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

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- 6 Abstract:

- **Background:** Cumulatively, rare diseases (RDs) affect more than 450 million people worldwide;
- 8 there is no universal agreement on what defines an RD. Medications used to prevent, diagnose,
- 9 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
- 14 ultra-orphan drugs (UODs), and provides insights into the rationale behind these definitions.
- 15 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
- 18 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
- 21 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.

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

Search strategy

review process.

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

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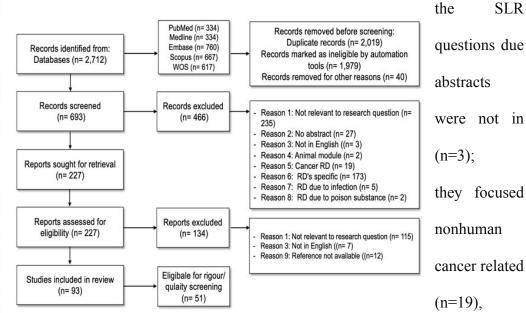
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The initial search yielded 2,712 studies identified from different databases. The published articles spanned from 1985 to 2021. A total of 2019 articles were duplicates and were removed; for example, title and abstract screening excluded 466 studies, and 235 studies were recorded as not relevant to



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)

data mining, Al training, and similar technologies

Protected by copyright, including for uses related

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).

Frequency of repeated definitions extracted from included studies

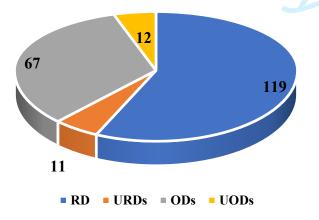


Figure 2. Repeated definitions included in the studies.

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 showcasingdifferences 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.

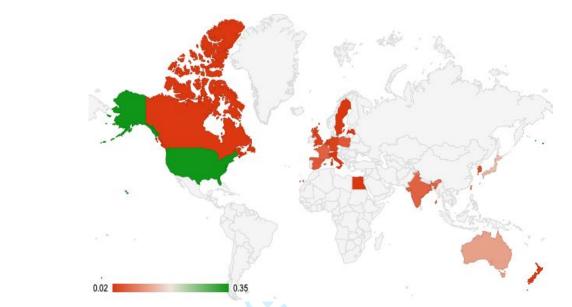


Figure 3. Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence)

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 ϵ 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.

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433	the Medical Research Council. These funders had no role in the development this study.
434	Competing interests None declared
435	Patient and public involvement The research's design, methodology, reporting, or distribution strategies did not
436	involve patients or public.
437	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

Abbreviations AGNSS= Advisory Group for National Specialised Services; AM= Amy Jayne McKnight; CM=

- - the data's accuracy and integrity. This study has no more unpublished data. There are no more statistics available.

 - 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.

References:

- 1. Gorini F, Coi A, Mezzasalma L, Baldacci S, Pierini A, Santoro M. Survival of patients with
- rare diseases: a population-based study in Tuscany (Italy). Orphanet Journal of Rare Diseases.
- 2021;16(1):1-9.
- 2. Repetto GM, Rebolledo-Jaramillo B. Rare Diseases: Genomics and Public Health. Applied
- Genomics and Public Health: Elsevier; 2020. p. 37-51.
- 3. Ma N, Nie W, Wang T, Li C. Current status and countermeasure of the research on rare diseases
- in China. Life Science Journal. 2013;10(2):11-4.
- 4. Forum WE. World Economic Forum Global Data Access for Solving Rare Disease—A Health
- Economics Value Framework 2020 [

- 5. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare disease
- terminology and definitions—a systematic global review: report of the ISPOR rare disease special
- interest group. Value in health. 2015;18(6):906-14.
- 6. Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer
- becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut.
- 2020;69(5):823-9.

- 7. Roeleveld N, Zielhuis GA, Gabreëls F. The prevalence of mental retardation: a critical review
- of recent literature. 1997.
- 8. Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two
- autoimmune bullous diseases: pemphigus and bullous pemphigoid. Archives of dermatological
- research. 2015;307:291-8.
- 9. Abozaid GM, Kerr K, McKnight A, Al-Omar HA. Criteria to define rare diseases and orphan
- drugs: a systematic review protocol. BMJ Open. 2022;12(7):e062126.
- 10. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare Disease
- Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease
- Special Interest Group. Value Health. 2015;18(6):906-14.
- 11. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al.
- Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J
- Hum Genet. 2020;28(2):165-73.
- 12. Alahdal H, Alshanbari H, Almazroa H, Alayesh S, Alrhaili A, Alqubi N, et al. Consanguinity,
- awareness, and genetic disorders among female university students in Riyadh, Saudi Arabia.
- Journal of Biochemical and Clinical Genetics. 2021;4(1):27-34.

- 13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting
- items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic
- reviews. 2015;4(1):1-9.
- 14. Dissementation UoYCfRa. Guidance notes for registering a systematic review protocol with
- PROSPERO. National Institute for Health Research. May 2016.
- 15. Innovation VH. Covidence systematic review software Melbourne, Australia February 4, 2019
- [Available from: https://www.covidence.org/.
- 16. Couban R. Covidence and Rayyan. Journal of the Canadian Health Libraries Association /
- Journal de l'Association des bibliothèques de la santé du Canada. 2016;37.
- 17. Tools CA. Internet. New York: UNICEF multiple indicator cluster surveys Guidelines and
- templates facilitate planning and design of surveys and help avoid pitfalls in implementation [cited
- 2014 Jul 14] Available from: http://www.childinfo.org/mics4_tools.html. 2020.
- 18. Barker TH, Stone JC, Sears K, Klugar M, Leonardi-Bee J, Tufanaru C, et al. Revising the JBI
- quantitative critical appraisal tools to improve their applicability: an overview of methods and the
- development process. JBI Evid Synth. 2023;21(3):478-93.
- 19. Baran A, Czech M, Kooiker C, Hołownia M, Sykut-Cegielska J. Bridging East with West of
- Europe-a comparison of orphan drugs policies in Poland, Russia and the Netherlands. Acta
- Poloniae Pharmaceutica-Drug Research. 2018;75(6):1409-22.
- 20. Regulation OMP. Regulation (EC) No 141/2000 of the European Parliament and of the
- Council of 16 December 1999 on orphan medicinal products. Off J. 2000;18:15.
- 21. Mukherjee S. The United States Food and Drug Administration (FDA) regulatory response to
- combat neglected tropical diseases (NTDs): A review. PLOS Neglected Tropical Diseases.
- 2023;17(1):e0011010.

Protected by copyright, including for uses related

- review of evidence-based clinical practice for rare diseases; what are the perceived and real barriers
- for improving the evidence and how can they be overcome? Trials. 2017;18:1-11.
- 23. Krajnovic D. Ethical and Social Aspects on Rare Diseases. Filozofija i drustvo.
- 2012;XXIII:32-48.

- 24. Kaywanga F, Alimohamed MZ, David AB, Maeda D, Mbarak S, Mayura T, et al. Rare
- diseases in Tanzania: a National Call for Action to address policy and urgent needs of individuals
- with rare diseases. Orphanet J Rare Dis. 2022;17(1):343.
- 25. Simoens S, Cassiman D, Dooms M, Picavet E. Orphan drugs for rare diseases: is it time to
- revisit their special market access status? Drugs. 2012;72:1437-43.
- 26. Vreman RA, de Ruijter AS, Zawada A, Tafuri G, Stoyanova-Beninska V, O'Connor D, et al.
- Assessment of significant benefit for orphan medicinal products by European regulators may
- support subsequent relative effectiveness assessments by health technology assessment
- organizations. Drug Discovery Today. 2020;25(7):1223-31.
- 27. Rode J. Rare diseases: understanding this public health priority. EURORDIS: Paris, France.
- 2005;5(1):3.
- 28. Mikami K. Orphans in the Market: The History of Orphan Drug Policy. Social History of
- Medicine. 2017;32(3):609-30.
- 29. Herkes GK. Orphan drugs in Australia. Expert Opinion on Orphan Drugs. 2016;4(12):1195-
- 7.
- 30. Leadley RM, Lang S, Misso K, Bekkering T, Ross J, Akiyama T, et al. A systematic review
- of the prevalence of Morquio A syndrome: challenges for study reporting in rare diseases.
- Orphanet journal of rare diseases. 2014;9(1):1-17.

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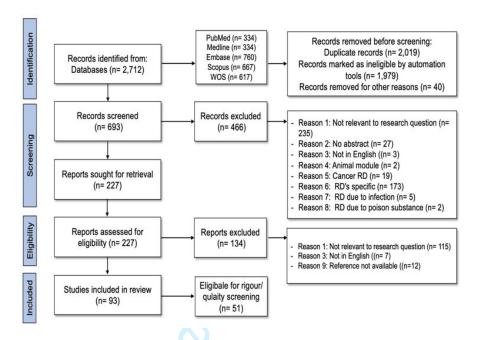


Figure 1. PRISMA flow chart of the study identification and screening process.

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Supplementary Table S1: List of included studies

*7	Country/	Study	A • · · ·		Definition 🚊 🕺		
Year	Jurisdiction / Organization	design	Aim	RD	OD T	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 Pharma Quidalla that are generally not considered to be attractional commercial development. Generally, orphasis and products are used in treating or preventing rare december 1975.		
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 dispersion on ditions that by definition, affect fewer than 2000 people (or up to 1 in 1300) in the United States and a conditions of the United States and a condition of the United States and a		
2003[20]	United States; Paris, France/ European Medicinal Evaluation Agency	Review	To analyse the American and European experience on the Orphan Medicinal Products.	eet.	A medical product can receive the designation and orphan medical product if it can be established that it intended for the diagnosis, prevention, or treatment iffe-threatening or chronically debilitating affecting not more than 5 in 10 thousand person if 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 the drug intended to treat either a rare disease or more common disease where the sponsor cannot make any production of the definition US FDA, Orphan drugs are those drugs used in diseases or circumstances which accurate infrequently in USA, that there is no remanable expectation that the cost of developing and makingly available, a drug for such disease or condition will be recovered from its sales in the USA. - The availability of orphan drugs to patients between the drug and the drug with the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is intended for the treatment of a serious when the drug is the drug the		
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.	hnologi	4	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 interest of the prevention, treatment or diagnosis of rare diseases has made necessary the creation of a number of incentives to stimulate the development of succeptions. 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 of treatment of the condition concerned is authorized, or if such method exists, the assumption that the product of the product of the condition of the condi		

	Country/	Study	,,		80		
Year	Jurisdiction / Organization	design	Aim	RD	OD CI	URD	UOD
	O gallization		~O		will be of significant benefit to those affected by the condition. -Criteria for orphan designation are the following instructions in the condition in the condition, i.e., condition affecting not more than 5 in 10,000 persons in the European Union. Alternatively a criterion is based on the low prevalence ("ind") of the condition, i.e., condition affecting not more than 5 in 10,000 persons in the European Union. Alternatively a can be shown that the development would not be conditionably sufficient financial return, i.e., if without incention is unlikely that the marketing of the medicinal condition in the Community would generate sufficient that is in the Community would generate sufficient that is in the Community would generate sufficient that is in the Community of the sponsor. Second calculations are in the condition in justified that is justified in the sponsor is invited to provide any scientific and calculations or seriously debilitating nature of the condition in justified the sponsors are also required to demonstrate the sponsors are also required to dem		
					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.	the sponsors are also required to demonstrate the sponsors are as required there exists no satisfactory method of demonstrate prevention, or treatment of the condition in question of such methods exist, that the medicinal production of significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to those affected by that conditions are significant benefit to the conditions are significant benefit t		
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	bmjoper Al trainin		
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.	Sy. Al training, and similar tegan. Serious, life-threatening disorders across the agonologasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the Act initially defined an orphan drug on the gasis of the gasis of the Act initially defined an orphan drug on the gasis of the gas		
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 and a constant of the const		
2010[28]	United States/ Orphan Drug Act	Review			The Act initially defined an orphan drug on the asis of unprofitability: one intended for the diagnosis, the unprofitability: one intended for the diagnosis, the unprofitability: one intended for the diagnosis, the unprofitability of a red diagnosis, the unprofitability of a red diagnosis, the unprofitability of the unprofitability of the diagnosis of a red diagnosis of a red diagnosis of the unprofitability. The Act initially defined an orphan drug on the diagnosis of a red diagnosis of a red diagnosis of a red diagnosis of the diagnosis of 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	bliographique		
			For peer review o	nly - http://bmjopen.bmj.com/site/ab	Ω		

	Country/	Study		Definition 🗒			
Year	Jurisdiction / Organization	design	Aim	RD	OD c S	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."	on 25 January 2025. De Enseignement en uses related to		
2010[31]	United States/ The Orphan Drug Act	Review	0/0		The Orphan Drug Act defined an ,orphan production that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United Science of Science	4	
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 ≤2000 Australians	Drugs used in the treatment of rare diseases significant unmet medical needs and are referred orphan drugs because, as described by EUERPHY (2011c), the pharmaceutical industry has little 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.	10,	In the European Union (EU), orphan drugs are the diagnosis, prevention, or treatment of life-thanceming or serious conditions that affects in 10,000 people (NOTE THE OVERLAP BETWEEN ORPHANDRUGAND RARE DISEASE DEFINITION)	<u> </u>	
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.	and sim		
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 gies. An orphan drug is a drug developed specifically gies.	4	
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.			
			For peer review o	nly - http://bmjopen.bmj.com/site/ab	out/guidelines.xhtml		

				BMJ Open	cted by copyrigh	36/bmjopen-2024		Page
Year	Country/ Jurisdiction /	Study design	Aim	RD	Definition OD	080	URD	UOD
	Organization			-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.		27 on 25 January Ensei	CALL)	
012 ^[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.	אמופע וכי ופאנ מווע עמ	7 on 25 January 2025. Downloaded fi Enseignement Superieur ()		
012[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 treatmend diseases.	AGES)		
012 ^[39]	Singapore, Taiwan, Korea, and China	Meeting Abstract	ussessment (1111) intucties the orphan ungs, market uptake.	-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 Police patients with life-threatening and severely ded diseases with no other treatment options to approved drugs prescribed by their practitiones. -In Korea, the Orphan Drug Centre supplies me for diseases affecting fewer than 1 in 20,000.	Dallowo Bitating		
)13 ^[40]	Middle East	Critical	We provide a critical review of the literature on the availability of orphan drugs in the Middle East.	10,000	An orphan drug is a drug developed specifically rare medical condition.	treat a		
013 ^[41]	United States; UK; and EU	Review 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 base number of patients affected by the disease (<200 patients and <5 in 10,000 EU patients). The requires that a satisfactory alternative treatment available or that the new drug is significantly be drugs currently marketed.	00 USD U also is not er than		
)[3[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, preverteatment of a life threatening or chronic deb condition. - The prevalence of the condition, for which the (orphan medicinal product) is intended, must than 5 in 10,000" - OMP has to fulfil following criteria: 1. Seriousness of the condition the investigat must be intended for diagnosis, prevent treatment of a life-threatening or debilitating condition.	te druge tion, ob		

V	Country/	Study	A 2-11		3		
Year	Jurisdiction / Organization	design	Aim	RD	OD CL S	URD	UOD
			~O		2. Low prevalence/irretrievable investment the prevalence of the condition, for which the MP is intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to prevalence sufficient return to justify the investment an some situations, the condition is defined as a moset of another frequent condition. To accept the sufficient recognizable and the investigated OMP with recognizable and the i		
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)	is one, the designated OMP must provide a significant benefit over the existing method. The significant street is given on the basis of/upon clinically chemical advantage or major contribution to patient except the existing method. The significant street is given on the basis of/upon clinically chemical advantage or major contribution to patient except the existing method in the patient of the existing method in the patient of the patient of the existing method in the patient of th		
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 newborn 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, present, on 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	treat rare diseases or pathologies that are serious or life threatening, and whose development costs are superior to the expected return on investment Similar technology Orphan designated drugs are those that are: in superior to the control of		
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	treat, prevent, or diagnose diseases or condition 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)	ence Biblio		
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	Country/	Study			Definition = 2		
Year	Jurisdiction / Organization	design	Aim	RD	OD CL		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.	on 25 January 202: Enseigner ding for uses related		
2014 ^[48]	Poland	Abstract	The aim of this study was to identify the cost-effectiveness threshold for an orphan designation in Poland.	ee _r to	According to criteria specified by the Lincolar Medicines Agency (EMA) a medicine must me a ricci criteria to qualify for orphan designation, treatment, prevention or diagnosis of a disease the life-threatening or chronically debilitating the prevalence level in the European Union (EU) ob progression of the series of the s		
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	Al trainin		
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 actended for diagnosis, prevention, or treatment of life threatening or very serious diseases affecting less than in 10 000 people in the European Union (EU). - These drugs are called ,orphans, becage the pharmaceutical industry has little interest, under market conditions, in developing and marketing products intended for only a small number of attentions 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.		echnologies.	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.	BDE		
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Year	Jurisdiction / Organization	design	Aim	RD	OD CL	URD	UOD
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." 	7 on 25 Janu En Iding for use		
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 ultrarare 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	ary 2025. Downloaded from http://bmjope. seignement Superieur (ABES) . s related to text and data mining, Al training.	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 ,ultraorphan disorders, has yet been adopted globally. Rather, this informal subcategory was	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 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 cost orded to treat rare diseases."		
2015[58]	United States (US) and European Union (EU),	Poster/Abstra ct 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 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: 4200,000 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		
2016 ^[60]	Italy	Review		Rare diseases (RDs), including those of genetic origin, are defined by the European Union (EU) as life-threatening or chronically	investment needed for its development.		

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	Country/	Study			Definition		
Year	Jurisdiction / Organization	design	Aim	RD	OD CL	URD	UOD
				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)	y for u		Ultra-orphan drug (prevaler ≤1:50,000)
2016[62]	France	Poster/Abstra ct 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 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 the targeted for orphan drug designation in April were excluded due to the short implementation credit. The prevalence was calculated as the rate per 1000 population using the number of patients with the religion.		
2016[64]	Asia-Pacific, Australia, Japan, Singapore, South Korea, and Taiwan	Poster/Abstra ct 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.	00.	- Australia: Prevalence threshold for orphan disease designation: 0.9 in 10,000 - Japan: Prevalence threshold for orphan designation: <3.9 in 10,000 - Singapore: Prevalence threshold: 37.7 in 10,000 South Koray: Powalence threshold: <40 in 10,000 South Koray: Powalence threshold: <10 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.		nin SES	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	- Taiwan: Prevalence threshold for orphan risesses designation: <1 in 10,000"		
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"	61	life-threatening diseases with no or limited mailable 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	ilar techno	Liltro rara dispassas hava a	
2017 ^[69]	French	Poster/Abstra ct 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 beed developed specifically to treat a rare dised itself referred to as an orphan disease. Often seed 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).	pout/quidalines yhtml		

bjective of this study was to evaluate National Institute for an and Care Excellence Highly Specialised Technology EHST) programme evaluations in the context of the changes seess the potential impact they may have on patient access to orphan treatments in England and Wales nultidisciplinary working group discussed the most relevant all and economic issues that are perceived to complicate the ffectiveness evaluation of orphan diseases and orphan inal products and to drive the high ICERs. Subsequently tital policy approaches are presented. ims of this study were to apply the MCDA framework that roposed by Hughes-Wilson et al. (Orphanet J Rare Dis 7:74, to a range of orphan drugs in different diseases, with a view ting the relationship between drug price and aggregated A scores for each product.	Prophan 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. Disease with a prevalence of 1 per 2,000 or less	Orphan drugs encompass pharmaceuticals that intended to treat these types of diseases	URD Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)	UOD
bjective of this study was to evaluate National Institute for a and Care Excellence Highly Specialised Technology EHST) programme evaluations in the context of the changes seess the potential impact they may have on patient access to sprphan treatments in England and Wales multidisciplinary working group discussed the most relevant al and economic issues that are perceived to complicate the ffectiveness evaluation of orphan diseases and orphan inial products and to drive the high ICERs. Subsequently inial policy approaches are presented. ims of this study were to apply the MCDA framework that roposed by Hughes-Wilson et al. (Orphanet J Rare Dis 7:74, to a range of orphan drugs in different diseases, with a view ting the relationship between drug price and aggregated A scores for each product.	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. Disease with a prevalence of 1 per 2,000 or less	Enseignement Superie Enseignement Ens	URD Ultra-orphan conditions are defined as diseases affecting <1000 people in England and Wales by the National Institute for Health and Care Excellence (NICE)	UOD
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al and economic issues that are perceived to complicate the ffectiveness evaluation of orphan diseases and orphan inal products and to drive the high ICERs. Subsequently inal policy approaches are presented. ims of this study were to apply the MCDA framework that roposed by Hughes-Wilson et al. (Orphanet J Rare Dis 7:74, to a range of orphan drugs in different diseases, with a view ting the relationship between drug price and aggregated A scores for each product.	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. Disease with a prevalence of 1 per 2,000 or less	nuary 2025. Download Enseignement Superie ses related to text and		
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		ed fro ur (A data		
s work we provide an up-to date analysis of drug target ctions for approved and clinical trial drugs and examine the 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 a intended to treat these types of diseases		
oal of this article is to provide an in-depth review of rare e policies and the reimbursement of ODs in 3 European ries, two EU members (Poland, the Netherlands) and a non- te (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)	ig, Altr	Ultra-rare being <1 in 50000 people'	
oal of this article is to provide an overview of the current of knowledge and latest developments in the field of MCDA A for orphan drugs, to review existing models, their design steristics, as well as to identify opportunities for further limprovement.	101	The disease prevalence threshold in the EU for appropriate drug designation is well-defined at ≤ 5 per 10.0 mg.		
primary objectives are to establish standardization for ration platform, to build biobanks of genomic data, and to 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.	of the Chinese Medical Association, experts main in the field of medical genetics proposed that (any discusses of prevalence lower than 1/500,000 in the overall pendiation or 1/10,000 among new-born's should be considered as O		
review identified special HTA, and reimbursement lerations introduced for assessment of orphan drugs and actions for manufacturers.		prevention, or treatment of rare disease 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 prophardrugs: 1. Higher P values for small sample sizes 2. Use of surrogate endpoints 3. Additional benefit is considered proven if the budged 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 proven significant additional therapeutic benefit compared without the provided of the possibly already approved drugs as part of the other possibly already approved drugs as part of the provided that the provided in the provided that the provided in the provided that the		-Currently, no offic definition of "ultra-orph disorders" has been adopt globally. This inform subcategory was introduc by the National Institute of Health and Care Excellen (NICE), which applied it drugs with indications of conditions with a prevalen of less than 1 per 50,0 persons. -In October 2018, a proce will be introduced to allk faster access to ultra-orph drugs: •The Scotti government will introduce new definition of ultra-orph medicines that can treat ve
primar ration partne	y objectives are to establish standardization for platform, to build biobanks of genomic data, and to reships for data sharing and research collaboration w identified special HTA, and reimbursement in introduced for assessment of orphan drugs and	y objectives are to establish standardization for platform, to build biobanks of genomic data, and to reships 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. We identified special HTA, and reimbursement introduced for assessment of orphan drugs and	The United States defines rare diseases as disorders affecting from platform, to build biobanks of genomic data, and to reships 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. 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 15/10,000. 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 15/10,000. 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 15/10,000. The United States defines rare diseases as disorders affecting fewer than 200,000 individuals while the European definition is different to the constitution of 1/10,000 among new-born's should be considered as rare disease. The United States defines rare diseases as disorders affecting fewer than 15/00,000 in the overall pollutions or 1/10,000 among new-born's should be considered as rare disease. The United States defines rare diseases as disorders affecting fewer than 15/00,000 in the overall pollution or 1/10,000 among new-born's should be considered as rare disease. The United States defines rare diseases as disorders affecting fewer than 15/00,000 in the overall pollution or 1/10,000 and nong new-born's should be considered as rare disease. The United States defines rare diseases with a prevalence lower than 15/00,000 in the overall pollution or 1/10,000 and nong new-born's should be considered as rare disease. The United States defined as rare diseases. The United States defined reference felled of medical as rare diseases. The United States defined special Pollution or 1/10,000 and nong new-born's should be considered as r	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. 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. 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. 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. 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. The United States defines rare diseases as disorders affecting fewer than 200,000 individuals while the European definition is different to reveal prevalence lower than 1/500,000 in the overall problem of 1/10,000 among new-born's should be considered to considered the considered of 1/10,000 among new-born's should be considered for 1/10,000 among new-born's should be considered for degrois as 0 revealence lower than 1/500,000 in the overall problem of 1/10,000 among new-born's should be considered for 1/10,000 among new-born's shoul

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					ding fo		rare conditions affectin fewer than 1 in 50,00 people—approximately 10 people or fewer in Scotland
I	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	iding for uses related to	2025 0	
	UK, England	Poster/Abstra ct only	This research aims to identify, compare, and evaluate willingness to pay (WTP) thresholds across countries		WHO recommends a WTP of <3 times CPP Capita/QALY		HST for ultra-orpha indications Euro113,900 341,700/QALY in England
	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.	and data mining	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 concenital	
	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.	_	!	
I	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	Al training, and sim		
	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.	ila	3	
	France	Poster/Abstra ct 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 opinions and designations are typically indicated in conditions that have a prevalence of below 5 in 12,000 of		
l	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	•	
	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 \$\leq 620\text{/million persons.}\$	Š.	Ultra-rare diseases (affecting	
	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	D D	
	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			
	WHO, and Europe	chapter	-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,	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 Diseases that are life-threatening or chronically debilitating are qualified as rare diseases (RD) in the EU if their prevalence is <5	diagnosis, prevention, or treatment of or Orphan drugs are those drugs having be non-orphan indications	gs used for the orphan disease. It is both orphan and	gs used for the proposed of th

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37.	Country/	Study	A:		Definition 📜 🗟		
Year	Jurisdiction / Organization	design	Aim	RD	Definition :	URD	UOD
	Š		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.		7 on 25 Januar Ense Iding for uses I		
2019[90]	UK	Abstract	TO _L		meet seven criteria, based on: a small and supplied in distinct patient population, a limited number of specialist treatment centres for the indication in question, treatment price, and severity of the coding of that do not meet HST criteria go through the xangar technology appraisal (TA) process, with a criteria control of criteria are met		
2019[91]	UK	Poster/Abstra ct 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	004	a n Br. or	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.	Ch.	OMPs are drugs intended for the treatment of course conditions affecting less than 5 in 10,000 people. The EU. AIFA may grant a medicine the status of impostative 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.	61	Treatments for diseases with a prevalence of <5 art 0,000 in the EU, which are life-threatening or severely are abling and have no satisfactory treatment available, are arranted orphan designation by the European Medicines Agence (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	sim		
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 denoised prevention, or treatment of life-threatening very serious conditions that affect no more than 5 in 0,000 (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	e 7, 2025 at Agence B nnologies.		
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 of the control of		

				BMJ Open	cted by copyrigh		Page 4
Year	Country/ Jurisdiction /	Study	Aim		Definition	00	
	Organization	design	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	RD	of high unmet need. Their approval may be based on a small or uncontrolled trial	2	UOD
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 1 n 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 ,orplands of targets a disease with a prevalence of <1 in 150 mpm as either having an official EU orphan designation of targets a disease with a prevalence of <1 in 150 mpm as Supper ieur registered medicine exists.		Effective from October 2: Scotland has introduced a definition for ultra-org drugs: "medicines that are to treat a condition wit prevalence of 1 in 50,000 less or around 100 peopl Scotland, which will most! used to facilitate early ac programs and reimburser 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 drug intended to treat a life-threatening or changed debilitating disease, provided a maximum prevention Europe of 5/10,000 and when no satisfactory at method can be authorised, or, if such a method ests, 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 ummet 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 lifethreatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union.	Al training, an	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 than 200,000 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 product assed in treatment, diagnosis, or prevention of rare disease.	3	
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 rehabilition or rare diseases Orphan drugs are also defined by their availability a pharmaceutical products or active ingredings 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 of treatment of a life-threatening or chronically debilitating condition affecting not more than five it 10 thousand persons in the community when the application is made, or that it is intended for the	0 7 2025 at Agence Bibliog	

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	Country/	Study					
Year	Jurisdiction / Organization	design	Aim	RD	OD och	URD	UOD
			10p	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 a life-threatening, seriously debilitating or serious and chronic condition in the community and that ithout incentives it is unlikely that the marketing of the medicinal product in the community would senerate sufficient return to justify the necessary in suf		
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	as an orphan medicinal product, the spond submit an application to the Agency at any stage of the development of the medicinal product be recurrently application for marketing authorization is not produced from European Union Cata mining		
2020[105]	China, Australia, Japan, South Korea, and Taiwan	Poster/Abstra ct 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"	http://bmjopen.bmj.co S) . ning, Al training, and s		
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 Strugger of Safety formulates ODs, which should satisfied to conditions related to the number of patients and the existence of alternatives. In other words, drugs used for disease with 20,000 or fewer patients (population with the disease) and diseases for which adequate transmitted or drugs have not yet been developed, or dress 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	significantly improve safety or efficacy compared to existing alternatives, are designated as OD. The, Orphan Medicinal Product Regulation telepines OMPs as products for the diagnosis, prevention, of 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 disabilityIn Europe, rare diseases are defended as those pathologies that affect less than 5 people per 10,000 inhabit	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 provide opportunities for research, development, and marketing opportunities for research opportunities fo	Ultra-rare, affecting less than 1 person per 50,000 inhabitants."	

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Year	Country/ Jurisdiction /	Study	Aim		Definition	.080 t, in		
1 cai	Organization	design	Aiiii	RD	OD	652 nclu	URD	UOD
			the preferences stated by different stakeholders, following the MCDA methodology.			di 7		
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		27 on 25 Janu Er uding for uses		
				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 Note: The perfect of the perfect		ary 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l seignement Superieur (ABES) . s related to text and data mining, Al training, and similar technologies.		

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Supplementary Table S2: Critical Appraisal Result

Critical Appraisal Result for Systemic Reviews and Research Syntheses studies

0 1 2 3 Studies 4 5 6	Q1) Is the review question clearly and explicitly stated?	Q2) Were the inclusion criteria appropriat e 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	s d is ? nuar 2025 Bownfoaded f Enseignement Superieur (, ses related to text and dat	Q10) Were recommendation s 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	from (ABES)	Yes	Yes
2. 2020 [84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	ղ <mark>այ</mark> ES	Yes	Yes
3. 2021 [110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	ing	Yes	Yes
2 1. Critical Appraisal Result for Text Opinion studies											

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 intergrate?	Q6) Is any incongruence with the literature/sources logically defended?
1.2003 [3]	Yes	Yes	Yes	Yes	₹es o	Yes
2.2005 [5]	Yes	Yes	Not applicable	No	Tes J	Yes
3.2006 [7]	Yes	Yes	Yes	Not applicable	es 5	No
4.2009 [9]	Yes	Yes	Yes	Not applicable	es 7	Not applicable
5.2010 [11]	Yes	Yes	Yes	Yes	7, 2025 Ologies	No
6.2010 [12]	Yes	Yes	Unclear	No	02! 9 7 es	No
7.2014 [33]	Yes	Yes	Yes	Yes	Ϋ́es ည	Yes
8.2017 [51]	Yes	Yes	Yes	Yes	Yes >	Yes
9.2017 [111]	Yes	Yes	Yes	Yes	Unclea ©	NO
10. 2019 ^[78]	Yes	Yes	Yes	NO	Yes 🕻	Yes
3 11. 1992 ^[1]	Yes	No	Yes	NO	Yes 👿	Not applicable
12. 2004	Yes	Yes	Yes	Yes	Yes E	Not applicable
13. 2008 [8]	Yes	Yes	Yes	Yes	Yes 💪	NO
14. 2010 [13]	Yes	Yes	NO	NO	Yes 🚨	Not applicable

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3 15. 2011	Yes	Yes	Yes	Yes	<u>₹</u> es 6	NO
4 16. 2013	Yes	Yes	Yes	Yes	7 es 6 5	NO
5 17. 2013	Yes	Yes	Yes	Yes	a es 7	NO
6 18. 2014	Yes	Yes	Yes	Yes	₩ es S	NO
7 19. 2016	Yes	Yes	NO	Yes	₹es 25	NO
8 20. 2018		Yes	Yes	Yes	Žes 🖢	Yes
9 21. 2018	Yes	Yes	Yes	Yes	ж Ш nu	NO
10 22. 2018	Yes	Yes	NO	Yes	ar) sei	NO
11 23. 2020	Yes	Yes	Yes	Yes	Jary 2025 Sejggjern	NO
12 24. 2020	Yes	Yes	Yes	Yes	D25	NO
13 25. 2020	112] Yes	Yes	Yes	Yes	5. Downloade legit Sugegie	NO
14 26. 2020	Yes	Yes	Yes	Yes	36.69 ≥	NO
15 27. 2021	Yes Yes	Yes	Yes	Yes	X 5 2	Yes
16 28. 2010		Yes	NO	Yes	oac egje	No applicable
17 29. 2018	Yes Yes	Yes	Yes	Yes	<u>ॲ</u> ॡ ਨੂ	NO
18 30. 2021	Yes	Yes	Yes	Yes		NO

2. Critical Appraisal Result for Economic Evaluations studies

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2 3 4 5 Studies 6 7	Q1) Is there a well- defined questio n?	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?	(9) Were analyses conducted to investigate a unsertainty in actimates of cost or sequences?	Q10) Do study results include all issues of concern to users?	Q11) Are the results generalizabl e to the setting of interest in the review?
8 1.2012 [21]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	≅ Notapplicable	Yes	Yes
9 2.2014 [34]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	No applicable	Yes	Yes
0 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	0 No	Yes	Yes
3 6.2017 [57]	Yes	Yes	Yes	Yes	Yes	Unclear	NO	NO	9 NO	Yes	Yes
5 6 3.	Critical A	Appraisal Resul	t for Analytical	Cross-Section	al Studies				5 at Age		

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?	Q Were the outcomes measured in a valid and reliable way?	Q8) Was appropriate statistical analysis used?
<u>)</u>							aphi	

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2012 [20]	Yes	Yes	Yes	Yes	Yes	Yes	ht, 1	Yes	Yes
2015 [41]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable)6527 nclud	Yes	Unclear
4.	Critical Appraisal R	esult for Qualitative	Research studies				on 25 Janu Er ding for use		

10 11 12 13 Studies 14 15	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) Areated Cyberie as related Q8) Areated Cyberie participants, their voice adequateless and represented and	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?
17 _{1.2014} [36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes da e	Yes	Yes
18 _{2.2021} [92]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes A A	Not applicable	Yes
193. 2021 [93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes mile Yes Not applicable	Not applicable	Yes
204. 2013 [30]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not application	Not applicable	Yes
21 5. 2019 [59]	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	Yes
22								₹ 5		

5. Critical Appraisal Result for Prevalence Studies

25 26 27 28 Studies 29	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?	Q Was there appropriate statistical analysis?	Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?
31 ¹ . 2016	Yes	Yes	NO	Yes	Yes	Yes	Yes	Yes	Yes
33 2. 2013 34	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	2025 Yes	Not applicable

6. Critical Appraisal Result for Cohort Studies

Q1) Were the Q2) Were the Q3) Was Q4) Were Q5) Were Q6) Were the Q7) Were Q8) Was the Q9) Was followed Q5) Were the Q7) Were Q8) Was the Q9) Was followed Q6) Were the Q7) Were Q8) Was followed Q6) Were the Q7) Were Q8) Was the Q9) Was followed Q6) Were the Q7) Were Q8) Was followed Q6) Were the Q7) Were Q8) Was the Q9) Was followed Q6) Were the Q7) Were Q8) Was the Q9) Was followed Q6) Were the Q7) Were Q8) Was the Q9) Was followed Q6) Were Q7) Were Q8) Was the Q9) Was followed Q8)	ow Q10) Were O11) Was
40 Studies two groups exposures the confounding strategies to groups/participants the follow up time up confounding	
similar and measured exposure deal with free of the outcomes reported and and if not, w	ere address appropriate

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3 4 5 6	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 resons to loss & follow lip described and oplored?	incomplete follow up utilized?	statistical analysis used?
O	Not applicable	Yes	Yes	NO	NO	Yes	Unclear	NO	5 Jan	Yes	Not applicable

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7 8	Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopted / developed
9 10				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	
11 12 13 14 15	North America	US (25)	24 (26%)	RDA ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare discondition' means any disease or condition which occurs so infrequently in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug'.	1983	developed
16 17 18 19	North			FDA	Define RD as 'any disease or condition that affects less than 200000 people 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 condition will be recovered from sales in the USA of such drug' Rare disease as one that afflicts less than 1 person in 200 000.		
20			2	CORD	Rare disease as one that afflicts less than 1 person in 200 000.		Aligned to EU
21		Canada (3)	(2%)		Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be wind with a rare disease		
22	South	Chile (1)	1 (1%)		Required the disease severity to be ,life threatening, and severely- or chronically,		
23	America	Peru (1)	(1,1)	41. D D'	debilitating.		
24 25				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	
26 27		UK (3)	(2%)	NHS	Some countries use additional definitions in situations where a condition is got officially defined as rare. classifies all conditions that require specialized needical care as rare if they occur in <500 citizens yearly		
28 29 30 31 32	ed	EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or chredically 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.		
33 34	Europe			European Commission on Public Health	Defines rare diseases as ,life-threatening or chronically debilitating disease which are of such low prevalence that special combined efforts are needed to address siems.		
35				Orphan Drug Regulation	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare	141/2000	
36				EMA	prevalence of rare disease < 5/10 000		
37		Germany (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
38		Latvia (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
39		Netherlands (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
40 41		Poland (2)	2 (2%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
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Continent	Country, frequency	# of articles; (%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) Diseases with a prevalence of 1.1/10 000 Diseases with a prevalence < 2000 individuals.	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				Diseases with a prevalence of 1.1/10 000		
				Diseases with a prevalence < 2000 individuals.		
	Australia (10)	10		Australia have set prevalence s of 1.16 per 100,000 individuals for a given the disease.		
	` ′	(11%)		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		
ı				Prevalence threshold for orphan disease designation: 0.9 in 10,000		
			U	The incidence rate is estimated to be 1 in 10,000 individuals for Australia Affecting less than 1:50,000 people, which is a considerably lower prevalence in the second of the second o		
	New Zealand (1)	1 (1%)	PHARMAC	than other nations that are from 5 to 76 per 100,000 people		
Asia				than other nations that are from 5 to 76 per 100,000 people Japan diseases with a prevalence of 4.0/10,000		
71314				Sapan diseases with a provincince of 4.0/10,000 <50,000 patients in Japan		
	Japan (13)	13		Intractable diseases, is a Japan-specific conception of diseases with (i) unknown		
	oupun (13)	(14%)		etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long-term terms.		
				The incidence rate is estimated to be ≤ 2.5 cases in 10,000 for Japan		
			Taiwan Foundation for	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical	2000	
		7	Rare Disorders	coverage.	2000	
	Taiwan (7)	7 (8%)	Physically and	T 2		
		(870)	Mentally Disabled	RD is one type of disability	2001	
			Citizens Protection Act	ji g		
	Cl.iv. (5)	5	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences in Newborn babies.		
	China (5)	(5%)		Incidence of the disease in adults or neonates is less than 1 in 500,000 and respectively.		
		-		Prevalence thresholds have been set at less than 1 per 20,000		
	South Korea (4)	5				
	, ,	(5%)		< 20,000 people in Korea (i.e., <4 per 10,000 population)		
	Singapore (2)	2		Prevalence threshold: <4.0 in 10,000 < 20,000 people in Korea (i.e., <4 per 10,000 population) Required the disease severity to be life threatening, and severely- or chronibally debilitating. Prevalence threshold: 37.7 in 10,000 Threshold for defining a disease as rare if it afflicts 1 in 5,000 individuals There is no specific definition for rare disease only levels of disability which define		
		(2%)		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 of the control of		
	Armenian	1 (1%)		There is no specific definition for rare disease only levels of disability which define		
	legislation (1)	1 (1/0)		whether the patient will receive the necessary medicines for free or not		
	Philippines		The DOH, upon recommendation of the RDTWG,	whether the patient will receive the necessary medicines for free or not		
Africa	Kenya		101110,	Required the disease severity to be ,life threatening, and severely- or chronically, debilitating.		
			For peer review	,debilitating. y only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		

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3	Continent	Country, frequency	# of articles; (%)		(RD) definition	-08652 ıt, inclı	Date	Adopted / developed	
7	Eastern Europe & Northern Asia.	Russia (1)	1 (1%)		Maximum prevalence for a rare disease is defined as 1 in 10,000	7 on 25 Ja Iding for u			
0 1 2 3	South-eastern Europe & Southwester n Asia	Turkey (1)	1 (1%)		Affect no more than 1 in 100,000, which is 50 times less frequent than th Union definition.	En:			
4 5 6		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.	ownloade it Superieu text and o			
/ 8 9		Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic et smaller percentage is autoimmune or infectious disorders, in addition to cancers."				
20	The Rare	Diseases Act (RDA; th	he Orphan Drug	Act (ODA; the Food and Dr	ug Administration (FDA); The Canadian Organization of Rare Diseases (CORD); N	ati zaCl<u>*</u>a lth Sei	rvice (NHS); - PHA	1RMAC	
21 22 23 24 25 26 27 28	(the Phan	maceutical Manageme	ent Agency); Org	anization for Rare Diseases definitions based o	India (ORDI)	.g, Al training, and simil			
9		# 00	f			ar t		Adopt	ı

0 1 Co	ontinent	Country, frequency	# of articles; (%)		n June 7, ; ar technol	Date	Adopt ed / develo ped
3 E	Europe	EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening chemically and seriously		
5			(==,,)		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		
7				NICE	The current NICE appraisal system means orphan drugs that do not meet HST criteria gethrough the standard		
8					technology appraisal (TA) process, with a cost-effectiveness threshold of £30 k/QALY, or £50 k/QALY when end-of-life criteria are met		
9				EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs and a referred to as orphan	(2011	
.0 .1					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.	(c)	

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4 5 6	Continent	Country, frequency	# of articles; (%)		(RD) definition (RD) definition	Date	ed / develo ped
7 8				The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-threatening or gery perious conditions that affect no more than 5 in 10,000 people in the European Union		
9				The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it targets a given with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered necessary.		
11 12 13				Poland	There is no specific formal threshold for orphan designations, there is only a general costal equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which is approximately € 26 800.		
14		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.		
15 16 17 18_		German (1)	1 (1%)		Certain special HTA criteria are applied to orphan drugs: Higher P values for small sand zes; Use of surrogate endpoints, Higher therapeutic benefit is automatically recognised for orphan drugs because drugs had to prove significant additional therapeutic benefit compared with other possibly already approved surses as part of the European marketing authorisation procedure. budget impact is less than €50 million per year for a participal rindication		
19 20 21	North America	US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a rare define one that affects less than 200, 000 persons in the USA' (which equates to approximately 6 to meets cost recovery provisions of the act'		
22 23 24 25 26 27 28				Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or restance 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 1934 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."		
26 27_					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		
28 29	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	
30		Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.		
31 32 33 34				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 existing alternatives, are designated as OD		
35 36		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 condition. Drug used for diseases affecting fewer than 1 in 10,000		
37 38 39		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 condition.		
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7	oplementar	ry Table :	S5: URDs definitio	BMJ Open BMJ op		Page 52
OContinent	Country, frequency	# of articles; (%)		(URD) definition	Date	Adopted / developed
2 3 Europe	UK	(,0)		Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 190,000 of the population (Hugheset al., 2005)		
14 15			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 ≤ 1 500		
6	Alberta		NICE	URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE, Alleign).		
18 19 20	England		Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in Englanding., ~1 in 100,000 of the English population)		
21	Ontario			An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per E ar h Ontario		
23				ultra-orphan diseases affecting <1/50000 inhabitants		
24 25 26			(EU regulation 536/2014)	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe		
27 28	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)"		
22 23 24 25 26 27 28 29 30 31 32	Poland			Poland uses the EU definition of 'Ultra-rare being <1 in 50000 people'		Adopted EU definition
34				rare disease there are "singular cases" or "individual cases", which are considered fultra-rare diseases" (prevalence: <1:10,000), including, for example MuSK-positive my there a gravis (prevalence 0.05–0.65/100,000 or congenital myasthenic syndrome (CMS)		
35 36				ultra-rare diseases (affecting <20/million persons)"		
36 37 38 39				the prevalence can be much lower, leading to the concept of the ,ultra-orphan disease, for diseases		
39				Ultra-rare, affecting less than 1 person per 50,000 inhabitants."		

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1 2				7-2024-(pyright,		
4 Conti 5	nent Country, frequency	# of articles; (%)		(URD) definition include the control of the control	Date	Adopted / developed
6 7				ultra-orphan (prevalence: <1:50,000)		
8 9 10 11			NICE Highly Specialised Technology Programme (HSTP) and the SMC	The NICE Highly Specialised Technology Programme (HSTP) and the SMC to be <1 in 50,000 and meeting other specialised criteria. "		
13 14 15 16	Supplementa	ry Table	S6: UODs definitio	ns based on continents as based on continents		Adopt

Supplementary Table S6: UODs definitions based on continents

			<u> </u>		
Country, frequency	# of articles; (%)		(UOD) definition	Date	Adopt ed / devel oped
			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 per 50,000 persons"		
			Indications approved for use in diseases with a prevalence of less than 1000 patiens (i.e. ultra-orphan drugs)		
			Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence ≤1,000) 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 (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence;		
	Scotland England	Scotland England	Scotland England WHO Scotland	Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or the standard persons. NICE: applied it to drugs with indications for conditions 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 ≤5:00,000) were consistent in most countries. Scotland The Scottish government The Scottish government	Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 or 25 ss b NICE: applied it to drugs with indications for conditions with a prevalence of less than 2 per 50,000 persons" Indications approved for use in diseases with a prevalence of less than 1000 patients (i.e. pultra-orphan drugs) Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence ≤5:0,000) were consistent in most countries. Scotland The Scottish government 50,000 people—approximately 100 people or fewer in Scotland HST for ultra-orphan indications Eurol13,900-341,700/QALY in England WHO WHO recommends a WTP of <3 times GDP per capita/QALY New definition for ultra-orphan drugs: ,medicines that are used to treat a condition with 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 No official definition of ,ultra-orphan disorders, has yet been adopted globally. Rather, but this informal subcategory was introduced by the National Institute for Health and Care biscellence

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RDs Qualitative and Quantitative descriptors and themes

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

ODs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Themes	Qualitative Descriptors
± 4 =	1. Medical Product	d d	21. No alternative treatment
latuı e of rodu	2. Agent	nm t lee	22. Treatment Price
Z	3. Biological Products		23. Lack profit

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

URDs Qualitative and Quantitative descriptors and themes

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

Theme	Qualitative	Theme	Qualitative	
	1. Very rare conditions		1. Indications	
	2.Medicines	Indication	2. Treat	
Nature	3.Drug		3. Approved for use	
	4.Disease	Dl-4'	1. Patients	
	5.Condition	Population Characteristics	2. Persons	
Theme	Quantitative	Characteristics	3. People	
1. Prevalence				
Measurements	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
	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	-
ure	9. Intractable	1	-	1	-
Nature	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
· · · · · · · · · · · · · · · · · · ·	19. Unknown Etiology	1	-	-	-
log	20. Genetic	7	-	1	-
Etiology	21. Hereditary	1	-	-	-
as le	22. Rare Diseases	40	4	16	-
Diseas e nature	23. Disab* (Disability & Disabling)	5	-	2	-
D ü	24. Life -Limiting	1	-	0	-

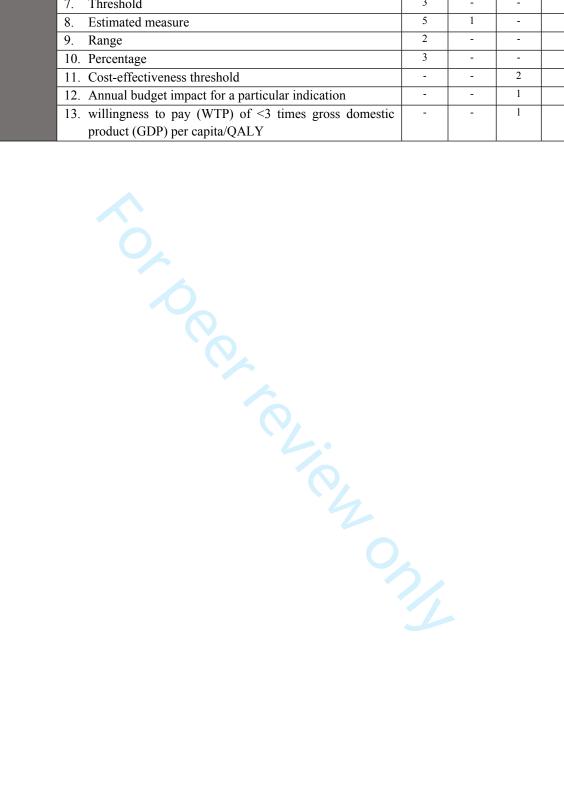
27. Long-Ter 28. Debilitati 29. Consider	al cause for early death rm Treatment ng able reduction in an individual's quality of life able reduction in socio- economic potential	23 1 1 21 1	- - -	20 0 0 10	- - -
28. Debilitati	m Treatment ng able reduction in an individual's quality of life able reduction in socio- economic potential	1 21		0	-
28. Debilitati	ng able reduction in an individual's quality of life able reduction in socio- economic potential	21		10	-
28. Debilitati	able reduction in an individual's quality of life able reduction in socio- economic potential	1	-		-
29. Consider 30. Consider	able reduction in socio- economic potential		-	0	
30. Consider	_	_		0	-
21 11		2	-	0	-
E e e e e e e e e e e e e e e e e e e	edical needs	3	-	3	-
30. Consider 31. Unmet m 32. Disease v centers 33. Common	vith limited number of specialist treatment	-	-	1	-
道 33. Common profit	disease where the sponsor cannot make any	-	-	1	-
34. Low Prev	valence	12	-	2	-
35. Low Occ	urrence	2	-	-	-
36. Rarely af 37. Small nu 38. Very sma 39. Population 39. Population	flict the population	1	-	-	-
36. Rarely at 37. Small nu 38. Very small nu 39. Population 39. Po	mber of patients	3	-	1	-
38. Very sma	all patient Population	-	1	-	-
	n	20	3	7	-
40. People		29	2	8	2
41. Inhabitan		6	2	-	-
E 42. Clinical a	dded value	-	-	1	-
43. Improve 44. Product v 45. New drug	safety or efficacy	-	-	1	-
43. Improve 44. Product v 45. New drug	vill be of significant benefit	-	-	2	-
Have the second state of t	g is significantly better than drugs currently	-	-	1	-
46. Indication	ns	-	-	4	4
47. Diagnosi	S	-	-	23	-
48. Treat* (T 49. Prevent*	reatment)	7	-	55	2
49. Prevent*	(Prevention)	1	-	23	-
50. Rehabilit	ation	-	-	1	-
51. Prophyla	xis	-	-	1	-

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

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

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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	-	-	1	1
	product (GDP) per capita/QALY				



BMJ Open

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

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- 6 Abstract:

- **Objectives** This study sheds light on the available global definitions, classifications and criteria
- 8 used for rare diseases (RDs), ultrarare diseases (URDs), orphan drugs (ODs), and ultra-orphan
- 9 drugs (UODs), and provides insights into the rationale behind these definitions.
- 10 Design A systematic literature review was conducted to identify existing definitions and the
- criteria used to define RDs, ODs, and their subtypes.
- 12 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
- 14 1985 to 2021.
- 15 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.
- 18 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.
- 32 Keywords: rare disease, ultra-rare, orphan drug, ultra-orphan drugs, qualitative, quantitative,33 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 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

treating a rare disease" (25).

- 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

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).

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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

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

3 of 118			BMJ Open BMJ open	
223 Tabl	e 1: A sum	nmary of RDs defini	BMJ Open BMJ Open tions is provided based on the country gh	
Country, frequency	# of articles; (%)		(RD) definition (RD) definition	Date
	-	Orphan Drug Regulation RDA	Defines RD according to prevalence: "rare disease' means any disease or condition that affects less than 200000 persons in the USA'.	1993
US (25)	24 (26%)	ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare the same or condition' means any disease or condition which occurs so infrequently in the USA there is no reasonable expectation that the cost of developing and making available in the USA to 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 & cost of developing and making available in the USA a drug for such disease or condition with the covered from sales in the USA of such drug'	
Canada	2	CORD	Rare disease as one that afflicts less than 1 person in 200 000.	
(3)	(2%)		Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease	
	2	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in 200 people. (i.e., a prevalence of 5 or less per 10,000)	2021
UK (3)	(2%)	NHS	Some countries use additional definitions in situations where a condition some officially defined as rare. classifies all conditions that require specialized medical care as rare of the occur in <500 citizens yearly	
EU (36)	35		Rare diseases, including those of genetic origin, are life-threatening or chronteally 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 stability of life or socioeconomic potential.	
EU (30)	(38%)	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

			BMJ Open	Page 14
Country, frequency	# of articles; (%)		(RD) definition (RD) definition	Date
		EMA		
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	
Taiwan (7)	7 (8%)	Taiwan Foundation for Rare Disorders Physically and Mentally Disabled Citizens Protection Act	Diseases affecting < 1 in 10,000 that are officially recognized are eligible in the large of the	2000
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.	
South Korea (4)	5 (5%)		Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively. 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) 30,000, respectively. 30,000, respectively. 	
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 cascers."	

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).

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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 (\sim 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 $\leq 1.50,000$ 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
the country asummary of URDs definitions is provided in Table 2

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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 He population (Hugheset al., 2005)
OK	NICE	2005) 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., ~ land the control of the English population)
Ontario		An incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year in Onterio
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)"
		nd similar technologies. 15 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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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 ϵ 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.

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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



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Country, frequency	# of article s; (%)		(RD) definition (RD) definition	Date										
		EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threaming or chronically and seriously debilitating condition affecting not more than 5 in 10 000 ELE prediction or that it is unlikely that marketing the drug in the EU would generate sufficient benefit to affected people and for the drug manufacturer to justify the investment											
		NICE	The current NICE appraisal system means orphan drugs that do not meet Hospitaria go through the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold th											
EU/UK (22)	19 (20%)	EURORDIS	Drugs used in the treatment of rare diseases address significant unmet receiped 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 one patients suffering from very rare condition.	(2011c)										
		The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-ture as ning 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 of ignormal 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 general cost-effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (fee CSA) or ICER/LYG (for CEA), which in 2014 is approximately € 26 800.							
	8	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's of the act'											
US (9)	(9%)	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 reasogable 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											

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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 to approve the treatment of diseases that affect fewer than 1,000 patients, underscoring their exceptionally granted for the treatment of diseases that affect fewer than 1,000 patients, underscoring their exceptionally granted for the frequency of the Highly Specialised Technologies (HST) Programme has implemented cost firesholds for UODs, while the WHO provides specific recommendations for cost thresholds for UODs, while the WHO provides specific recommendations for cost thresholds for UODs definitions affecting fewer than 1 is 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 and similar technologies.

Table 4 provide a summary of UODs definitions based on the country of the data mining Al training and similar technologies.

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		1t, 4-0	
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 5 green less or around 100	Effective from
Scotland		people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processed 3 5	October 2018
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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)

Quantitative criteria

(Supplementary Table 10).

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

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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.

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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

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

410	treatments. It is imperative for each country to develop a local definition or reporting system or establish
411	a national registration program. This approach would not only facilitate the collection of vital health
412	information but also foster a more effective health care ecosystem that addresses the needs of individuals
413	affected by these conditions.
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430	important scientific content. GMA, KK, and HiA contributed to data acquisition. All authors contributed to the interpretation
431	of results and approved the final version submitted for publication and agreed to be accountable for all aspects of this
432	research. GMA is responsible for the overall content as guarantor.

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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.
- 442 Patient consent for publication Not required
- **Provenance and peer review** External peer review; not commissioned.

States; WHO = World Health Organization; WTP= Willingness To Pay.

- 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

456 References:

1. Aronson J. Rare diseases, orphan drugs, and orphan diseases. BMJ. 2006;333:127-8.

- Fehr A, Prütz F. Rare diseases: a challenge for medicine and public health. Journal of health
- monitoring. 2023;8:3-6.
- Gorini F, Coi A, Mezzasalma L, Baldacci S, Pierini A, Santoro M. Survival of patients with rare 3.
- diseases: a population-based study in Tuscany (Italy). Orphanet Journal of Rare Diseases. 2021;16(1):1-
- 9.
- 4. Repetto GM, Rebolledo-Jaramillo B. Rare Diseases: Genomics and Public Health. Applied
- Genomics and Public Health: Elsevier; 2020. p. 37-51.
- Ma N, Nie W, Wang T, Li C. Current status and countermeasure of the research on rare diseases 5.
- in China. Life Science Journal. 2013;10(2):11-4.
- Forum WE. World Economic Forum Global Data Access for Solving Rare Disease—A Health 6.
- Economics Value Framework 2020 [
- Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare disease 7.
- terminology and definitions—a systematic global review: report of the ISPOR rare disease special
- interest group. Value in health. 2015;18(6):906-14.
- Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer 8.
- becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut.
- 2020;69(5):823-9.
- Roeleveld N, Zielhuis GA, Gabreëls F. The prevalence of mental retardation: a critical review 9.
- of recent literature. 1997.
- Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two
- autoimmune bullous diseases: pemphigus and bullous pemphigoid. Archives of dermatological
- research. 2015;307:291-8.

Al training, and similar technologies

- Abozaid GM, Kerr K, McKnight A, Al-Omar HA. Criteria to define rare diseases and orphan 11.
- drugs: a systematic review protocol. BMJ open. 2022;12(7):e062126.
- Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare Disease 12.
- Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special
- Interest Group. Value Health. 2015;18(6):906-14.
- Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. 13.
- Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum
- Genet. 2020;28(2):165-73.

- 14. Alahdal H, Alshanbari H, Almazroa H, Alayesh S, Alrhaili A, Alqubi N, et al. Consanguinity,
- awareness, and genetic disorders among female university students in Riyadh, Saudi Arabia. Journal of
- Biochemical and Clinical Genetics. 2021;4(1):27-34.
- 15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting
- items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic
- reviews. 2015;4(1):1-9.
- Dissementation UoYCfRa. Guidance notes for registering a systematic review protocol with 16.
- PROSPERO. National Institute for Health Research. May 2016.
- Innovation VH. Covidence systematic review software Melbourne, AustraliaFebruary 4, 2019 17.
- [Available from: https://www.covidence.org/.
- 18. Couban R. Covidence and Rayyan. Journal of the Canadian Health Libraries Association
- Journal de l'Association des bibliothèques de la santé du Canada. 2016;37.
- Tools CA. Internet. New York: UNICEF multiple indicator cluster surveys Guidelines and 19.
- templates facilitate planning and design of surveys and help avoid pitfalls in implementation [cited 2014]
- Jul 14] Available from: http://www.childinfo.org/mics4_tools.html. 2020.

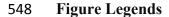
- Barker TH, Stone JC, Sears K, Klugar M, Leonardi-Bee J, Tufanaru C, et al. Revising the JBI 20.
- quantitative critical appraisal tools to improve their applicability: an overview of methods and the
- development process. JBI Evid Synth. 2023;21(3):478-93.
- Baran A, Czech M, Kooiker C, Hołownia M, Sykut-Cegielska J. Bridging East with West of 21.
- Europe-a comparison of orphan drugs policies in Poland, Russia and the Netherlands. Acta Poloniae
- Pharmaceutica-Drug Research. 2018;75(6):1409-22.
- Regulation OMP. Regulation (EC) No 141/2000 of the European Parliament and of the Council 22.
- of 16 December 1999 on orphan medicinal products. Off J. 2000;18:15.
- Mukherjee S. The United States Food and Drug Administration (FDA) regulatory response to 23.
- combat neglected tropical diseases (NTDs): A review. PLOS Neglected Tropical Diseases.
- 2023;17(1):e0011010.
- Rath A, Salamon V, Peixoto S, Hivert V, Laville M, Segrestin B, et al. A systematic literature 24.
- review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for
- improving the evidence and how can they be overcome? Trials. 2017;18:1-11.
- Krajnovic D. Ethical and Social Aspects on Rare Diseases. Filozofija i drustvo. 2012;XXIII:32-25.
- 48.
- Kaywanga F, Alimohamed MZ, David AB, Maeda D, Mbarak S, Mayura T, et al. Rare diseases 26.
- in Tanzania: a National Call for Action to address policy and urgent needs of individuals with rare
- diseases. Orphanet J Rare Dis. 2022;17(1):343.
- 27. Simoens S, Cassiman D, Dooms M, Picavet E. Orphan drugs for rare diseases: is it time to revisit
- their special market access status? Drugs. 2012;72:1437-43.
- Vreman RA, de Ruijter AS, Zawada A, Tafuri G, Stoyanova-Beninska V, O'Connor D, et al. 28.
- Assessment of significant benefit for orphan medicinal products by European regulators may support

Al training, and similar technologies

Protected by copyright, including for uses

- subsequent relative effectiveness assessments by health technology assessment organizations. Drug
- Discovery Today. 2020;25(7):1223-31.
- 29. Rode J. Rare diseases: understanding this public health priority. EURORDIS: Paris, France.
- 2005;5(1):3.

- Mikami K. Orphans in the Market: The History of Orphan Drug Policy. Social History of 30.
- Medicine. 2017;32(3):609-30.
- Herkes GK. Orphan drugs in Australia. Expert Opinion on Orphan Drugs. 2016;4(12):1195-7. 31.
- Leadley RM, Lang S, Misso K, Bekkering T, Ross J, Akiyama T, et al. A systematic review of 32.
- the prevalence of Morquio A syndrome: challenges for study reporting in rare diseases. Orphanet journal
- of rare diseases. 2014;9(1):1-17.
- Mehta G, Macek M, Mehta A. Cystic fibrosis across Europe: EuroCareCF analysis of 33.
- demographic data from 35 countries. Journal of Cystic Fibrosis. 2010;9:S5-S21.
- Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic 34.
- fibrosis care: a global perspective. The Lancet Respiratory Medicine. 2020;8(1):65-124.
- 35. Bin Zuair A, Aldossari S, Alhumaidi R, Alrabiah M, Alshabanat A. The Burden of Sickle Cell
- Disease in Saudi Arabia: A Single-Institution Large Retrospective Study. Int J Gen Med. 2023;16:161-
- 71.
- Moeti MR, Brango P, Nabyonga-Orem J, Impouma B. Ending the burden of sickle cell disease 36.
- in Africa. The Lancet Haematology. 2023;10(8):e567-e9.
- 37. Bell V, Varzakas T, Psaltopoulou T, Fernandes T. Sickle Cell Disease Update: New Treatments
- and Challenging Nutritional Interventions. Nutrients. 2024;16(2).



- 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
- gure 3 prevalence) in Figure 3

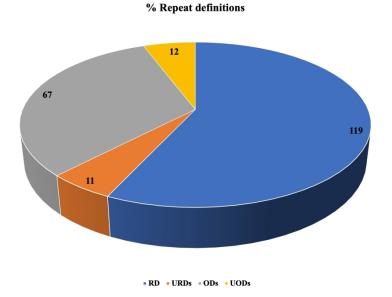


Figure 2. Repeated definitions included in the studies. $224x134mm (300 \times 300 DPI)$

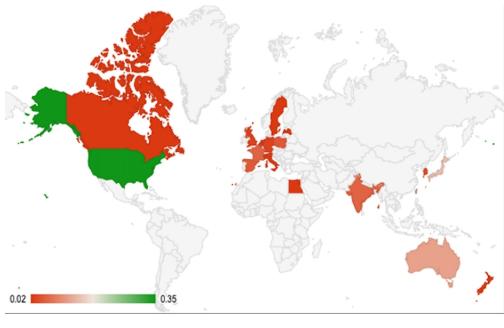


Figure 3. Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence)

117x72mm (600 x 600 DPI)

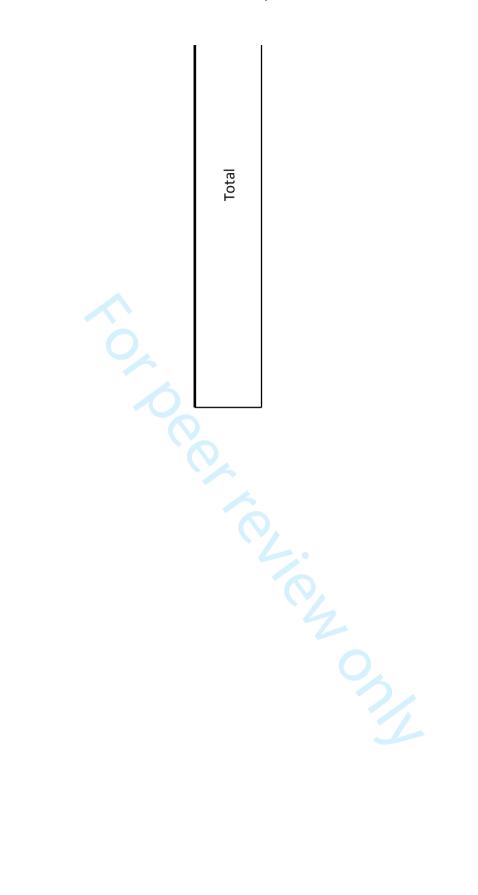
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1	Standard*[All Fields] OR	Fields] OR Description [All Fields]	disease*"[All Fields] OR "Rare	OR "Orphan medicinal product*"	[All Fields] OR Measure*[All Fields] OR	
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+	11,155,322	14,855,618	78.992	2.409	435 5	334
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_	classification or Measure* or	Character* or Explan* or delineate	or Rare disorder* or Rare disability*	Orphan product* or Orphan		
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3		standard* OR classification OR	mean* OR description OR	OR "Rare condition*" OR "Rare	medicinal product*" OR "Orphan	measure* OR condition* OR principle* R requirement* OR	
9		measure* OR condition* OR	character* OR explan* OR	disorder*" OR "Rare disability*" OR	product*" OR "Orphan subset*"	scale* OR parameter* OR indicat 66 * TOR norm*)) OR (
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1 1		indicator* OR norm*)	illustrate OR exemplify)	frequency disease*" OR "life-	OR "Priority review drug*" OR	OR determine OR elucidate OR illegate OR exemplify)	
11		•		threatening disease*" OR	"Orphan Drug Production*" OR	Character* OR explan* OR delineate or illetail OR interpret OR determine OR elucidate OR illetail OR interpret OR determine OR elucidate OR illetail OR exemplify) AND (TITLE-ABS-KEY ("Orphan the see OR "Rare condition*" OR "Rare disorder*" OR "Albertail disability*" OR "Neglected disease*" OR "Undiagnose disease*" OR "Low- frequency disease*" OR "life-threading of Sease*" OR "Abbilitation disease*" OR "OR "Interpretable	
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14	•			on have bisease y		"debilitating disease*" OR "severed seeds of "intractable disease*" OR "Rare Disease*"))	
15						disease*" OR "Rare Disease*")) AND TELE-ABS-KEY (
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16						specialized technolog*" OR "Prior Ry Ry drug*" OR	
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20		measure* OR condition* OR	explan* OR delineate OR detail	disorder*" OR "Rare disability*" OR	OR "Orphan subset*" OR	CPCI-S, CPCI-SHOST.	
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21		scale* OR parameter* OR indicator* OR norm*)	elucidate OR illustrate OR exemplify)	"Undiagnosed disease*" OR "Low- frequency disease*" OR "life-	specialized technolog*" OR "Priority review drug*" OR	, <u>, </u>	
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23	WOS	EXPANDED, SSCI, A&HCI, CPCI-S,	EXPANDED, SSCI, A&HCI, CPCI-S,	"debilitating disease*" OR "severe	"Orphan Drug*")	ira J	
24		CPCI-SSH, ESCI., CPCI-S, CPCI-SSH, ESCI.	CPCI-SSH, ESCI.	disease*" OR "intractable disease*"	Timespan: All years. Indexes: SCI- EXPANDED, SSCI, A&HCI, CPCI-S,	in b	
25		55H, E5CI.		OR "Rare Disease*") Timespan: All years. Indexes: SCI-	CPCI-SSH, ESCI.	n _c	
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Concept 2	
Concept 3	64037
Concept 4	



Research ques What are the criteria to define Rare Disea

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	PubMed
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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	

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limit to english and human	334

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ases and Orphan Drugs globally?

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	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 subheading 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 Lowfrequency 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

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

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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
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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
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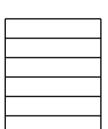
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ALL FIELDS: (criteria OR standard* OR classification OR measure* OR condition* OR principle* OR requirement* OR scale* OR parameter* OR indicator* OR norm*) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	20,665,577
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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

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Duplication	1656

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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 source

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

TOTAL INCLUDED = 66



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	2005 Tawarda ay Outinal Oughan Madisiral Duadrata (OMIDistanbural Davison Casura
	2005 Towards an Optimal Orphan Medicinal Products (OMIBiotechnol Review Scopus
	2009 Orphan-Drug Applications Guidebook Scopus
A la al a II a la IV	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 randomized Clin Epidemiol
Abrahamya	2014 Using value-of-information methods when the diseased 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 \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, (2013 PW02-027 - CAPS and cost-effectiveness analysis proj Pediatric Rheumatology
Albinana, √	2011 Hereditary haemorrhagic telangiectasia (Rendu-Osler-Haemophilia
Alghamdi, ،	2014 APhA2014 abstracts of contributed papers
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, Vei	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 Introductic Scopus
Anastasaki,	2017 Orphan Drug Reimbursement In Europe: Do Less Strin Value in Health
Andersen,	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 polic 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 recExpert Opii Article Scopus
Antoniu, Sa	2015 Fresh from the designation pipeline: orphan drugs recExpert Opii Article Scopus
Armstrong,	2013 Is scorpion antivenom cost-effective as marketed in the Toxicon
Arnould, B.	2018 Role of patient-reported outcome evaluation in the at 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 FValue 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, N	2018 Orphan Drugs and Their Impact on Pharmaceutical DeTrends Pha Erratum Scopus
Aulois-Grio	2018 Psy135 - Access to Orphan Drugs – Regulation within † Value in Health

_	
Ayme, S.	2011 Poster Presentations FEBS Journal
Ayme, Sego	2012 State of the art of rare disease activities in Europe: A l'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. anı	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 ZeBMJ 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., Bi	2013 Strategic biomarkers for drug development in treating AAPS J
Baiardi, Pac	2010 Clinical trial design and management PharmaceuShort SurveScopus
Bakker, Em	2017 Current and prospective pharmacotherapies for the ti Expert Opinion on Orphan Drugs
Baldovino,	2016 Rare Diseases in Europe: from a Wide to a Local Persplsr 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, Ada	2011 Orphan drugs: pricing, reimbursement and patient ac Internation 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 anaActa Polon Article Scopus
Baran-Kooi	2018 Multi-Criteria Decision Analysis (MCDA) Models in Hei Front Public Health
Baran-Kooi	2019 Overview of Regulatory Initiatives in the European UnActa 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, §	2013 Emergence of pediatric rare diseases: Review of prese Rare Dis
Belgaied, V	2018 Comparison of Orphan Drugs Prices Between Europe (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-deExpert Opinion on Orphan Drugs
Bewicke-Co	2019 Pro156 Approaches to the Collection of Utility Values Value in Health
Bhalla, Ash	2007 Patents on therapeutics in developing countries: the 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 neurology
Bin Sawad,	2020 Nd3 Orphan Drug Market Access Challenges in Europ∈ 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-Da	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, N	2017 Miltefosine: A case study of a product development p Tropical Medicine and Internation
Boncheva,	2020 PRO74 Is IT Possible to Accelerate the Access of Patier Value in Health
Bonner, N.,	2016 Challenges and solutions associated with patient-cent Value in Health
Boon, W., I	2015 Governance of conditional reimbursement practices in Health Policy
Boon, W. a	2008 Exploring emerging technologies using metaphorsa (Soc Sci Med
Bosone, En	2017 Timely Access to Priority Medicines in Europe Medicine Access @ Point of Care

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48 49

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57

58

```
2012 Abstracts of the 9th Annual ENETS (European Neuroe Neuroendocrinology
Bovce. M.
                2013 Effectiveness of Centruroides scorpion antivenom cor Toxicon
Bover, L. V.
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
                2019 Pro105 a Review of Six Years of the Nice Highly Specia Value in Health
Brown, R. J
                2012 Strategic Corporate Social Responsibility and Orphan Journal of I Article
Bruyaka, O
                                                                                                 Scopus
                2015 Bringing regenerative medicines to the clinic: The futuRegenerati Review
                                                                                                 Scopus
Bubela, T.,
                2010 Engineering tumors: a tissue engineering perspective Tissue Eng Part B Rev
Burdett, E.,
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
                2011 Abstracts of the 2011 Joint Annual Meeting of the Gei Br J Clin Pharmacol
Cap, M., Ki
Carr, D. R. a
                2016 An early assessment of nice highly specialised technol Value in Health
                2016 Gene therapies: the challenge of super-high-cost trea Regen Med
Carr, D. R. a
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
                2002 Orphan drug development: David and goliath
Cato, A., W
                                                                          Clinical Dru Scopus
Chan, Adrie
                2019 Orphan drugs-access and unmet needs in 194 countri The Lancet
Charco, J. N
                2021 Prion Diseases: History, Diversity, and Socioeconomic Araucaria-Revista Iberoamericana
Chaves Res
                2018 Psy185 - Alternative Methodologies Implemented by Value in Health
                2018 Psy183 - Scope Review of Orphan Drug Public Policies Value in Health
Chaves Res
Chen, C., D
                2014 Orphan drugs and rare diseases: A scientometric reviεExpert Opiι Review
                                                                                                Scopus
                2019 Pro82 Reimbursement and Pricing of Orphan Drugs in Value in Health
Cheng, C. Y
                2021 Orphan drugs in different countries and development Intractable & Rare Diseases Resea
Cheng, H. F
                2019 Pns216 Nice Highly Specialised Technology Assessmer Value in Health
Child, A.
Chirveches
                2016 Systematic review of international models of care on Value in Health
Chisolm, St
                2014 Partnering in medical education: rare disease organiz; 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 develournal of Biopharmaceutical Stat
Church, L. I
                2008 Long term management of patients with cryopyrin-as: Biologics Review
Ciafaloni, E
                2019 Efficacy and Safety of Dichlorphenamide for Primary F 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 f Value in Health
Contesse, 1
                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., Ł
                2013 Abstracts of the 17th Annual Meeting of French Socie Fundam Clin Pharmacol
Cornu, C., 1
                2017 Focused Workshop
                                                                           European Journal of Neurology
                2005 Pulmonary alveolar proteinosis: a new autoimmune d Sarcoidosis Vasc Diffuse Lung Dis
Costabel, L
                2014 Opportunity cost of funding drugs for rare diseases: tl Med Decis Making
Coyle, D., C
Coyle, D., C
                2020 HTA methodology and value frameworks for evaluatic Eur J Health Econ
                2020 PRO81 Is EU Orphan Medicine Status Working? a Retr Value in Health
Coyle, S., N
Crausaz, S.
                2015 Competing for public funding of medicines to treat rai Bull World Health Organ
Crossnohei
                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 He; Value in Health
Cutillo, C. N
                2017 A Global Approach to Rare Diseases Research and Orr Rare Diseases Epidemiology: Upd
```

Feng, S., Liı

Czech, M.,	2020 A Review of Rare Disease Policies and Orphan Drug Re		
Czech, M.,	2018 BRIDGING EAST WITH WEST OF EUROPE - A COMPARI Acta Poloniae Pharmaceutica		
Dabbous, C	2019 Ro2 Assessing the Relationship between Lifelong Value	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 McArticle 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 IRI	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, (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,	2014 A US perspective on newborn screening: a powerful to Expert Opinion on Orphan Drugs		
Della Casa	2015 The RaDiCEA project: Cost of illness (COI) analysis app	Pediatric Rheumatology	
DeRidder, I	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, (2021 Cost-effectiveness analysis of caplacizumab in the new		
Diab, D., d€	2020 PRO87 Limited Target Population: IMPACT on Medica		
Diop, A. G.	2015 Advocacy in resource limited world	Journal of the Neurological Science	
Divino, V.,	2015 The budget impact of orphan drugs in the us and Cana	_	
Divino, Vict	2014 The budget impact of orphan drugs in the U.S.: A 200		
Djambazov	2020 PNS135 A Comparative Analysis on Application of Ma		
Djambazov	2020 PNS187 Differences and Similarities in the LEVEL of Ev		
Djambazov	2020 PNS168 Differences and Similarities in the LEVEL of Ev		
Djambazov	2020 PNS148 Differences and Similarities in the LEVEL of Ev		
Dodman, S	2020 PRO67 Does Society Support The Prioritisation Of High		
Donadieu,	2020 How Many Patients Have Congenital Neutropenia? a		
Donadieu,	2016 Abstracts From the 32nd Annual Meeting of the Histig		
Dooms, Ma	2014 Understanding off-label use and the new challenges		
Doux, J.	2015 Barriers and Opportunities: A View across the Develop		
Dusza, M.,	2019 Pro98 Ultra-Orphan Medicinal Products Assessment:		
Dusza, M.,	2019 Pro108 Analysis of Nice and Us Icer Hta Outcomes for		
E. Haffner,	2019 F10108 Analysis of Nice and Os iter Hta Outcomes for 2010 The U.S. Food and Drug Administration and the regula		
•	_	•	
Edfjall, Cata	2012 Leveraging existing opportunities for improved Orpha	-	
Efthymiadc	2018 Differentiation of Health-Related Quality of Life Outco		
Ekins, S., Pı	2020 Repurposing the Dihydropyridine Calcium Channel Inl		
Ensor, Chri	2012 Abstracts and Index of Authors	Pharmacotherapy: The Journal of	
Ethgen, O.,	2012 PHP102 From Value to Price: What Should Be the Patl		
Faduola, Pa	2013 Monoclonal biologics in Acute Myeloid Leukemia (AM		
Faeh, Andr	2012 A Just Distribution of Health Care in the Case of Orpha	•	
Falk, K., Bro	2015 Similarities and differences in orphan drug reimburse Value in Health		
Fecarotta,	2011 The videofluoroscopic swallowing study shows a susta		
Feldman, N	2011 Sodium oxybate for the treatment of excessive sleepi		

2018 National Rare Diseases Registry System of China and FHuman Gel 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 ResiScopus
Fiorentino,	2012 Non-Speaker Abstracts Haemophilia
Foltánová,	2012 Orphan drugs used for treatment in pediatric patientsActa 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 publicatin 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
Franceschii	2020 PRO99 Real-World Application of Multiple Criteria De Value in Health
Freiberg, N	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 Sanc	2016 Review of the recommendations made by the nationa Value in Health
Garcia Sanc	2016 Review of health technology assessment (HTA) requir Value in Health
Gardiner, R	2014 Innovation May Drive Streamlined Access to New Bior Value Health
Gea, E., Gil	2013 41st ESCP symposium on clinical pharmacy:
	rnational Journal of Clinical Pharmacy
Giannuzzi,	2018 9th European Conference on Rare Diseases & Orphan Orphanet Journal of Rare Disease
Gilabert-P€	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
Gombocz, I Gordon, Au	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs
Gombocz, I Gordon, Au Goshua, Ge	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood
Gombocz, I Gordon, At Goshua, Ge Gottwald, S	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in dei Article Scopus
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski,	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski,	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development in Health Aff (Millwood)
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in dei Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. E	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development in Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development in Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 1985 Orphan drug development in the United States CPJ Article Scopus
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in dei Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 1985 Orphan drug development in the United States CPJ Article Scopus 2009 Collaborative research efforts and related activities of Italian Jour Article Scopus
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in dei Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 1985 Orphan drug development in the United States CPJ Article Scopus 2009 Collaborative research efforts and related activities of Italian Jour Article Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in der Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternatior Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 1985 Orphan drug development in the United States CPJ Article Scopus 2009 Collaborative research efforts and related activities of Italian Jour Article Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2018 Symposium Summaries Pediatric Pulmonology
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor,	2020 Public spending on orphan medicines: a review of the J Pharm Po Article Scopus 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in dei Article Scopus 2005 Increasing R&D Incentives for Neglected Diseases: LesInternatior Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 1985 Orphan drug development in the United States CPJ Article Scopus 2009 Collaborative research efforts and related activities of Italian Jour Article Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2018 Symposium Summaries Pediatric Pulmonology 2011 Orphan drugs face tougher scrutiny in securing favora Value in Health
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in del Article 2005 Increasing R&D Incentives for Neglected Diseases: LesInternatior Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS Journal of the American College c 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 1985 Orphan drug development in the United States CPJ Article Scopus 2009 Collaborative research efforts and related activities of Italian Jour Article 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2018 Symposium Summaries Pediatric Pulmonology 2011 Orphan drugs face tougher scrutiny in securing favora Value in Health 2011 Poster Session Pediatric Nephrology
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Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N Grzywacz, I Gungor, D. Guo, D., Jin	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in dei Article 2005 Increasing R&D Incentives for Neglected Diseases: LesInternatior Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2039 Collaborative research efforts and related activities of Italian Jour Article 2040 Symposium Summaries 2050 Pediatric Pulmonology 2050 Orphan drugs face tougher scrutiny in securing favora Value in Health 2051 Poster Session 2051 Pediatric Nephrology 2052 Pediatric Nephrology 2053 The Office of Rare Diseases Threshold For Orphan Designa Value Health 2054 The Cost-Effectiveness Threshold For Orphan Designa Value Health 2055 Pediatric Pulmonology 2056 Pediatric Nephrology 2057 The Office of Rare Diseases Threshold For Orphan Designa Value Health 2058 The International Society for Biological and Environm Biopresery Biobank
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N Grzywacz, I Gungor, D. Guo, D., Jin Haffner, M	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtlicheEthik in del Article 2005 Increasing R&D Incentives for Neglected Diseases: LesInternatior Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2022 Orphan drug development in the United States 2023 Copus 2024 Collaborative research efforts and related activities of Italian Jour Article 2029 Collaborative research efforts and related activities of Italian Jour Article 2020 TAFOMIDIS: The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2011 Orphan drugs face tougher scrutiny in securing favora Value in Health 2011 Poster Session 2014 The Cost-Effectiveness Threshold For Orphan Designa Value Health 2011 Survival and associated factors in 268 adults with Pon Orphanet J Rare Dis 2018 The International Society for Biological and Environma Biopreserv Biobank 2017 Support for orphan drug development: legislation in the United States, Japan and Europ
Gombocz, I Gordon, At Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Gras, J. Griffin, Jan Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N Grzywacz, I Gungor, D. Guo, D., Jin Haffner, M	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Thron Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in dei Article 2005 Increasing R&D Incentives for Neglected Diseases: LesInternatior Scopus 2015 The roles of patents and research and development ir Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2039 Orphan drug development in the United States 2040 Collaborative research efforts and related activities of Italian Jour Article 2050 Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2011 Orphan drugs face tougher scrutiny in securing favora Value in Health 2011 Poster Session 2014 The Cost-Effectiveness Threshold For Orphan Designa Value Health 2011 Survival and associated factors in 268 adults with Pon Orphanet J Rare Dis 2018 The International Society for Biological and Environme Biopreserv Biobank 2019 Support for orphan drug development: legislation in the United States, Japan and Europ 2019 Evaluation of orphan products by the U.S. Food and DInt J Techni Article Scopus
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Griffin, Jan Grimm, S. E Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N Grzywacz, I Gungor, D. Guo, D., Jin Haffner, M Hajimiri, S.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Throm Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in dei Article 2005 Increasing R&D Incentives for Neglected Diseases: Les Internation Scopus 2015 The roles of patents and research and development in Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2029 Collaborative research efforts and related activities of Italian Jour Article 2030 Scopus 2040 Collaborative research efforts and related activities of Italian Jour Article 2050 Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2011 Orphan drugs face tougher scrutiny in securing favora Value in Health 2011 Poster Session 2014 The Cost-Effectiveness Threshold For Orphan Designa Value Health 2011 Survival and associated factors in 268 adults with Pon Orphanet J Rare Dis 2018 The International Society for Biological and Environma Biopresery Biobank 2019 Toppan drug development: legislation in the United States, Japan and Euro; 2019 Pro92 an Analysis of Orphan Medicines Expenditure ir Value in Health
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Griffin, Jan, Grimm, S. I Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N Grzywacz, I Gungor, D., Guo, D., Jin Haffner, M Hajimiri, S. Haley, C. J.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Throm Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in dei Article 2005 Increasing R&D Incentives for Neglected Diseases: LesInternation Scopus 2015 The roles of patents and research and development in Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2029 Collaborative research efforts and related activities of Italian Jour Article 2020 Symposium Summaries 2021 Symposium Summaries 2021 Orphan drugs face tougher scrutiny in securing favora Value in Health 2021 Poster Session 2024 The Cost-Effectiveness Threshold For Orphan Designa Value Health 2021 Survival and associated factors in 268 adults with Pom Orphanet J Rare Dis 2028 The International Society for Biological and Environma Biopreserv Biobank 2029 Support for orphan drug development: legislation in the United States, Japan and Europ 2030 Support for orphan products by the U.S. Food and Dint J Techn Article 2040 Scopus 2050 Scopus 2051 Pro92 an Analysis of Orphan Medicines Expenditure ir Value in Health 2060 The Minor Use and Minor Species Animal Health Act: Food and E Review 2060 Scopus
Gombocz, I Gordon, Au Goshua, Ge Gottwald, S Grabowski, Grabowski, Gras, J. Griffin, Jan Grimm, S. E Groft, S. C. Groft, S. C. Groft, Step Grosse, Scc Grosvenor, Gruppen, N Grzywacz, I Gungor, D. Guo, D., Jin Haffner, M Hajimiri, S.	2020 Public spending on orphan medicines: a review of the J Pharm Po Article 2014 The Progeria Research Foundation: its remarkable jou Expert Opinion on Orphan Drugs 2020 Cost Effectiveness of Caplacizumab in Acquired Throm Blood 2013 Personalisierte Medizin als Orphanisierung: rechtliche Ethik in dei Article 2005 Increasing R&D Incentives for Neglected Diseases: Les Internation Scopus 2015 The roles of patents and research and development in Health Aff (Millwood) 2016 LANADELUMAB Prop INN; USAN Anti-KLKB1 (plasma k Drugs of the Future 2021 Berotralstat. Plasma kallikrein (KLKB1) inhibitor, Treat Drugs of the Future 2020 TAFAMIDIS: THE COST TO OUR PATIENTS 2021 Building a trusted framework for uncertainty assessm Orphanet J Rare Dis 2029 Collaborative research efforts and related activities of Italian Jour Article 2030 Scopus 2040 Collaborative research efforts and related activities of Italian Jour Article 2050 Scopus 2010 The Office of Rare Diseases Research: Serving a coord Small Mole Scopus 2011 Orphan drugs face tougher scrutiny in securing favora Value in Health 2011 Poster Session 2014 The Cost-Effectiveness Threshold For Orphan Designa Value Health 2011 Survival and associated factors in 268 adults with Pon Orphanet J Rare Dis 2018 The International Society for Biological and Environma Biopresery Biobank 2019 Toppan drug development: legislation in the United States, Japan and Euro; 2019 Pro92 an Analysis of Orphan Medicines Expenditure ir Value in Health

	2046 Commenter of the Lorente of each and a standard with Males to Hardin		
Hanna, E., ·	2016 Comparison of the trends of orphan drugs designation 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 Pharmac		
Hassan, Ma	2014 Comparative effectiveness research and the rise of or Internation Article Scopus		
Hauk, M., S	2019 M043 Two Day 20-Step Desensitization for Galsulfase Annals of Allergy, Asthma & Immi		
Hendrich, J	2019 Pro14 Is the Reimbursement of Orphan Medical ProduValue 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 FValue in Health		
Hillcoat, B.	1998 Rare diseases and "orphan" drugs Med J Aust Editorial Scopus		
Hiort, Olaf	2011 ESPE Working Groups Hormone Research in Paediatrics		
Hirai, T.	1997 System for the orphan drug development in Japan		
Hivert, Virg	2010 New functionalities in Orphanet for orphan drugs, R& Orphanet Journal of Rare Disease		
Hoffman, C	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		
Houyez, Fra	2012 Compassionate use programmes for rare diseases: ProOrphanet Journal of Rare Disease		
Houyez, Fra	2014 Health care cost-containment measures in the contex Orphanet Journal of Rare Disease		
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		
Hughes, D.	2006 Rationing of drugs for rare diseases Pharmacoeconomics		
Hughes-Wi	2012 A coordinated EU approach to informed access decisic Orphanet Journal of Rare Disease		
Hutchings,	2012 PHP100 Defining Elements of Value for Rare Disease TValue in Health		
Hutchings,	2013 Payer Assessment and Reimbursement Policy for Rare Value in Health		
Hutchings,	2014 Estimating the budget impact of orphan drugs in Swe(Orphanet J Rare Dis		
Huyard, Ca	2012 The emergence of the cause of rare diseases and rare Orphanet Journal of Rare Disease		
Hyde, R. an	2010 Orphan drug pricing and payer management in the UrAmerican F 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		
Iskrov, G., I	2017 Health Technology Assessment and Appraisal of Thera Rare Diseases Epidemiology: Upd		
Iskrov, G. C	2013 Insight into reimbursement decision-making criteria irFolia Med (Article Scopus		
Ismail, A. a	2013 Orphan Drug Access: Risk/Reward Analysis of Local Cli 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, Sanja _\	2016 Utilising Nanotechnology and Nanosystems for TreatrPharmacet Review Scopus		
Jain, S., Ed\	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		
Janzen, Ruc	2018 Off-Label Use in Rare Diseases: Myasthenia Gravis, La Neurology International Open		
Jeffrey, P.,	2016 Rare Diseases, Extraordinary Aspirations. Highlights fr Drugs of the Future		
Jeppesen, I	2013 Short bowel syndrome – characterisation of an orpha Expert Opinion on Orphan Drugs		
Jobard, M.,	2011 39th ESCP European symposium on clinical pharmacy International Journal of Clinical PI		
Jobjornssoı	2016 Late-stage pharmaceutical R&D and pricing policies urJ Health Ec Article Scopus		
Johnson, S.	2010 The ERS guidelines for LAM: trying a rationale approacRespir Med		
Johnston, L	2014 The impact of integrated omics technologies for patie Expert Opinion on Orphan Drugs		
Jones, C., A	2020 PRO90 Investigating Potential Benefits of Nice - Cadth Value in Health		
Jones, C. A.	2018 Market access for advanced therapy medicinal produc 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 patien Haemophilia		
Joshi, M. aı	2020 Pns14 Value Assessment of Orphan Drugs Value in Health		

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Jubert, H.,
                2016 Impact of post-inscription studies on reassessment in Value in Health
                2020 Regulatory Overview on Rare Diseases and Orphan Dr International Journal of Pharmace
Jyothi, M. S
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
                2020 Clinical and economic assessment of nusinersen: the I Expert Opinion on Orphan Drugs
Kamusheva
Kang, D., C
                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
                2010 A conceptual model for Pompe disease: The backbone Value in Health
Kanters, T.
                2012 PHP15 The Impact of Orphan Drug Incentives on Inno Value in Health
Kapur, A. K
                2017 Orphan drug policies and use in pediatric nephrology Pediatr Nephrol
Karpman, [
Kartha, R. \
                2020 Patients with Gaucher disease display systemic oxidat Mol Genet Metab Rep
Kasper, Dav
                2020 Challenges for newborn screening and rare disease di Molecular Genetics and Metaboli
Kawalec, P.
                2016 The correlation between HTA recommendations and I Orphanet J Rare Dis
Kelly, S.
                2018 Psy187 - the Quantity and Quality of Evidence Suppor Value in Health
                2019 Pns164 Pharmacoeconomic Assessment and Drug Cos Value in Health
Kennedy, C
Kerr, K. W.
                2020 Effective Market Exclusivity of New Molecular Entities Pharmaceut Med
Kesselheim
                2011 An empirical review of major legislation affecting drug Milbank Q
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
                2016 The future of pharmacoeconomic policy - does value-Journal of l'Article
                                                                                                Scopus
Kiernan, Fig
Kinch, M. S
                2015 An analysis of FDA-approved drugs for metabolic dise Drug Discov Today
Kishore, A.,
                2016 Association Study for 26 Candidate Loci in Idiopathic F Front Immunol
Klepacki, R.
                2015 APhA2015 abstracts of contributed papers
                                                                           Journal of the American Pharmac
                2012 PCN134 Expenditures and Availability of Orphan Drug Value in Health
Klimes, J., [
Klug, B., Ce
                2012 Regulatory structures for gene therapy medicinal proc Methods Enzymol
                2019 Pro75 Patient Access to Orphan Medicines in Turkey Value in Health
Kockaya, G
                2012 Classification and codification of rare diseases
Kodra, Y., F
                                                                          J Clin Epidemiol
                2016 Potential impact of the implementation of multiple-cr Orphanet J Rare Dis
Kolasa, K., I
Kolasa, K., I
                2018 Revealed preferences towards the appraisal of orphar Orphanet J Rare Dis
Kole, A. and
                2010 Rare diseases social epidemiology: analysis of inequal Adv Exp Med Biol
Koromina, M., Fanara: Ethics and equity in rare disease research and healthcPersonaliz: Review; Early Access
Koury, C. D
                2013 Rapid economic evaluation review for rare diseases tr Value in Health
                2020 PNS25 MULTI-LEVEL Cost-Effectiveness Thresholds in Value in Health
Kovács, S.,
Krishnan, N
                2020 Advances in the diagnosis and treatment of HIV-assoc Expert Opinion on Orphan Drugs
                2014 An European Overview of the Future Changes in Evide Value in Health
Krueger, L.
Kucukkeles
                2019 Small Numbers, Big Concerns: Practices and Organizat Academy of Management Discove
Kum, F., W
                2018 Establishing a rare stone disease service: 10 years of ε European Urology, Supplements
Kumar, J. a
                2011 Pricing and reimbursement of orphan drugs in Canada Value in Health
Kunneman
                2019 10th World Orphan Drug Congress (WODC) (Novembe Drugs Today (Barc)
Lagasse, H.
                2017 Recent advances in (therapeutic protein) drug develor F1000Res Review
                                                                                                Scopus
Landfeldt, I
                2017 Economic Evaluation in Duchenne Muscular Dystroph Pharmacoeconomics
Latchford, A
                2014 Strategies for improving patient outcome in patients \Expert Opinion on Orphan Drugs
Le, T. T.
                2017 Incentivizing Orphan Product Development: United St Rare Diseases Epidemiology: Upd
Lebioda, A.
                2013 Orphan Drugs in the German Early Benefit Assessmen Value in Health
Lee, C. K., F
                2017 Access To Medicines For Rare Diseases In Australia: Th Value in Health
Leffell, D., (
                2018 Php46 - Is Europe Waking up to Biopharmaceutical Ini Value in Health
Léger, Jean
                2017 Investigated and emerging treatments for chronic infl Expert Opinion on Orphan Drugs
                2018 Pharmacy budget impact of orphan drugs for chronic Journal of Managed Care and Spe
Li, Q., Weh
Li, S. X., Ch
                2020 Nd1 Access and Unmet Needs of Orphan Drugs in 194 Value in Health
Li, T.
                2016 Compare policies and research situation of rare disea: Value in Health
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McCabe, E.

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Li. X. F., Zha
                2021 Rare disease awareness and perspectives of physician Orphanet Journal of Rare Disease
                2020 Heart Rate Recovery After Exercise Is Associated With Circ Arrhythm Electrophysiol
Lieve, K. V.
Lin, Hsiang
                2007 Prader-Willi syndrome in Taiwan
                                                                           Pediatrics international: official ic
Lin, J. D., Li
                2013 Reported numbers of patients with rare diseases base Res Dev Disabil
Lloyd, A., D
                2018 Prm209 - How Do We Measure Utilities Outside of Tri Value in Health
Lloyd, A., G
                2015 How do we estimate quality adjusted life years (Qalys Value in Health
Lo, Andrew
                2019 Risk and Reward in the Orphan Drug Industry
                                                                          The Journal of Portfolio Managen
                2016 Value assessment of orphan drugs for treatment of ra Value in Health
Lockhart, C
                2014 Trends in individual reimbursement of orphan drugs i 4th International Interdisciplinary
Logviss, K.,
                2021 Meeting the affordability challenges posed by orphan J Manag Care Spec Pharm
Lopata, E.,
                2019 Pro19 the Role Played by Social Costs in Economic Eva Value in Health
Lopez Basti
López, Estr
                2016 Overview of existing initiatives to develop and improv Expert Opinion on Orphan Drugs
Lopez-Bast
                2010 Cost of Illness and Economic Evaluation in Rare Diseas Rare Diseases Epidemiology
Lopez-Onie
                2017 Induced pluripotent stem cells derived from Bernard-Stem Cell Res
                2016 Generation of a human induced pluripotent stem cell Stem Cell Res
Lopez-Onie
Low, L. A. a
                2016 Tissue Chips to aid drug development and modeling fc Expert Opin Orphan Drugs
                2016 Development of chidamide for peripheral T-cell lympl Intractable Rare Dis Res
Lu, X., Ning
Luisetti, M.
                2010 The problems of clinical trials and registries in rare dis Respir Med
                2015 Rare diseases and effective treatments: are we delive Lancet
Luzzatto, L.
                2018 Outrageous prices of orphan drugs: a call for collabora Lancet
Luzzatto, L.
Lynn, S., Lo
                2012 S.P.46 Rare disease policies: An important perspective Neuromuscular Disorders
Ma, H., O'C
                2021 Management of Angioimmunoblastic T-Cell Lymphom Seminars in Hematology
Ma, Lian, V
                2014 Abstracts Accepted for American Conference on Phari J Pharmacokinet Pharmacodyn
                2013 Current status and countermeasure of the research oiLife Science Article
Ma, N., Nie
                                                                                                Scopus
Ma, Y., Guc
                2019 Moyamoya disease: A retrospective study of 198 case Med Clin (Barc)
Macaulay,
                2015 Encouraging orphan designation for new Ebola treatm Value in Health
Macaulay,
                2019 Pns84 Eams Vs. Atu: Comparing Early Access to Unlice Value in Health
                2018 Psy134 - Has the Nice Hst Process Been a Success? Co Value in Health
Macaulay,
Macaulay,
                2019 Pro112 the Hst Test: Good, Better, Best?
Macaulay,
                2018 Psy136 - a Comparison of P&R Requirements for Orph Value in Health
Macchia, F
                2014 Differential pricing: Solidarity at times of financial cris Orphanet Journal of Rare Disease
                2018 Can Severity Outweigh Smaller Numbers? A Deliberat Value Health
Magalhaes
                2016 Cost effectiveness of icatibant for hereditary angioed (Value in Health
Magliano, (
Malinowsk
                2015 Evaluation of United States schools and colleges of ph Molecular Genetics and Metaboli
Malinowsk
                2020 Health technology assessment and reimbursement pc Orphanet J Rare Dis
Malladi, Ru
                2018 Original Abstracts from the 14th Annual Meeting of IS Curr Med Res Opin
Manrique-I
                2016 Individualized therapy in patients with Fabry disease: Expert Opinion on Orphan Drugs
Mantel-Te
                2011 Abstracts of the 27th International Conference on Pha Pharmacoepidemiol Drug Saf
Maresova,
                2015 Cooperation Policy of Rare Diseases in the European L5th Iceepsy International Confere
Marini, Pac
                2019 Abstracts from the 4th International PPRI Conference Journal of Pharmaceutical Policy ?
                2005 Orphan drugs and the NHS: consider whom drug regu BMJ
Marshall, T
Martins, Iv
                2018 9th European Conference on Rare Diseases & Orphan Orphanet Journal of Rare Disease
Matijašević
                2011 Drugs for rare diseases: An example of modified gluccArhiv za Fa Article
Matsuo, M
                2015 Investigational treatments and therapeutic targets in Expert Opinion on Orphan Drugs
Matthews,
                2019 Pro89 Too Ultra-Rare for Care? Orphan Drug Availabil Value in Health
Mavris, Ma
                2010 EURORDIS summer school for patient advocates in clir Orphanet Journal of Rare Disease
Mayer, Gee
                2013 Treatment options in narcolepsy
                                                                           Expert Opinion on Orphan Drugs
                2016 A quantitative analysis of health technology assessme Value in Health
Mazumder
                2005 Orphan drugs and the NHS: should we value rarity?
McCabe, C.
```

1996 Gaucher disease. Current issues in diagnosis and treatJAMA: The Conference Scopus

McCormick	2018 Common drug review recommendations for orphan d Orphanet J Rare Dis
Medic, G.,	2017 Do payers value rarity? An analysis of the relationship Value in Health
Meekings,	2012 Orphan drug development: an economically viable str Drug Discov Today
Mennezein	2017 Orphan Drugs In France: Key Market Access Incentive: Value in Health
Mereles, D	2016 Diagnosis of cardiac involvement in systemic amyloid Expert Opinion on Orphan Drugs
Mertens, P	2012 Spina Bifida and primary prevention Orphanet Journal of Rare Disease
Mestre-Fer	2019 An analysis of orphan medicine expenditure in Europe Orphanet J Rare Dis
Metais, Car	2018 9th European Conference on Rare Diseases & Orphan Orphanet Journal of Rare Disease
Metzinger,	2015 'Approved for use in uveitis': drug approval for an orp Expert Opinion on Orphan Drugs
Meyers, A.	2003 The orphan medicinal products: An international challMinerva Bi Article Scopus
Mildred, M	2015 The rise of orphan drugs in europe vs the United State Value in Health
Millikan, L.	1999 Anecdotal therapies Rheumaderm: Current Issues in R
Mincarone	2015 Reimbursed price of orphan drugs: A value based fran Value in Health
Minder, Eli	2016 Existing therapies and therapeutic targets for erythro Expert Opinion on Orphan Drugs
Mingoranc	2018 The evolving orphan drug development model Basic and Clinical Pharmacology a
Mirasol, F.	2004 Orphan Drugs Open Door to Opportunity in Small MarChemical N Review Scopus
Mishima, T	2019 Perry disease: recent advances and perspectives Expert Opinion on Orphan Drugs
Miteva-Kat	2017 Patients' registries as a key tool in rare disease managRare Disea: Scopus
Mittal, L. K	2016 Reimbursement decision landscape for orphan drugs Value in Health
Mizoguchi,	2016 Research and drug development activities in rare dise Drug Discov Today
Moliner, A.	2009 The european union action in the field of rare disease Italian Jour Article Scopus
Moliner, A.	2010 Creating a European Union Framework for Actions in Rare Diseases Epidemiology
Moliner, A.	2017 The European Union Policy in the Field of Rare Diseas Rare Diseases Epidemiology: Upd
Montilva, J	2016 Impact of national orphan drug policy and reimburser Value in Health
Montserrat	2012 Abstracts of the XXX International Congress of the Wc Haemophilia
Moorhouse	2018 Policies and processes applicable to drugs for very rar Value in Health
Morales, Jc	2015 Complexities in transitioning a child with a rare disord Expert Opinion on Orphan Drugs
Morel, T., /	2013 Reconciling uncertainty of costs and outcomes with thorphanet J Rare Dis
Morginstin	2019 Abstracts from the 7th International Jerusalem Conferlsr J Health Policy Res
Moutier, H	2018 Psy109 - What Interpretation of Icers in Orphan Disea Value in Health
Mueller-La	2014 DeSScipher, a jump in the future Clinical and Experimental Rheuma
Mukku, S.,	2011 PHP131 How Can Pharma Industry Prepare Itself for tl Value in Health
Mumford,	2020 PNS185 Solutions to the Comparator Question in the 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
Mwamburi	2016 Provisions and special considerations for rare disease: Value in Health
Mwamburi	2016 Special considerations and patient access schemes for Value in Health
Nacar, S., A	2018 Php162 - Licenced Orphan Medicines Expenditure in TValue in Health
Nakamura,	2018 Promotion and challenges of Development for Orphai Annals of Oncology
Ndri, Η., Ηι	2011 39th ESCP European symposium on clinical pharmacy International Journal of Clinical Pl
Nellesen, D	2016 Economic burden of multiple chronic comorbidities as Expert Opinion on Orphan Drugs
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
Ng, K., Titu	2020 An International Multicenter Evaluation of Inheritance Circulation
Nicholson,	2017 How Will Proposed Changes To The Nice Highly Specia Value in Health
Nicholson,	2019 Pro103 the Patient Perspective in Health Technology , Value in Health
Nicod, E.	2014 To What Extent Do Disease and Treatment Characteri Value Health
Nicod, E., K	2016 Dealing with uncertainty and accounting for social val Value in Health

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42 43

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48 49

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54 55

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57

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59 60

Putzeist, M

```
Nicod, E., V
                2020 Are supplemental appraisal/reimbursement processe; Orphanet J Rare Dis
                2017 Mucopolysaccharidosis type III: current clinical trials, Expert Opinion on Orphan Drugs
Nijmeijer, S
Nony, P., K
                2014 A methodological framework for drug development ir Orphanet J Rare Dis
Norcliffe-Ka
                2016 Mother-induced hypertension in familial dysautonom Clin Auton Res
Norman, Po
                2013 Repurposing as a strategy for orphan drug developme Expert Opinion on Orphan Drugs
Norman, Po
                2013 Orphan drug approvals in Europe since 2001: an analy Expert Opinion on Orphan Drugs
Norman, Po
                2014 Pulmonary arterial hypertension: a rare disease that ε Expert Opinion on Orphan Drugs
                2016 Orphan drug approvals of 2015: Europe and the Unite Expert Opinion on Orphan Drugs
Norman, Po
                2017 Clinical and economic issues complicating cost-effecti The EuroBiotech Journal
Nuijten, Ma
O'Connell,
                2014 Clinical trial safety population size: analysis of drug ap Expert Opinion on Orphan Drugs
O'Connor,
                2019 Commonly setting biological standards in rare disease Expert Opinion on Orphan Drugs
O'Connor,
                2014 Coping with small populations of patients in clinical tr Expert Opinion on Orphan Drugs
Ogbah, Rar
                2015 Orphan medicinal products - A european process over Regulatory Rapporteur
Oliver, L., K
                2019 Pro107 Understanding the Pricing and Reimbursemen Value in Health
                2020 10th European Conference on Rare Diseases & Orpha Orphanet J Rare Dis
Olry, Annie
Olsen, Bjor
                2015 Translational Medical Research
                                                                          Research ir Scopus
                2015 Pathophysiology and emerging therapeutic strategies Expert Opinion on Orphan Drugs
Osaka, Hitc
Padula, W.
                2018 Is the orphan drug act being used as a loophole to ext Value in Health
Padula, W.
                2018 Psy128 - How Long Can the Orphan Drug Exclusivity P. Value in Health
                2014 Treatment of idiopathic retroperitoneal fibrosis
Palmisano,
                                                                          Expert Opinion on Orphan Drugs
Pariser, An
                2012 Clinical Development of Products to Treat Rare Diseas Molecular Genetics and Metaboli
Pariser, A.
                2012 Characteristics of rare disease marketing applications Drug Discov Today
Pariser, An
                2013 Rare Diseases and Orphan Drugs
                                                                          Pediatric D Scopus
Park, T., Gr
                2015 Cost Effectiveness of Monoclonal Antibody Therapy fc BioDrugs
Patel, B., N
                2020 PRO82 How Do RARE Disease Patient Numbers in Ger Value in Health
                2014 Global HTA Assessments of Ultra-Orphan Products: A Value Health
Paul, A., M
                2015 Value-based reimbursement decisions for orphan dru Pharmacoeconomics
Paulden, M
Pavlović, N
                2013 Low availability of orphan medicines in Serbia
                                                                          Value in Health
Pavlović. N
                2014 An Insight on Differences in Availability and Reimburs Biotechnol Review
                                                                                                Scopus
Paz, S., Cor
                2015 Experts consensus on the future of rare diseases care Value in Health
Pearl, Philli
                2013 Inherited pediatric metabolic epilepsies
                                                                          Expert Opinion on Orphan Drugs
                2019 11th Excellence in Pediatrics Conference – 2019 Book Cogent Medicine
Pediatrics,
Peila, E., Fc
                2011 Extemporaneous orphan drugs and preparations for r EJHP Practice
Pereira, L. a
                2017 Rare or next competitive landscape
                                                                          Value in Health
Petrongona
                2017 Orphan drugs' pharmacoeconomic data and the impa European Journal of Hospital Pha
Petrova, Ev
                2020 Advances in understanding of Netherton syndrome ar Expert Opinion on Orphan Drugs
Peyvandi, F
                2015 Speaker Abstracts
                                                                          Haemophilia
Picavet, E.,
                2012 Market uptake of orphan drugs--a European analysis J Clin Pharm Ther
Picavet, E.,
                2013 Clinical evidence for orphan medicinal products-a cau Orphanet J Rare Dis
Picavet, E.,
                2014 Reimbursement of orphan drugs in Belgium: what (els Orphanet J Rare Dis
Piras, Desic
                2016 Rare disease: a focus on metabolomics
                                                                          Expert Opinion on Orphan Drugs
                2018 Enhancing data retrieval and analysis skills among Dor Pharmacy Education
Pizzuto, Ma
                2019 Pro15 Orphan Drug Methodology Challenges in the Di Value in Health
Ploug, U. a.
Polizzi, A., I
                2014 Rare diseases research and practice
Pontes, C.,
                2015 Milestones on orphan medicinal products developme Clinical Therapeutics
Potashnik,
                2019 Abstracts from the 4th International PPRI Conference Journal of Pharmaceutical Policy;
Potter, B. K
                2013 Achieving the "triple aim" for inborn errors of metabc Genet Med
                2019 Pro115 Development and Validation of a Mcda Frame Value in Health
Poveda, J. I
Prada, M.,
                2017 Orphan drugs to treating rare diseases: The Italian wa Value in Health
```

2012 Determinants for successful marketing authorisation (Drug Discov Today

Puyol, A.	2021 Political Fraternity and Rare Diseases	Araucaria-Revista Iberoamericana
Qiu, T., Har	2018 Europe-China Comparison of Orphan Drugs Approvals	
Qiu, T., Har	2020 PRO11 Policy Initiatives to Facilitate the Patient Acces	_
Quijada, A.	2013 SEFC 2013. Oral Communications	Basic & Clinical Pharmacology & T
Quirland-La	2017 Main components of public policies and financing stra	Value in Health
Rath, A., Sa	2017 A systematic literature review of evidence-based clini	Trials
Raycheva,∣	2018 VP81 Health Technology Assessment And Rare Diseas	International Journal of Technolo
Reddy, DSa	2014 Orphan regulations for orphan drug development in I	Asian Jourr Review Scopus
Reidenberg	2006 Are drugs for rare diseases "essential"?	Bull World Health Organ
Repetto, G	2020 Rare Diseases: Genomics and Public Health	Applied Ge Scopus
Resemann,	2018 Original Abstracts from the 2018 European Meeting of	Curr Med Res Opin
Revah, Fréc	2014 Genethon: patient-empowered research	Expert Opinion on Orphan Drugs
Riemer, J.,	2017 Does The Presence of An Orphan Drug Polcy Affect HT	Value in Health
Rivaud, M.	2018 Enhanced late sodium current underlies pro-arrhythm	Int J Cardiol
Rizzo, W. B	2016 Genetics and prospective therapeutic targets for Sjog	Expert Opin Orphan Drugs
Roberts, E.	2015 Fair pricing of "old" orphan drugs: considerations for	CMAJ
Rodrigues,	2014 Orphan Drug Approvals In Europe: Historical Review a	Value Health
Romero-Lo	2017 45th ESCP-NSF international symposium on clinical ph	Int J Clin Pharm
Rost, Moni	2014 An introduction to value dossiers for early benefit ass	Regulatory Rapporteur
Rothwell, E	2017 How Does The Scottish Medicines Consortium Assess	Value in Health
Roy, S., Des	2011 39th ESCP European symposium on clinical pharmacy	International Journal of Clinical Pl
Roy, S., Des	2011 Cysteamine eyedrops: optimisation of the manufactu	International Journal of Clinical Pl
Ruperto, N	2014 SP0191 How to Deal with Methodology in Orphan Dis	Annals of the Rheumatic Diseases
Sakushima,	2013 Clinical data packages of drug approval for neurologic	Journal of the Neurological Scienc
Salvatore, \	2018 Evaluating the impact of peer support and connection	Expert Opinion on Orphan Drugs
Scarpa, Ma	2016 Orphan Drugs	Drug Disco Scopus
Schey, C., I	2014 Assessing The Relationship Between Individual Attribu	.Value Health
Schey, C., K	2017 Multi-criteria decision analysis (MCDA): testing a prop	Orphanet J Rare Dis
Schlander,	2008 The use of cost-effectiveness by the National Institute	J Med Ethics
Schlander,	2008 Has NICE got it right? An international perspective con	Curr Med Res Opin
Schlander,	2014 Incremental cost per quality-adjusted life year gained	J Comp Eff Res
Schlander,	2016 Drugs for rare (and ultra-rare) diseases in Europe: Ana	Value in Health
Scholten, J.	2014 National Rare Disease Strategies: The Current State for	Value Health
Scholz, C., S	2013 Abstract 24. Jahrestagung	medizinische genetik
Schubert, J	2017 Eculizumab for the treatment of hemolytic paroxysma	Expert Opinion on Orphan Drugs
Schuller, Y.	2018 Oncologic orphan drugs approved in the EU - do clinic	Orphanet J Rare Dis
Schuller, Y.	2017 Factors Contributing to the Efficacy-Effectiveness Gap	Drugs
Schultz, N.	2014 A Probabilistic Budget Impact Analysis Of Cystic Fibros	·Value in Health
Senturk, A.	2016 Orphan drug market analysis in Turkey	Value in Health
Serrano-Ag	2015 Recruitment procedures for descriptive socio-econom	Expert Opinion on Orphan Drugs
Serrano-Ag	2016 Patient participation in the development of a clinical §	Expert Opinion on Orphan Drugs
Shafie, A. A	2020 Rare disease in Malaysia: Challenges and solutions	PLoS One
Sharma, D.	2018 Cost-effectiveness analysis of lumacaftor and ivacafto	Orphanet J Rare Dis
Sheehan, N	2005 Orphan drugs and the NHS: fairness in health care ent	BMJ
Sheikh, Zar	2017 Is there a role for inhaled anti-inflammatory drugs in	Expert Opinion on Orphan Drugs
Shelley, W.	1988 The orphan patient	N Engl J McLetter 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. i	2014 Orphan Drug Policy: Approaches To Market Access In	Value Health
Shih, Shaw	2018 Advances in genetic understanding of gorlin syndrome	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, Nico	2017 Introduction Rare Disea: Scopus
Sireau, Nico	2017 Rare Diseases Scopus
Skeldon, G.	2020 PRO95 Patient Engagement Process in Rare Disease: FValue 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 assoc Expert Opinion on Orphan Drugs
Sollie, A., S	2013 A new coding system for metabolic disorders demons Hum Mutat
Song, Peip€	2013 Rare disease patients in China anticipate the sunlight Drug Discoveries & Therapeutics
Song, Peip€	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 norJAMA
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, N	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., Duı	2012 PHP76 Evidence Requirements for Pricing and Reimbi Value in Health
Tanaudom	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,	2014 Concerns about unapproved meningococcal vaccinati Orphanet J Rare Dis
Tankovic, 🤆	2013 Designing robust clinical trials for orphan drugs Orphan Dru 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: 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 FE 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 PhaPharmacoepidemiol Drug Saf
Tinelli, C., [2005 The Italian register for diffuse infiltrative lung disorde Sarcoidosis Vasc Diffuse Lung Dis

2

4

5

6

7 8

9

10

11

12

13

14

15

16

17

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40

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```
Tinglev. K..
                2018 Using a meta-narrative literature review and focus gro Orphanet J Rare Dis
                2012 Assessment of health-related quality of life as an outc Arthritis Care Res (Hoboken)
Tomasson,
Tomeo, F., Mariz, S., BHaemophilia, 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
Tomita, N.,
                2010 Accessibility to orphan drugs in Japan-Has the orphan Value in Health
Torrent-Fai
                2001 The EU challenges on the designation of orphan medi Pharmace Article
Torres, Ros
                2019 Current understanding of Lesch-Nyhan disease and pc Expert Opinion on Orphan Drugs
                2014 Impact Of Advanced Therapy Medicinal Products Cost Value in Health
Toumi, M.,
Trad, M., B
                2017 Advancing drug development in neuro-orphan indicat Journal of the Neurological Science
                2015 Cost-effectiveness analysis and prevention effects of Pediatric Rheumatology
Trieste, L.,
                2014 Multi-Criteria Decision Analysis for Reimbursing Orphi Value Health
Trip, A. M.,
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
                2019 Abstracts from the 52nd European Society of Human (European Journal of Human Gene
Tumiene, B
Tzouma, V.
                2017 Value assessment criteria for orphan drugs across eigl Value in Health
                2014 Pseudoxanthoma Elasticum: Diagnostic Features, Clas Expert Opin Orphan Drugs
Uitto, J., Jia
Ulrich, Lind
                2010 Efforts to develop orphan drugs: The FDA experience Pharmace L Short Surve Scopus
                2012 Program for SIMD annual meeting
Utz, Jeanin
                                                                          Molecular Genetics and Metaboli
van der Bei
                2012 Clinical features and predictors for disease natural pro 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: identil Orphanet J Rare Dis
                2018 Php243 - Do Disease Severity and/or Quality of Clinica Value in Health
Vandewalle
                2020 An Economic Evaluation of Voretigene Neparvovec fo Adv Ther Article
Viriato, D.,
                                                                                                Scopus
                2020 1586MO Pivotal trial endpoints of drugs for rare and r Annals of Oncology
Vokinger, k
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
                2016 Challenges in Using MCDA for Reimbursement DecisicValue Heal Editorial
Walker, A.
                2010 Designation, plausibility, protocol assistance, clinical tPharmaceιShort Survε Scopus
Walker, Ch
                2019 Pro101 Orphan Drug Reimbursement in England and I Value in Health
Walker, S.,
Wallraven,
                2013 Abstracts of the American Society of Gene & Cell Ther Mol Ther
Walsh, M.,
                2013 Plasma exchange and glucocorticoid dosing in the trea Trials
Walshe, J. I
                2005 The management of rare diseases
                                                                          Clin Med (LLetter
                                                                                                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 Technolog
Wang, G., I
                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
                2017 Message Passing on Factor Graph: A Novel Approach Advances in Data Mining. Applica
Wang, Yun
                2020 PRO86 Approaches to the Collection of Utility Values | Value in Health
Warnants,
                2020 10th European Conference on Rare Diseases & Orpha Orphanet J Rare Dis
Watson, Al
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
                2010 The US Orphan Drug Act: rare disease research stimul Health Policy
Wellman-L
Wells, D., F
                2015 The TREAT-NMD Advisory Committee for Therapeutic Neuromuscular Disorders
                2010 The COMP perspective
Westermar
                                                                          PharmaceuShort 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 fInternation 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 Dru Scopus	
Wilson, Caı	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, Jacqı	2018 US drugs were granted breakthrough approval on wei Bmj Note Scopus	
Wolf, Sarał	2019 Inpatient drug reimbursement: Approaches for a dem International Journal of Technological)
Wonder, N	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	Š
Wong-Rieg	2017 Orphan disease overview: Status of rare disease and cJournal of Pharmacy and Pharma	1(
Wong-Rieg	2018 OP100 How Health Technology Assessment Is Adaptir International Journal of Technology)
Wood, J., S	2013 Multifaceted roles of ultra-rare and rare disease patie Drug Discov Today	
Wu, Jasma	2018 Abstract Pharmacoepidemiology and Drug	3
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 fraInternation 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 Pharmace Short Surve Scopus	
Zelei, T., M	2020 Pro63 Systematic Literature Review of Traditional and Value in Health	
Zelei, T., Mend	ola, 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	1
Zhang, Xiar	2021 A comprehensive analysis of rare diseases in China thi Molecular Genetics and Metabol	i
Zhang, Yan	2011 Abstracts of the 27th International Conference on Pha Pharmacoepidemiol Drug Saf	
Zhao, M. aı	2018 Rare Diseases: Drug Discovery and Informatics Resour Interdiscip Sci	
Zuluaga Sa	2019 Pro14 Improved Quality of Life and Life-Years in Patie Value in Health	



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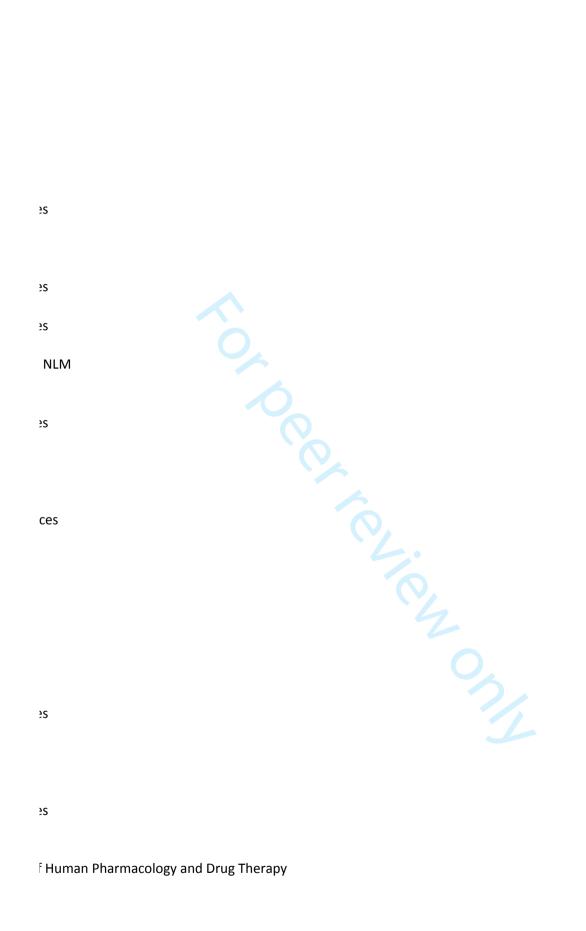


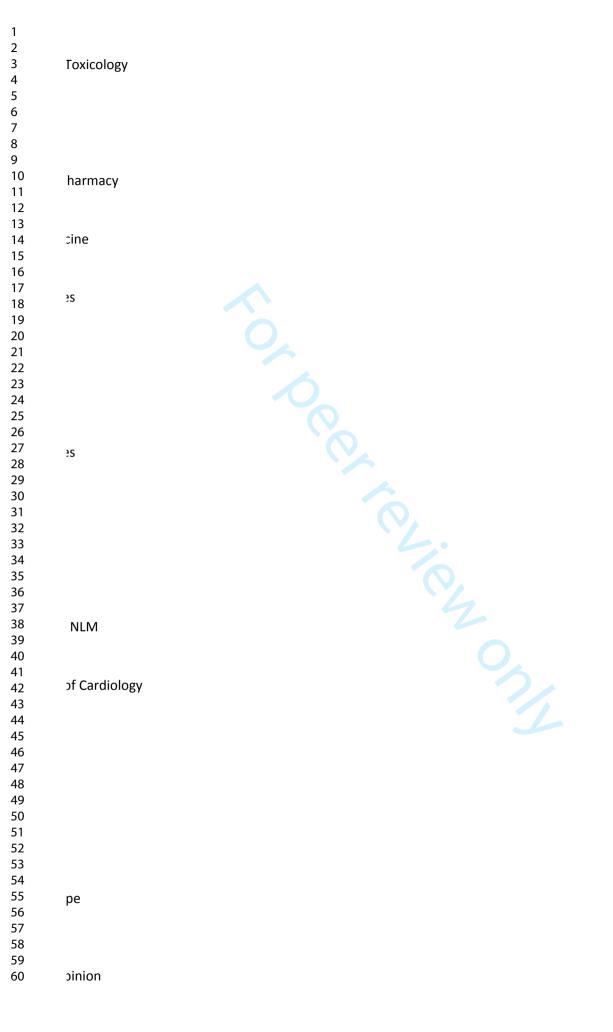


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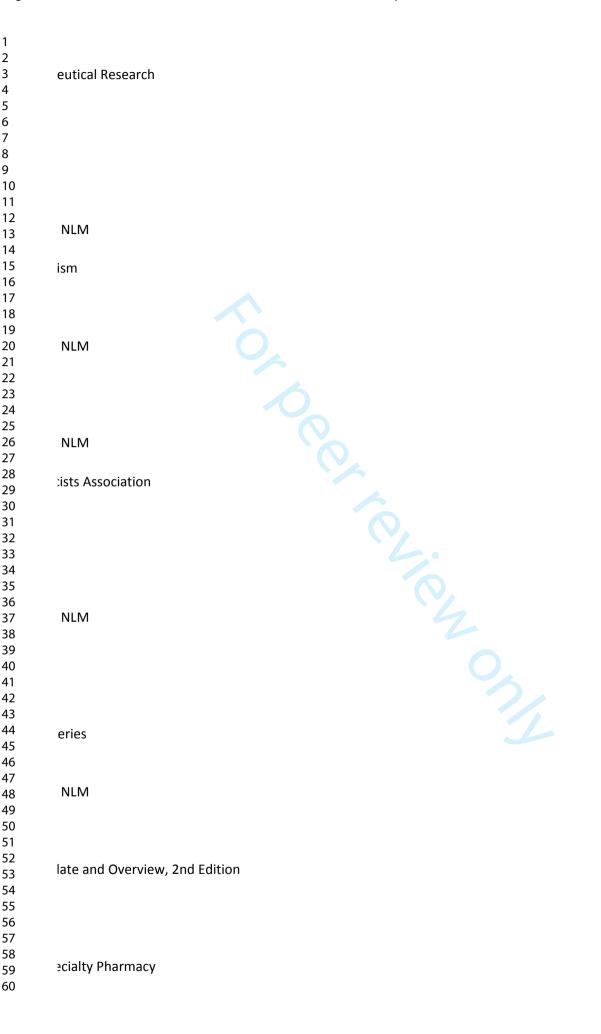
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Supplementary Table 3: List of included studies

	Country/	Study	۸٠		Definition S		
Year	Jurisdiction / Organization	design	Aim	RD	OD Or u	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 Pharmachus and that are generally not considered to be attracted to commercial development. Generally, orphamical products are used in treating or preventing rare to me.		
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 dispersional conditions that by definition, affect fewer than 2000 per ic people (or up to 1 in 1300) in the United States. and		
2003 ^[20]	United States; Paris, France/ European Medicinal Evaluation Agency	Review	To analyse the American and European experience on the Orphan Medicinal Products.	eet.	A medical product can receive the designating and and orphan medical product if it can be established to a finite intended for the diagnosis, prevention, or treatment if if-threatening or chronically debilitating and affecting not more than 5 in 10 thousand person in 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 the drug- intended to treat either a rare disease or more common- disease where the sponsor cannot make any prob- As per the definition US FDA, Orphan drugs are those drugs used in diseases or circumstances which course infrequently in USA, that there is no reasonable expectation that the cost of developing and makingly 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 of SFDA designated orphan drug with t-IND (toptameno Investigational New Drug) in some cases suching when the drug is intended for the treatment of a serious or life threatening disease, when no alternative and treatment is available, and thirdly, the product in the process of clinical trials and in an active 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.	nologii		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 interested for the prevention, treatment or diagnosis of rare disease has made necessary the creation of a number of incentives to stimulate the development of sucception of the stream of the development of sucception of the sucception of the development of sucception of the EU a medicinal product to treat rare diseased of either a demonstrated insufficient return on investment or the rarity of the condition and, the absence satisfactory method of diagnosis, prevention of treatment of the condition concerned is authorized, of it such method exists, the assumption that the product of the product of the condition concerned is authorized.		

Countr	Study	A		Definition 🚆 🗟	00	
Year Jurisdict Organiza	on /	Aim	RD	OD SE S	URD	UOD
	decian		RD	will be of significant benefit to those affects by the condition. -Criteria for orphan designation are the following risstly, a criterion is based on the low prevalence ("ngb")" of the condition, i.e., condition affecting not more wan 5 is 10,000 persons in the European Union. Alternatively, the sponsor can apply for more frequent condition the sponsor can apply for more frequent condition is unlikely that the marketing of the medicinal condition is unlikely that the marketing of the medicinal condition in the Community would generate sufficient that is unlikely that the marketing of the medicinal condition in the community would generate sufficient that is unlikely that the marketing of the medicinal condition in pushing the investment by the sponsor. Secondary of debilitating nature of the condition is justified that sponsor is invited to provide any scientific and medical references that may support the life-the angular medical references that the support the life-the angular medical references that the medicinal provided will be a support to the support of significant benefit to those affected by that challenges and the support that the medicinal production is such methods exist, that the medicinal production is supported to demonstrate the support of significant benefit to those affected by that challenges are supported to demonstrate the support of significant benefit to those affected by that challenges are supported to demonstrate the support of significant benefit to those affected by that challenges are supported to demonstrate the support of significant benefit to those affected by that challenges are supported to demonstrate the support of the s	7 CD 25 CD 2	UOD
		/ _		prevention, or treatment of the condition in questic for if such methods exist, that the medicinal production of significant benefit to those affected by that conditions		
2006 ^[24] USA Orphai Act, Euro		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.	mining,		
2008 ^[25] United St	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	omjoper Ni trainin		
United Sta America, Jap Australia, Taiwa	nn, EU, and 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.	g, and sir	hminom	
United St. 2010 ^[27] Orphan Drug 1983		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 agena.	1	
2010 ^[28] United St. Orphan Dr.				The Act initially defined an orphan drug on the sais of unprofitability: one intended for the diagnosis, to the orphan drug on 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 of condition of interest in the United States as a surrogation of the lack of profitability.	2* *	
2010 ^[29] United State Office of Diseases Re	Rare Book-	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	pout/guidelines.xhtml		

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World nisation, pan and States Book- Chapter Chapter Review O, US	Aim	million to 30 million people in the United States have a rare disease or condition." -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. Acustralia, 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."	OD Enseignement Spanlary 2025. Doubling for uses related to the spanlary spanlary spanlary that is intended to treat a rare disease or conditions that is intended to treat a rare disease or conditions affects fewer than 200,000 people in the Uniting		UOD
es/The ug Act Review		disease or condition." -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	7 on 25 January 2025. Down Enseignement Enseignement of the state of t		
es/The ug Act Review	10 /0	-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	Innuary 2025. Down Enseignement uses related to the south that is intended to treat a rare disease or conditions.		
ug Act Review	0/0		that is intended to treat a rare disease or condition affects fewer than 200,000 people in the United Section 200,000 people 200,000 peop		
) lie	mi		affects fewer than 200,000 people in the Unit		
J. US General Japan, review ia:	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 in significant unmet medical needs and are referred orphan drugs because, as described by EUEDITIA (2011c), the pharmaceutical industry has little under normal market conditions in developing an 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	
n Abstract	We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU.	1/0,	the diagnosis, prevention, or treatment of life-thattening		
la 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.	and sim		
(Egypt, y, Iraq, abia, syria, trab ' UAE, rdan, Dman, Dman, Policy Forum and us the ian of the and the trip			on June 7, 2025 at liar technologies. An orphan drug is a drug developed specificallygier rare medical condition		
tates 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. 	Bibliogra		
(I)	Abstract Egypt, Iraq, joia, ria, ab JAE, an, man, tar, nd ts the n the dthe p	Abstract We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU. 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. Egypt, Iraq, via, ria, ab JAE, an, man, tar, and tar, and tar, and tar, and tar, and the man of	Abstract Abstra	We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU. 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. The Canadian Organization of Rare Diseases (CORD) defines a rare disease as one that afflicts less that 1 person in 200 000. The Canadian Organization of Rare Diseases (CORD) defines a rare disease as one that afflicts less that 1 person in 200 000. An orphan drug is a drug developed specifically of the properties of the prop	Abstract Abstra

	Country/	Study	A ****		cted by copyright.	36/bmjopen-2024-08	
Year	Jurisdiction / Organization	design	Aim	RD	OD c	S 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.			
012 ^[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.	Enseignement Superieur (, iding for uses related to text and dat	2025. Downloaded f	
012[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 diseases.	rom ht	
012 ^[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 Policinal Policinal Policinal Infe-threatening and severely deminated diseases with no other treatment options to accumproved drugs prescribed by their practitiones approved drugs prescribed by their practitiones. -In Korea, the Orphan Drug Centre supplies readicing for diseases affecting fewer than 1 in 20,000.	p://bmjop	
)13 ^[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 trea	ı Ş	
013 ^[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 number of patients affected by the disease (<2020001 patients and <5 in 10,000 EU patients). The OU a requires that a satisfactory alternative treatment is available or that the new drug is significantly begin the drugs currently marketed.	use 1857 1900 1900 1900	
013 ^[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 treatment of a life threatening or chronic debilitatic condition. - The prevalence of the condition, for which the ON (orphan medicinal product) is intended, must be let than 5 in 10,000° - OMP has to fulfil following criteria: 1. Seriousness of the condition the investigated drugst be intended for diagnosis, prevention, treatment of a life-threatening or chrodebilitating condition.	Agence B	

V	Country/	Study	Aim	Definition 8			
Year	Jurisdiction / Organization	design	Ailli	RD	OD OD	URD	UOD
			\O_\		2. Low prevalence/irretrievable investment the prevalence of the condition, for which the MP in intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to be nearly sufficient return to justify the investment—in some situations, the condition is defined as a disease of another frequent condition. To accept the state it is needed to prove that the subset is reading it is needed to prove that the subset is reading it is needed to prove that the subset is reading it is needed to prove that the subset is reading to the condition per se. 3. Medical need No other treatment is one, the designated OMP must provide a significant is one, the designated OMP must provide a significant benefit over the existing method. The significant is given on the basis of/upon clinically setting advantage or major contribution to patient of the CK-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)	rom ABES a mir		
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 500 000 of the incidences in newborn 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, present, on treat rare diseases or pathologies that are serior or life threatening, and whose development costs are surrior 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	similar technolo		
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: in detect treat, prevent, or diagnose diseases or condition 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)	ence Biblio		
			For peer review o	nly - http://bmjopen.bmj.com/site/ab	graphique d		

¥7	Country/	Study	Aim		Definition = 8		
Year	Jurisdiction / Organization	design	Aim	RD			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. 	5527 on 25 January 2025 Enseignem cluding for uses related		
2014 ^[48]	Poland	Abstract	The aim of this study was to identify the cost-effectiveness threshold for an orphan designation in Poland.	e _{er}	According to criteria specified by the European Medicines Agency (EMA) a medicine must me a pictoriteria to qualify for orphan designation, criteria to qualify for orphan designation, criteria to qualify for orphan designation, criteria to qualify for orphan designation or diagnosis of a disease that life-threatening or chronically debilitating allows prevalence level in the European Union (EU) of the prevalence level in the European Union (EU) of the prevalence sevel in the European Union (EU) of the prevalence sevel in the European Union (EU) of the prevalence satisfactory method of disease diagnosis, procuring treatment or if such method exists, the drug multiple significant benefits to patients. In Poland there is no specific formal three specific orphan designations, there is only a general effectiveness threshold that equals 3 x GDP (EQCEA) or ICER/LYG (EQCEA) 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	Al trainii		
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 are not diagnosis, prevention, or treatment of life threatening or very serious diseases affecting less than 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 not products intended for only a small number of actient 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.		technologies.	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.	Biblio		
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V	Country/ Jurisdiction /	Study	Aim		Definition 📜 🗟		
Year	Organization	design	Allii	RD	OD Clu	URD	UOD
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." 	noluding for uses r		
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 ultrarare 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	ary 2025. Downloaded from http://bmjopuseignement Superieur (ABES) . seignement Superieur (ABES) . related to text and data mining, Al train	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	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 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 Drughan drug legislation by the U.S. Food the Drughan drughan drughan drughan development cost of develop drugs that have low development cost or treat rare diseases."		
2015 ^[58]	United States (US) and European Union (EU),	Poster/Abstra ct 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 at treating rare diseases or disorders OD tend to consider the prevalence of the dicesses and the estimation of the population affected by the session of the population affected by the session of the population affected by the session of th		
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			
2016 ^[60]	Italy	Review	For peer review o	by the European Union (EU) as life-threatening or chronically nly - http://bmjopen.bmj.com/site/ab	grap phique nout/guidelines.xhtml		

	Country/	Study	A :		Definition 🗒 🗟		
Year	Jurisdiction / Organization	design	Aim	RD	OD CL	URD	UOD
				debilitating conditions whose prevalence is so low (less than 5 per 10,000)	iding		
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)	for u		Ultra-orphan drug (prevalen ≤1:50,000)
2016 ^[62]	France	Poster/Abstra ct 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 treate 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 were excluded due to the short implementation; and the prevalence was calculated as the rate per oppulation using the number of patients with the calculation of the prevalence was calculated as the rate per oppulation using the number of patients with the calculations of the prevalence was calculated as the patients with the calculations of the prevalence was the patients of the prevalence when the patients with the calculations of the prevalence was the patients of the prevalence when the patients with the patients of the prevalence was the patients of the prevalence when the patients of the		
2016 ^[64]	Asia-Pacific, Australia, Japan, Singapore, South Korea, and Taiwan	Poster/Abstra ct 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.	0	designation: 0.9 in 10,000 - Japan: Prevalence threshold for orphan additions of the signation: 4.9 in 10,000 - Singapore: Prevalence threshold: 4.0 in 10,000 - South Korea: Prevalence threshold or orphan additions of the signation: 4.0 in 10,000 - Taiwan: Prevalence threshold or orphan additions of the signation: 4.0 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.		3. B.	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	ng, Al tr		
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"	61	Orphan medicinal products (OMPs) are used to severe life-threatening diseases with no or limited 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	ilar techno	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe (EU regulation 536/2014).	
2017 ^[69]	French	Poster/Abstra ct 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 os been developed specifically to treat a rare disestation referred to as an orphan disease. Often sector and disabling, affecting a limited number of people (that 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).	Europe). Gence Bibliographique applique appliqu		

¥7	Country/	Study	A :		Definition				
Year	Jurisdiction / Organization	design	Aim	RD	OD clu		UOD		
2017 ^[71]	UK, England, and Wales	Poster/Abstra ct 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		7 on 25 Ja Iding for u	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.	nuary 2025. Downloaded fro Enseignement Superieur (A ses related to text and data				
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	raded from the control of the contro				
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 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)	p://bm, ig, Al tr	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.	101	The disease prevalence threshold in the EU for appropriate drug designation is well-defined at ≤ 5 per 10.0 mg.				
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 Genetic Society of the Chinese Medical Association, experts mainly in the field of medical genetics proposed that (any dispases 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 definition, orphan drugs are intended for demonsing 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 the particular indication. - Certain special HTA criteria are applied the orphandrugs: 1. Higher P values for small sample sizes 2. Use of surrogate endpoints 3. Additional benefit is considered proven if the budgen impact is less than €30 million per year for particular indication. - Higher therapeutic benefit is automatically recognized for orphan drugs because these drugs had to proven 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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Year	Country/ Jurisdiction /	Study	Aim		Definition 🚊 🗟	3	
rear	Organization	design	Allii	RD	OD C	URD	UOD
					iding for		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 ALSThis 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 20,000 persons and 50,000, respectively. The EU defines rare diseases as fewer than 5 per 10,000 persons	or uses related to		
2018[80]	UK, England	Poster/Abstra ct only	This research aims to identify, compare, and evaluate willingness to pay (WTP) thresholds across countries		WHO recommends a WTP of <3 times Process		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.	erieur (ABES) . erieur (ABES) . and data mining.	Rare diseases are "singular cases" or "individual cases", which are considered "ultra-rare	
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	training, an	-	
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.	similar		
2018[85]	France	Poster/Abstra ct 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 opinions and designations are typically indicated in conditions that have a prevalence of below 5 in 2000 0		
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 disconsisting the Company of the Compa		
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 paediatries and adults.	A rare disease was defined as a condition with a prevalence of \$\leq 620\frac{million persons.}\$	s.	Ultra-rare diseases (affecting	
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	ogra		
			For peer review o	nly - http://bmjopen.bmj.com/site/ab	oout/guidelines.xhtml	:	

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Year	Jurisdiction / Organization	design	Aim	RD	OD O	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.		Ense uding for uses r	7 on 25 Januar	
2019 ^[90]	UK	Abstract	Corp		- For a drug to be appraised via the HST proces	2025 Down	
2019 ^[91]	UK	Poster/Abstra ct 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	004	ur (ABI data m	<u> </u>	
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.	· (e)	OMPs are drugs intended for the treatment of conditions affecting less than 5 in 10,000 peops. In the EU. AIFA may grant a medicine the status of impostative 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.	101	Treatments for diseases with a prevalence of <5 \$\frac{1}{10,000}\$ in the EU, which are life-threatening or severely washing and have no satisfactory treatment available, a granted orphan designation by the European Medicines Agenc (EMA)		The NICE Highly Specialis Technology Program (HSTP) and the SMC consicultra-orphan to be <1 in 50,0 and meeting other specialis 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	sim	com/	
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 prevention, or treatment of life-threatening are very serious conditions that affect no more than 5 (are diseases) in the European Union (EU).	ح	
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	nologies.	e 7. 2025 at Agence Bi	
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	, canada a process	Many of the treatments developed for rare diseases wil have an Orphan Medicinal Product (OMP) designation indicating that they are likely to deliver benefit in an area	8	
2020[97]	Belgium		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.		

V-	Country/	Study	A :		15. ir				
Year	Jurisdiction / Organization	design	Aim	RD	OD 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 be a consult or uncontrolled trial				
2020 ^[08]	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 or the second of the se		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 the drug intended to treat a life-threatening or changed debilitating disease, provided a maximum prevention. Europe of 5/10,000 and when no satisfactory a method can be authorised, or, if such a method can be a method can				
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 lifethreatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union.	bmjopen.bmj. Al training, an	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 than 200,000 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 productured in 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 rehabilition of rare diseases. - Orphan drugs are also defined by their availability and developed, imported, or registered owing so commercial returns and unfavorable marketing conditions. Countries/areas such as China and Vietnam acknowledged orphan drug designation from referenced competent authorities. A medicinal product shall be designated as an orphan medicinal product if its sponsoccan establish: (a) that it is intended for the diagnosis, prevention of treatment of a life-threatening or chronically debilitating condition affecting not more than five if 10 thousand persons in the community when the papilication is made, or that it is intended for the diagnosis is intended for the diagnosis.				
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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) A	osis, prevention or treatment of a life or condition in the community and the orithout it was it is unlikely that the marketing of the inal product in the community would senerate ent return to justify the necessary in the original product in the community of the senerate ent return to justify the necessary in the original side of the condition in product with the senerate ent return to justify the necessary in the original side of the condition in product with the senerate enter of the medicinal product the senerate of the medicinal product the spone or near the necessary in the product of the condition in the original product the spone or near the necessary in the necessary i
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500,000 population.	후 길
We sought to identify the regulations and policies related to market - South Korea: Rare disease defined as that affecting: Less than access for orphan drugs in five major markets from the APAC 20,000 people in Korea (i.e., <4 per 10,000 population)	<u>≅</u> . <mark>♀</mark>
China, Australia, Poster/Abstra Region with the sim of providing an overview of the factors Lapan. Rare disease defined as that affecting Less than 50 000	<u>⊒</u> . <mark>ĕ</mark>
Japan, South Korea, ct only designed to support sporsors of orphan medicinal products and part 10,000 population)	<u>.</u> 6
and Taiwan and Ta	- <u>-</u>
South Korea, and Taiwan 10,000 population.	ا ج ج ا
- Australia: Rare disease defined as that affecting less than 5 per	
10,000 population"	≟. →
	Korea, the Korea Ministry of Food and Drug
This paper reviews key factors that should be considered in the	related to the number of patients and the
process of development, regulation, and market access of orphan existence o	of alternatives. In other words, drugs used for
O21 106 South Korea Crisis South Korea drugs in South Korea with a particular focus on the pricing and disease with	of alternatives. In other words, drugs used for \$\frac{1}{2}\$ th 20,000 or fewer patients (population) in the
reimbursement review process.	nd diseases for which adequate treatments on
drugs havi	ve not yet been developed, or drues that
significant	tly improve safety or efficacy compred to tematives, are designated as OD.
existing att	ter not yet been developed, or and the stand ly improve safety or efficacy commend to termatives, are designated as OD. han Medicinal Product Regulation terms or the diagnosis, prevention, or of life-threatening or very serious conditions.
This review provides an overview of the strengths and limitations Solution of the strengths and limitations with low prevalence; occurring in less than one in 2,000 people OMPs as	products for the .diagnosis, preve g on, or
021 ^[107] UK Review of value assessment frameworks (VAFs) for the reimbursement of in Europe.	of life-threatening or very serious condition
orphan drugs in Europe and may serve as a guide for decision— makers. They are defined as life-threatening or chronically debilitating, that affect	Union
	Union Q
This study aimed to determine the most relevant criteria for the reimbursement of OMPs in Spain, from a multi-stakeholder -Rare diseases are diseases of low prevalence and high Orphan me	edicinal products (OMPs), which are intenden
perspective and using multi-criteria decision analysis (MCDA) complexity that can lead to death or chronic disability to diagnose	e prevent or treat rare diseases, have a shared
021 ¹⁰⁸¹ Spain Research The objective of this study was twofold; first, to review, discuss, - In Europe, rare diseases are defended as those pathologies that	y procedure for being designated as such in the
and reach a consensus on the most relevant criteria for decision-	y procedure for being designated as such in the Ultra-rare, affecting less than 1 person per 50,000 inhabitants."
making about pricing and financing OMPs in Spain; and second, opportunitie	ies for research, development, and marketing
to prioritize them according to their relative importance based on	ğ
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Year	Country/ Jurisdiction / Organization	Study design	Aim the preferences stated by different stakeholders, following the	RD	Definition OD	.08 <u>65</u> 2	URD	UOD
2021[109]	New Zealand	Online survey	MCDA methodology. 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		27 on 25 Janu Er uding for use		
				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 100,000 people nly - http://bmjopen.bmj.com/site/abo		ary 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l seignement Superieur (ABES) s related to text and data mining, Al training, and similar technologies.		
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Supplementary Table 4: Critical Appraisal Result

Critical Appraisal Result for Systemic Reviews and Research Syntheses studies

9 10 11 12 13 Studies 14 15 16	Q1) Is the review question clearly and explicitly stated?	Q2) Were the inclusion criteria appropriat e 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	s d io grand of the control of the c	Q10) Were recommendation s for policy and/or practice supported by the reported data?	Q11) Were the specific directives for new research appropriate?
10 1. 2018 [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	a 6 2 S	Yes	Yes
2. 2020 [84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	n S	Yes	Yes
3. 2021 [110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes) Yes	Yes	Yes
22 23 1. Crit 24	ical Appraisal Result for	Text Opinion	n studies		(0	4	etated position		://bmjopen.		

1. Critical Appraisal Result for Text Opinion studies

24						inir þe	
25 26 27	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?
2 8 29	1.2003 [3]	Yes	Yes	Yes	Yes	Y es ⊕	Yes
29	2.2005 [5]	Yes	Yes	Not applicable	No	n J	Yes
30	3.2006 [7]	Yes	Yes	Yes	Not applicable	es un	No
31	4.2009 ^[9]	Yes	Yes	Yes	Not applicable	es 7	Not applicable
3Z	5.2010 [11]	Yes	Yes	Yes	Yes	, 2 o jo s	No
33	6.2010 ^[12]	Yes	Yes	Unclear	No	9 es 02	No
34	7.2014 [33]	Yes	Yes	Yes	Yes	es a	Yes
35	8.2017 ^[51]	Yes	Yes	Yes	Yes	Yes >	Yes
36	9.2017 [111]	Yes	Yes	Yes	Yes	Unclea	NO
37	10. 2019 ^[78]	Yes	Yes	Yes	NO	Yes C	Yes
38	11. 1992 ^[1]	Yes	No	Yes	NO	Yes 👿	Not applicable
39	12. 2004	Yes	Yes	Yes	Yes	Yes 5	Not applicable
40	13. 2008 ^[8]	Yes	Yes	Yes	Yes	Yes 🙆	NO
41	14. 2010 ^[13]	Yes	Yes	NO	NO	Yes a	Not applicable
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3	15. 2011 ^[15]	Yes	Yes	Yes	Yes	<u>∯</u> es -08	NO
4	16. 2013 ^[25]	Yes	Yes	Yes	Yes	29	NO
5	17. 2013 ^[28]	Yes	Yes	Yes	Yes	27	NO
6	18. 2014 ^[37]	Yes	Yes	Yes	Yes	inges on	NO
7	19. 2016 ^[44]	Yes	Yes	NO	Yes	¥es 25	NO
8	20. 2018 ^[55]	Yes	Yes	Yes	Yes	Žes Ja	Yes
9	21. 2018 ^[59]	Yes	Yes	Yes	Yes	nu Eg	NO
10	22. 2018 ^[65]	Yes	Yes	NO	Yes	Jary 2025 Isejg∌em	NO
11	23. 2020 ^[80]	Yes	Yes	Yes	Yes	, 20 9 势 海	NO
12	24. 2020 ^[86]	Yes	Yes	Yes	Yes)25 egn læd	NO
13	25. 2020 ^[112]	Yes	Yes	Yes	Yes	. D	NO
14	26. 2020 ^[88]	Yes	Yes	Yes	Yes	TOWN	NO
15	27. 2021 ^[91]	Yes	Yes	Yes	Yes	P.TX Gn ogn	Yes
16	28. 2010 [14]	Yes	Yes	NO	Yes	oac egje anc	No applicable
17	29. 2018 ^[61]	Yes	Yes	Yes	Yes	vnloaded Sugegeer ਮੌਮਰਮਹ ਕੋਰ	NO
18	30. 2021 ^[91]	Yes	Yes	Yes	Yes	a Se fro	NO

2. Critical Appraisal Result for Economic Evaluations studies

22										>		
223 24 25 26 27	Studies	Q1) Is there a well- defined questio n?	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?	trainstead to investigate a univertainty in attinutes of cost or si-colored to colored t	Q10) Do study results include all issues of concern to users?	Q11) Are the results generalizabl e to the setting of interest in the review?
20	1.2012 [21]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Yes
29	2.2014 [34]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	No applicable	Yes	Yes
30	3.2014 [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	4.2018 [63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
32	5.2018 [67]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Yes	olo	Yes	Yes
33	6.2017 [57]	Yes	Yes	Yes	Yes	Yes	Unclear	NO	NO	O2: O2:	Yes	Yes
34	·									5 at		
35 36 3. Critical Appraisal Result for Analytical Cross-Sectional Studies												

7							7	
8 9 Studies 0	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?	Q Were the outcomes measured in a valid and reliable way?	Q8) Was appropriate statistical analysis used?
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. 2012 [20]	Yes	Yes	Yes	Yes	Yes	Yes	<u>, r</u>	4 -08	Yes	Yes
2. 2015 ^[41]	Yes	Not applicable	nclud	6527	Yes	Unclear				

4. Critical Appraisal Result for Qualitative Research studies

9 10 11 12 13 Studies 14 15	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?	wary 2025. Downloade inseignement Superie es related for the participants for their voice participants for their voice adequate and represente represente	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 da d	Yes	Yes
18 _{2.2021} [92]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes a l	Not applicable	Yes
19 _{3.2021} [93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes Not application	Not applicable	Yes
204. 2013 [30]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Yes
2 1 ₅ . 2019 [59]	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes g	NO	Yes
22 23 24 25	Critical Appra	isal Result for	Prevalence Str	udies		"Vio		bmjopen. ∖\I training		

25 26 27 28 Studies 29	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?	Qö) Was there appropriate statistical analysis?	Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?
31 ¹ . 2016 [47]	Yes	Yes	NO	Yes	Yes	Yes	Yes	Yes	Yes
33 2. 2013 [26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes 2025	Not applicable

6. Critical Appraisal Result for Cohort Studies

U Studies I two groups I exposures I the I 2 I strategies to I groups/participants I the I tollow up time I up complete. I strategies to I	9	Q1) Were the	Q2) Were the	Q3) Was	Q4) Were	Q5) Were	Q6) Were the	Q7) Were	Q8) Was the	Q9) Was follow	Q10) Were	Q11) Was
	0 Studies	two groups	exposures	the	confounding	strategies to	groups/participants	the	follow up time	up cemplete,	strategies to	appropriate
similar and measured exposure comounting deal with free of the outcomes reported and and if and, were address approximation appr	1	similar and	measured	exposure	comounting	deal with	free of the	outcomes	reported and	and if not, were	address	арргорпас

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Supplementary Table 5: RDs definitions based on continents

Continent	Country, frequency	# of articles; (%)		(RD) definition of 25	Date	Adopted / developed
			Orphan Drug Regulation	Defines RD according to prevalence: "rare disease' means any disease of the disea	1993	
			RDA	, <u>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</u>	2002	
North America	US (25)	24 (26%)	ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare and or condition' means any disease or condition which occurs so infrequently have USA that there is no reasonable expectation that the cost of developing and making and pable in the USA a drug for such disease or condition will be recovered from sale where USA of such drug'.	1983	developed
North			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 expendition that the cost of developing and making available in the USA a drug for such disease condition will be recovered from sales in the USA of such drug' Rare disease as one that afflicts less than 1 person in 200 000.		
		2	CORD	Rare disease as one that afflicts less than 1 person in 200 000.		Aligned to EU
	Canada (3)	(2%)		Estimated that I in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease		
South	Chile (1)	1 (1%)		Required the disease severity to be ,life threatening, and severely- or chronically-,		
America	Peru (1)	1 (170)		debilitating.		
		2	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 is 200 people. (i.e., a prevalence of 5 or less per 10,000)	2021	
	UK (3)	2 (2%)	NHS	Some countries use additional definitions in situations where a conditional officially defined as rare. classifies all conditions that require specialized medical care as rare if they occur in <500 citizens yearly		
Europe	EU (36)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or derong ally debilitating diseases which are of such low prevalence (less than 5 per 16,000 persons in the European Union) that special combined efforts are needed to address than 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.		
Bur			European Commission	Defines rare diseases as ,life-threatening or chronically debilitating diseases & hich are		
			on Public Health	of such low prevalence that special combined efforts are needed to address then.		
			Orphan Drug	A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for	141/2000	
			Regulation	rare		
	Germany (1)	1 (1%)	EMA	prevalence of rare disease < 5/10 000 Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		
	Latvia (1)	1 (1%)		` ' 1		
	Netherlands (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) 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 (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) 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 givernate disease. Affecting <11/100,000 inhabitants or ,≤2000 Australians Prevalence threshold for orphan disease designation: 0.9 in 10,000		
Oceania				Diseases with a prevalence of 1.1/10 000		
				Diseases with a prevalence < 2000 individuals.		
	Australia (10)	10		Australia have set prevalence's of 1.16 per 100,000 individuals for a giver are disease.		
	()	(11%)		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 Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold		
	New Zealand (1)	1 (1%)	PHARMAC	Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold		
A -:-	` ′			than other nations that are from 5 to 76 per 100,000 people Japan diseases with a prevalence of 4.0/10,000		
Asia			\sim	sapan diseases with a prevalence of 4.0/10,000 Sapan disease with a prevalence with a prevalence of 4.0/10,000 Sapan disease with a prevalence with a prevale		
	Japan (13)	13		Intractable diseases, is a Japan-specific conception of diseases with (i) unknown		
	Japan (13)	(14%)		etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long reatment		
				The incidence rate is estimated to be ≤ 2.5 cases in 10,000 for Japan		
			Taiwan Foundation for	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical		
		_	Rare Disorders	coverage.	2000	
	Taiwan (7)	7	Physically and			
	()	(8%)	Mentally Disabled	RD is one type of disability	2001	
			Citizens Protection Act	i i i i i i i i i i i i i i i i i i i		
	GI: (5)	5	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidence fin Newborn babies.		
	China (5)	(5%)		Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 is 10,000, respectively.		
		-		Prevalence thresholds have been set at less than 1 per 20,000		
	South Korea (4)	5 (5%)		Prevalence threshold: <4.0 in 10,000		
		(3%)		< 20,000 people in Korea (i.e., <4 per 10,000 population) 6 5		
	Singapore (2)	2		Required the disease severity to be life threatening, and severely- or chronically-, debilitating.		
		(2%)	_	Prevalence threshold: 37.7 in 10,000		
	India (1)	1 (1%)	ORDI	Threshold for defining a disease as fare if it affilets 1 in 5,000 individuals	•	
	Armenian legislation (1)	1 (1%)		whether the patient will receive the necessary medicines for free or not		
	Philippines		The DOH, upon recommendation of the RDTWG,	ence Bi		
Africa	Kenya			Required the disease severity to be ,life threatening, and severely- or chronic dy, ,debilitating.		

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Continent	Country, frequency	# of articles; (%)		(RD) definition	en-2024 <mark>-0865</mark> 2	Date	Adopted / developed
Eastern Europe & Northern Asia.	Russia (1)	1 (1%)		Maximum prevalence for a rare disease is defined as 1 in 10,000	7 on 25		
South- eastern Europe & Southwester n Asia	Turkey (1)	1 (1%)	5	Affect no more than 1 in 100,000, which is 50 times less frequent than the Union definition. Rare disease affects at most 6.5 out of every 10,000 individuals.	inuaryopean Ensetunemer		
	WHO (5)	5 (5%)	Or (C	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.	/nloade		
	Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetic et smaller percentage is autoimmune or infectious disorders, in addition to cancers."	og∰ and a Madare m ∃		

The Rare Diseases Act (RDA; the Orphan Drug Act (ODA; the Food and Drug Administration (FDA); The Canadian Organization of Rare Diseases (CORD) (Construction of Rare Diseases (CORD)) (Construction of Rare Diseases

Continen	Country, frequency	# of articles; (%)		(RD) definition (RD) definition	Date	Adopt ed / develo ped
Europe	EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or hronically 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 criteriage through the standard technology appraisal (TA) process, with a cost-effectiveness threshold of £30 k/QALY, of £50 k/QALY when end-of-life criteria are met		
			EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs an 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)	

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Continent	Country, frequency	# of articles; (%)		(RD) definition (RD) definition	Date	Adopt ed / develo ped
			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 Defines orphan drug, as either having an official EU orphan designation or if it targets as as with a prevalence of		
			The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it target a sewith a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered receiving exists		
			Poland	There is no specific formal threshold for orphan designations, there is only a general case effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which 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: unmetatical 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 and the 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 the same approved to the European marketing authorisation procedure. budget impact is less than €50 million per year for the European marketing authorisation procedure.		
North America	US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a range see or condition, which is one that affects less than 200,000 persons in the USA' (which equates to approximately see 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, profession 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 1982 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease. condition of interestin 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 week 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 that 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 for 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		
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Supplementary Table 7: URDs definitions based on continents

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Continent	frequency	articles; (%)		(URD) definition	Date	developed
Europe	UK			Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 50,000 of the population (Hugheset al., 2005)		
} 5			NICE	Ultra-orphan diseases affect a very small patient population, defined by the hand Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of \$\frac{1}{2} \frac{1}{2} \frac{1}{2},000\$		
	Alberta		NICE	URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE rta).		
3	England		Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in English population)		
2	Ontario			An incidence rate of fewer than 1 in 150,000 live births or new diagnoses por year in Ontario		
3				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		
3	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
2 3 4 4 5 5				rare disease there are "singular cases" or "individual cases", which are conselered "ultra-rare diseases" (prevalence: <1:10,000), including, for example MuSK-positive management gravis (prevalence 0.05-0.65/100,000 or congenital myasthenic syndrome (CMS)		
5				ultra-rare diseases (affecting <20/million persons)"		
3				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."		

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					en-2024 >opyrigh		
	Continent	Country, frequency	# of articles; (%)		(URD) definition (URD) definition	Date	Adopted / developed
					ultra-orphan (prevalence: <1:50,000)		
0				NICE Highly Specialised Technology Programme (HSTP) and the SMC	The NICE Highly Specialised Technology Programme (HSTP) and the SM to be <1 in 50,000 and meeting other specialised criteria. "		
3 4 5 6 7	s	Supplement	ary Tabl	e 8: UODs definition	ultra-orphan (prevalence: <1:50,000) The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained of the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained to the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained to the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained to the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained to the special sed criteria. " The NICE Highly Specialised Technology Programme (HSTP) and the SM contained to the special sed criteria. " The NICE Highly Specialised Technology Program		Adom

Supplementary Table 8: UODs definitions based on continents

			<u> </u>		
Continent Counti			(UOD) definition	Date	Adopt ed / devel oped
			Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 ♣ r 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 patents die.: ultra-orphan drugs)		
			Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence 1:50,000) were consistent in most countries.		
Scotlar	d	The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting gewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland		
Englar	d	_	HST for ultra-orphan indications Euro113,900-341,700/QALY in England		
		WHO	WHO recommends a WTP of <3 times GDP per capita/QALY		
Scotlar	d		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 faculate 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 Cast 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 per 50,000 persons"	2000	

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RDs Qualitative and Quantitative descriptors and themes

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

ODs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Themes	Qualitative Descriptors
Natur e of Produ ct	1. Medical Product	ie d	21. No alternative treatment
	2. Agent	Jnm t Nee	22. Treatment Price
	3. Biological Products	Ď Z	23. Lack profit

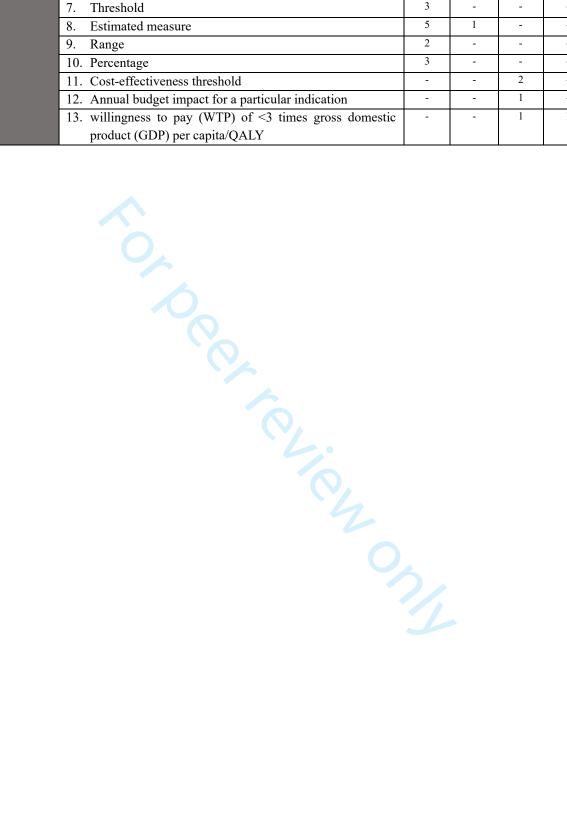
	7. Drug				
	8. Rare Diseases		28. Clinical added value		
's	9. Life-Threatening Condition	s s	29. Improve safety or efficacy		
Disease nature affecting the pt.'s Society.	10. Debilitating Disease	Benefits from taking the treatments	30. Product will be of significant benefit		
ng t	11. Disease with a limited	ned aki rea	31. New drug is significantly		
ctir '.	number of specialist	Be t t	better than drugs currently		
ffe	treatment centers		marketed		
re affec Society.	12. Serious Condition		32. Indications		
utur S	13. Rare medical condition		33. Diagnosis		
3 ne	14. Interactable diseases		34. Treatment		
ase	15. Unmet medical needs	Indication	35. Prevention		
ise	16. Common disease where		36. Prophylaxis		
	the sponsor cannot make any profit		37. Rehabilitation		
	17. Low prevalence				
Population	18. Small number of patients				
Characteristics	19. Population	• //			
	20. People				
Quantitative De	scriptors				
	1. Prevalence				
es	2. Cost-effectiveness threshold				
sur	3. Annual budget impact for a	particular indica	tion		
Measures	4. Number of cases reference				
2	5. Willingness to pay (WTP) o capita/QALY	f < 3 times gross	domestic product (GDP) per		
	Suprim VIIII		~//		

Theme	Qualitative	Theme	Qualitative		
Nature	1. Very rare conditions		1. Indications		
	2.Medicines	Indication	2. Treat		
	3.Drug		3. Approved for use		
	4.Disease	Danulation	1. Patients		
	5.Condition	Population Characteristics	2. Persons		
Theme	Quantitative	Characteristics	3. People		
	1.Prevalence				
Measurements	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
	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	-
Nature	9. Intractable	1	-	1	-
Nat	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
Σ:	19. Unknown Etiology	1	-	-	-
golo	20. Genetic	7	-	1	-
Etiology	21. Hereditary	1	-	-	-
as re ti	22. Rare Diseases	40	4	16	=
Diseas e nature affecti	23. Disab* (Disability & Disabling)	5	-	2	-
D E	24. Life -Limiting	1	-	0	-

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	-	-	1	1
product (GDP) per capita/QALY				



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

2 Literature Review

- 3 Ghada Mohammed Abozaid^{1,2*}, Katie Kerr¹, Hiba Alomary³, Hussain Abdulrahman Al-
- 4 Omar^{4,5,6}, Amy Jayne McKnight¹
- *Corresponding author: gabozaid01@Qub.ac.uk.
- 6 Abstract:

- **Objectives** This study sheds light on the available global definitions, classifications and criteria
- 8 used for rare diseases (RDs), ultrarare diseases (URDs), orphan drugs (ODs), and ultra-orphan
- 9 drugs (UODs), and provides insights into the rationale behind these definitions.
- 10 Design A systematic literature review was conducted to identify existing definitions and the
- criteria used to define RDs, ODs, and their subtypes.
- 12 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
- 14 1985 to 2021.
- 15 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.
- 18 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 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 noncancerous 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-

Patient and public involvement

to-date evidence in the analysis.

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

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

individuals in Australia.

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

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%),

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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



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

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258 Tabl	e 1: A sun	ımary of RDs defini	BMJ Open BMJ Open by copyrigh tions is provided based on the country	
Country, frequency	# of articles; (%)		(RD) definition (RD) definition (RD) definition	Date
	24 (26%)	Orphan Drug Regulation RDA	Defines RD according to prevalence: "rare disease" means any disease or condition that affects less than 200000 persons in the USA.	1993 2002
US (25)		ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare descriptors' means any disease or condition which occurs so infrequently in the USA and there is no reasonable expectation that the cost of developing and making available in the USA of 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 the USA or affects >200000 in the USA and for which there is no reasonable expectation that affects of developing and making available in the USA a drug for such disease or condition with the decovered from sales in the USA of such drug'	
Canada	2	CORD	Rare disease as one that afflicts less than 1 person in 200 000.	
(3)	(2%)		Estimated that 1 in 12 Canadians, or about 2.8 million individuals, may be living with a rare disease	
	2 (2%)	the Rare Disease Framework	Defined RD based on prevalence, as a condition affecting fewer than 1 in people. (i.e., a prevalence of 5 or less per 10,000)	2021
UK (3)		NHS	Some countries use additional definitions in situations where a condition of officially defined as rare. classifies all conditions that require specialized medical care as rare of they occur in <500 citizens yearly	
EU (26)	35 (38%)		Rare diseases, including those of genetic origin, are life-threatening or claron early 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 state of life or socioeconomic potential.	
EU (36)		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 (RD) definition inc.	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 diseases with a prevalence of 4.0/10,000	
	13		<50,000 patients in Japan	
Japan (13)	(14%)		Intractable diseases, is a Japan-specific conception of diseases with (i) una problem etiology (ii) no	
	(1770)		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	
	7 (8%)	Taiwan Foundation	Diseases affecting < 1 in 10,000 that are officially recognized are eligible an edical coverage.	2000
		for Rare Disorders	Discases affecting < 1 in 10,000 that are officially recognized are engions in incurcal coverage.	2000
Taiwan		Physically and	lata	
(7)		Mentally Disabled	RD is one type of disability	2001
		Citizens Protection	ning	
		Act	, <u>A</u>	
China (5)	5 (5%)	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidences who have been babies.	
			Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 to 10,000, respectively.	
Courth	5 (5%)		Prevalence thresholds have been set at less than 1 per 20,000	
South Korea (4)			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.	
			Fraguency 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%)		Disease inventory, it is evident that the majority of RDs are of genetic etiology, and a smaller	
(1)			percentage is autoimmune or infectious disorders, in addition to some rare cageers."	

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).

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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 $\leq 1.50,000$ 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

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Country, frequency		(URD) definition
UK		Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 1 in 50,000 Bathe population (Hugheset al., 2005)
	NICE	Ultra-orphan diseases affect a very small patient population, defined by the National Instruction 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., ~ land (i.e., ~
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)"
		d similar technologies. 17 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 ϵ 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.

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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



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1 Tabl	BMJ Open Table 3: A summary of ODs definitions is provided based on the country. BMJ Open St. 4 Summary of ODs definitions is provided based on the country. St. 36 bn jop population of Open summary of ODs definitions is provided based on the country.						
Country, frequency	# of article s; (%)		(RD) definition (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 ELE people or that it is unlikely that marketing the drug in the EU would generate sufficient benefit to 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 Head in the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, with a cost-effectiveness threshold the standard technology appraisal (TA) process, which is the standard technology app				
		EURORDIS	Drugs used in the treatment of rare diseases address significant unmet receiped 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 on patients suffering from very rare condition.	(2011c			
			The Orphan Medicinal Product Regulation	Defines OMPs as products for diagnosis, prevention, or treatment of life-the earning 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 of igtargets 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 general cost- effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (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's 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				

			BMJ Open BMJ open	Page 2
Country, frequency	# of article s; (%)		(RD) definition (RD) definition	Date
			affected by the disease. condition of interest in the United States as a surro attended to the lack of profitability." Orphan product, as one that is intended to treat a rare disease or condition at a ffects fewer than	
			200,000 people in the United States OR as a product which will not be prograble within seven years of approval by the FDA	
		the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.	
Korea (2)	2 (2%)	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 ignificantly 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 the developed, imported, or registered owing to low commercial returns and under the developed of the developed.	
			conditions. Agence Bibliographique de Stranger de la com/site/about/guidelines.xhtml	
			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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 the provided approval for the treatment of diseases that affect fewer than 1,000 patients, underscoring their exceptionally granted for the fighty. The England, the Highly Specialised Technologies (HST) Programme has implemented cost thresholds for UODs, while the WHO provides specific recommendations for cost thresholds for UODs, while the WHO provides specific recommendations for cost thresholds for UODs definitions affecting fewer than 1 is 50,000 individuals. Furthermore, Seotland 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 of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals. Table 4 provide a summary of UODs definitions based on the country of the provide approximately 100 individuals.

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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	new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people—approximately 100	
	government	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 symbol or less or around 100	Effective from
		people in Scotland, which will mostly be used to facilitate early access programs and reimbursement processed 3 %	October 2018
		Drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons" new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 per legis, approximately 100 people or fewer in Scotland HST for ultra-orphan indications Eurol 13,900-341,700/QALY in England WHO recommends a WTP of ≺3 times GDP per capita/QALY New definition for ultra-orphan drugs: "medicines that are used to treat a condition with a prevalence of 1 in 30,000 per 10,000 pe	
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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)

Quantitative criteria

(Supplementary Table 10).

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

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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.

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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

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** ¹Centre 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 ²Pharmacy 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 ³Department of Applied Linguistics, College of Languages, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. https://orcid.org/my-orcid?orcid=0000-0001-7476-0561 ⁴Department 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 ⁵Health Technology Assessment Unit, College of Pharmacy, King Saud University, P.O. Box: 2457, Riyadh, Zip Code: 11451, Saudi Arabia. ⁶Center of Health Technology Assessment, Ministry of Health, Riyadh, Saudi Arabia. Acknowledgements We would like to thank the library information specialist, Richard Fallis from Queens Belfast University, who revised the search terms and strategy used in this SLR. Contributions GMA, AM, and HAA contributed to study conceptualisation, study design and revised the manuscript for important scientific content. GMA, KK, and HiA contributed to data acquisition. All authors contributed to the interpretation of results and approved the final version submitted for publication and agreed to be accountable for all aspects of this research. GMA is responsible for the overall content as guarantor.

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Competing interests None declared

- 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.
- References:
- 1. Aronson J. Rare diseases, orphan drugs, and orphan diseases. BMJ. 2006;333:127-8.
- 2. Fehr A, Prütz F. Rare diseases: a challenge for medicine and public health. Journal of health
- monitoring. 2023;8:3-6.

- 3. Gorini F, Coi A, Mezzasalma L, Baldacci S, Pierini A, Santoro M. Survival of patients with rare
- diseases: a population-based study in Tuscany (Italy). Orphanet Journal of Rare Diseases. 2021;16(1):1-
- 9.
- 4. Repetto GM, Rebolledo-Jaramillo B. Rare Diseases: Genomics and Public Health. Applied
- Genomics and Public Health: Elsevier; 2020. p. 37-51.
- 5. Ma N, Nie W, Wang T, Li C. Current status and countermeasure of the research on rare diseases in
- China. Life Science Journal. 2013;10(2):11-4.
- 6. Forum WE. World Economic Forum Global Data Access for Solving Rare Disease—A Health
- Economics Value Framework 2020 [
- 7. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare disease terminology
- and definitions—a systematic global review: report of the ISPOR rare disease special interest group.
- Value in health. 2015;18(6):906-14.
- 8. Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer becoming
- a rare disease? A global assessment of predicted incidence trends to 2035. Gut. 2020;69(5):823-9.
- 9. Roeleveld N, Zielhuis GA, Gabreëls F. The prevalence of mental retardation: a critical review of
- recent literature. 1997.
- 10. Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune
- bullous diseases: pemphigus and bullous pemphigoid. Archives of dermatological research.
- 2015;307:291-8.
- 11. Abozaid GM, Kerr K, McKnight A, Al-Omar HA. Criteria to define rare diseases and orphan drugs:
- a systematic review protocol. BMJ open. 2022;12(7):e062126.

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- 12. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare Disease
- Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special
- Interest Group. Value Health. 2015;18(6):906-14.
- 13. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating
- cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet.
- 2020;28(2):165-73.

- 14. Alahdal H, Alshanbari H, Almazroa H, Alayesh S, Alrhaili A, Alqubi N, et al. Consanguinity,
- awareness, and genetic disorders among female university students in Riyadh, Saudi Arabia. Journal of
- Biochemical and Clinical Genetics. 2021;4(1):27-34.
- 15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items
- for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews.
- 2015;4(1):1-9.
- 16. Dissementation UoYCfRa. Guidance notes for registering a systematic review protocol with
- PROSPERO. National Institute for Health Research. May 2016.
- 17. Innovation VH. Covidence systematic review software Melbourne, Australia February 4, 2019
- [Available from: https://www.covidence.org/.
- 18. Couban R. Covidence and Rayyan. Journal of the Canadian Health Libraries Association / Journal
- de l'Association des bibliothèques de la santé du Canada. 2016;37.
- 19. Tools CA. Internet. New York: UNICEF multiple indicator cluster surveys Guidelines and
- templates facilitate planning and design of surveys and help avoid pitfalls in implementation [cited 2014
- Jul 14] Available from: http://www.childinfo.org/mics4_tools.html. 2020.

- 20. Barker TH, Stone JC, Sears K, Klugar M, Leonardi-Bee J, Tufanaru C, et al. Revising the JBI
- quantitative critical appraisal tools to improve their applicability: an overview of methods and the
- development process. JBI Evid Synth. 2023;21(3):478-93.
- 21. Baran A, Czech M, Kooiker C, Hołownia M, Sykut-Cegielska J. Bridging East with West of
- Europe-a comparison of orphan drugs policies in Poland, Russia and the Netherlands. Acta Poloniae
- Pharmaceutica-Drug Research. 2018;75(6):1409-22.
- 22. Regulation OMP. Regulation (EC) No 141/2000 of the European Parliament and of the Council of
- 16 December 1999 on orphan medicinal products. Off J. 2000;18:15.
- 23. Mukherjee S. The United States Food and Drug Administration (FDA) regulatory response to
- combat neglected tropical diseases (NTDs): A review. PLOS Neglected Tropical Diseases.
- 2023;17(1):e0011010.
- 24. Rath A, Salamon V, Peixoto S, Hivert V, Laville M, Segrestin B, et al. A systematic literature
- review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for
- improving the evidence and how can they be overcome? Trials. 2017;18:1-11.
- 25. Krajnovic D. Ethical and Social Aspects on Rare Diseases. Filozofija i drustvo. 2012;XXIII:32-48.
- 26. Kaywanga F, Alimohamed MZ, David AB, Maeda D, Mbarak S, Mayura T, et al. Rare diseases in
- Tanzania: a National Call for Action to address policy and urgent needs of individuals with rare diseases.
- Orphanet J Rare Dis. 2022;17(1):343.
- 27. Simoens S, Cassiman D, Dooms M, Picavet E. Orphan drugs for rare diseases: is it time to revisit
- their special market access status? Drugs. 2012;72:1437-43.
- 28. Vreman RA, de Ruijter AS, Zawada A, Tafuri G, Stoyanova-Beninska V, O'Connor D, et al.
- Assessment of significant benefit for orphan medicinal products by European regulators may support

Protected by copyright, including for uses

- subsequent relative effectiveness assessments by health technology assessment organizations. Drug
- Discovery Today. 2020;25(7):1223-31.
- 29. Rode J. Rare diseases: understanding this public health priority. EURORDIS: Paris, France.
- 2005;5(1):3.

- 30. Mikami K. Orphans in the Market: The History of Orphan Drug Policy. Social History of Medicine.
- 2017;32(3):609-30.
- 31. Herkes GK. Orphan drugs in Australia. Expert Opinion on Orphan Drugs. 2016;4(12):1195-7.
- 32. Leadley RM, Lang S, Misso K, Bekkering T, Ross J, Akiyama T, et al. A systematic review of the
- prevalence of Morquio A syndrome: challenges for study reporting in rare diseases. Orphanet journal
- of rare diseases. 2014;9(1):1-17.
- 33. Mehta G, Macek M, Mehta A. Cystic fibrosis across Europe: EuroCareCF analysis of demographic
- data from 35 countries. Journal of Cystic Fibrosis. 2010;9:S5-S21.
- 34. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis
- care: a global perspective. The Lancet Respiratory Medicine. 2020;8(1):65-124.
- 35. Bin Zuair A, Aldossari S, Alhumaidi R, Alrabiah M, Alshabanat A. The Burden of Sickle Cell
- Disease in Saudi Arabia: A Single-Institution Large Retrospective Study. Int J Gen Med. 2023;16:161-
- 71.
- 36. Moeti MR, Brango P, Nabyonga-Orem J, Impouma B. Ending the burden of sickle cell disease in
- Africa. The Lancet Haematology. 2023;10(8):e567-e9.
- 37. Bell V, Varzakas T, Psaltopoulou T, Fernandes T. Sickle Cell Disease Update: New Treatments
- and Challenging Nutritional Interventions. Nutrients. 2024;16(2).

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579 Figu	re Legends
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- 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 gure 3

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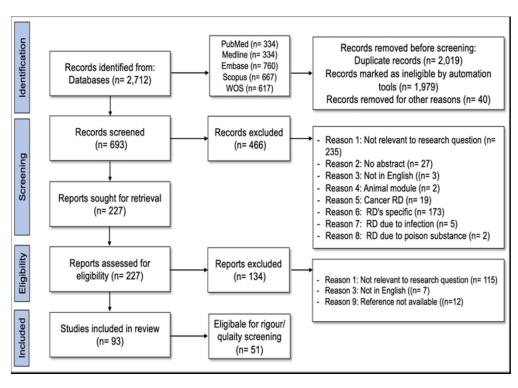


Figure 1. PRISMA flow chart of the study identification and screening process.

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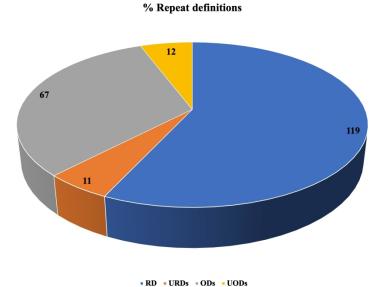


Figure 2. Repeated definitions included in the studies. $224x134mm (330 \times 330 DPI)$

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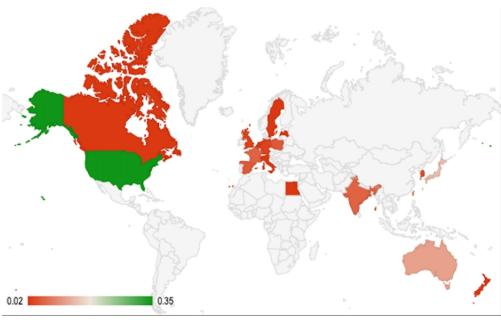


Figure 3. Global insight into RD prevalence (dark red indicates low prevalence, and dark green indicates greater prevalence)

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18 – 19 20 21 22 23 24 25 26	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 "debilitating disease*" OR "debilitating disease*" OR "General disease*" OR "Rare Disease*" OR "Rare Disease*" OR "Rare Disease*" OR "Severe Disease*" OR "Rare Disease*" OR "General disease*" OR "CRANDED, 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.	782 ts. 782 ts. #7 AND #6 AND #9 Timespan: All years. Indexes: SCE First JOER, SSCI, A&HCI, CPCI-S, CPCI-SH (4850). Lesg. Al training, amiliary and the state of the stat	007
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Rese	olementary Table 2: Study Selectionarch question: What are the criteriept 1: Criteria / Concept 2: Define	ria to defin	e Rare Diseases and Orphan					n-2024-08 pyright, i		
		PubMed		Medline		Embase		Sc. Sc.		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 subheading 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*)	on 25 January 202	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 Characte*[All Fields] OR Characte*[All Fields] OR delineate [All Fields] OR detail [All Fields] OR interpret[All Fields] OR detail [All Fields] OR or elucidate[All Fields] OR detail [All Fields] OR elucidate[All Fields] OR flucidate[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 subheading word, keyword heading word, organism supplementary concept word, protocol 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)	January 2025. Downloaded from Enseignement Superleur (ABE)	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 diseases" [All Fields] OR "Rare conditions" [All Fields] OR "Rare disorders" [All Fields] OR "Rare disabilitys" [All Fields] OR "Neglected diseases" [All Fields] OR "Undiagnosed diseases" [All Fields] OR "Low-frequency diseases" [All Fields] OR "the wife-threating diseases" [All Fields] OR "debilitating diseases" [All Fields] OR "severe diseases" [All Fields] OR "intractable diseases" [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, loating sub-heading word, keyword heading word, organism supplementary concept word, rare disease 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 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, expword, floating subheading word, candidate term word]	160,442	TITLE-ABS-KEY ("Orphan disease*" OR "Rare condition*" OR "Arer 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*")	http://bmjopergbmj.com/ on . 6) . hng, Al training, and similar	ALL FIELDS: ("Orphan diseases" OR "Rare conditions" OR "Rare disorders" OR "Rare disorders" OR "Rare disorders" OR "Undiagnosed diseases" OR "Undiagnosed diseases" OR "Ioseases" OR "life-threatening diseases" OR "debilitating diseases" OR "severe diseases" OR "mtractable diseases" OR "mtractable diseases" OR "Rare Diseases" OR "Rare Diseases" OR "Rare Diseases" OR "Severe diseases" OR "Rare Diseases" OR "Severe diseases" OR "Rare Diseases" OR "Severe diseases" OR "Se	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 subset* 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, are 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* 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	TTTLE-ABS-KEY ("Orphan medicinal product*" OR "Orphan product*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Production*" OR "Orphan Drug Production*" OR "Orphan Drug Production*" OR "Orphan Drug*")	June 7, 2025 at ∯gence Bibliograp lechnologies.	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 "Orphan Drug "Orphan Drug "Orphan Drug "Orphan Drug "Soron Scholes SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	3,462

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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 Condition*[All Fields] OR Requirement*[All Fields] OR Scale*[All Fields] OR Parameter*[All Fields] OR Indicator*[All Fields] OR Norm*[All Fields] OR OR Description [All Fields] OR Mean*[All Fields] OR Description [All Fields] OR Character*[All Fields] OR Explan*[All Fields] OR determine[All Fields] OR educidate[All Fields] OR determine[All Fields] OR exemplify[All Fields] OR character*[All Fields] OR exemplify[All Fields] OR "Corphan disease*[All Fields] OR "Rare disorder*[All Fields] OR "Rare disorder*[All Fields] OR "Rare disorder*[All Fields] OR "Rare disorder*[All Fields] OR "Corphan disease*[All Fields] OR "Low-frequency disease*[All Fields] OR "Low-frequency disease*[All Fields] OR "Low-frequency disease*[All Fields] OR "Low-frequency disease*[All Fields] OR "Corphan Drug Production*[All Fields] OR "Orphan Drug Producter*[All Fields] OR "Orphan Drug Producter*[All Fields] OR "Orphan product*[All Fields] OR "Priority review drug*[All Fields] OR "Orphan Drug*[All Fields] OR "Priority review drug*[All Fields] OR "Orphan Drug*[A	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 "Low-frequency disease*" OR "Low-frequency disease*" OR "fife-threatening disease*" OR "debilitating disease*" OR "severe disease*" OR "intractable disease*" OR "Rare Disease*")) AND (TITLE-ABS-KEY "Orphan medicinal product*" OR "Orphan subset*" OR "Orphan indication*" OR "Highly specialized technolog*" OR "Priority review drug*" OR "Orphan Drug Production*"))	086527 on 25 January 2025. Downloaded from hi Enseignement Superieur (ABES) including for uses related to text and data mini	#7 AND #6 AND #5 Timespan: All years. Indexes: SCI- EXPANDED, SSCI, A&HCI, CPCI-S, CPCI- SSH, ESCI. Less	646
<u> </u>	limit to english and human	334		334	101	760	limited to english	y	limited to english	617
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Supplementary Table 3: List of included studies

	Country/	Study	٠.				
Year	Jurisdiction / Organization	design	Aim	RD	OD T	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 Pharms with a that are generally not considered to be attractive to commercial development. Generally, orphagnically products are used in treating or preventing rare		
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 discussions conditions that by definition, affect fewer than 2000 or in 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.	ee,	A medical product can receive the designation and orphan medical product if it can be established that it intended for the diagnosis, prevention, or treatment if it-threatening or chronically debilitating entry of affecting not more than 5 in 10 thousand personal threatment in the chronical behavior of		
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 the drug intended to treat either a rare disease or more common disease where the sponsor cannot make any probability. As per the definition US FDA, Orphan drugs are those drugs used in diseases or circumstances which accur so infrequently in USA, that there is no real polarity of the 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 being granted a Marketing Authorization is possible as SFD designated orphan drug with t-IND (grameno Investigational New Drug) in some cases such wheel the drug is intended for the treatment of a serious of life threatening disease, when no alternative using the drug is disease, when no alternative using the process of clinical trials and in an active was ease of the drug of the drug in the process of clinical trials and in an active was ease of the drug of the drug in the process of clinical trials and in an active was ease of the drug of the drug in the process of clinical trials and in an active was ease of the drug of the drug in the process of clinical trials and in an active was ease of the drug		
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.	nologii		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 interested for the prevention, treatment or diagnosis of rare diseases has made necessary the creation of a number of incentives to stimulate the development of superpoducts. These drugs are known as orphan drugs. In the EU a medicinal product to treat rare diseased 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 satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorized, of it such method exists, the assumption that the product		

Country/	Study	A :				
Year Jurisdiction / Organization	design	Aim	RD	OD SE S	URD	UOD
	design		RD	will be of significant benefit to those affected by the condition. -Criteria for orphan designation are the following ristly: -criteria is based on the low prevalence ("ngb") of the condition, i.e., condition affecting not more than 5 is 10,000 persons in the European Union. Alternatively, the sponsor can apply for more frequent condiguing the sponsor can apply for more frequent condiguing the sponsor can apply for more frequent condition is unlikely that the marketing of the medicinal condition in the Community would generate sufficient sponsor in the Community would generate sufficient sponsor seconds of the condition in the condition in the condition in pushing or debilitating nature of the condition in justify the investment by the sponsor is invited to provide any scientific and or seriously debilitating nature of the condition in question or seriously debilitating nature of the condition in question or seriously debilitating nature of the condition in question or seriously debilitating nature of the condition in question of significant benefit to those affected by that challed the condition of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of significant benefit to those affected by that challed the condition in question of th		UOD
			In the USA Orphan Drug Act, the definition relates to an absolute	prevention, or treatment of the condition in question of if such methods exist, that the medicinal production of significant benefit to those affected by that conditions to the condition of the condition of the condition in question of the 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.	mining,		
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	NI trainin		
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.	Al training, and similar technal serious, life-threatening disorders across the agent		
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 agency	1	
2010 ^[28] United States/ Orphan Drug Act	Review			The Act initially defined an orphan drug on the asis of unprofitability: one intended for the diagnosis, to the orphan drug 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 of condition of interest in the United States as a surrogate for the lack of profitability.	2 2 3 5 5	
United States/ the Office of Rare Diseases Research	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	pout/guidelines.xhtml		

Year	Country/ Jurisdiction /	Study	Aim		Definition = S		
rear	Organization	design	Ailli	RD	OD oct	URD	UOD
				million to 30 million people in the United States have a rare disease or condition."	ding		
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."	25 January 2025. D Enseignement for uses related to		
2010 ^[31]	United States/ The Orphan Drug Act	Review	0/0		that is intended to treat a rare disease or condescribed affects fewer than 200,000 people in the United Steep OR as a product which will not be profitable with years of approval by the FDA. There are one 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 ≤2000 Australians	Drugs used in the treatment of rare diseases of the significant unmet medical needs and are referred or orphan drugs because, as described by EUERITIA (2011c), the pharmaceutical industry has little under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition.		
2011 ^[33]	Spain	Abstract	We assessed the characteristics and outcomes of the new drug development for rare diseases in the EU.	1/0,	In the European Union (EU), orphan drugs are the form the diagnosis, prevention, or treatment of life-the diagnosis, prevention or serious conditions that affect5 in 10,000 people (NOTE THE OVERLAP BETWEEN ORPHAISDRUGAND 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.	and sim		
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 gies. An orphan drug is a drug developed specifically gies.		
2012 ^[36]	United States	Editorial		-The terms, ophan 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 populationThe US Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, as does Japan.	Sibliogra		

Year	Country/ Jurisdiction/	Study	Aim		Definition 8		
2011	Organization	design	******	RD	0D OD	URD	UOD
				-The European Commission on Public Health defines rare	27 on 25 January Enseig uding for uses re		
				diseases as ,life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts	ກູເກັ		
				are needed to address them.	g 2		
				-The definition of ,low prevalence, varies between countries but	<u>o</u> 5		
				usually ranges from 1/1,000 to 1/200,000	. Ja		
				-The alternative term, orphan disease, is used in reference to a	S E E		
				combination of the paucity of treatment availability, lack of	es de la companya de		
				resources, and severity of disease.	Z <u>Q.</u> Z		
			- In this article we present the findings of this analysis, which,		gr 2		
			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		<u> </u>		
			additional resources might be directed.		t % D		
			- In this work we provide an up-to date analysis of drug, target	Rare diseases, which are disorders affecting less than 200,000	ry 2025. Downloade eignement Superieu related to text and o		
2012[37]	United States	Review	interactions for approved and clinical trial drugs and examine the	persons in the USA, also have considerable unmet medical needs.	S S N		
			major developments and trends in pharmaceutical development				
			- For the purpose of supporting rare disease product development,		an erioa		
			we undertook an evaluation of CDER, rare disease marketing		d e e		
			application history, focusing on a recent five-year period (2006 - 2010).		는 등 등 등 등 등 등 등 등 등 등 등 등 등 등 등 등 등 등 등		
			The aim of this study was to quantify both the sales and volume		Orphan drugs are drugs intended for the treatment of the diseases		
2042(29)	European Union		uptake of orphan drugs in Europe and to assess whether a country,	In the European Union, a rare disease is defined as a life-	Orphan drugs are drugs intended for the treatment		
2012[38]	countries	Review	gross domestic product (GDP) and/or health technology	threatening or chronically debilitating disease with the prevalence among 50 per 100 000 people or less	Orphan drugs are drugs intended for the treatment diseases.		
			assessment (HTA) influences the orphan drugs, market uptake.		₹`		
				-Since 1991, Singapore, Orphan Drugs Policy allows patients	ĝ. · <u>p</u>		
				with life-threatening and severely debilitating diseases with no	-Since 1991, Singapore, Orphan Drugs Police allowo		
				other treatment options to access approved drugs prescribed by their practitioner.			
				-The Taiwan Foundation for Rare Disorders helped secure the	-Since 1991, Singapore, Orphan Drugs Police allow		
				Rare Disease and Orphan Drugs Act in 2000. Diseases affecting	patients with life-threatening and severely demittating		
2012 ^[39]	Singapore, Taiwan,	Meeting		fewer than 1 in 10,000 that are officially recognized are eligible	diseases with no other treatment options to acces		
2012	Korea, and China	Abstract		for medical coverage.	diseases with no other treatment options to access approved drugs prescribed by their practitione		
				-In Korea, the Orphan Drug Centre supplies medicines for	In Korea, the Orphan Drug Centre supplies modicines for diseases affecting fewer than 1 in 20,000.		
				diseases affecting fewer than 1 in 20,000.	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 	s <u>o</u>		
				epidemiological studies for diseases affecting fewer than 1 in	simil		
				10,000			
2013 ^[40]	Middle East	Critical	We provide a critical review of the literature on the availability of		An orphan drug is a drug developed specifically treat		
		Review	orphan drugs in the Middle East.		rare medical condition. Criteria for Orphan designation is generally base on the		
			We examined the characteristics of orphan drug (OD) designations		number of patients affected by the disease (<20,000 USD		
	United States; UK;		and approvals by the US Food and Drug Administration (FDA)		patients and <5 in 10,000 EU patients). The EU also		
2013 ^[41]	and EU	Review	and the European Medicines Agency (EMA) between 2000 and		requires that a satisfactory alternative treatment is not		
			2011.		available or that the new drug is significantly begin that		
					drugs currently marketed		
					- The orphan drug intended for diagnosis, prevation on		
			- The presentation provides a brief review of all supportive incentives in the field of orphan medicinal products as: the		treatment of a life threatening or chronic debilitating		
			European orphan medicinal product (OMP) regulation, Guideline		- The prevalence of the condition, for which the OMO		
			on Clinical Trials in Small Populations and Commission		- The prevalence of the condition, for which the OMO (orphan medicinal product) is intended, must be less		
2013 ^[42]	UK	Conference	Regulation (EC) No 2049/2005 / support of small and medium		than 5 in 10,000"		
			enterprises (SMEs)."		- OMF has to fulfil following criteria.		
			- It also introduces the concept of Clinical added value of orphan		Seriousness of the condition the investigated dru		
			medicinal products, as one of the key instruments to increase the		must be intended for diagnosis, prevention, o		
			availability of orphan medicinal products in the member states."		treatment of a life-threatening or chronio debilitating condition.		
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•	Country/	Study	A :		08		
Year	Jurisdiction / Organization	design	Aim	RD	OD C	URD	UOD
			~O		2. Low prevalence/irretrievable investment the prevalence of the condition, for which the JMP intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to general sufficient return to justify the investment is some situations, the condition is defined as a most of another frequent condition. To accept the it is needed to prove that the subset is modelling recognizable and the investigated OMP of the effective only in this subset and no condition per se. 3. Medical need No other treatment is one, the designated OMP must provide a solicitant benefit over the existing method. The significant benefit over the existing method. The significant section is given on the basis of/upon clinically selected advantage or major contribution to patient and 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)	ABES a mir		
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 500 000 of the incidences in newborn babies. -Rare diseases are serious chronic diseases, difficulties in obtaining timely, accurate diagnoses and are often lifethreatening	Orphan drugs are those intended to diagnose, pre- treat rare diseases or pathologies that are serion or life threatening, and whose development costs are superior to	5	
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	the expected return on investment ing, and similar technological and similar a		
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: in the ded to treat, prevent, or diagnose diseases or condition 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.	71 0 	
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)	e i ce		
			For peer review o	nly - http://bmjopen.bmj.com/site/ab	out/guidelines.xhtml		

V.	Country/	Study	Aim			.080	
Year	Jurisdiction / Organization	design	Alm	RD		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.	Enseig for uses re	7 on 25 January 2025	
2014 ⁽⁴⁸⁾	Poland	Abstract	The aim of this study was to identify the cost-effectiveness threshold for an orphan designation in Poland.	ee _r	-According to criteria specified by the Europa Medicines Agency (EMA) a medicine must me a process of a qualify for orphan designation, treatment, prevention or diagnosis of a disease that it life-threatening or chronically debilitating prevalence level in the European Union (EU) or or than 5 cases in 10,000 patients is necessary in the satisfactory method of disease diagnosis, prevention of the satisfactory method of disease diagnosis of disease diagnosis of the satisfactory method of disease diagnosis of dise	- Downloade	
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	Al traini	bmjope	
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 tende for diagnosis, prevention, or treatment of life threatening or very serious diseases affecting less than in 10 000 people in the European Union (EU). - These drugs are called ,orphans, because the pharmaceutical industry has little interest, under horma market conditions, in developing and notice in products intended for only a small number of attents suffering from very rare conditions.	micom/on J	
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.		nologies.	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 \(\leq 1 \): 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.	_	Biblio	
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X 7.	Country/	Study	Α ****		Definition 📜 😸		
Year	Jurisdiction / Organization	design	Aim	RD	OD <u>c</u> 5	URD	UOD
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." 	27 on 25 Januar Ense uding for uses r		
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 ultrarare 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	ary 2025. Downloaded from http://bmjope.seignement Superieur (ABES) . selated to text and data mining, Al train	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 Health and Clinical Excellence.	National Institute for and Care Excellence (for the Institute for Healt Clinical Excellence, ar Institute for C Excellence; NICE), drug indications for condition a prevalence of less thar 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 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 fo diseases with a prevale less than 1000 patient 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 committee develop drugs that have low development coxin order to treat rare diseases."		
2015 ^[58]	United States (US) and European Union (EU),	Poster/Abstra ct 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 production at treating rare diseases or disorders. OD tend to consider the prevalence of the dicesses and the estimation of the population affected by the diseases. In the USA a rare disease is defined as: 400,000 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	graphique de		

*7	Country/	Study	Aim		Definition = S		
Year	Jurisdiction / Organization	design	Aim	RD	OD och	URD	UOD
				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)	ng for a		Ultra-orphan drug (prevalence ≤1:50,000)
2016 ^[62]	France	Poster/Abstra ct 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 treate 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 paties. Survived targeted for orphan drug designation in April 1990, were excluded due to the short implementation of the prevalence was calculated as the rate per 1900,000, population using the number of patients with the 1900,000 disease provided by the MILW website 0		
2016 ^[64]	Asia-Pacific, Australia, Japan, Singapore, South Korea, and Taiwan	Poster/Abstra ct 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.	0	- Australia: Prevalence threshold for orphan displayed designation: 0.9 in 10,000 - Japan: Prevalence threshold for orphan displayed designation: doi.org/10.000 - South Korea: Prevalence threshold: doi.org/10.000 - South Korea: Prevalence threshold for orphan displayed designation: doi.org/10.000 - Taiwan: Prevalence threshold for orphan displayed designation: doi.org/10.000		
2017[65]	Spain	Abstract	Identify if the official criteria of Spanish P&R process are related with P&R approval for ODs.		nin n nin n	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	ng, Al tr		
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"	61	Orphan medicinal products (OMPs) are used the severed life-threatening diseases with no or limited 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	ilar techno	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe (EU regulation 536/2014).	
2017 ^[69]	French	Poster/Abstra ct 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 so been developed specifically to treat a rare dise. a itself referred to as an orphan disease. Often so the 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).	gence Bibliographique de graphique de graphi		

Year	Country/ Jurisdiction /	Study	Aim		Definition	086	
	Organization	design	73111	RD	OD <u>ō</u>	55 URD	UOD
2017 ^[71]	UK, England, and Wales	Poster/Abstra ct 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		ding for u	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.	Orphan drugs encompass pharmaceuticals that intended to treat these types of diseases	nuary 2025. Downk	
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	and data	baded fro	
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 a intended to treat these types of diseases	m ht	
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)	<u>≯</u>	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.	101	The disease prevalence threshold in the EU for a ph drug designation is well-defined at ≤ 5 per 10.0000	opaen.brr	
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 Genetic Socio of the Chinese Medical Association, experts mainty in field of medical genetics proposed that (any discossed prevalence lower than 1/500,000 in the overall parallation or 1/10,000 among new-born's should be considered a rare disease).	thom	
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 gen definition, orphan drugs are intended for dragos prevention, or treatment of rare diseases who conditions affect no more than 5 in 10,000 persons. - OD proven at marketing authorization if the annumbudget impact is less than €30 million per transparticular indication. - Certain special HTA criteria are applied transparticular indication. 1. Higher P values for small sample sizes 2. Use of surrogate endpoints 3. Additional benefit is considered proven if the budgin impact is less than €50 million per year for particular indication. - Higher therapeutic benefit is automatically recognize for orphan drugs because these drugs had to prosignificant additional therapeutic benefit compared wother possibly already approved drugs as part of the European marketing authorization procedure.	<u>ne 7, ⊋025 at Agence Bibji</u>	Currently, no o definition of "ultra-odisorders" has been at globally. This inil subcategory was intro by the National Institut Health and Care Exce (NICE), which applied drugs with indication conditions with a prevalence of less than 1 per 5 persons. In October 2018, a provide the provided rugs: The Sc government will introduced to faster access to ultra-odrugs: The Sc government will introduce the definition of ultra-one wedicines that can trea

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V	Country/	Study	Aim		Definition	80		
Year	Jurisdiction / Organization	design	Aim	RD	OD G	652	URD	UOD
					iding fo			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 personsIn 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		7 on 25 January 2025. D Enseignement		
2018[80]	UK, England	Poster/Abstra ct only	This research aims to identify, compare, and evaluate willingness to pay (WTP) thresholds across countries		WHO recommends a WTP of <3 times capita/QALY	ownio Supe		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.	nd data	oaded from http: erieur (ABES)	which are considered "ultra-rare diseases" (prevalence:	
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.	AI	-		
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	training, and similar			
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/Abstra ct 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 Continuous and designations are typically indext conditions that have a prevalence of below 5 in	ted in		
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 discases	7, 2025		
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 \$\leq 620\text{/million persons.}\$	9	at Age	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 diagnosis, prevention, or treatment of orphan dise. Orphan drugs are those drugs having both orphan non-orphan indications	ase. On in an O		
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		ograp		
			For peer review o	nly - http://bmjopen.bmj.com/site/ab	out/guidelines.xhtml	phique de l		

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Year	Country/ Jurisdiction /	Study	Aim		Definition = 8		
rear	Jurisdiction / Organization	design		RD	OD 652	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.		7 on 25 January Ense Iding for uses r		
2019 ^[90]	UK	Abstract	10 ₁ 0		-For a drug to be appraised via the HST processing the meet seven criteria, based on: a small and distinct patient population, a limited number of specialist treatment centres for the indication in question, treatment price, and severity of the coding of		
2019 ^[91]	UK	Poster/Abstra ct 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	00%	d from (AB	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.	· (e)	OMPs are drugs intended for the treatment of conditions affecting less than 5 in 10,000 people. EU. AIFA may grant a medicine the status of impovative 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.	61	Treatments for diseases with a prevalence of <5 10,000 in the EU, which are life-threatening or severely mablings and have no satisfactory treatment available, argument orphan designation by the European Medicines Agence (EMA)		The NICE Highly Special Technology Program (HSTP) and the SMC cons ultra-orphan to be <1 in 50, and meeting other speciali 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	d sim		
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 prevention, or treatment of life-threatening revery serious conditions that affect no more than 5 100,000 (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	e 7, 2025 at Agence Bi hnologies.		
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 with have an Orphan Medicinal Product (OMP) designation indicating that they are likely to deliver benefit in an area.		

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Country/	Study			Definition		
Year Jurisdiction / Organization	design	Aim	RD		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	3	
Western Eurasiar region: Armenia, France, Germany Kazakhstan, Latvi The Netherlands, Poland, Romania Russia, Turkey, Ukraine, and the United Kingdom		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 , orping as either having an official EU orphan designation at targets a disease with a prevalence of <1 in 150,000 me shows a clinically proven therapeutic benefit and shows a clinically proven the registered medicine exists.)))	Effective from October 2 Scotland has introduced a definition for ultra-org drugs: medicines that are to treat a condition wit prevalence of 1 in 50,00 less or around 100 peopl Scotland, which will most used to facilitate early ac programs and reimburser 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 likely drug intended to treat a life-threatening or changed debilitating disease, provided a maximum prevention. Europe of 5/10,000 and when no satisfactory a method can be authorised, or, if such a method ests, 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 lifethreatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union.	Al training, an	Prevalence can be much lower, leading to the concept of the, ultra-orphan disease, for diseases with an estimated prevalence of	
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 than 200,000 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 productors of treatment, diagnosis, or prevention of rare disease.	3	
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	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 ingredicts 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 of treatment of a life-threatening or chronicallidebilitating condition affecting not more than five it 10 thousand persons in the community when the	7 2025 at Agence Biblio	

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	Country/	Study	Aim		Definition = 5		
Year	Jurisdiction / Organization	design	Ailii	RD	OD C	URD	UOL
			~O	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 chiefe threatening, seriously debilitating or seriously debilitating or seriously and thoughout incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary in strength and (b) that there exists no satisfactory method of chiefe prevention, or treatment of the condition in the prevention, or treatment of the condition in the community of the prevention of the condition in the designation of a medicinal product. In order to obtain the designation of a medicinal product as an orphan medicinal product, the spond as submit an application to the Agency at any stage of the condition in the development of the medicinal product between the application for marketing authorization is the condition in	25 January 2025 D	
			* <i>/</i>		European Union	ί .	
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." 	rieur (ABES) . nd data mining,		
2020 ^[105]	China, Australia, Japan, South Korea, and Taiwan	Poster/Abstra ct 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	- RDs are a highly heterogeneous group of disorder - "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.	Al training, and s		
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 Drus Safety formulates ODs, which should sate two conditions related to the number of patients and the existence of alternatives. In other words, drugs ugd for 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. The, Orphan Medicinal Product Regulation of the safety of the saf		
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 clefine OMPs as products for the diagnosis, prevedon, or treatment of life-threatening or very serious condition that affect no more than 5 in 10,000 people in the European Union	2 2 3	
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 share community procedure for being designated as such in the European Union, and this community approach provide opportunities for research, development, and marketing	Ultra-rare, affecting less than 1 person per 50,000 inhabitants."	

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Year	Country/ Jurisdiction /	Study	Aim		Definition	086 t, im	
	Organization	design		RD	OD	652 nclu	URD
			the preferences stated by different stakeholders, following the MCDA methodology.			7 oı din	
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		າ 25 Janເ Er g for use	
				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		5527 on 25 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Biblic Erseignement Superieur (ABES) . reluding for uses related to text and data mining, Al training, and similar technologies.	

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1. Critical Appraisal Result for Text Opinion studies

Yes

Yes

Supplementary Table 4: Critical Appraisal Result

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Yes

Yes

Yes

Yes

Critical Appraisal Result for Systemic Reviews and Research Syntheses studies

O 1 2 2 3 Studies 4 5 5 6 7 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Q1) Is the review question clearly and explicitly stated?	Q2) Were the inclusion criteria appropriat e for the review question?	Q3) Was the search strategy appropriate ?	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	ded f ieur (nd dat	Q10) Were recommendation s 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	ro≤ AYB an	Yes	Yes
2. 2020 ^[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	n 🗳 ES	Yes	Yes

Yes

Yes

Yes

NO

Yes

Yes phique de I

Yes

Not applicable

Yes

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 laterature?	Q6) Is any incongruence with the literature/sources logically defended?
1.2003 [3]	Yes	Yes	Yes	Yes	n xi es	Yes
2.2005 [5]	Yes	Yes	Not applicable	No	aries Tes	Yes
3.2006 [7]	Yes	Yes	Yes	Not applicable	un e c	No
4.2009 ^[9]	Yes	Yes	Yes	Not applicable	es 7	Not applicable
5.2010 [11]	Yes	Yes	Yes	Yes	oes N	No
6.2010 ^[12]	Yes	Yes	Unclear	No	02! ဇွန် gie	No
7.2014 [33]	Yes	Yes	Yes	Yes	er es	Yes
8.2017 [51]	Yes	Yes	Yes	Yes	Yes >	Yes
9.2017 [111]	Yes	Yes	Yes	Yes	Unclea	NO
10. 2019 ^[78]	Yes	Yes	Yes	NO	Yes (Yes
3 11. 1992 ^[1]	Yes	No	Yes	NO	Yes 👿	Not applicable
12. 2004	Yes	Yes	Yes	Yes	Yes E	Not applicable
13. 2008 [8]	Yes	Yes	Yes	Yes	Yes 🙆	NO

NO

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3 15. 2011 [15]	Yes	Yes	Yes	Yes	Ý.es 🕏	NO
4 16. 2013 ^[25]	Yes	Yes	Yes	Yes	rates of	NO
5 17. 2013 ^[28]	Yes	Yes	Yes	Yes	₹ es 27	NO
6 18. 2014 [37]	Yes	Yes	Yes	Yes	₹es S	NO
7 19. 2016 [44]	Yes	Yes	NO	Yes	¥es ≥	NO
8 20. 2018 [55]	Yes	Yes	Yes	Yes	Žes 🖢	Yes
9 21. 2018 [59]	Yes	Yes	Yes	Yes	<u>क्ष</u> स्मा प्र	NO
10 22. 2018 [65]	Yes	Yes	NO	Yes	sei.	NO
11 23. 2020 [80]	Yes	Yes	Yes	Yes	36 2	NO
12 24. 2020 [86]	Yes	Yes	Yes	Yes	025 tegn	NO
13 25. 2020 [112]	Yes	Yes	Yes	Yes	₹® 0	NO
14 26. 2020 [88]	Yes	Yes	Yes	Yes	# % ×	NO
15 27. 2021 [91]	Yes	Yes	Yes	Yes	2 2 2 2 1	Yes
16 28. 2010 ^[14]	Yes	Yes	NO	Yes	nloade ugege x∺and	No applicable
17 29. 2018 [61]	Yes	Yes	Yes	Yes	<u>ਕ</u>	NO
18 30. 2021 [91]	Yes	Yes	Yes	Yes	ã ® ₹	NO

2. Critical Appraisal Result for Economic Evaluations studies

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Studies	Q1) Is there a well- defined questio n?	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?	trees of cost or seconds consequences?	Q10) Do study results include all issues of concern to users?	Q11) Are the results generalizabl e 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	No₅applicable	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	olo 7, No	Yes	Yes
6.2017 [57]	Yes	Yes	Yes	Yes	Yes	Unclear	NO	NO	02 NO	Yes	Yes
35 36 3. Critical Appraisal Result for Analytical Cross-Sectional Studies											

3. Critical Appraisal Result for Analytical Cross-Sectional Studies

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8 9 Studies 0	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?	QD) Were the outcomes measured in a valid and reliable way?	Q8) Was appropriate statistical analysis used?
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. 2012 [20]	Yes	Yes	Yes	Yes	Yes	Yes	<u>,†</u>	Yes	Yes
. 2015 ^[41]	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	6527 nclud	Yes	Unclear
4.	Critical Appraisal Re	esult for Qualitative I	Research studies				on 25 Jan E ling for us		

10 11 12 13 Studies 14 15	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?	Nary 2025. Downloade inseignement Superie Res related Superie Participants, their voice adequated and represented and	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?
$7_{1.2014}$ [36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes da d		Yes
18 _{2.2021} [92]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes a A o	Not applicable	Yes
19 _{3.2021} [93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes Not application	Not applicable	Yes
204. 2013 [30]	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not application	Not applicable	Yes
21 _{5. 2019} [59]	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes G	NO	Yes
22 23 5. 24	Critical Appra	nisal Result for	Prevalence Str	udies		"Vio		bmjopen. ∖\I training		

25 26 27 28 Studies 29 30	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?	Qo) Was there appropriate statistical analysis?	Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?
31 ¹ . 2016 [47]	Yes	Yes	NO	Yes	Yes	Yes	Yes	ne Yes	Yes
33 2. 2013 [26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	2025	Not applicable

6. Critical Appraisal Result for Cohort Studies

U Studies I two groups I exposures I the I 2 I strategies to I groups/participants I the I tollow up time I up complete. I strategies to I	9	Q1) Were the	Q2) Were the	Q3) Was	Q4) Were	Q5) Were	Q6) Were the	Q7) Were	Q8) Was the	Q9) Was follow	Q10) Were	Q11) Was
	0 Studies	two groups	exposures	the	confounding	strategies to	groups/participants	the	follow up time	up cemplete,	strategies to	appropriate
similar and measured exposure comounting deal with free of the outcomes reported and and if and, were address approximation appr	1	similar and	measured	exposure	comounting	deal with	free of the	outcomes	reported and	and if not, were	address	арргорпас

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3 4 5 6		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?	pyrightine rescribed ind con 2	incomplete follow up utilized?	statistical analysis used?
8 1.	2018 [61]	Not applicable	Yes	Yes	NO	NO	Yes	Unclear	NO	5 Var	Yes	Not applicable
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45							(or at the moment of exposure)? Yes mjopen.bmj.com/si			© 5 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . for uses related to text and data mining, Al training, and similar technologies.		

Supplementary Table 5: RDs definitions based on continents

				36/bm jopen BMJ Open		Page 64	
Sur		able 5 : RD	s definitions based o	-2024-)yrighi			
Continent	Country, frequency	articles;		<u> </u>	Date	Adopted / developed	
			Orphan Drug Regulation	Defines RD according to prevalence: "rare disease' means any disease of confiction that affects less than 200000 persons in the USA'.	1993		
North America	US (25)	24 (26%)	RDA ODA	Defined RDs based on qualitative descriptors as follows: 'the term 'rare to condition' means any disease or condition which occurs so infrequently for the USA that there is no reasonable expectation that the cost of developing and making and the USA a drug for such disease or condition will be recovered from sale usale usa	1983	developed	
North				FDA	Define RD as 'any disease or condition that affects less than 200000 people with the USA or affects >200000 in the USA and for which there is no reasonable expected that the cost of developing and making available in the USA a drug for such disease 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 with a rare disease		Aligned to EU	
South America	Chile (1) Peru (1)	1 (1%)		Required the disease severity to be ,life threatening, and severely- or chronically-,			
America	UK (3)	2 (2%)	the Rare Disease Framework	debilitating. 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) Some countries use additional definitions in situations where a condition of some condition of state of sta	2021		
Europe	EU (36)	35 (38%)		as rare if they occur in <500 citizens yearly Rare diseases, including those of genetic origin, are life-threatening or deproposally debilitating diseases which are of such low prevalence (less than 5 per 18,000 persons in the European Union) that special combined efforts are needed to address than so as to prevent significant morbidity or perinatal or early mortality or a consequence reduction in an individual's quality of life or socio-economic potential.			
Eu			European Commission on Public Health	Defines rare diseases as ,life-threatening or chronically debilitating dise shich are of such low prevalence that special combined efforts are needed to address then. A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for			
			Orphan Drug Regulation EMA	a disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare prevalence of rare disease < 5/10 000 Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)	141/2000		
	Germany (1)	1 (1%)	EIVIA	Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000)		+	
	Latvia (1)	1 (1%)		9		+	
	Netherlands (1)	1 (1%)		Affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) 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 (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) 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 givernate disease. Affecting <11/100,000 inhabitants or ,≤2000 Australians Prevalence threshold for orphan disease designation: 0.9 in 10,000			
Oceania				Diseases with a prevalence of 1.1/10 000			
				Diseases with a prevalence < 2000 individuals.			
	Australia (10)	10		Australia have set prevalence's of 1.16 per 100,000 individuals for a giver are disease.			
	()	(11%)		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 Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold			
	New Zealand (1)	1 (1%)	PHARMAC	Affecting less than 1:50,000 people, which is a considerably lower prevalence threshold			
A -:-	` ′			than other nations that are from 5 to 76 per 100,000 people Japan diseases with a prevalence of 4.0/10,000			
Asia			\sim	sapan diseases with a prevalence of 4.0/10,000 Sapan disease with a prevalence with a prevalence of 4.0/10,000 Sapan disease with a prevalence with a prevale			
	Japan (13)	13		Intractable diseases, is a Japan-specific conception of diseases with (i) unknown			
	Japan (13)	(14%)		etiology (ii) no effective treatment, (iii) rare status (iv) necessity of long reatment			
				The incidence rate is estimated to be ≤ 2.5 cases in 10,000 for Japan			
			Taiwan Foundation for	Diseases affecting < 1 in 10,000 that are officially recognized are eligible for medical			
		_	Rare Disorders	coverage.	2000		
	Taiwan (7)	7	Physically and				
	()	(8%)	(8%)	Mentally Disabled	RD is one type of disability	2001	
			Citizens Protection Act	i i i i i i i i i i i i i i i i i i i			
	GI: (5)	5	the Chinese Society of Genetic Medicine	Genetic disorders affect with less than one over 50,000 of the incidence fin Newborn babies.			
	China (5)	(5%)		Incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 is 10,000, respectively.			
		-		Prevalence thresholds have been set at less than 1 per 20,000			
	South Korea (4)	5 (5%)		Prevalence threshold: <4.0 in 10,000			
		(3%)		< 20,000 people in Korea (i.e., <4 per 10,000 population) 6 5			
	Singapore (2)	2		Required the disease severity to be life threatening, and severely- or chronically-, debilitating.			
		(2%)	_	Prevalence threshold: 37.7 in 10,000			
	India (1)	1 (1%)	ORDI	Threshold for defining a disease as fare if it affilets 1 in 5,000 individuals	•		
	Armenian legislation (1)	1 (1%)		whether the patient will receive the necessary medicines for free or not			
	Philippines		The DOH, upon recommendation of the RDTWG,	ence Bi			
Africa	Kenya			Required the disease severity to be ,life threatening, and severely- or chronic dy, ,debilitating.			

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Continent	Country, frequency	# of articles; (%)		(RD) definition	-08652	Date	Adopted / developed
Eastern Europe & Northern Asia.	Russia (1)	1 (1%)		Maximum prevalence for a rare disease is defined as 1 in 10,000	7 on 25 Ja Iding for u		
South-eastern Europe & Southwester n Asia	Turkey (1)	1 (1%)	<i>F</i>	Affect no more than 1 in 100,000, which is 50 times less frequent the Union definition.	nuary 2025. I Enseignemer ses related to		
	WHO (5)	5 (5%)	C	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 populati Rare disease as affecting 65/100 000~100/100 000 persons.	de ieu d		
	Orphanet, (1)	1 (1%)		Disease inventory, it is evident that the majority of RDs are of genetismaller percentage is autoimmune or infectious disorders, in addition cancers."	n to so he are		
The Ro	are Diseases Act (RDA	; the Orphan D	rug Act (ODA; the Food and	Drug Administration (FDA); The Canadian Organization of Rare Diseases (CO Rare Diseases India (ORDI)	RD) Exa ti <mark>z</mark> nal Health S	Service (NHS); -	
		J	nt Agency); Organization for s definitions based	er er	p://bmjopen.bmj.com/ o g, Al training, and simil:		
	# 0	2			= 0		Ado

Continent	Country, frequency	# of articles; (%)		(RD) definition	Date	Adopt ed / develo ped
Europe	EU/UK (22)	19 (20%)	EMA	If the drug is intended for the diagnosis, prevention, or treatment of a life-threatening or hronically 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, of £50 k/QALY when end-of-life criteria are met		
			EURORDIS	Drugs used in the treatment of rare diseases address significant unmet medical needs an 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 (RD) definition	Date	Adopt ed / develo ped
				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		
0				The Netherlands	Defines orphan drug, as either having an official EU orphan designation or if it target the larget that a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered receives		
1 2 3				Poland	There is no specific formal threshold for orphan designations, there is only a general case effectiveness threshold that equals 3 x GDP per capita for ICUR/QALY (for CUA) or ICER/LYG (for CEA), which is approximately € 26 800.		
4		Italian (1)	1 (1%)	Medicines Agency (AIFA)	AIFA may grant a medicine the status of innovative drug according to 3 criteria: unmetatical needs, clinical added value and quality of evidence.		
5 5 7 8		German (1)	1 (1%)		Certain special HTA criteria are applied to orphan drugs: Higher P values for small and the 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 approver as a part of the European marketing authorisation procedure. budget impact is less than €50 million per year for the European marketing authorisation procedure.		
))	North America	US (9)	8 (9%)	FDA	The defines an OD as 'one intended for the treatment, prevention or diagnosis of a range was en condition, which is one that affects less than 200, 000 persons in the USA' (which equates to approximately was per 10,000 population) 'or meets cost recovery provisions of the act'		
3 4 5				Orphan Drug Act (ODA)	Orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, pr 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 1988 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."		
5 7					Orphan product, as one that is intended to treat a rare disease or condition that affects weethan 200,000 people in the United States OR as a product which will not be profitable within seven years of approval by the FDA		
3	Asia	Singapore (1)	1(1%)	Orphan Drugs Policy	Allows patients with life-threatening and severely debilitating diseases with no other that the patients to access approved drugs prescribed by their practitioner.	1991	
0		Korea (2)	2 (2%)	the Orphan Drug Centre	Supplies medicines for diseases affecting fewer than 1 in 20,000.		
1 2 3 4				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 for efficacy compared to existing alternatives, are designated as OD		
5 5		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		
7 8 9		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		
0 1 2 3 4				For po	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		

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Supplementary Table 7: URDs definitions based on continents

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0	Continent	Country, frequency	# of articles; (%)		(URD) definition (URD) definition	Date	Adopted / developed
2 3	Europe	UK		^_	Ultra-orphan diseases, the term refers to chronic diseases with a prevalence of 50,000 of the population (Hugheset al., 2005)		
4 5				NICE	Ultra-orphan diseases affect a very small patient population, defined by the small Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of \$\frac{1}{20}\$,000		
6		Alberta		NICE	URD: conditions with a prevalence of less than 1 per 50,000 persons (NICE rta).		
8 9 0		England		Advisory Group on National Specialized Services (AGNSS).	The qualifier required by AGNSS was less than 500 persons affected in English population)		
2		Ontario			An incidence rate of fewer than 1 in 150,000 live births or new diagnoses por year in Ontario		
3					ultra-orphan diseases affecting <1/50000 inhabitants		
4 - 5 6				(EU regulation 536/2014)	Ultra-rare diseases have a prevalence of 1 in 50,000 individuals or less in Europe		
7 8		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)"		
9 0 1		Poland			Poland uses the EU definition of 'Ultra-rare being <1 in 50000 people'		Adopted EU definition
2 3 4					rare disease there are "singular cases" or "individual cases", which are conselered "ultra-rare diseases" (prevalence: <1:10,000), including, for example MuSK-positive by as genia gravis (prevalence 0.05-0.65/100,000 or congenital myasthenic syndrome (CMS)"		
6					ultra-rare diseases (affecting <20/million persons)"		
7 8					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 "		
9 0 L					Ultra-rare, affecting less than 1 person per 50,000 inhabitants."		

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	Continent	Country, frequency	articles; (%)		(URD) definition include 27	Date	Adopted / developed
					ultra-orphan (prevalence: <1:50,000)		
ე 1 2				NICE Highly Specialised Technology Programme (HSTP) and the SMC	The NICE Highly Specialised Technology Programme (HSTP) and the SM special sed rultra-orphan to be <1 in 50,000 and meeting other specialised criteria. "		
3					d men to to		

Supplementary Table 8: UODs definitions based on continents

18 19 20 21	Continent	Country, frequency	# of articles; (%)		(UOD) definition (UOD) definition	Date	Adopt ed / devel oped
22					Ultra-Orphan Drug define as drug for diseases with a prevalence of 0.18/10 000 to 18/10 000 to 1		
23 24					NICE: applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons"		
25 26					Indications approved for use in diseases with a prevalence of less than 1000 patents c.: ultra-orphan drugs)		
27 28					Definitions of orphan (prevalence ≤5:10,000) and ultra-orphan drug (prevalence 1:30,000) were consistent in most countries.		
29 30		Scotland		The Scottish government	new definition of ultra-orphan medicines that can treat very rare conditions affecting gewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland		
31 32		England			HST for ultra-orphan indications Euro113,900-341,700/QALY in England		
33 34				WHO	WHO recommends a WTP of <3 times GDP per capita/QALY		
35 36 37		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	
38 39 40 41				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 per 50,000 persons.		

RDs Qualitative and Quantitative descriptors and themes

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

ODs Qualitative and Quantitative descriptors and themes

Themes	Qualitative Descriptors	Themes	Qualitative Descriptors
Natur e of Produ ct	1. Medical Product	ne d	21. No alternative treatment
	2. Agent	Jnm t Nee	22. Treatment Price
	3. Biological Products		23. Lack profit

LIRDs Qualitative and	Quantitative	descriptors	and themes

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

UODs Qualitative and Quantitative descriptors and themes

Theme	Qualitative	Theme	Qualitative			
	1. Very rare conditions		1. Indications			
	2.Medicines	Indication	2. Treat			
Nature	3.Drug		3. Approved for use			
	4.Disease	Donulation	1. Patients			
	5.Condition	PopulationCharacteristics	2. Persons			
Theme	Quantitative	Characteristics	3. People			
	1.Prevalence					
Measurements 2. Willingness to pay (WTP) of <3 times gross domestic product (GDP 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
	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	-
Nature	9. Intractable	1	-	1	-
Nat	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
>:	19. Unknown Etiology	1	-	-	-
Etiology	20. Genetic	7	-	1	-
Etic	21. Hereditary	1	-	-	-
as re ti	22. Rare Diseases	40	4	16	=
Diseas e nature affecti	23. Disab* (Disability & Disabling)	5	-	2	=
a E	24. Life -Limiting	1	-	0	-

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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	-
	29. Considerable reduction in an individual's quality of life	1	-	0	-
re t. 's	30. Considerable reduction in socio- economic potential	2	-	0	-
natu he p ty	31. Unmet medical needs	3	-	3	-
Disease nature affecting the pt.'s Society	32. Disease with limited number of specialist treatment centers	-	-	1	-
Di	33. Common disease where the sponsor cannot make any profit	-	-	1	-
	34. Low Prevalence	12	-	2	-
70	35. Low Occurrence	2	-	-	-
Population Characteristics	36. Rarely afflict the population	1	-	-	-
Population haracteristii	37. Small number of patients	3	-	1	-
opul ract	38. Very small patient Population	-	1	-	-
Pc Cha	39. Population	20	3	7	-
J	40. People	29	2	8	2
	41. Inhabitant* (s)	6	2	-	-
Ш	42. Clinical added value	-	-	1	-
enefits fror taking the treatment	43. Improve safety or efficacy	-	-	1	-
nefits fro aking the reatment	44. Product will be of significant benefit	-	-	2	-
Benefits from taking the treatment	45. New drug is significantly better than drugs currently marketed	-	-	1	-
	46. Indications	-	-	4	4
	47. Diagnosis	-	-	23	-
Indication	48. Treat* (Treatment)	7	-	55	2
ndic	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
	1. Prevalence	51	10	22	6
ıts	2. Absolute # of patients	1	-	-	-
mer	3. Incidence	7	1	-	-
Measurements	4. Incidence rate	2	1	-	-
eas	5. Frequency	1	-	-	-
\boxtimes	6. Number of* (cases reference, patients, people, prevalent	6	-	5	-
	cases, and individuals)				

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	-	-	1	1
	product (GDP) per capita/QALY				

