involved content analysis of the qualitative data, with coding employed to explore themes. Descriptive statistics were performed and included frequencies and percentages to report and summarize the quantitative criteria from the included studies. This process was intended to illustrate the key themes and numerical information presented in these definitions by using two independent coders (GMA and HiA) with different backgrounds; conflicts were resolved through collaborative discussion. The analyses aimed to identify key elements defining RDs, URDs, ODs, and UODs qualitatively and quantitatively.

Ethical Considerations

As this study is a SLR that analysed existing definitions and criteria for RDs, ODs, and their subtypes, ethical approval was not required. The research involved the review of published literature, which did not include direct interaction with human participants or primary data collection. All studies included in the review were openly accessible, and data extraction was conducted from existing publications.

Findings

PRISMA and quality assessment

The initial search yielded 2,712 studies identified from different databases. The published articles spanned from 1985 to 2021. A total of 2019 articles were duplicates and were removed; for example, title and abstract screening excluded 466 studies, and 235 studies were recorded as not relevant to the SLR research questions due to a lack of abstracts (n=27) or were not in English (n=3); instead, they focused on nonhuman (n=2), cancer related RDs (n=19), specific RDs (n=173), or infections (n=5) or poisonings (n=227) (**Supplementary Table 2**). The final review included 93 studies whose full texts were retrieved (**Figure 1**)

A total of 93 articles met the inclusion criteria, and 209 distinct definitions were extracted. Specifically, 93 of these articles mentioned RDs, 11 URDs, 67 ODs, and 12 UODs. Fifty-one studies were considered in the final quality assessment. A full list of included studies is provided in (**Supplementary Table 3**). Likewise, the critical appraisal results for systematic reviews and research syntheses, economic evaluations, text opinion studies, analytical cross-sectional studies, qualitative research, prevalence studies, and cohort studies were outlined and provided in (**Supplementary Table 4**).

Geographical overview of the definitions

A total of 209 definitions were identified in the 93 included articles; these were for RDs (n=119, 56.93%); URDS (n=11, 5.26%); ODs (n=67, 32.06%); and UODs (n=12, 5.75%) (**Figure 2**).

RD and OD definitions were often linked. Nonetheless, the most frequent definition employed for RDs, and ODs was the European Union (EU) definition, accounting for approximately 40% and 24%, respectively, of the cases. EU nations employ both qualitative and quantitative criteria to define RDs as "*diseases that are life-threatening or chronically debilitating illnesses with*

extremely low prevalence (less than 5 per 10,000)" [21, 22]. Similarly, the United States of America (USA) Food and Drug Administration (FDA) defines RDs as *"any ailment or condition that impacts fewer than 200,000 individuals in the USA or that affects over 200,000 people in the USA, with no foreseeable likelihood of recuperating the expenses associated with developing and providing a drug for such a disease or condition through sales of the drug in the USA"* [23, 24]. An OD in the EU is typically defined as *"a pharmaceutical product for diagnosing, preventing, or treating a rare disease"* [25].

The geographical analysis presented in this SLR examined the global distribution of RD (**Supplementary Table 5**), OD (**Supplementary Table 6**), URD (**Supplementary Table 7**), and UOD (**Supplementary Table 8**) criteria used to define them across different geographic regions.

Rare disease definitions

In Europe, 48 studies discussed RD definitions. Specifically, the EU (36), the United Kingdom (UK) (3), Germany (1), Latvia (1), the Netherlands (1), Poland (2), Romania (1), France (2), and Ukraine (1) had studies that defined RDs as diseases with a prevalence of 5 or fewer cases per 10,000 individuals. The UK defines RDs based on a prevalence threshold of fewer than 1 in 2,000 people. In Eastern Europe and Northern Asia, Russia had one article; in Southeast Europe, Southwestern Europe and Asia, Turkey had an article discussing RD definitions, both showcasing differences in prevalence thresholds compared to the EU definition.

In North America, 28 studies were identified, 24 from the USA and 2 from Canada. The USA defines RDs based on a prevalence of less than 200,000 individuals living with an RD. In addition, the Rare Disease Act (RDA) defines RDs based on qualitative criteria indicating that it occurs so

infrequently in the USA that there is no reasonable expectation for the cost of developing and making a drug available in the USA for such a disease or condition to be recuperated from its sales. However, the Canadian Organization for Rare Disorders (CORD) suggested that 1 in 12 Canadians, approximately 2.8 million individuals, might be living with an RD. South America contributed 2 studies—one from Chile and one from Peru—where RDs were defined by disease severity, categorizing them as "life-threatening" and "severely or chronically debilitating" (**Supplementary Table 5**).

Oceania had differing prevalence thresholds according to RD definitions: Australia (10) and New Zealand (1) used a disease prevalence of 1.1 per 10,000 individuals. Australia has established a prevalence rate of 1.16 per 100,000 individuals for an RD. The prevalence threshold for orphan disease designation is 0.9 in 10,000 individuals. The estimated incidence rate is 1 in 10,000 individuals in Australia.

Asian countries (Japan, Taiwan, China, South Korea, Singapore, India, Armenia, and the Philippines) each defined RDs based on varying criteria such as prevalence rates, genetic disorders, disease severity, and incidence thresholds (**Supplementary Table 5**).

In Africa, Egypt and Kenya were the only countries to mention and discuss RD definitions based on specific conditions and disease severity.

The majority of the definitions extracted were from Europe [EU (43%), the UK (22%), France (6%), Poland (5%), Spain (5%), Belgium (4%), Germany (3%), the Netherlands (3%), England (3%), Scotland (3%), Lativa (2%), Italy (2%), and Sweden (2%)], followed by North America [US (35%) and Canada (2%)] and Asia and Oceania [Japan (15%), Australia (12%), Taiwan (9%),

India (6%), South Korea (4%), New Zealand (2%) and Singapore (2%)]. Global perspectives on RD definitions from the World Health Organization (WHO) and Orphanet revealed further variations in prevalence thresholds and disease severity criteria (**Figure 3**). **A summary of RDs definitions is provided based on the country provided in Table 1**

258 **Table 1: A summary of RDs definitions is provided based on the country**

Country, frequency	# of articles; (%)		(RD) definition	Date
US (25)	24 (26%)	Orphan Drug Regulation	Defines RD according to prevalence: ‘‘rare disease’ means any disease or condition that affects less than 200000 persons in the USA’.	1993
		RDA		2002
		ODA	Defined RDs based on qualitative descriptors as follows: ‘the term ‘rare disease or condition’ means any disease or condition which occurs so infrequently in the USA that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug’.	1983
		FDA	Define RD as ‘any disease or condition that affects less than 200000 people in the USA or affects >200000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug’	
Canada (3)	2 (2%)	CORD	Rare disease as one that afflicts less than 1 person in 200 000.	
			Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease	
UK (3)	2 (2%)	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in 2000 people. (i.e., a prevalence of 5 or less per 10,000)	2021
		NHS	Some countries use additional definitions in situations where a condition is not officially defined as rare. classifies all conditions that require specialized medical care as rare if they occur in <500 citizens yearly	
EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000persons in the European Union) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential.	
		European Commission on Public Health	Defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them.	
		Orphan Drug Regulation	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare	141/2000

Country, frequency	# of articles; (%)		(RD) definition	Date
		EMA	prevalence of rare disease < 5/10 000	
France (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)	
Japan (13)	13 (14%)		Japan diseases with a prevalence of 4.0/10,000	
			<50,000 patients in Japan	
			Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment	
			The incidence rate is estimated to be ≤2.5 cases in 10,000 for Japan	
Taiwan (7)	7 (8%)	Taiwan Foundation for Rare Disorders	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical coverage.	2000
		Physically and Mentally Disabled Citizens Protection Act	RD is one type of disability	2001
China (5)	5 (5%)	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences in Newborn babies.	
			Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.	
South Korea (4)	5 (5%)		Prevalence thresholds have been set at less than 1 per 20,000	
			Prevalence threshold: <4.0 in 10,000	
			< 20,000 people in Korea (i.e., <4 per 10,000 population)	
WHO (5)	5 (5%)		Rare disease affects at most 6.5 out of every 10,000 individuals.	
			Frequency of 6.5-10/ 10,000 inhabitants	
			Incidence ranges approximately from 0.65-1% in the whole population.	
			Rare disease as affecting 65/100 000~100/100 000 persons.	
Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic etiology, and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers."	

The Rare Diseases Act (RDA; the Orphan Drug Act (ODA; the Food and Drug Administration (FDA); The Canadian Organization of Rare Diseases (CORD); National Health Service (NHS).

Ultrarare disease definitions

The definitions of URDs primarily originated from the European continent, encompassing the UK, Poland, and North America, and including, e.g., Alberta and Ontario; URDs typically affect ≤1 in 50,000 or fewer individuals within a population. Additional criteria for classifying URDs varied by region and authority. The Advisory Group for National Specialized Services stipulates that in England, the prevalence should be less than 500 individuals affected (~2500/100,000 of the population). The National Institute for Health and Care Excellence (NICE) further narrows this definition, classifying URDs as those with a prevalence of ≤1:50,000 people. Ontario employs a criterion of fewer than 1 in 150,000 live births or new diagnoses per year, while the definition in Poland aligns with the EU definition, designating URDs as affecting fewer than 1 in 50,000 people. URDs may also be termed "singular cases" or "individual cases," given their exceptionally low prevalence (**Supplementary Table 7**). **Based on the country asummary of URDs definitions is provided in Table 2**

Table 2: A summary of URDs definitions is provided based on the country.

Country, frequency		(URD) definition
UK		Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population (Hugheset al., 2005)
	NICE	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000
England	Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~ less than 1/100,000 of the English population)
Ontario		An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario
England and Wales	NICE	"Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)"

Orphan drug definitions

Nineteen studies described OD definitions within Europe, with one from Italy and another from Germany both adopting the European Medicines Agency (EMA) definition, indicating that a drug can be defined as an OD if it is intended for the diagnosis, prevention, or treatment of life-threatening or chronically serious debilitating conditions affecting no more than 5 in 10,000 individuals. Similarly, one study from Italy followed the Italian Medicines Agency (AIFA) criteria, focusing on three aspects: unmet medical needs, clinical added value, and quality of evidence. Moreover, 1 study from Germany suggested that specific health technology assessment (HTA) criteria be used for the definition of ODs; these criteria are associated with higher *p* values when sample sizes are limited, when surrogate endpoints are utilized, when therapeutic benefit is added, and when the annual budget impact for a given indication is less than €50 million.

In North America, there were nine studies, all of which aligned with the USA FDA regulations, indicating that an OD represents a condition affecting fewer than 200,000 persons in the USA or meets the cost recovery provisions.

In Asia, six studies described ODs, one from Singapore, one from Vietnam, and two from China, all of which contributed to the body of evidence on orphan drugs. It was also reported in two studies that the OD Centre in Korea provides medications for diseases affecting fewer than 1 in 20,000 individuals. These encompass illnesses lacking adequate treatments or drugs or drugs that notably enhance safety or efficacy compared to existing alternatives. In contrast, in China, ODs are characterized by their availability as pharmaceutical products or active ingredients that are not developed, imported, or registered due to low commercial returns and unfavourable marketing conditions. These drugs are designated for diseases affecting fewer than 1 in 10,000 individuals.

Similarly, ODs in Vietnam are described by their availability as pharmaceutical products or active ingredients not developed, imported, or registered due to low commercial returns and unfavourable marketing conditions (**Supplementary Table 6**). **A summary of ODs definitions is provided based on the country in Table 3**

301 **Table 3: A summary of ODs definitions is provided based on the country.**

Country, frequency	# of articles; (%)		(RD) definition	Date
EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically and seriously debilitating condition affecting not more than 5 in 10 000 EU people or that it is unlikely that marketing the drug in the EU would generate sufficient benefits for the affected people and for the drug manufacturer to justify the investment	
		NICE	The current NICE appraisal system means orphan drugs that do not meet HTA criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of ¬£30 k/QALY, or ¬£50 k/QALY when end-of-life criteria are met	
		EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs and are referred to as orphan drugs because, the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	(2011c)
		The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union	
		The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered medicine exists	
		Poland	There is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.	
US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200, 000 persons in the USA' (which equates to approximately 6 cases per 10,000 population) 'or meets cost recovery provisions of the act'	
		Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons	

Country, frequency	# of articles; (%)		(RD) definition	Date
			affected by the disease. condition of interest in the United States as a surrogate for the lack of profitability."	
			Orphan product, as one that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA	
Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.	
		the Korea Ministry of Food and Drug Safety formulates ODs	Drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments or drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD	
China (2)	2 (2%)		Orphan drugs are defined by their availability as pharmaceutical products of active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions.	

Ultra-orphan drug definitions

One study from the UK defined UODs as drugs for diseases with an extremely low prevalence, often less than 0.18 per 10,000 individuals. Three studies introduced the NICE definition for "ultra-orphan" drugs as those targeting conditions with less than 1 case per 50,000 persons. These drugs are typically granted approval for the treatment of diseases that affect fewer than 1,000 patients, underscoring their exceptional rarity. In England, the Highly Specialised Technologies (HST) Programme has implemented cost-effectiveness thresholds for UODs, while the WHO provides specific recommendations for cost thresholds. Scotland has introduced a distinct definition that places emphasis on conditions affecting fewer than 1 in 50,000 individuals. Furthermore, Scotland has also redefined its criteria for UODs to facilitate early access programs and streamline reimbursement processes, with a particular focus on conditions impacting approximately 100 individuals. **Table 4 provide a summary of UODs definitions based on the country**

314 **Table 4: A summary of UODs definitions is provided based on the country.**

Country, frequency		(UOD) definition	Date
UK	NICE	Drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"	
Scotland	The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people – approximately 100 people or fewer in Scotland	
England		HST for ultra-orphan indications Euro113,900-341,700/QALY in England	
	WHO	WHO recommends a WTP of <3 times GDP per capita/QALY	
Scotland		New definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes	Effective from October 2018

Qualitative criteria

The review identified 35 qualitative criteria for RDs, 37 for ODs, 7 for URDs, and 11 for UODs. The identified qualitative criteria were categorized into 7 themes related to RDs, URDs, ODs, and UODs: nature, aetiology, disease nature affecting the patients, disease nature affecting the patient's society, population characteristics, benefits from taking the treatment, and indications (**Supplementary Table 9**).

The most frequent qualitative criteria used in defining RDs and URDs were "disease" 148 times and 13 times, respectively, and "condition" 30 times and 3 times, respectively. For ODs and UODs, the most frequent qualitative criteria were "drugs" 83 times and 8 times, respectively, and "medical products" 36 times and 2 times, respectively. In terms of aetiology, the term "genetic" was used 7 times for RDs and once for ODs. Interestingly, "hereditary" was exclusively reported for ODs. The qualitative criterion "life-threatening" was found 23 times and "debilitating" 21 times for RDs, while for ODs, these qualitative criteria appeared 20 and 10 times, respectively. Some qualitative criteria were used to assess the extent of the impact on society, whether the disease was rare or common. The subtheme "low prevalence" appeared 12 times in definitions related to RDs, similarly describing "low-occurrence criteria", "infrequent population affliction", and a "small number of patients with RDs". However, no data pertaining to URDs, ODs, or UODs were identified. Notably, the theme "benefits from taking the treatment" was found to be associated only with ODs. In the indications theme, the qualitative criteria "treatment and prevention" were used repeatedly (55 and 23 for ODs and 7 and 1 for RDs, respectively) (**Supplementary Table 10**).

Quantitative criteria

These quantitative criteria yielded 10 criteria for RDs, five criteria for ODs, four for URDs and three for UODs (**Supplementary Table 9**).

In the context of defining RDs, ODs, and their subtypes, quantitative criteria were less common than qualitative criteria. The most popular metric was "prevalence", rather than "incidence", "incidence rate", "number of cases", "threshold", "estimated measures", "range", "percentage", or "frequency". Quantitative criteria such as "cost-effective threshold" and "annual budget impact for a particular indication", as well as "willingness-to-pay", were exclusively recorded for ODs (**Supplementary Table 11**).

Discussion

This review sheds light on various definitions and criteria used by different countries and stakeholders, provides deeper insights into different elements, promoting the development of strong criteria, and facilitates policy dialogue. The present analyses revealed inconsistency in definitions; regional disparities in RD occurrence range from approximately 5,000 to 8,000 [26]; and various terminologies and criteria used to define RDs, ODs and their subtypes.

Some definitions rely on qualitative criteria, such as disease severity, life-threatening or hereditary nature, or the presence of alternative treatment options [7, 27]. These subjective criteria lack substantial evidence and vary based on the specific organization that uses the term. However, the UK [28] adopts similar criteria to those used by the EMA to define RDs, suggesting a degree of alignment in the RD classification between Europe and the UK. The European Organisation for Rare Diseases (EURORDIS) definition has a broader scope because it includes both RDs and neglected diseases within the

classification of ODs [29]. This inclusion acknowledges diseases that may be neglected even if they are not strictly rare.

Additionally, we observe that historical differences in definitions have had tangible consequences on healthcare outcomes and drug development priorities over recent decades. For instance, the variation in prevalence thresholds between the USA (fewer than 200,000 individuals) and the EU (fewer than 1 in 2,000) has influenced patient eligibility for support and access to treatments, with different thresholds potentially limiting access in regions with more restrictive definitions. These discrepancies have also shaped pharmaceutical investment strategies, as varying definitions impact the perceived market size and economic feasibility of developing treatments for rare diseases in different regions.

There has been controversy surrounding the term "orphan" in the context of ODs, reflecting differences in interpretations across countries. Initially coined in the early 1960s to describe a class of drugs for RDs, the term highlighted the economic disincentives for developing treatments due to limited profitability. However, by the 1990s, government incentives made RD drug development more viable [30]. In the UK, the use of the term "orphan" has been criticized, particularly by Rosalind Hurley of the European Medicines Agency (EMA), who expressed regret over its usage [30]. Despite this criticism, Richter [12] argues that the term is consistent in referring to technologies for RDs. In Australia, ODs refer to medicines, vaccines or in vivo diagnostic agents used to treat, prevent or diagnose or not available to treat, prevent or diagnose another disease [31]. This provides a broader understanding of the term and its application in different regions.

Disease severity is considered a critical criterion in evaluating the impact of ODs on health-related outcomes in patients, considering that diseases can substantially affect both health and health-related quality of life [41]. Haendal et al. [39] recommended that a multitude of overlapping terminologies,

models, and metadata exist for the identification and classification of RDs. Failure to do so can have substantial consequences, affecting drug approvals, market entry prices, and reimbursement recommendations and ultimately impeding patient access to ODs.

Additionally, some definitions depend on quantitative criteria, such as the disease prevalence threshold, which constitutes the favoured epidemiological element utilized in 58% of RD definitions [7]. However, establishing a prevalence threshold poses challenges due to diverse information sources. This challenge is exacerbated by the absence of firmly established diagnostic criteria or coding systems necessary to gather these data [32]. As a result, certain diseases could be deemed rare in one country but not in another owing to genetic population diversity, environmental or societal pressures, and variations in survival challenges across different regions [10].

One study [12] presented a comprehensive overview of RD definitions worldwide, collating 296 definitions from 1109 organizations across 32 international jurisdictions. The findings indicated the common use of terms such as "RDs" and "ODs," while descriptive qualifiers such as "life-threatening" were less prevalent. Moreover, 88% of the investigations specified prevalence thresholds ranging from 5 to 76 cases per 100,000 people, with 66% of jurisdictions adopting thresholds between 40 and 50 cases per 100,000 individuals. The study [12] underscored the substantial diversity in defining RDs across various jurisdictions and organizational structures. This highlights the necessity for standardization, particularly in objective criteria such as prevalence thresholds, while recommending the avoidance of subjective qualifiers to achieve a harmonized definition of rare diseases. Despite the widespread use of terms such as "RDs" and "ODs", the study emphasized the importance of focusing on standardized metrics to ensure clarity and consistency in identifying RDs globally.

This SLR emphasizes the importance of developing a local definition for each country, regardless of the criteria applied. Subjective qualifiers can occasionally provide additional context or complexity to the description of RDs, ODs, and their subtypes. However, relying too heavily on subjective standards may lead to inconsistent results and implementation challenges. For comprehensive definitions of RDs, ODs, and their subtypes, it is better to combine qualitative and quantitative criteria, which should be reviewed and updated periodically.

Additionally, differences in disease classification across regions can lead to significant disparities in patient care, research funding, and access to treatments. For instance, cystic fibrosis [33] is classified as rare in Europe and North America, where it benefits from orphan drug designations, incentivizing pharmaceutical companies to develop treatments. However, in regions where it is less common, the lack of this classification can limit research initiatives and access to specialized care [34]. Similarly, sickle cell anemia is considered rare in the US [35] and UK [35] but is more common in parts of Africa [36], the Middle East [36], eastern and southwestern regions of Saudi Arabia [35], where healthcare systems are better equipped to handle it. In contrast, in countries where sickle cell is classified as rare, patients may face limited treatment options and fewer specialists [37]. These examples highlight how the classification of a disease as rare in one country and common in another can lead to inconsistencies in care, treatment availability, and research focus, underscoring the importance of harmonizing definitions across regions.

In summary, an exploration of the worldwide definitions of RDs, ODs, and their subtypes provides a comprehensive understanding of their complex nature. The diversity in criteria among nations and institutions accentuates the problem of defining them, influenced by genetic variations, societal factors, and regional disparities. This important fact illuminates the critical challenges and factors required to address these conditions and advance the development of treatments for individuals affected by RDs globally.

Recommendations for future use

This study highlights the importance of establishing a country-specific consensus on the definition of the distinctive combination of genetic, phenotypic, and environmental characteristics as well as sociocultural and economic factors. RDs should be linked toto individuals to steer the research and enhance the diagnosis and care of patients with RDs and the availability of treatments [38] based on scientific principles. Qualitative and quantitative criteria and subthemes should be included in the definition. Therefore, understanding the economic and ethical principles of and health care burdens associated with RDs, ODs, and their subtypes is essential for policymakers to shape policies, especially in underdeveloped policy areas. Moreover, there is a need for international collaboration and data exchange to improve the global understanding and treatment of RDs, which in turn can affect pricing, reimbursement, and patient access to ODs. Additionally, more robust evidence is needed to effectively implement the United Nations (UN) 2030 Agenda principles and Sustainable Development Goals of '*leaving no one behind*', '*reducing inequalities*', and '*addressing the needs of those furthest behind first*' to support the RD community.

Conclusion

A comprehensive study on RD, OD and subtype definitions across countries is lacking. In particular, these definitions are considered outdated, with no scientific grounding. There is a need to address problems associated with diseases that impact only a small percentage of the population. These definitions are meant to provide a framework for identifying and supporting the development of ODs. Therefore, local evaluations of qualitative and/or quantitative criteria are needed to shift therapeutic outcomes from treatment to transformative and curative treatment, to gather comprehensive patient data, to accurately determine disease prevalence, and to ensure equity and equality in accessing appropriate

treatments. It is imperative for each country to develop a local definition or reporting system or establish a national registration program. This approach would not only facilitate the collection of vital health information but also foster a more effective health care ecosystem that addresses the needs of individuals affected by these conditions.

Author affiliations

[1]Centre for Public Health, Institute of Clinical Sciences B, Royal Victoria Hospital, Queen's University Belfast School of Medicine, Dentistry and Biomedical Sciences, Belfast, UK. https://orcid.org/0000-0002-8469-8885; https://orcid.org/0000-0002-7482-709X

[2]Pharmacy Practice Department, College of Pharmacy, Princess Nourah bint Abdulrahman University, PO Box 84428, Riyadh, Zip Code: 11451, Saudi Arabia. https://orcid.org/0000-0002-4523-0577 ; email: gaabozeed@pnu.edu.sa

[3]Department of Applied Linguistics, College of Languages, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. https://orcid.org/my-orcid?orcid=0000-0001-7476-0561

[4]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia. https://orcid.org/0000-0002-0765-0466

[5]Health Technology Assessment Unit, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia.

[6]Center of Health Technology Assessment, Ministry of Health, Riyadh, Saudi Arabia.

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Data sharing statement All of the study's data were fully accessible to the author(s), who also bear responsibility for the data's accuracy and integrity. This study has no more unpublished data. There are no more statistics available.

Abbreviations AGNSS= Advisory Group for National Specialised Services; AM= Amy Jayne McKnight; CM= Consanguineous Marriage; CMS= Congenital Myasthenic Syndrome; DOH = Department of Health; EMA= European Medicines Agency; EU= European Union; FDA= Food and Drug Administration, GMA = Ghada Mohammed Abozaid; HiA= Hiba Alomary; HAA= Hussain Abdulrahman Al-Omar; HST= Highly Specialised Technology Programme; JBI= Joanna Briggs Institute; KK = Katie Kerr; NICE= National Institute for Health and Care Excellence; OD= orphan drugs; ORDI = Organization For Rare Diseases India; PNU= Princess Nourah Bint Abdulrahman University; PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RD = Rare Diseases; RDTWG = Rare Diseases Technical Working Group; SA= Saudi Arabia; SLR= Systematic Literature Review; TFRD = The Taiwan Foundation for Rare Disorders; UOD= Ultra- Orphan Drug; UK= United Kingdom; URD= Ultra- Rare disease; US= United States; WHO = World Health Organization; WTP= Willingness To Pay.

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Figure Legends

Figure 1: Description of PRISMA flow chart in **Figure 1**.

Figure 2: Description of of Repeated definitions included in the studies in **Figure 2**

Figure 3: Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence) in **Figure 3**

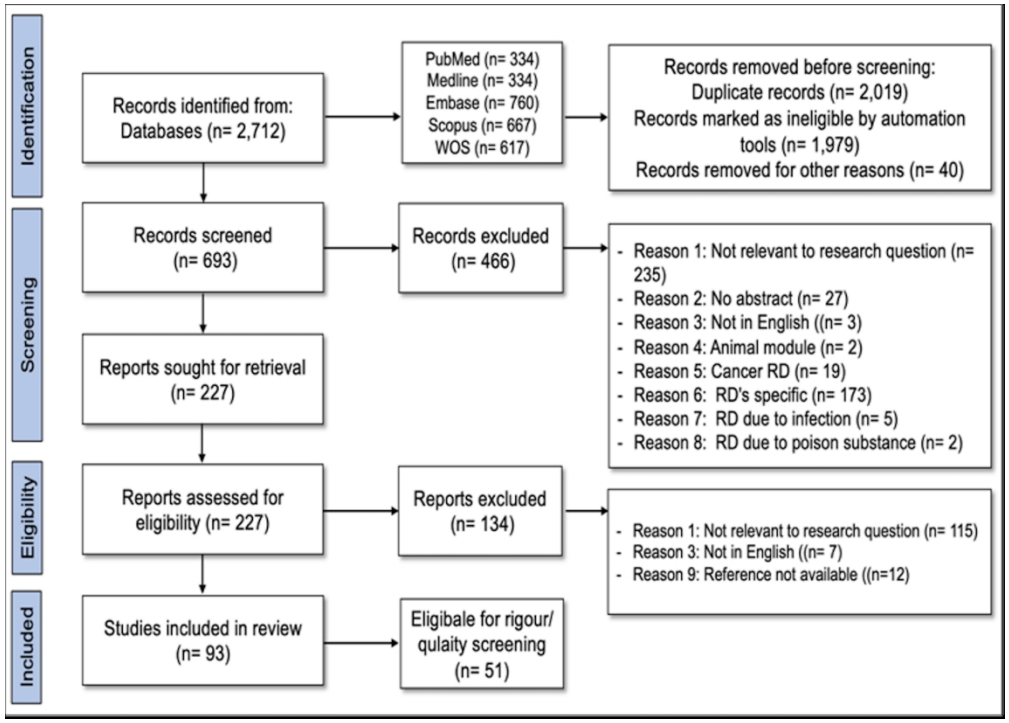

Figure 1. PRISMA flow chart of the study identification and screening process.

117x83mm (762 x 762 DPI)

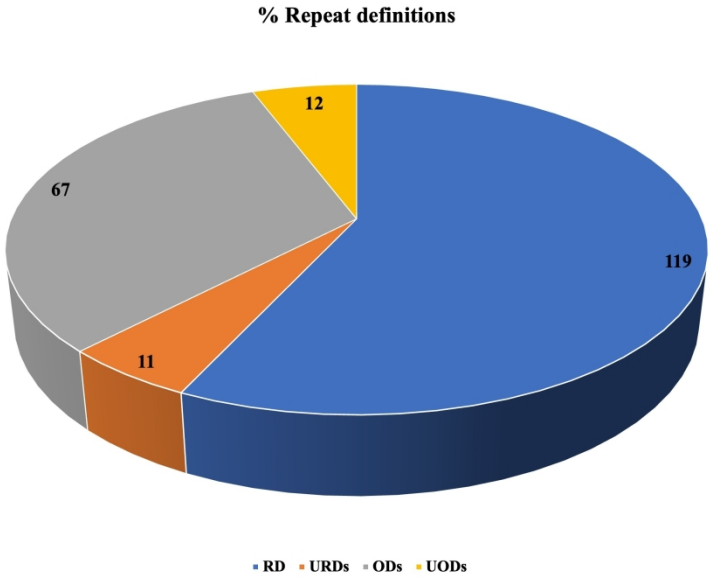

Figure 2. Repeated definitions included in the studies.

224x134mm (330 x 330 DPI)

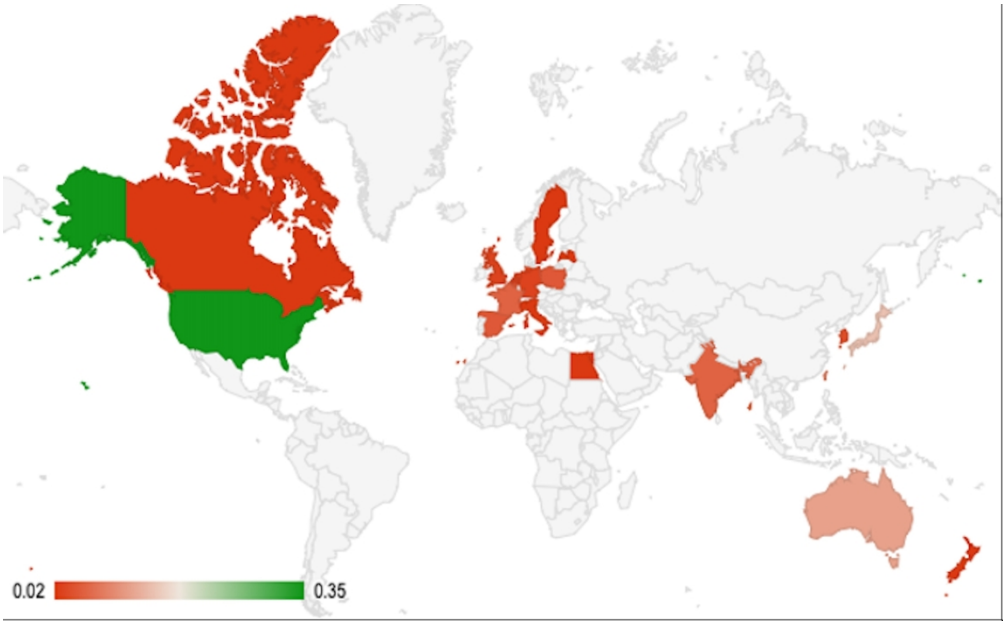

Figure 3. Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence)

117x72mm (762 x 762 DPI)

Supplementary Table 1: Research question: What are the criteria to define Rare Diseases and Orphan Drugs globally?

Concept 1: Criteria / Concept 2: Define/ Concept 3: Rare Disease(s)/ Concept 4: Orphan Drug(s)

	Concept 1	Concept 2	Concept 3	Concept 4	Total	limit to english & human
PubMed	Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]	Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields]	"Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields]	"Orphan Drug Production"[Mesh] OR "Orphan medicinal product*"[All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields]	((((Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]) OR (Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields])) AND ("Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields])) AND ("Orphan Drug Production"[Mesh] OR "Orphan medicinal product*" [All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields])	
	11,155,322	14,855,618	78,992	2,409	435	334
Medline	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1 OR 2 And 3 and 4	
	10,653,511	7,966,623	98,302	2,236	510	334
Embase	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, heading word, drug	1 OR 2 And 3 and 4	

	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	name, keyword, floating subheading word, candidate term word]	Disease*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]		
	13,859,313	10,574,947	160,442	4828	1,010	760
Scopus	TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)	TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)	TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")	TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*")	(TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)) OR (TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)) AND (TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")) AND (TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*"))	
	29,871,274	21,496,075	134,422	4,160	782	667
WOS	ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI., CPCI-S, CPCI-SSH, ESCI.	ALL FIELDS: (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	ALL FIELDS: ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	ALL FIELDS: ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	#7 AND #6 AND #5 Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. ...Less	
	20,665,577	18,096,480	90,196	3,462	646	617
					Total	2,712

Supplementary Table 2: Study Selection and Exclusion Proces
Research question: What are the criteria to define Rare Diseases and Orphan Drugs globally?
Concept 1: Criteria / Concept 2: Define/ Concept 3: Rare Disease(s)/ Concept 4: Orphan Drug(s)

		PubMed		Medline		Embase		Scopus		WOS
Concept 1	Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]	11,155,322	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	10,653,511	(Criteria or Standard* or classification or Measure* or Condition* or Principle* or Requirement* or Scale* or Parameter* or Indicator* or Norm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13,859,313	TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)	21,313,274	ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	20,665,577
Concept 2	Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields]	14,855,618	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7,966,623	(Defin* or Mean* or Description or Character* or Explan* or delineate or detail or interpret or determine or elucidate or illustrate or exemplify).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	10,574,947	TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)	17,[illegible]2,075	ALL FIELDS: (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	18,096,480
Concept 3	"Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields]	78,992	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	98,302	(Orphan disease* or Rare condition* or Rare disorder* or Rare disability* or Neglected disease* or Undiagnosed disease* or Low-frequency disease* or life-threatening disease* or debilitating disease* or severe disease* or intractable disease* or Rare Disease*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	160,442	TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")	134,422	ALL FIELDS: ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	90,196
Concept 4	"Orphan Drug Production"[Mesh] OR "Orphan medicinal product*" [All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields]	2,409	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2,236	(Orphan medicinal product* or Orphan product* or Orphan subset* or Orphan indication* or Highly specialized technolog* or Priority review drug* or Orphan Drug* or Orphan Drug Production*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4828	TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*")	4,[illegible]50	ALL FIELDS: ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*" OR "Orphan Drug*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	3,462

		PubMed		Medline		Embase			WOS
Total	(((Criteria [All Fields] OR Standard*[All Fields] OR classification [All Fields] OR Measure*[All Fields] OR Condition*[All Fields] OR Principle*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields]) OR (Defin*[All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR determine[All Fields] OR elucidate[All Fields] OR illustrate[All Fields] OR exemplify[All Fields])) AND ("Rare Diseases"[Mesh] OR "Orphan disease*"[All Fields] OR "Rare condition*"[All Fields] OR "Rare disorder*"[All Fields] OR "Rare disability*"[All Fields] OR "Neglected disease*"[All Fields] OR "Undiagnosed disease*"[All Fields] OR "Low-frequency disease*"[All Fields] OR "life-threatening disease*"[All Fields] OR "debilitating disease*"[All Fields] OR "severe disease*"[All Fields] OR "intractable disease*"[All Fields])) AND ("Orphan Drug Production"[Mesh] OR "Orphan medicinal product*" [All Fields] OR "Orphan product*"[All Fields] OR "Orphan subset*"[All Fields] OR "Orphan indication*"[All Fields] OR "Highly specialized technolog*"[All Fields] OR "Priority review drug*"[All Fields] OR "Orphan Drug*"[All Fields])	435	1 OR 2 And 3 and 4	510	1 OR 2 And 3 and 4	1,010	(TITLE-ABS-KEY (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*)) OR (TITLE-ABS-KEY (defin* OR mean* OR description OR character* OR explan* OR delineate OR detail OR interpret OR determine OR elucidate OR illustrate OR exemplify)) AND (TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Rare disorder*" OR "Rare disability*" OR "Neglected disease*" OR "Undiagnosed disease*" OR "Low-frequency disease*" OR "life-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")) AND (TITLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*"))	2	#7 AND #6 AND #5 Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. ...Less	646
	limit to english and human	334		334		760	limited to english	6	limited to english	617

Supplementary Table 3: List of included studies

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
1992[18]	USFAD/ Orphan Drug Act, P.L. 97-414, 1983.	Review	This paper examines some of the special problems that are associated with the design and implementation of studies to evaluate the safety and efficacy of orphan drugs.	The legal definition of a rare disease or condition is one that "either (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation than 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.	Orphan drug and biological products are Pharmaceuticals that are generally not considered to be attractive for commercial development. Generally, orphan drug products are used in treating or preventing rare diseases		
2002[19]	United States	Book - Chapter	The information presented is directed both at the fortunate individuals al-ready involved in drug development and at those adventuresome sorts who are considering entering the field. We hope this book will provide readers with in-sights into this exciting arena and begin to explain the complicated process of developing a promising new drug		Orphan products are used to treat rare diseases or conditions that by definition, affect fewer than 200,000 people (or up to 1 in 1300) in the United States.		
2003[20]	United States; Paris, France/ European Medicinal Evaluation Agency	Review	To analyse the American and European experience on the Orphan Medicinal Products.		A medical product can receive the designation of an orphan medical product if it can be established that it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 thousand persons in the EU. American definition of OD not clear		
2004[21]	United States; India, Japan, Australia/ US FDA	Review	This article reviews the bias for classification of orphan drugs, the discovery of orphan drugs, and attempts by pharmaceutical industries, academician (scientist) and practicing physician, with their respective perspectives, advantages and disadvantages in discovery and development of orphan drugs and some historical aspects.	Rare disease or condition is any disease or condition which affects less than two hundred thousand persons in the United States or affects more than two hundred thousand persons in the United States, but for which there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in US.	- Orphan Drugs have been defined in USA as those drugs intended to treat either a rare disease or more common disease where the sponsor cannot make any profit. - As per the definition US FDA, Orphan drugs are those drugs used in diseases or circumstances which occur so infrequently in USA, that there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in the USA. - The availability of orphan drugs to patients before being granted a Marketing Authorization is possible. USFDA designated orphan drug with t-IND (treatment Investigational New Drug) in some cases such as when the drug is intended for the treatment of a serious or life-threatening disease, when no alternative drug or treatment is available, and thirdly, the product is in the process of clinical trials and in an active phase of Marketing Authorization application		
2005[22]	UK, United States, Japan, Australia	Education and debate	We examine the justifications for special status for rare diseases and ask whether the cost effectiveness of drugs for rare or very rare diseases should be treated differently from that of other drugs and intervention.	Definitions of orphan disease: United States diseases with a prevalence of 7.5/10 000; Japan diseases with a prevalence of 4.0/10 000; Australia diseases with a prevalence of 1.1/10 000; and EU diseases with a prevalence of 5.0/10 000.			The UK defines Ultra Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or less
2006[23]	European Union Regulation (EC) No 141/2000	Book - Chapter		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. As a guide, low prevalence is taken as prevalence of less than 5 per 10,000 persons in the European Union [1]"	-The lack of drug development for products intended for the prevention, treatment or diagnosis of rare diseases has made necessary the creation of a number of incentives to stimulate the development of such products. These drugs are known as orphan drugs. - In the EU a medicinal product to treat rare diseases is designated as an orphan medicinal product based on either a demonstrated insufficient return on investment or the rarity of the condition and, the absence of satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorized, or if such method exists, the assumption that the product		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
					will be of significant benefit to those affected by the condition. -Criteria for orphan designation are the following. Firstly, a criterion is based on the low prevalence ("rarity") of the condition, i.e., condition affecting not more than 5 in 10,000 persons in the European Union. Alternatively, the sponsor can apply for more frequent conditions if it can be shown that the development would not be justified by sufficient financial return, i.e., if without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the investment by the sponsor. Secondly, it is necessary for designation that the life-threatening or debilitating nature of the condition is justified. The sponsor is invited to provide any scientific and medical references that may support the life-threatening or seriously debilitating nature of the condition. Finally, the sponsors are also required to demonstrate that either there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question or, if such methods exist, that the medicinal product will be of significant benefit to those affected by that condition.		
2006[24]	USA Orphan Drug Act, European	Policy And Practice	In this paper we propose selection criteria for an Orphan Medicines Model List that could form a departure point for future work towards an extensive WHO Orphan Medicines Programme.	In the USA Orphan Drug Act, the definition relates to an absolute number (<200 000 patients in the USA), while the European regulation uses a relative measure (<5 cases per 10 000 inhabitants) and requires disorders to be life threatening and/or chronically debilitating.			
2008[25]	United States	Book - Chapter		The legislative definition for a rare disease in the United States is one with a prevalence of less than 200,000 persons or, if over 200,000 persons, one for which there is no reasonable expectation of recovering drug development costs within seven years of market approval			
2009[26]	United States of America, Japan, EU, Australia, and Taiwan	Review		A rare disease is defined as a disease or condition affecting fewer than 200,000 persons in the United States of America. <50,000 patients in Japan, The EU defines rare diseases as life threatening or chronically debilitating diseases which are of such low prevalence in 2,000) that special combined efforts are needed to address them. Australia: < 2000 individuals. Taiwan: < 1 in 10,000 people.			
2010[27]	United States/ Orphan Drug Act of 1983	Book	- To provide a convenient repository for the substantial work that has been accomplished by individual investigators treating rare genetic disorders with simple molecules. - To provide a handbook that will enable potential clinician/ scientists and others to rapidly survey the field, thus ascertaining what has been done and what can yet be done.	In that legislation, an orphan disease was defined as a condition that affects fewer than 200,000 Americans." Serious, life-threatening disorders across the age span.	Serious, life-threatening disorders across the age span.		
2010[28]	United States/ Orphan Drug Act	Review			The Act initially defined an orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease or condition of interest in the United States as a surrogate for the lack of profitability.		
2010[29]	United States/ the Office of Rare Diseases Research (ORDR)	Book-Chapter	This chapter will focus on many of the activities of the ORDR and include other significant activities related to rare diseases research and orphan products development	The disorders and conditions in the rare diseases category are defined by the prevalence figure of fewer than 200,000 people in the United States with the specific disease. An estimated 25			

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				million to 30 million people in the United States have a rare disease or condition."			
2010[30]	UK; EU, World Health Organisation, Australia, Japan and the United States	Book-Chapter		-Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual, quality of life or socio-economic potential. -According to the World Health Organisation, a rare disease affects at most 6.5 out of every 10,000 individuals. -Australia, Japan, and the United States have set prevalence's of 1.16, 4.07 and 6.68 per 100,000 individuals respectively for a given rare disease."		
2010[31]	United States/ The Orphan Drug Act	Review			The Orphan Drug Act defined an ,orphan product' as a drug that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA. There are over 6000 conditions that meet the definition of a rare disease		
2011[32]	UK, WHO, US FDA, EU, Japan, Australia:	General review	This article aims to provide a description of principal aspects of policy and practice associated with orphan drugs and treatments of rare diseases and give perspectives for 2011 on new and emerging approaches for addressing patient access." "This article summarizes the current state of international orphan drug patient access and describes developments up to 2011. Emerging policies and practices that will affect patient access in 2011 and beyond are also explored."	-WHO: Frequency of 6.5-10/ 10,000 inhabitants US FDA: Affecting, <7 patients/10,000 residents (estimated to affect about 200,000 patients/year -EU: Affecting ≤ 5 patients/10,000 residents (estimated to affect about 30 million EU citizens) -Japan: Affecting <40/100,000 of the population. -Australia: Affecting <11/100,000 inhabitants or ≤2000Australians	Drugs used in the treatment of rare diseases address significant unmet medical needs and are referred to as orphan drugs because, as described by EURORDIS (2011c) , the pharmaceutical industry has little incentive under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	Ultra-orphan diseases, in the UK, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population	
2011[33]	Spain	Abstract	We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU.		In the European Union (EU), orphan drugs are used for the diagnosis, prevention, or treatment of life-threatening or serious conditions that affect5 in 10,000 people (NOTE THE OVERLAP BETWEEN ORPHAN DRUG AND RARE DISEASE DEFINITION)		
2011[34]	Canada	Abstract	The scope of this study is to describe the ODs regulations in Canada, evidence requirements by the national regulatory agency, national and regional funding criteria, market access challenges associated with ODs, and approaches to obtain access to ODs in Canada.	The Canadian Organization of Rare Diseases (CORD) defines a rare disease as one that afflicts less that 1 person in 200 000.			
2012[35]	Middle East (Egypt, Iran, Turkey, Iraq, Saudi Arabia, Yemen, Syria, United Arab Emirates or UAE, Israel, Jordan, Lebanon, Oman, Kuwait, Qatar, Bahrain, and Cyprus) plus the Palestinian territories of the West Bank and the Gaza Strip	Policy Forum			An orphan drug is a drug developed specifically to treat a rare medical condition		
2012[36]	United States	Editorial		-The terms, orphan diseases, and, rare diseases, are commonly used interchangeably worldwide and have been defined as ,any disease or condition that affects a small percentage of the population. -The US Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, as does Japan.			

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				-The European Commission on Public Health defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. -The definition of ,low prevalence, varies between countries but usually ranges from 1/1,000 to 1/200,000 -The alternative term, orphan disease, is used in reference to a combination of the paucity of treatment availability, lack of resources, and severity of disease.			
2012[37]	United States	Review	- In this article we present the findings of this analysis, which, consistent with the IOM recommendation, are intended to identify factors correlating with rare disease product approvals that could inform future development programs, and to identify areas where additional resources might be directed. - In this work we provide an up-to date analysis of drug, target interactions for approved and clinical trial drugs and examine the major developments and trends in pharmaceutical development - For the purpose of supporting rare disease product development, we undertook an evaluation of CDER, rare disease marketing application history, focusing on a recent five-year period (2006 - 2010).	Rare diseases, which are disorders affecting less than 200,000 persons in the USA, also have considerable unmet medical needs.			
2012[38]	European Union countries	Review	The aim of this study was to quantify both the sales and volume uptake of orphan drugs in Europe and to assess whether a country, gross domestic product (GDP) and/or health technology assessment (HTA) influences the orphan drugs, market uptake.	In the European Union, a rare disease is defined as a life-threatening or chronically debilitating disease with the prevalence among 50 per 100 000 people or less	Orphan drugs are drugs intended for the treatment of rare diseases.		
2012[39]	Singapore, Taiwan, Korea, and China	Meeting Abstract		-Since 1991, Singapore, Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. -The Taiwan Foundation for Rare Disorders helped secure the Rare Disease and Orphan Drugs Act in 2000. Diseases affecting fewer than 1 in 10,000 that are officially recognized are eligible for medical coverage. -In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000. -In China, in 2011, medical professionals called for legislation to support healthcare, research, orphan drug development, and epidemiological studies for diseases affecting fewer than 1 in 10,000	-Since 1991, Singapore, Orphan Drugs Policy allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner. -In Korea, the Orphan Drug Centre supplies medicines for diseases affecting fewer than 1 in 20,000.		
2013[40]	Middle East	Critical Review	We provide a critical review of the literature on the availability of orphan drugs in the Middle East.		An orphan drug is a drug developed specifically to treat a rare medical condition.		
2013[41]	United States; UK; and EU	Review	We examined the characteristics of orphan drug (OD) designations and approvals by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2000 and 2011.		Criteria for Orphan designation is generally based on the number of patients affected by the disease (<200,000 US patients and <5 in 10,000 EU patients). The EU also requires that a satisfactory alternative treatment is not available or that the new drug is significantly better than drugs currently marketed.		
2013[42]	UK	Conference	- The presentation provides a brief review of all supportive incentives in the field of orphan medicinal products as: the European orphan medicinal product (OMP) regulation, Guideline on Clinical Trials in Small Populations and Commission Regulation (EC) No 2049/2005 / support of small and medium enterprises (SMEs)." - It also introduces the concept of Clinical added value of orphan medicinal products, as one of the key instruments to increase the availability of orphan medicinal products in the member states."		- The orphan drug intended for diagnosis, prevention or treatment of a life threatening or chronic debilitating condition. - The prevalence of the condition, for which the OMP (orphan medicinal product) is intended, must be less than 5 in 10,000" - OMP has to fulfil following criteria: 1. Seriousness of the condition the investigated drug must be intended for diagnosis, prevention, or treatment of a life-threatening or chronic debilitating condition.		

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					2. Low prevalence/irretrievable investment: the prevalence of the condition, for which the OMP is intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to generate sufficient return to justify the investment. In some situations, the condition is defined as a subset of another frequent condition. To accept this subset it is needed to prove that the subset is medically recognizable and the investigated OMP is clearly effective only in this subset and not in the condition per se. 3. Medical need No other treatment authorised in EU for this condition or if there is one, the designated OMP must provide a significant benefit over the existing method. The significant benefit is given on the basis of/upon clinically relevant advantage or major contribution to patient EC/847/200		
2013[43]	Taiwan, and Republic of China	Registry data analysis	- This paper aims to describe the prevalence of RDs over time from 2002 to 2011 based on the national RDs registry data in Taiwan". - To describe a general demographic picture of patients with rare diseases in Taiwan and particularly focuses on the prevalence of rare diseases over time, age, and gender distributions.	- Rare disease as a disease whose prevalence is less than 1 in 10,000 in Taiwan. - Taiwan officially included RDs as one type of disability and initiated the RDs disability registry in the social welfare system in 2002 (the Physically and Mentally Disabled Citizens Protection Act, 2001)			
2013[3]	China	Review	In this article, the primary tasks faced by China have been proposed: to call on the government to legislate as soon as possible; to establish information platform of rare diseases and orphan drugs for sharing the global rare diseases resources; to establish Rare Disease Outpatient Service (RDOPS)for improving the level of diagnosis and treatment; to carry out tertiary prevention of the rare diseases; to establish the rare diseases epidemiological surveillance system in our country	- World Health Organization (WHO) defines a rare disease as affecting 65/100 000~100/100 000 persons. A disease is considered as rare when it affects 1 person per 2,000 in Europe, <200 000 people in the United States, <50 000 people (1 person per 2500) in Japan and 1 person per 10 000 in Taiwan. In China, the Chinese Society of Genetic Medicine defines rare disease as 'diseases affect less than one over 500 000 and genetic disorders affect with less than one over 50 000 of the incidences in new-born babies. - Rare diseases are serious chronic diseases, difficulties in obtaining timely, accurate diagnoses and are often life-threatening	Orphan drugs are those intended to diagnose, prevent, or treat rare diseases or pathologies that are serious or life-threatening, and whose development costs are superior to the expected return on investment		
2013[44]	Seven European countries, Belgium	Review	This study aimed to identify, describe, and classify MEAs applied to orphan medicinal products (OMPs) by national payers and to analyse their practice in Europe. The present study, focusing on seven European countries, had three main objectives, namely to: (i) examine the processes through which MEAs are implemented by national healthcare payers, (ii) identify, describe, and classify MEAs applied to OMPs by national healthcare payers, and (iii) analyse and compare identified MEAs related to OMPs within and between countries.	Life-threatening or chronically debilitating diseases with a prevalence of 5 out of 10,000 or less			
2013[45]	United States/ Orphan Drug Act (ODA)	Book - Chapter		- Rare diseases, also referred to as orphan diseases, are defined in the United States (US) by the Orphan Drug Act (ODA) as diseases or conditions that affect fewer than 200,000 persons in the US. - Most rare diseases are serious, life-limiting, or life-threatening conditions	Orphan designated drugs are those that are: intended to treat, prevent, or diagnose diseases or conditions affecting fewer than 200,000 persons in the US; and have shown promise, based on supporting evidence, in the treatment of the disease or condition.		
2013[46]	Netherlands	Research Article	In the Netherlands, we decided to build a registry for patients with metabolic disorders and also to optimize the codes for national use in medical and clinical genetics. With these purposes in mind, we developed, with a dedicated group of clinical specialists, a clinically oriented annotation system for metabolic disorders based on two existing national coding systems.	Rare diseases are life threatening or chronically debilitating diseases with a prevalence of up to five per 10,000 inhabitants in the European Union (EU)			

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2013[47]	China, WHO, United States, Japan, and Australia	Commentary		- A rare disease is referred to as any disease that affects an extremely small percentage of the population. - The World Health Organization (WHO) defines a disease as a rare disease when its incidence ranges approximately from 0.65-1% in the whole population. - Rare disease is identified in the United States (US), Japan, and Australia when it afflicts less than 200,000 (approx. 0.75% of the population), 50,000 (approx. 0.4% of the population), and 2,000 (approx. 0.1% of the population) people, respectively. - Expert consensus indicates that a rare disease could be identified in China when the incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.			
2014[48]	Poland	Abstract	The aim of this study was to identify the cost-effectiveness threshold for an orphan designation in Poland.		- According to criteria specified by the European Medicines Agency (EMA) a medicine must meet 3 criteria to qualify for orphan designation, i.e.: the treatment, prevention or diagnosis of a disease is life-threatening or chronically debilitating; the prevalence level in the European Union (EU) of no more than 5 cases in 10,000 patients is necessary; no satisfactory method of disease diagnosis, prevention or treatment or if such method exists, the drug must still deliver significant benefits to patients. - In Poland there is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.		
2014[49]	UK, US	Review	We aim to highlight how the emergence of omics technologies and the development of integrated , systems medicine, approaches might offer ways to overcome research challenges in rare disease and allow patients to ultimately reap the benefits of better scientific understanding of their condition.	Rare diseases are defined in the European Union as those with a prevalence of < 5 in 10,000 and in the US as diseases that affect fewer than 200,000 US citizens			
2014[50]	Latvia	Conferences	This study aims to determine the trends in reimbursement of ODs in Latvia within the framework of individual reimbursement system in 2008, 2011.	Rare diseases, also related to as orphan diseases, are life-threatening or chronically debilitating conditions of different origin. Disease is considered as rare if it affects not more than 5 in 10 000 people in the EU.	- Orphan drugs (ODs) are medicinal products intended for diagnosis, prevention, or treatment of life-threatening or very serious diseases affecting less than 5 in 10 000 people in the European Union (EU). - These drugs are called ‚orphans, because the pharmaceutical industry has little interest, under normal market conditions, in developing and marketing products intended for only a small number of patients suffering from very rare conditions		
2014[51]	National Institute for Health and Care Excellence (NICE)	Abstract	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000. Medicines for these indications are difficult to develop in part due to challenges associated with recruiting for clinical trials from a small patient population. Within this context, global payer bodies have assessed these therapies with modified evidence requirements and opportunity for very high prices. We performed a health technology assessment (HTA) review of two ultra-orphan products – eculizumab/Soliris and iduronate-2-sulfatase (IDS)/Elaprase – to gain insight into the evolving HTA evidence requirements for ultra-orphan medicines and comparatively evaluate key decision drivers across geographies.			Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1: 50,000.	
2014[52]	Belgium	Qualitative research	The aim of this study is to use a combination of qualitative research methods to examine which official and non-official factors influence reimbursement decisions for orphan drugs in Belgium.	In Europe, rare diseases are defined as life-threatening or chronically debilitating diseases with a prevalence of 50 out of 100000 individuals or less.			

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2014[53]	India, US, Europe, and Japan	Review	An attempt has been made to put forward the challenges faced by rare disease drug development and the current scenario of orphan drug legislations in India. The objective of this review is to look into Indian orphan drug regulations and an emphasis has been laid on Orphan Drugs Act (ODA) of US and orphan drug policies of other developed countries such as Europe, Japan, and Australia, thus showing the requirement of adopting ODA like legislation in India.	- In United States (US), the Orphan Drugs Act (ODA) is a federal law concerning rare diseases that affect fewer than 200,000 people or are of low prevalence (<7.5/10,000 in the community) - A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000) - Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan, definition of rare disease."			
2014[54]	USA, EU, Japan, Australia, Taiwan, South Korea, Alberta, and Ontario	Perspective-workshop	The present paper sets out to explain the rationale underlying a recent expert consensus, recommending a more rigorous assessment of the clinical effectiveness of ultra-rare disorders (URDs,) applying established standards of evidence-based medicine.	- Definitions for, orphan disorders, typically include a criterion of prevalence or incidence and differ somewhat between jurisdictions. - In the USA, these are disorders with a prevalence of less than 200,000 affected persons (according to the Orphan Drug Act of 1983, and Orphan Drug Regulation of 1993) - In the EU, prevalence must be less than 1 per 2000 (or less than 0.05%) of the population (according to EU Regulation CE No. 141/2000 of 2000) - Strict criteria have also been set in Japan (fewer than 4 per 10,000, according to Orphan Drug Regulation of 1993) - Australia (less than 1.1 per 10,000, according to Orphan Drug Policy of 1997) - In Taiwan and South Korea, prevalence thresholds have been set at less than 1 per 10,000 and 1 per 20,000, respectively		- URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE, Alberta). The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~1 in 100,000 of the English population). An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario - No official definition of ‚ultra-orphan disorders, has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE) conditions with a prevalence of less than 1 per 50,000 persons"	National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"
2014[55]	United States	Position Statement	This article examines the trends in public discussion of high-cost drugs and the potential consequences for orphan drug development.	Prevalence of under 200,000 people in the United States	Drugs to treat conditions defined as rare, that is with a prevalence of under 200,000 people in the United States		
2015[56]	United States	Abstract	We assessed trends in approvals of new drugs with orphan indications in the US and in the prevalence of orphan drugs approved by the FDA from 1983 to 2014 compared to non-orphan drug approvals in the same time frame		Orphan drugs are indicated for rare diseases and conditions.		Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e.: ultra-orphan drugs)
2015[57]	Egypt, U.S.	Chapter	We introduce in this study a system that classifies the orphan drugs according to their probability of structural similarity		- Orphan drugs are a treatment for rare diseases. - Orphan drug legislation by the U.S. Food and Drug Administration (FDA) is motivating drug companies to develop drugs that have low development costs in order to treat rare diseases."		
2015[58]	United States (US) and European Union (EU),	Poster/Abstract only	The objective of this research is to identify the number of medicines that have been granted orphan designation in the United States (US) and European Union (EU) and analyse the approval trends over a ten-year time horizon with a specific focus on the number of ODs with an oncology indication.		- OD may be defined as a pharmaceutical product aimed at treating rare diseases or disorders. - OD tend to consider the prevalence of the disease and the estimation of the population affected by the disease. - In the USA a rare disease is defined as: <200,000 patients (<6.37 in 10,000, based on US population of 314m) - In Europe a rare disease is defined as: <5 in 10,000 (<250,000 patients, based on EU population of 506m).		
2016[59]	EU, Germany	Forum	Here we examine the factors that account for these failures and describe a variety of possible remedies. This analysis focuses on the EU perspective, though many findings are relevant toother global markets.		An orphan designation is granted to a product when the prevalence of the treated condition in the EU is not more than 5 in 10,000 or it is unlikely that marketing of the product would generate sufficient returns to justify the investment needed for its development.		
2016[60]	Italy	Review		Rare diseases (RDs), including those of genetic origin, are defined by the European Union (EU) as life-threatening or chronically			

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				debilitating conditions whose prevalence is so low (less than 5 per 10,000)			
2016[61]	UK; (EU15 plus Nordics and Poland)	Abstract	To review HTA requirements currently in place for treatments for rare diseases in selected European countries (EU15 plus Nordics and Poland), to identify and evaluate differences between country requirements.	Definitions of orphan (prevalence ≤5:10,000)			Ultra-orphan drug (prevalence ≤1:50,000)
2016[62]	France	Poster/Abstract only	This study aims to analyse their impact on reassessment with a specific focus on orphan medicines.		Orphan designation is a status assigned to a drug intended to treat a rare condition.		
2016[63]	Japan and Europe	Model	This study focused on the difference of rare disease prevalence between Japan and Europe, classified the rare diseases comprehensively using cluster analysis and analysed the influence of prevalence on research activity and drug development.	Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment	Designated intractable diseases over 50,000 patients are targeted for orphan drug designation in April ,2015 were excluded due to the short implementation. The prevalence was calculated as the rate per 100,000 population using the number of patients with the intractable disease provided by the MHLW website		
2016[64]	Asia-Pacific, Australia, Japan, Singapore, South Korea, and Taiwan	Poster/Abstract only	To evaluate the impact of national orphan drug policy and existing reimbursement mechanisms over the implementation of managed entry agreements (MEAs) for orphan drugs in the context of five Asia-Pacific countries.		- Australia: Prevalence threshold for orphan disease designation: 0.9 in 10,000 - Japan: Prevalence threshold for orphan disease designation: <3.9 in 10,000 - Singapore: Prevalence threshold: 37.7 in 10,000 - South Korea: Prevalence threshold: <4.0 in 10,000 - Taiwan: Prevalence threshold for orphan disease designation: <1 in 10,000"		
2017[65]	Spain	Abstract	Identify if the official criteria of Spanish P&R process are related with P&R approval for ODs.			Ultra-orphan diseases affecting <1/50000 inhabitants	
2017[66]	China	Commentary	The current authors proffered 300,000 to 500,000 cases as a reference threshold with which to define rare diseases in China. This proposal linked the concept of rare diseases with orphan drugs, so it is highly useful in terms of Chinese policymaking on rare diseases	- Disorders with a prevalence less than 1/500,000 or with an incidence less than 1/10,000 among new-borns - More recent - 300,000 to 500,000 cases as a reference threshold with which to define rare diseases in China			
2017[67]	Bulgarian	Text and opinion	- To highlight the possible trends in the further development of requirements for orphan medicines entering the Bulgarian market on the basis of the global situation and trends." - The goals of the current study are to determine the access of orphan medicines to the Bulgarian pharmaceutical market considering the currently available legislation on Health Technology Assessment (HTA) and reimbursement strategies for orphan medicines, the current number of orphan medicines included in the PDL and their total financial burden"		Orphan medicinal products (OMPs) are used in severe life-threatening diseases with no or limited available therapeutic options		
2017[68]	Sweden	Editorial Commentary	Processes related to drug pricing, reimbursement, and thereby availability, vary between countries, thus having implications on patient care. These processes are discussed, with specific focus on three drugs used in paediatric nephrology: a galsidase beta (for Fabry disease), eculizumab (for atypical haemolytic uremic syndrome), and cysteamine bitartrate (for cystinosis).	Rare diseases are severe, chronic, debilitating, and/or life-threatening conditions that are often hereditary and, by definition, affect less than 1 in 2000 individuals in the European Union, or fewer than 200,000 individuals in the USA, at any given time		Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe (EU regulation 536/2014).	
2017[69]	French	Poster/Abstract only	- To explore French stakeholders, policy, implicit or explicit, toward orphan drugs on both Transparency Committee (TC) assessment and pricing decisions - To compare authorities, decisions between two periods of time (2006-2010 and 2011-2016) in order to describe variations on assessment and price lifecycle."	In Europe orphan disease is defined by a prevalence of less than 5 in 10 000 inhabitants which represent a maximum target population of 30 000 patients in France.	An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare disease itself referred to as an orphan disease. Often severe and disabling, affecting a limited number of people (the threshold admitted for the prevalence is 1 in 2000 in Europe).		
2017[70]	Europe	Book - Chapter	Is to bring together the necessary elements for an efficient overall strategy, hence the adoption of Commission Communication COMM (2008) 679 final on 11 November 2008 1. Making rare diseases more visible 2. Encouraging Member States to develop national rare diseases plans in their health policies. 3. Providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared	Rare diseases, are defined by the European Union as life-threatening or chronically debilitating diseases with low prevalence (less than 5 per 10,000).			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
2017[71]	UK, England, and Wales	Poster/Abstract only	The objective of this study was to evaluate National Institute for Health and Care Excellence Highly Specialised Technology (NICE HST) programme evaluations in the context of the changes and assess the potential impact they may have on patient access to ultra-orphan treatments in England and Wales			Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)	
2017[72]	Europe	Research article	Our multidisciplinary working group discussed the most relevant clinical and economic issues that are perceived to complicate the cost-effectiveness evaluation of orphan diseases and orphan medicinal products and to drive the high ICERs. Subsequently potential policy approaches are presented.	Orphan disease is defined in the EU Orphan Regulation 141/2000 (10) as: 1. A disease that is Life-threatening or chronically debilitating. 2. Prevalence of the condition in the EU of less than 5 in 10,000 or unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and 3. No satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorized in the EU, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.			
2017[73]	UK	Research	The aims of this study were to apply the MCDA framework that was proposed by Hughes-Wilson et al. (Orphanet J Rare Dis 7:74, 2012) to a range of orphan drugs in different diseases, with a view to testing the relationship between drug price and aggregated MCDA scores for each product.	Disease with a prevalence of 1 per 2,000 or less			
2018[74]	Sweden	Review	In this work we provide an up-to date analysis of drug target interactions for approved and clinical trial drugs and examine the major developments and trends in pharmaceutical development	Rare diseases are defined in the US as a disease or condition affecting less than one in 200 000 people.	Orphan drugs encompass pharmaceuticals that are intended to treat these types of diseases		
2018[75]	Poland, Netherlands, and Russia	Review	The goal of this article is to provide an in-depth review of rare disease policies and the reimbursement of ODs in 3 European countries, two EU members (Poland, the Netherlands) and a non-EU one (Russia).	Poland uses the EU definition of rare disorders, which considers a disease as rare if it affects less than 1 in 2000 people (< 5 in 10000 people)		Ultra-rare being <1 in 50000 people'	
2018[76]	Poland	Systematic review	The goal of this article is to provide an overview of the current state of knowledge and latest developments in the field of MCDA in HTA for orphan drugs, to review existing models, their design characteristics, as well as to identify opportunities for further model improvement.		The disease prevalence threshold in the EU for an orphan drug designation is well-defined at ≤ 5 per 10.000		
2018[77]	China	Research	The primary objectives are to establish standardization for registration platform, to build biobanks of genomic data, and to create partnerships for data sharing and research collaboration	The United States defines rare diseases as disorders affecting fewer than 200,000 individuals while the European definition is diseases with a prevalence of lower than 5/10,000.	In 2010, at a seminar conducted by the Genetics Society of the Chinese Medical Association, experts mainly in the field of medical genetics proposed that (any diseases of prevalence lower than 1/500,000 in the overall population or 1/10,000 among new-born's should be considered as a rare disease).		
2018[78]	UK, Scotland	Review	This review identified special HTA, and reimbursement considerations introduced for assessment of orphan drugs and implications for manufacturers.		- According to the European Medicines Agency definition, orphan drugs are intended for diagnosis, prevention, or treatment of rare diseases, whose conditions affect no more than 5 in 10,000 persons. - OD proven at marketing authorization if the annual budget impact is less than €30 million per year for particular indication. - Certain special HTA criteria are applied to orphan drugs: 1. Higher P values for small sample sizes 2. Use of surrogate endpoints 3. Additional benefit is considered proven if the budget impact is less than €50 million per year for particular indication. - Higher therapeutic benefit is automatically recognized for orphan drugs because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorization procedure.		- Currently, no official definition of "ultra-orphan disorders" has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons. - In October 2018, a process will be introduced to allow faster access to ultra-orphan drugs: •The Scottish government will introduce a new definition of ultra-orphan medicines that can treat very

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
							rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland
2018[79]	Taiwan, United States, EU, and Japan	Research article	- The objectives of this study were to examine 2003,2014 longitudinal trends in the prevalence and expenditure of rare diseases in Taiwan. We also analysed these trends for two specific rare diseases, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), because ALS is the main targeted rare disease in the ice bucket challenge activity, and MS is another rare disease with similar symptoms to those of ALS. - This study examined the national trends in the prevalence of rare diseases and their health-related economic burden (including medication costs) in Taiwan.	- The general definition of a rare disease in Taiwan is <1/10,000 persons. - In the United States and Japan, a rare disease is one with a prevalence of fewer than 200,000 persons and 50,000, respectively. The EU defines rare diseases as fewer than 5 per 10,000 persons			
2018[80]	UK, England	Poster/Abstract only	This research aims to identify, compare, and evaluate willingness to pay (WTP) thresholds across countries		WHO recommends a WTP of <3 times GDP per capita/QALY		HST for ultra-orphan indications Euro113,900-341,700/QALY in England
2018[81]	Germany	Review	- The valid guidelines and the regulations of the German health system are discussed in this article. - The criteria for indication and monitoring of off-label use are shown, especially focused on the problem of refractory myasthenia gravis.	- Since 2000, diseases with a prevalence of < 5 out of every 10,000 people in the EU have been defined as "rare diseases." - According to a statement by Orphanet regarding **myasthenia gravis** in Europe, this amounts to a prevalence of 1–9/100,000 population.		Rare diseases are "singular cases" or "individual cases", which are considered "ultra-rare diseases" (prevalence: <1:10,000), including, for example MuSK-positive myasthenia gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS)	
2018[82]	United States	Abstract	To estimate the pharmacy budget impact (per member per month [PMPM]) of five orphan drugs with single chronic indications.	There are up to 7,000 rare diseases, defined as a condition affecting fewer than 200,000 people.			
2018[83]	Canada, Scotland, Australia, and New Zealand	Research	The objective of the present study was to analyse the basis for Common Drug Review (CDR) orphan drug recommendations and to compare recommendations to those in other jurisdictions. In the current study we have reviewed CDR recommendations for orphan drugs, defined the parameters involved in decision making, and compared recommendations with those made in Scotland, Australia, and New Zealand.	- (Canada) proposed definition of a rare or orphan disease as one that affects < 1in 2000 persons, a definition aligned to that used in the European Union - Approximately 7000 such diseases have been identified and it is estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease			
2018[84]	Spain	Meeting Abstract	This presentation will review these forces and the multiple business models for pursuing orphan indications that they offer and discuss some of the unique scientific and business aspects that make the orphan space unique, including the crucial central role of rare disease patient organizations.	Rare diseases, which are those affecting <5 in 10,000 people in Europe.			
2018[85]	France	Poster/Abstract only	The aim of this analysis was to discuss ICERs of orphan drugs and their characterizations issued by the CEESP		Orphan drugs according to the Transparency Committee's opinions and designations are typically indicated in conditions that have a prevalence of below 5 in 10,000		
2018[86]	Japan	Symposium	Overview the designation and supporting systems for development of orphan drugs in Japan and foreign country, and introduce our experience of promoting the orphan drug in neuromuscular fields	- Rare diseases are any diseases that affected the relatively small number of patients, and generally chronically debilitating, life threatening. - Rare disease is definitely in the space of unmet medical needs.	Orphan drugs, which are the drugs for rare diseases		
2018[87]	United States	Review	The purpose of this study was to compare published ICER estimates, as a measure of relative value, across several orphan drugs which are indicated to treat rare diseases in paediatrics and adults.	A rare disease was defined as a condition with a prevalence of ≤620/million persons.		Ultra-rare diseases (affecting <20/million persons)"	
2019[88]	United States, WHO, and Europe	Book - chapter		- WHO, orphan disease refers to a disease with a low prevalence of less than 6.5–10 cases in 10,000 people. - USA, orphan disease is defined as one that affects less than 200,000 individuals. - Europe, disease with prevalence of less than 5 in 10,000 people	- Orphan drugs are defined as the drugs used for the diagnosis, prevention, or treatment of orphan disease. - Orphan drugs are those drugs having both orphan and non-orphan indications		
2019[89]	UK	Model	- Our study tested the criteria preferences and possibilities for implementation of the EVIDEM MCDA framework for orphan drugs with a diverse group of 140 stakeholders in Kazakhstan,	Diseases that are life-threatening or chronically debilitating are qualified as rare diseases (RD) in the EU if their prevalence is <5 per 10.000			

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
			Netherlands, Poland, Romania, Russia, Turkey, and Ukraine (KZ, NL, PL, RO, RU, TR, UA). - The purpose of the study was to perform a weight elicitation for the EVIDEM rare disease model (v3.0) in a wider region in Eurasia with a sizeable group of experts (100-200), in order to identify key differences between countries and types of stakeholders as well as to compare weighting results from other studies. A secondary goal was to test the usefulness of a questionnaire tool designed for this purpose.				
2019[90]	UK	Abstract			- For a drug to be appraised via the HST process, it must meet seven criteria, based on: a small and defined distinct patient population, a limited number of specialist treatment centres for the indication in question, treatment price, and severity of the condition. - The current NICE appraisal system means orphan drugs that do not meet HST criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of¬£30 k/QALY, rising to £50 k/QALY when end-of-life criteria are met		
2019[91]	UK	Poster/Abstract only	This research compares NICE Highly Specialised Technologies (HST) appraisal outcomes with corresponding guidance by other European HTA bodies, stratified by payer archetype: cost-effectiveness versus clinical effectiveness			Ultra-orphan disease (prevalence: <1:50,000)	
2019[92]	Italy	Meeting Abstracts	This paper aims to give some insights into the Italian Pricing & Reimbursement (P&R) Policies on Orphan Medical Products (OMPs) highlighting the strengths and weaknesses of the system.		- OMPs are drugs intended for the treatment of seriously conditions affecting less than 5 in 10,000 people in the EU. - AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmet medical needs, clinical added value, and quality of evidence.		
2019[93]	UK (England and Scotland)	Review/ Poster	This research reviewed recent assessments of orphan and ultra-orphan drugs by NICE and the SMC, and disparities in availability for NHS patients between England and Scotland.		Treatments for diseases with a prevalence of <5 in 10,000 in the EU, which are life-threatening or severely disabling and have no satisfactory treatment available, are granted orphan designation by the European Medicines Agency (EMA)		The NICE Highly Specialised Technology Programme (HSTP) and the SMC consider ultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "
2019[94]	UK	Review	This review provides an overview of NIBSC, work in rare diseases and highlights the positive impact of the work of standardization institutions in this field	Rare diseases are defined as conditions not affecting more than 5 in 10,000 people in Europe			
2019[95]	Spain	Review	The present study aims to develop a reflective MCDA framework, based on EVIDEM methodology, with relevant criteria that allows the evaluation and positioning of OD to aid decision-making at the national level in Spain.		Orphan Drugs (ODs) are intended for the diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 (rare diseases) in the European Union (EU).		
2020[96]	India, Organization for Rare Diseases India (ORDI), WHO, EU, US, Japan, and Australia	Review	This review provides a brief account on RDs and their prevalence, followed by a discussion on the major RDs-associated challenges in general, an account on the methods that can be adopted for conducting fruitful molecular genetic studies of monogenic diseases, and the experiences of genetic research in Indian context with a special reference to a genetically vulnerable and low resource region like J&K - India.	- Organization for Rare Diseases India (ORDI) has suggested a threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals in India. - The base prevalence rate of RDs set by the World Health Organization (WHO) is approximately 1 in 2,000 people. - A genetic disorder prevalent in the European Union (EU) is considered rare only if it affects 5 or less per 10,000 cases, whereas the incidence rate for RDs in the United States is 7 or less per 10,000 individuals. These numbers translate to nearly 30 million Europeans and 25 million North Americans (approximately 1 in every 10) affected by any of the known RDs. - The incidence rate is estimated to be ≤2.5 cases in 10,000 and 1 in 10,000 individuals for Japan and Australia, respectively			
2020[97]	Belgium	Position Statement	The current paper aims to set a further step and translate the findings and recommendations from the many existing initiatives into a pragmatic and realistic methodology. The proposed tool will provide guidance to inform multi-stakeholder discussions and		Many of the treatments developed for rare diseases will have an Orphan Medicinal Product (OMP) designation, indicating that they are likely to deliver benefit in an area		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
			reimbursement decision making about specialised treatments for rare diseases." "Additionally, the paper provides guidance on the potential of Real-World Evidence (RWE) ,i.e., data collected outside the context of RCTs to help address such uncertainties.		of high unmet need. Their approval may be based on a small or uncontrolled trial		
2020[98]	Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom.	Systematic Review	This study aimed to create a comprehensive and in-depth overview of rare diseases policies and reimbursement of OMPs in a selection of 12 countries in the Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom. the aim of this article is to bridge the identified gaps by presenting an overview and comparison of current rare disease policies, HTA and reimbursement processes for orphan drugs in a broader range of Eurasian countries.	- The EU has officially defined rare diseases as being rare when they affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) and in most of the selected countries this definition is used [FR, DE, LV, NL, PL, RO, UK, and UA - In Russia the maximum prevalence for a rare disease is defined as 1 in 10,000 - Some countries use additional definitions in situations where a condition is not officially defined as rare, such as in the UK, where the National Health Service (NHS) classifies all conditions that require specialized medical care also as rare if they occur in <500 citizens yearly. - Turkey defines a rare disease when they affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition. - There is no specific definition for ,rare disease, in Armenian legislation, only ,levels of disability, which define whether the patient will receive the necessary medicines for free or not	The Netherlands defines the classification ,orphan drug, as either having an official EU orphan designation or one that targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no registered medicine exists.		Effective from October 2018, Scotland has introduced a new definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes
2020[99]	France	Review	To detect among the drugs approved for limited populations any impact of the orphan status on the assessment outcome of medical benefit (SMR) or improvement in medical benefit (ASMR) carried out by the French authority for health (HAS)	Prevalence of rare disease < 5/10 000 as per EMA"	An orphan designation is granted by EMA for all medicinal drug intended to treat a life-threatening or chronically debilitating disease, provided a maximum prevalence in the Europe of 5/10,000 and when no satisfactory authorised method can be authorised, or, if such a method exists, the medicine must be of significant benefit to patients.		
2020[100]	UK	Commentary	This paper explores the successes and limitation of both the regulation and its implementation mechanisms in the current regulatory context, and suggests some improvements that could maximise its benefits and boost rare disease research even further	- Rare diseases are categorized as ,orphan diseases, because their occurrence in a small number of patients means that, despite apparent high unmet medical need, there is limited scientific understanding, making it difficult to justify the development risk and investment to develop new treatments. - The European Union defines a rare (or ,orphan,) disease as a life-threatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union.		Prevalence can be much lower, leading to the concept of the, ultra-orphan disease, for diseases with an estimated prevalence of <1 in 50,000 people	
2020[101]	India	Abstract	The purpose of this paper is to identify the hurdles in the field of orphan drugs in India and suggest solutions to address the same.	An orphan disease is defined as a condition that affects fewer than200,000 people nationwide	Orphan Drug is used to treat such a condition.		
2020[102]	India	Review	To understand orphan drugs and national policy on treatments of rare diseases. To overview the condition for pricing of orphan drugs in India and government schemes which are helping out for patient needs. To highlight the need of regulations on orphan drugs for sale and manufacture of orphan drugs in India.	A rare disease is a health disorder of low occurrence that affects a limited number of people in the general population as opposed to other prevalent diseases.	Orphan drugs are the drugs and natural products used in treatment, diagnosis, or prevention of rare diseases.		
2020[103]	194 World Health Organization member countries and other areas (Hong Kong, Kosovo, Macau, Palestine, Sahrawi, Republic, Philippines and Taiwan)"	Health Policy Analysis	This study aims to provide an up-to-date global overview of ODP (Orphan drug policies) in the era of innovative medicine and to reflect associated changes in drug regulation policy. This review provides an overview of global policies that optimize development, licensing, pricing, and reimbursement of orphan drugs.	- Rare diseases are typically defined as conditions with limited treatment alternatives, with an average prevalence of fewer than 40 to 50 cases per 100 000 population or that affect a small number of patients compared with the total population. - When defining rare diseases, most countries/ areas adhered to the European Union definition of low prevalence (0.05%), whereas others followed the number of prevalent cases, such as Australia (< 2000), South Korea (<20 000), and the United States (<200 000). Countries/areas such as Chile, Kenya, Peru, and Singapore required the disease severity to be, life threatening, and severely- or chronically-,debilitating. - Rare disease or condition, means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 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	- Orphan drugs are often defined as drugs intended for the treatment, diagnosis, prophylaxis, or rehabilitation of rare diseases. - Orphan drugs are also defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions. Countries/areas such as China and Vietnam acknowledged orphan drug designation from reference competent authorities. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the community when the application is made, or that it is intended for the		

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
				condition will be recovered from sales in the United States of such drug (United States) - Designation of rare diseases: The DOH, upon recommendation of the RDTWG, shall have the authority to designate any disease that is recognized to rarely afflict the population of the country as a rare disease. (The Philippines)	diagnosis, prevention or treatment of life-threatening, seriously debilitating or serious and chronic condition in the community and that without incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment, and (b) that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in the EU that has been authorized in the Community or, if such a method exists, that the medicinal product will be of significant benefit to those affected by that condition. - In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorization in the European Union		
2020[104]	Santiago de Chile	Book - Chapter		- Rare diseases (RDs) or orphan diseases, by definition, are conditions that affect a small number of individuals most RDs are chronic and debilitating and are a substantial cause for disability and early death. - Based on Orphanet, disease inventory, it is evident that the majority of RDs are of genetic etiology, and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers." - RDs are a highly heterogeneous group of disorder			
2020[105]	China, Australia, Japan, South Korea, and Taiwan	Poster/Abstract only	We sought to identify the regulations and policies related to market access for orphan drugs in five major markets from the APAC Region, with the aim of providing an overview of the factors designed to support sponsors of orphan medicinal products. Specifically, we focused on policies in Australia, China, Japan, South Korea, and Taiwan	- "China: Rare disease defined as that affecting less than 1 per 500,000 population. - South Korea: Rare disease defined as that affecting: Less than 20,000 people in Korea (i.e., <4 per 10,000 population) - Japan: Rare disease defined as that affecting: Less than 50,000 people in Japan (i.e., <4 per 10,000 population). - Taiwan: Rare disease defined as that affecting less than 1 per 10,000 population. - Australia: Rare disease defined as that affecting less than 5 per 10,000 population"			
2021[106]	South Korea	Expert Opinion	This paper reviews key factors that should be considered in the process of development, regulation, and market access of orphan drugs in South Korea with a particular focus on the pricing and reimbursement review process.		In South Korea, the Korea Ministry of Food and Drug Safety formulates ODs, which should satisfy two conditions related to the number of patients and the existence of alternatives. In other words, drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments of drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD.		
2021[107]	UK	Review	This review provides an overview of the strengths and limitations of value assessment frameworks (VAFs) for the reimbursement of orphan drugs in Europe and may serve as a guide for decision-makers.	- Rare diseases are a group of diverse diseases, each characterized with low prevalence: occurring in less than one in 2,000 people in Europe. - They are defined as life-threatening or chronically debilitating, and are mostly caused by a genetic predisposition	The, Orphan Medicinal Product Regulation defines OMPs as products for the ,diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union		
2021[108]	Spain	Research	This study aimed to determine the most relevant criteria for the reimbursement of OMPs in Spain, from a multi-stakeholder perspective, and using multi-criteria decision analysis (MCDA). The objective of this study was twofold: first, to review, discuss, and reach a consensus on the most relevant criteria for decision-making about pricing and financing OMPs in Spain; and second, to prioritize them according to their relative importance based on	- Rare diseases are diseases of low prevalence and high complexity that can lead to death or chronic disability. - In Europe, rare diseases are defended as those pathologies that affect less than 5 people per 10,000 inhabitants.	Orphan medicinal products (OMPs), which are intended to diagnose, prevent, or treat rare diseases, have a shared community procedure for being designated as such in the European Union, and this community approach provides opportunities for research, development, and marketing	Ultra-rare, affecting less than 1 person per 50,000 inhabitants."	

Year	Country/ Jurisdiction / Organization	Study design	Aim	Definition			
				RD	OD	URD	UOD
			the preferences stated by different stakeholders, following the MCDA methodology.				
2021[109]	New Zealand	Online survey	The objectives of this study were to measure the relative societal importance of values of New Zealanders in informing drug funding decisions and to determine how New Zealanders trade of funding in various scenarios between common and rare diseases.	A rare disorder is defined by PHARMAC (the Pharmaceutical Management Agency) as affecting less than 1:50,000 people in the New Zealand population, which is a considerably lower prevalence threshold than other nations that are from 5 to 76 per 100,000 people			

Supplementary Table 4: Critical Appraisal Result

Critical Appraisal Result for Systemic Reviews and Research Syntheses studies

Studies	Q1) Is the review question clearly and explicitly stated?	Q2) Were the inclusion criteria appropriate for the review question?	Q3) Was the search strategy appropriate?	Q4) Were the sources and resources used to search for studies adequate?	Q5) Were the criteria for appraising studies appropriate?	Q6) Was critical appraisal conducted by two or more reviewers independently?	Q7) Were there methods to minimize errors in data extraction?	Q8) Were the methods used to combine studies appropriate?	Q9) Was likelihood publicatio s assessed?	Q10) Were recommendations for policy and/or practice supported by the reported data?	Q11) Were the specific directives for new research appropriate?
1. 2018 [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. 2020 [84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. 2021 [110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1. Critical Appraisal Result for Text Opinion studies

Studies	Q1) Is the source of the opinion clearly identified?	Q2) Does the source of opinion have standing in the field of expertise?	Q3) Are the interests of the relevant population the central focus of the opinion?	Q4) Is the stated position the result of an analytical process, and is there logic in the opinion expressed?	Q5) Is there reference to the extant literature?	Q6) Is any incongruence with the literature/sources logically defended?
1.2003 [3]	Yes	Yes	Yes	Yes	Yes	Yes
2.2005 [5]	Yes	Yes	Not applicable	No	Yes	Yes
3.2006 [7]	Yes	Yes	Yes	Not applicable	Yes	No
4.2009 [9]	Yes	Yes	Yes	Not applicable	Yes	Not applicable
5.2010 [11]	Yes	Yes	Yes	Yes	Yes	No
6.2010 [12]	Yes	Yes	Unclear	No	Yes	No
7.2014 [33]	Yes	Yes	Yes	Yes	Yes	Yes
8.2017 [51]	Yes	Yes	Yes	Yes	Yes	Yes
9.2017 [111]	Yes	Yes	Yes	Yes	Unclear	NO
10. 2019 [78]	Yes	Yes	Yes	NO	Yes	Yes
11. 1992 [1]	Yes	No	Yes	NO	Yes	Not applicable
12. 2004	Yes	Yes	Yes	Yes	Yes	Not applicable
13. 2008 [8]	Yes	Yes	Yes	Yes	Yes	NO
14. 2010 [13]	Yes	Yes	NO	NO	Yes	Not applicable

15. 2011 [15]	Yes	Yes	Yes	Yes	Yes	NO
16. 2013 [25]	Yes	Yes	Yes	Yes	Yes	NO
17. 2013 [28]	Yes	Yes	Yes	Yes	Yes	NO
18. 2014 [37]	Yes	Yes	Yes	Yes	Yes	NO
19. 2016 [44]	Yes	Yes	NO	Yes	Yes	NO
20. 2018 [55]	Yes	Yes	Yes	Yes	Yes	Yes
21. 2018 [59]	Yes	Yes	Yes	Yes	Yes	NO
22. 2018 [65]	Yes	Yes	NO	Yes	Yes	NO
23. 2020 [80]	Yes	Yes	Yes	Yes	Yes	NO
24. 2020 [86]	Yes	Yes	Yes	Yes	Yes	NO
25. 2020 [112]	Yes	Yes	Yes	Yes	Yes	NO
26. 2020 [88]	Yes	Yes	Yes	Yes	Yes	NO
27. 2021 [91]	Yes	Yes	Yes	Yes	Yes	Yes
28. 2010 [14]	Yes	Yes	NO	Yes	Yes	No applicable
29. 2018 [61]	Yes	Yes	Yes	Yes	Yes	NO
30. 2021 [91]	Yes	Yes	Yes	Yes	Yes	NO

2. Critical Appraisal Result for Economic Evaluations studies

Studies	Q1) Is there a well-defined question?	Q2) Is there comprehensive description of alternatives?	Q3) Are all important and relevant costs and outcomes for each alternative identified?	Q4) Has clinical effectiveness been established?	Q5) Are costs and outcomes measured accurately?	Q6) Are costs and outcomes valued credibly?	Q7) Are costs and outcomes adjusted for differential timing?	Q8) Is there an incremental analysis of costs and consequences?	Q9) Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Q10) Do study results include all issues of concern to users?	Q11) Are the results generalizable to the setting of interest in the review?
1.2012 [21]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Yes
2.2014 [34]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes
3.2014 [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.2018 [63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.2018 [67]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Yes	No	Yes	Yes
6.2017 [57]	Yes	Yes	Yes	Yes	Yes	Unclear	NO	NO	NO	Yes	Yes

3. Critical Appraisal Result for Analytical Cross-Sectional Studies

Studies	Q1) Were the criteria for inclusion in the sample clearly defined?	Q2) Were the study subjects and the setting described in detail?	Q3) Was the exposure measured in a valid and reliable way?	Q4) Were objective, standard criteria used for measurement of the condition?	Q5) Were confounding factors identified?	Q6) Were strategies to deal with confounding factors stated?	Q7) Were the outcomes measured in a valid and reliable way?	Q8) Was appropriate statistical analysis used?

. 2012 [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
. 2015 [41]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Unclear

4. Critical Appraisal Result for Qualitative Research studies

Studies	Q1) Is there congruity between the stated philosophical perspective and the research methodology?	Q2) Is there congruity between the research methodology and the research question or objectives?	Q3) Is there congruity between the research methodology and the methods used to collect data?	Q4) Is there congruity between the research methodology and the representation and analysis of data?	Q5) Is there congruity between the research methodology and the interpretation of results?	Q6) Is there a statement locating the researcher culturally or theoretically?	Q7) Is the influence of the researcher on the research, and vice- versa, addressed?	Q8) Are participants, their voices adequately represented?	Q9) Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Q10) Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?
1. 2014 [36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. 2021 [92]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
3. 2021 [93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes
4. 2013 [30]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Yes
5. 2019 [59]	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	Yes

5. Critical Appraisal Result for Prevalence Studies

Studies	Q1) Was the sample frame appropriate to address the target population?	Q2) Were study participants sampled in an appropriate way?	Q3) Was the sample size adequate?	Q4) Were the study subjects and the setting described in detail?	Q5) Was the data analysis conducted with sufficient coverage of the identified sample?	Q6) Were valid methods used for the identification of the condition?	Q7) Was the condition measured in a standard, reliable way for all participants?	Q8) Was there appropriate statistical analysis?	Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?
1. 2016 [47]	Yes	Yes	NO	Yes	Yes	Yes	Yes	Yes	Yes
2. 2013 [26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Not applicable

6. Critical Appraisal Result for Cohort Studies

Studies	Q1) Were the two groups similar and	Q2) Were the exposures measured	Q3) Was the exposure	Q4) Were confounding	Q5) Were strategies to deal with	Q6) Were the groups/participants free of the	Q7) Were the outcomes	Q8) Was the follow up time reported and	Q9) Was follow up complete, and if not, were	Q10) Were strategies to address	Q11) Was appropriate

	recruited from the same population?	similarly to assign people to both exposed and unexposed groups?	measured in a valid and reliable way?	factors identified?	confounding factors stated?	outcome at the start of the study (or at the moment of exposure)?	measured in a valid and reliable way?	sufficient to be long enough for outcomes to occur?	the reasons to loss to follow up described and explored?	incomplete follow up utilized?	statistical analysis used?
1. 2018 [61]	Not applicable	Yes	Yes	NO	NO	Yes	Unclear	NO	NO	Yes	Not applicable

Supplementary Table 5: RDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
North America	US (25)	24 (26%)	Orphan Drug Regulation	Defines RD according to prevalence: "rare disease' means any disease or condition that affects less than 200000 persons in the USA'.	1993	developed
			RDA		2002	
			ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare disease or condition' means any disease or condition which occurs so infrequently in the USA that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug'.	1983	
			FDA	Define RD as 'any disease or condition that affects less than 200000 people in the USA or affects >200000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug'		
	Canada (3)	2 (2%)	CORD	Rare disease as one that afflicts less than 1 person in 200 000.		Aligned to EU
				Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease		
South America	Chile (1)	1 (1%)		Required the disease severity to be ,life threatening, and severely- or chronically-, debilitating.		
	Peru (1)					
Europe	UK (3)	2 (2%)	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in 2000 people. (i.e., a prevalence of 5 or less per 10,000)	2021	
			NHS	Some countries use additional definitions in situations where a condition is not officially defined as rare. classifies all conditions that require specialized medical care as rare if they occur in <500 citizens yearly		
	EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000 persons in the European Union) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential.		
			European Commission on Public Health	Defines rare diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them.		
			Orphan Drug Regulation	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare	141/2000	
			EMA	prevalence of rare disease < 5/10 000		
	Germany (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Latvia (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Netherlands (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Poland (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
	Romania (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	France (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Ukraine (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
Oceania	Australia (10)	10 (11%)		Diseases with a prevalence of 1.1/10 000		
				Diseases with a prevalence < 2000 individuals.		
				Australia have set prevalence's of 1.16 per 100,000 individuals for a given rare disease.		
				Affecting <11/100,000 inhabitants or ,≤2000 Australians		
				Prevalence threshold for orphan disease designation: 0.9 in 10,000		
				The incidence rate is estimated to be 1 in 10,000 individuals for Australia		
	New Zealand (1)	1 (1%)	PHARMAC	Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold than other nations that are from 5 to 76 per 100,000 people		
Asia	Japan (13)	13 (14%)		Japan diseases with a prevalence of 4.0/10,000		
				<50,000 patients in Japan		
				Intractable diseases, is a Japan-specific conception of diseases with (i) unknown etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term treatment		
				The incidence rate is estimated to be ≤2.5 cases in 10,000 for Japan		
	Taiwan (7)	7 (8%)	Taiwan Foundation for Rare Disorders	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical coverage.	2000	
			Physically and Mentally Disabled Citizens Protection Act	RD is one type of disability	2001	
	China (5)	5 (5%)	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences in Newborn babies.		
				Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively.		
	South Korea (4)	5 (5%)		Prevalence thresholds have been set at less than 1 per 20,000		
				Prevalence threshold: <4.0 in 10,000		
				< 20,000 people in Korea (i.e., <4 per 10,000 population)		
	Singapore (2)	2 (2%)		Required the disease severity to be life threatening, and severely- or chronically-, debilitating.		
				Prevalence threshold: 37.7 in 10,000		
	India (1)	1 (1%)	ORDI	Threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals.		
	Armenian legislation (1)	1 (1%)		There is no specific definition for rare disease only levels of disability which define whether the patient will receive the necessary medicines for free or not		
	Philippines		The DOH, upon recommendation of the RDTWG,			
Africa	Kenya			Required the disease severity to be ,life threatening, and severely- or chronically- ,debilitating.		

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
Eastern Europe & Northern Asia.	Russia (1)	1 (1%)		Maximum prevalence for a rare disease is defined as 1 in 10,000		
South-eastern Europe & Southwestern Asia	Turkey (1)	1 (1%)		Affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition.		
	WHO (5)	5 (5%)		Rare disease affects at most 6.5 out of every 10,000 individuals.		
				Frequency of 6.5-10/ 10,000 inhabitants		
				Incidence ranges approximately from 0.65-1% in the whole population.		
				Rare disease as affecting 65/100 000~100/100 000 persons.		
	Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic etiology and a smaller percentage is autoimmune or infectious disorders, in addition to some rare cancers."		

The Rare Diseases Act (RDA; the Orphan Drug Act (ODA; the Food and Drug Administration (FDA); The Canadian Organization of Rare Diseases (CORD); National Health Service (NHS); - PHARMAC (the Pharmaceutical Management Agency); Organization for Rare Diseases India (ORDI)

Supplementary Table 6: ODs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
Europe	EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically and seriously debilitating condition affecting not more than 5 in 10 000 EU people or that it is unlikely that marketing the drug in the EU would generate sufficient benefit for the affected people and for the drug manufacturer to justify the investment		
			NICE	The current NICE appraisal system means orphan drugs that do not meet HST criteria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of £30 k/QALY, or £50 k/QALY when end-of-life criteria are met		
			EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs and are referred to as orphan drugs because, the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.	(2011 c)	

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
			The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union		
			The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered medicine exists		
			Poland	There is no specific formal threshold for orphan designations, there is only a general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.		
	Italian (1)	1 (1%)	Medicines Agency (AIFA)	AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmet medical needs, clinical added value and quality of evidence.		
	German (1)	1 (1%)		Certain special HTA criteria are applied to orphan drugs: Higher P values for small patient sizes; Use of surrogate endpoints, Higher therapeutic benefit is automatically recognised for orphan drugs because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorisation procedure. budget impact is less than €50 million per year for a particular indication		
North America	US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200, 000 persons in the USA' (which equates to approximately 6.4 cases per 10,000 population) 'or meets cost recovery provisions of the act'		
			Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1985 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease. condition of interest in the United States as a surrogate for the lack of profitability."		
				Orphan product, as one that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA		
Asia	Singapore (1)	1(1%)	Orphan Drugs Policy	Allows patients with life-threatening and severely debilitating diseases with no other treatment options to access approved drugs prescribed by their practitioner.	1991	
	Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.		
			the Korea Ministry of Food and Drug Safety formulates ODs	Drugs used for a disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate treatments or drugs have not yet been developed, or drugs that significantly improve safety or efficacy compared to existing alternatives, are designated as OD		
	China (2)	2 (2%)		Orphan drugs are defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions.		
				Drug used for diseases affecting fewer than 1 in 10,000		
	Vietnam (1)	1(1%)		Orphan drugs are defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions		

Supplementary Table 7: URDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
Europe	UK			Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 1 in 50,000 of the population (Hugheset al., 2005)		
			NICE	Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1/50,000		
	Alberta		NICE	URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE Alberta).		
	England		Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in England (i.e., ~1 in 100,000 of the English population)		
	Ontario			An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Ontario		
				ultra-orphan diseases affecting <1/50000 inhabitants		
			(EU regulation 536/2014)	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe		
	England and Wales		NICE	"Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)"		
	Poland			Poland uses the EU definition of 'Ultra-rare being <1 in 50000 people'		Adopted EU definition
				rare disease there are “singular cases” or “individual cases”, which are considered “ultra-rare diseases” (prevalence: <1:10,000), including, for example MuSK-positive myasthenia gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS)		
				ultra-rare diseases (affecting <20/million persons)"		
				the prevalence can be much lower, leading to the concept of the ‚ultra-orphan disease, for diseases with an estimated prevalence of <1 in 50,000 people "		
				Ultra-rare, affecting less than 1 person per 50,000 inhabitants."		

Continent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
				ultra-orphan (prevalence: <1:50,000)		
			NICE Highly Specialised Technology Programme (HSTP) and the SMC	The NICE Highly Specialised Technology Programme (HSTP) and the SMC consider ultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "		

Supplementary Table 8: UODs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopted / developed
				Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or less		
				NICE: applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"		
				Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e.: ultra-orphan drugs)		
				Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence ≤1:50,000) were consistent in most countries.		
	Scotland		The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland		
	England			HST for ultra-orphan indications Euro113,900-341,700/QALY in England		
			WHO	WHO recommends a WTP of <3 times GDP per capita/QALY		
	Scotland			New definition for ultra-orphan drugs: ,medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processes	Effective from October 2018	
			NICE	No official definition of ,ultra-orphan disorders, has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), who applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"		

Continent	Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopted / developed
			NICE	Currently, no official definition of “ultra-orphan disorders” has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons.		

Supplementary Table 9: Qualitative and Quantitative descriptors and themes

RDs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Theme	Qualitative Descriptors
Nature	1. Disease	Disease nature affecting the pt.	17. Rare
	2. Condition		18. Disable
	3. Disorder		19. Life-Limiting condition
	4. Pathologies		20. Life-threatening
	5. Status		
	6. Severe		21. Substantial cause for early death
	7. Chronic		22. Long-Term Treatment
	8. Serious		23. Debilitating
	9. Intractable	Disease nature affecting the pt.'s Society	24. Considerable reduction in an individual's quality of life
	10. High Complexity		
	11. Medic* (medical, Medicinal, Medically, & Medicine)		
	12. Drugs		
	13. Heterogeneous Group		
Etiology	14. Unknown Etiology		25. Considerable reduction in socio-economic potential
	15. Genetic		
	16. Hereditary		
Quantitative Descriptors			26. Unmet medical needs
Measures	1. Prevalence	Population characteristics	27. Low Prevalence
	2. Absolute # of patients		28. Small number of patients
	3. Incidence		29. Low Occurrence
	4. Incidence rate		30. Rarely afflict the population
	5. Frequency		31. Population
	6. Number of case references		32. People
	7. Threshold		33. Inhabitant* (s)
	8. Range	Indication	34. Treat* (Treatment)
	9. Percentage		35. Prevent* (Prevention)
	10. Estimated measure		

ODs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Themes	Qualitative Descriptors
Nature of Product	1. Medical Product	Unmet Need	21. No alternative treatment
	2. Agent		22. Treatment Price
	3. Biological Products		23. Lack profit

	4. Product		24. Lack of drug development
	5. Pharmaceutical Product		25. Little interest
	6. Active Ingredients not developed, imported, or registered		26. No/limited available therapy
			27. Attractive for commercial development
	7. Drug		
Disease nature affecting the pt.'s Society.	8. Rare Diseases	Benefits from taking the treatments	28. Clinical added value
	9. Life-Threatening Condition		29. Improve safety or efficacy
	10. Debilitating Disease		30. Product will be of significant benefit
	11. Disease with a limited number of specialist treatment centers		31. New drug is significantly better than drugs currently marketed
	12. Serious Condition	Indication	32. Indications
	13. Rare medical condition		33. Diagnosis
	14. Interactable diseases		34. Treatment
	15. Unmet medical needs		35. Prevention
	16. Common disease where the sponsor cannot make any profit		36. Prophylaxis
			37. Rehabilitation
Population Characteristics	17. Low prevalence		
	18. Small number of patients		
	19. Population		
	20. People		
Quantitative Descriptors			
Measures	1. Prevalence		
	2. Cost-effectiveness threshold		
	3. Annual budget impact for a particular indication		
	4. Number of cases reference		
	5. Willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY		

URDs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Quantitative
Nature	1. Disease	**Measurements**	1. Prevalence
	2. Chronic		2. Incidence
Population Characteristics	Very small patient		3. Incidence rate
	Population		4. Estimated measure
	People		
	Persons		
	Inhabitants		

UODs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Qualitative
Nature	1.Very rare conditions	Indication	1. Indications
	2.Medicines		2. Treat
	3.Drug		3. Approved for use
	4.Disease	Population Characteristics	1. Patients
	5.Condition		2. Persons
Theme	Quantitative		3. People
Measurements	1.Prevalence		
	2. Willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY.		

Supplementary Table 10: Qualitative criteria frequently used for RDs, ODs, URDs, and ODs in the definition.

Theme	Qualitative Descriptor	RD	URD	OD	UODs
Nature	1. Disease	148	13	60	2
	2. Condition	30	3	52	4
	3. Disorder	18	1	2	1
	4. Pathologies	1	-	1	-
	5. Status	1	-	2	-
	6. Sever*	5	-	5	-
	7. Chronic	22	1	7	-
	8. Serious	3	-	12	-
	9. Intractable	1	-	1	-
	10. High Complexity	1	-	-	-
	11. Heterogeneous	1	-	-	-
	12. Product	-	-	35	-
	13. Medic* (medical, Medicinal, Medically, & Medicine)	5	-	36	2
	14. Agent	-	-	1	-
	15. Biological Products	-	-	1	-
	16. Pharmaceutical Product	-	-	2	-
	17. Active Ingredient not developed, imported, or registered	-	-	1	-
	18. Drugs	8	-	83	8
Etiology	19. Unknown Etiology	1	-	-	-
	20. Genetic	7	-	1	-
	21. Hereditary	1	-	-	-
Disease nature affecti	22. Rare Diseases	40	4	16	-
	23. Disab* (Disability & Disabling)	5	-	2	-
	24. Life -Limiting	1	-	0	-

Theme	Qualitative Descriptor	RD	URD	OD	UODs
	25. Life-threatening	23	-	20	-
	26. Substantial cause for early death	1	-	0	-
	27. Long-Term Treatment	1	-	0	-
	28. Debilitating	21	-	10	-
Disease nature affecting the pt.'s Society	29. Considerable reduction in an individual's quality of life	1	-	0	-
	30. Considerable reduction in socio- economic potential	2	-	0	-
	31. Unmet medical needs	3	-	3	-
	32. Disease with limited number of specialist treatment centers	-	-	1	-
	33. Common disease where the sponsor cannot make any profit	-	-	1	-
Population Characteristics	34. Low Prevalence	12	-	2	-
	35. Low Occurrence	2	-	-	-
	36. Rarely afflict the population	1	-	-	-
	37. Small number of patients	3	-	1	-
	38. Very small patient Population	-	1	-	-
	39. Population	20	3	7	-
	40. People	29	2	8	2
	41. Inhabitant* (s)	6	2	-	-
Benefits from taking the treatment	42. Clinical added value	-	-	1	-
	43. Improve safety or efficacy	-	-	1	-
	44. Product will be of significant benefit	-	-	2	-
	45. New drug is significantly better than drugs currently marketed	-	-	1	-
Indication	46. Indications	-	-	4	4
	47. Diagnosis	-	-	23	-
	48. Treat* (Treatment)	7	-	55	2
	49. Prevent* (Prevention)	1	-	23	-
	50. Rehabilitation	-	-	1	-
	51. Prophylaxis	-	-	1	-

Supplementary Table 11: Quantitative criteria frequency used of RDs, ODs, URDs, and ODs in the definition.

Theme	Quantitative Descriptor	RD	URD	OD	UOD
Measurements	1. Prevalence	51	10	22	6
	2. Absolute # of patients	1	-	-	-
	3. Incidence	7	1	-	-
	4. Incidence rate	2	1	-	-
	5. Frequency	1	-	-	-
	6. Number of* (cases reference, patients, people, prevalent cases, and individuals)	6	-	5	-

	7. Threshold	3	-	-	-
	8. Estimated measure	5	1	-	-
	9. Range	2	-	-	-
	10. Percentage	3	-	-	-
	11. Cost-effectiveness threshold	-	-	2	-
	12. Annual budget impact for a particular indication	-	-	1	-
	13. willingness to pay (WTP) of <3 times gross domestic product (GDP) per capita/QALY	-	-	1	1