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The Economic Evaluation of Rare Disease Medicines

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Abstract

Economic evaluation of rare diseases and orphan drugs has gained prominence among scientists, managers, and the general public. This challenging problem requires evaluation and analysis from a variety of perspectives. Economic assessment of technologies can support decision-making and resource allocation. The research objective describes and discusses several important issues when addressing economic evaluation in rare diseases and orphan drugs. The method used in this article review is searching the Pubmed, Scopus, and ScienceDirect databases using specific keywords for research articles published in English between 2016 and 2021. We found 537 studies that economically evaluated the cost of treating rare diseases. The selected studies met the eligibility criteria that had been established. To assess the quality of the selected papers, we used a 10-point checklist derived from Drummond's criteria for economic evaluation. Seven papers were reviewed from the initial 20 articles that met the eligibility criteria, and 537 records were initially found across the three databases. The quality of the selected papers ranged from 70% to 100% in meeting Drummond's 10-point checklist. The conclusion of this research is to consistently and continuously identify cost-effective and cost-saving solutions that may help achieve good clinical outcomes and reduce the burden of disease. Future research should focus on the clinical implementation of interventions along with accompanying economic evaluations.

Introduction

According to the 1983 Orphan Drugs Act, Orphan drugs are defined as products that could address an unmet clinical need but have low investment potential due to the small population affected (Postma *et al*., 2022). A rare disease (RD) is a pathologic condition affecting fewer than 200,000 individuals (Haendel *et al*., 2020; Pearson *et al*., 2018). Approximately 80% of the 5,000–8000 rare diseases that have been identified worldwide are genetic in origin (Haendel *et al*., 2020; Makarova *et al*., 2021). Furthermore, the current estimate suggests there are approximately 10.000 rare diseases (Fermaglich & Miller, 2023; Haendel *et al*., 2020; Taruscio *et al*., 2011). The medicines proposed for diagnosing, preventing, and treating RDs are orphan drugs (Mazzucato *et al*., 2022). The total economic burden of 379 RDs in the United States in 2019 was estimated to be $997 billion, including $449 billion in direct medical costs and an additional $548 billion in indirect, non-medical costs and healthcare costs not covered by insurance (non-covered costs) (Yang *et al*., 2022).

RDs are often associated with early mortality and long-severe impairment. Although RDs have distinct clinical and pathogenetic characteristics (Haendel *et al*., 2020), they share many traits in terms of their social and health consequences, rendering RDs a public health concern. Less than one percent of

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rare diseases have effective treatments because their pathogenesis remains largely unknown (Cai *et al*., 2019; Tumiene & Graessner, 2021). Orphan provides a clear example of the limitations of standard market settings. These pharmaceuticals aim to treat life-threatening or chronically debilitating conditions that affect a small portion of the population, and their limited market potential for recovering development costs necessitates the establishment of a specific legislative framework to support orphan drug development and ensure economic viability (Taruscio *et al*., 2011). These conditions have a profound impact on affected individuals, as well as on their families, caregivers, healthcare systems, and society (Delaye *et al*., 2022). In recent decades, there has been an increasing awareness of the significance of rare diseases as a prominent public health concern (Delaye *et al*., 2022). Accessing therapeutic interventions and appropriate medications may be challenging, as treatment options may be unavailable, restricted, or prohibitively expensive (Angelis *et al*., 2015). Most research priorities typically focus on the economic impacts, whereas political and public discussions mainly revolve around the frequently outrageous expenses associated with their therapies and administration (Gammie *et al*., 2017). The high cost of treating rare diseases can be attributed to the time-consuming and expensive process of bringing orphan drugs to market. Moreover, clinical trials should be considered in terms of their challenges and expenses (Adachi *et al*., 2023; Taruscio *et al*., 2011). Some orphan drugs, which are used to treat various diseases, may be assumed to be effective for a rare disease that was not claimed on the label or the formulation. If an effective pharmaceutical product remains unaffordable for many patients due to unreasonably high costs, it can become a significant obstacle to achieving positive clinical outcomes.

The commercialization of items with an insufficient cost-effectiveness assessment has occurred in specific circumstances. In such cases, post-marketing surveillance is highly suggested to collect the missing data needed for a comprehensive assessment of cost-effectiveness, clinical relevance, and safety profiles. There were specific reasons for conducting this study to systematically review the cost-effectiveness analysis of rare disease medicines or orphan drugs.

Method

Systematic searches were conducted in Pubmed, Science Direct, and Scopus to explore articles related to the economic evaluation of rare disease drugs published between 2016 to 2021. Publications in languages other than English and those categorized as "systematic review," "meta-analysis," or "books" were excluded. The review aimed to examine the economic evaluation of the orphan drug to give an overview of the cost of rare disease therapy. The search methods involving MeSH terms were "economic evaluation" "rare disease" AND "orphan drug," which were used in Pubmed and Science Direct databases. In Scopus, the search terms used were "economic evaluation" OR "cost analysis" OR "cost studies" AND "rare disease" OR "orphan drug.

Furthermore, to select the article-based inclusion criteria, PICO was used as an inclusion criterion, where P stands for uncommon disease, I stands for orphan drugs, C stands for no intervention, and O stands for the outcome. Therefore, the study conducted full economic evaluations of orphan drugs as its methodology and focused on rare diseases as an indication for orphan drugs. In contrast, the exclusion criteria included qualitative studies, articles in languages other than English, and those with unavailable full text or only abstract available. The PRISMA diagram was used to depict the process of including reviewed papers. After collecting the selected study to review, a quality assessment of included articles was carried out, using Drummond's 10-point checklist. This critical appraisal done by EKU and PO will count the number of the met or unmet criteria on each paper. The extracted data from the included articles are the authors, the intervention or name of orphan drugs, the study subject, the types of outcomes, the economic evaluation model, and the analysis.

Result and Discussion

The PRISMA diagram guided the selection of studies (Fig. 1). From Pubmed, Scopus, and ScienceDirect database searches, it was identified 538 publications with an

additional three records. After removing duplicates, a total of 538 studies remained for the screening process. The titles and abstracts of these 538 studies were screened for eligibility, resulting in the exclusion of 518 studies based on the exclusion criteria. This left 20 studies for assessment in the qualitative synthesis. Ultimately, seven papers were selected as the final studies for examining the cost-effectiveness of orphan drugs in treating rare diseases.

The 10 points of the Drummond Methodological Quality Assessment were used to evaluate the quality of economics evaluation journals (Drummond *et al*., 2015). Seven studies that met the review's inclusion criteria were continued to assess the quality of the method in economic evaluation. Papers were marked with (V) if they fully met the criteria, while an (X) indicated that the study did not meet the criteria, and an (O) signified that the paper only partially met the criteria or contained some confusing information.) The quality assessment for these studies is presented in Table 1. The Drummond Methodological Quality Assessment revealed a score range of 7-10, equivalent to (70%-100%). The highest score of 10 was achieved by articles authored by (Hagendijk *et al*., 2021; Jalali *et al*., 2020), and the lowest score of 7 was given to articles authored by (Giudice *et al*., 2017). The 10-point Drummond checklist emphasizes key aspects of economic evaluation methodology, including perspective covered, cost considerations, sensitivity analysis, and discount rates used to estimate future treatment costs.

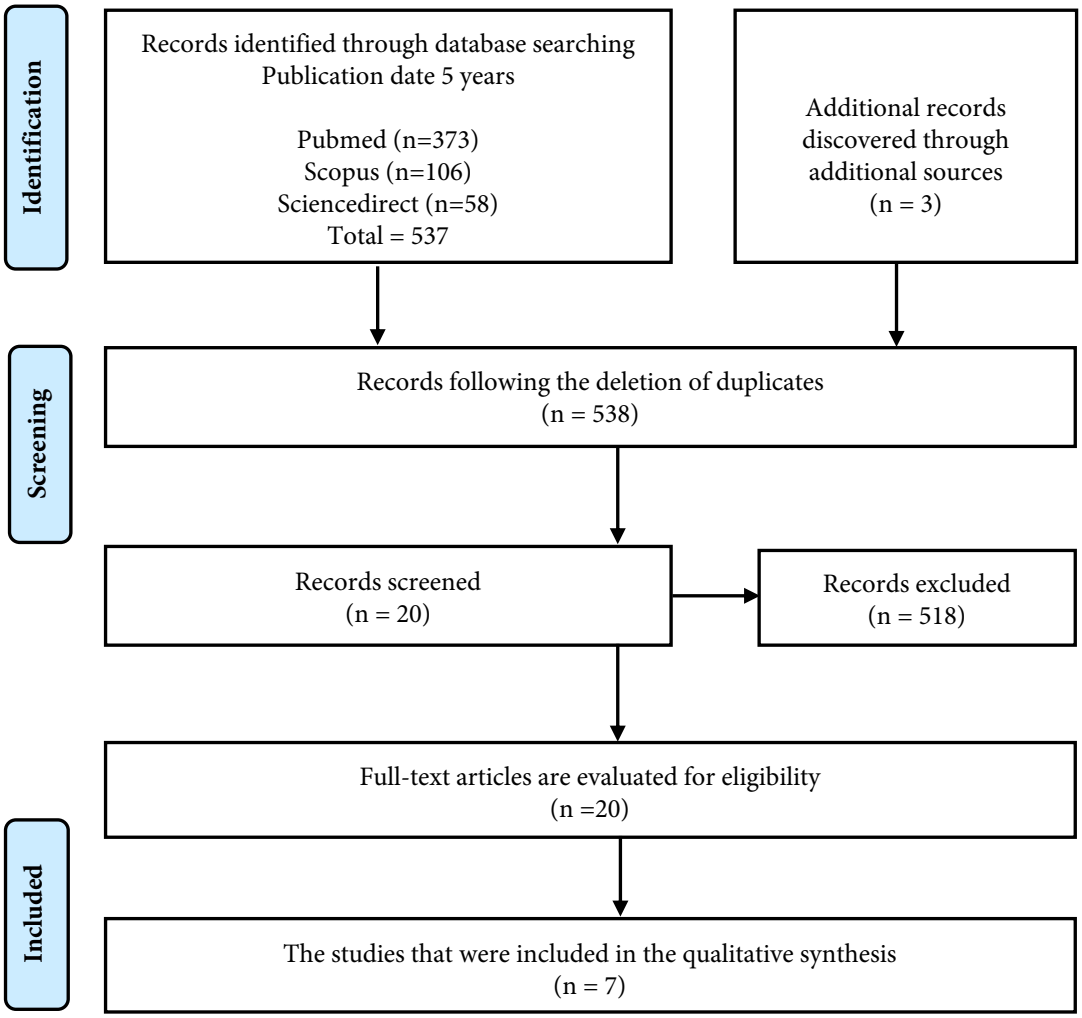

Figure 1. Flow-Chart Summary of Literature Search.

Table 1. Quality Assessment of Reviewed Papers.

No	Questions	Jalali et al. (2020)	Marita et al. (2019)	Wherry et al. (2020)	Kazi et al. (2020)	Giudice et al. (2017)	Galan et al. (2021)	Hagendijk et al. (2021)
1.	Was a well-defined question posed in an answerable form?	V	V	V	V	V	V	V
2.	Was a comprehensive description of the competing alternatives given?	V	V	V	V	V	V	V
3.	Was the effectiveness of the programs or services established?	V	V	V	V	V	V	V
4.	Where are all the important and relevant costs and consequences for each alternative identified?	V	V	V	V	V	V	V
5.	Were costs and effects measured accurately in appropriate physical units (e.g., QALYs)?	V	X	V	V	V	V	V
6.	Were costs and effects valued credibly?	V	X	V	V	V	V	V
7.	Were costs and effects adjusted for differential timing?	V	V	O	V	X	X	V
8.	Was an incremental analysis of costs and effects of alternatives performed?	V	V	V	V	X	V	V
9.	Were allowances made for uncertainty in the estimates of costs and effects?	V	V	V	V	X	X	V
10.	Did the presentation and discussion of study results include all issues of concern to users?	V	V	V	V	V	V	V

Yes: V

No: X

Not clear: O (in cases where the information provided was not satisfactory, thus making it difficult for the reviewer to conclude.

QALY, Quality-Adjusted Life Years; ICER, Incremental Cost-Effectiveness Ratio; IRD, Inherited Retinal Disease; VN, voretigene neparvovec; CF, Cystic Fibrosis; CFTR, Cystic Fibrosis Conductance Regulator; ATTR-CM, Transthyretin Amyloid Cardiomyopathy; TBSA, Total Body Surface Area; ICU/SICU, Intensive Care Unit/ Subintensive Care Unit; NXB, NexoBridâ; TTR, Transthyretin; O-LAR, Octreotide Long-Acting Release; LO, Lutetium-Octreotate

Based on Table 2, we formulated the following Economic evaluation characteristics: 1) Study setting. With four investigations (Jalali *et al*., 2020; Kazi *et al*., 2020; Marita *et al*., 2019; Wherry *et al*., 2020), Italy (Giudice *et al*., 2017), Spain (Galan *et al*., 2021), and the Netherlands (Hagendijk *et al*., 2021) were among the nations where the studies were conducted. These studies used a variety of techniques, including two cohort studies, four Markov model studies, and one retrospective research. 2) Time horizon. The duration of the intervention, as well as the monitoring of costs, effects, and benefits, should all be included in the time horizon. It should ideally reflect current clinical procedures. A time horizon

Table 2. Study Summary of Economic Evaluation in Rare Disease Treatments

Study	Country	Study Population	Method	Type of Evaluation	Intervention	Type of Outcome	Type of Cost	Perspective	Result
Jalali (2020)	US	Infants with spinal muscular atrophy	Markov model	Cost-Effectiveness Analysis	Universal screening and treatment with versus without Nusinersen injection.	QALY	Direct cost	Societal	ICER for nusinersen with screening and treatment was more saved.
Marita (2019)	US	The mean age of 15 years old, biallelic RPE65-mediated IRD	Markov model	Cost-Utility Analysis	Voretigene neparvovec (VN) gene therapy vs. standard of care treatment (regular physician visits and supportive care).	QALY	Direct costs Indirect Cost	Health care system and modified Societal perspective	VN offered 1.3 QALY's; from a healthcare system perspective, resulting in ICER $643 800/QALY and ICER $480 100/QALY from a modified societal perspective
Wherry (2020)	US	CF patients with the G551D mutation	Cohort	Cost-Effectiveness	Best supportive care plus ivacaftor (CFTR) vs. best supportive care alone	QALY	Lifetime Cost	Societal	The ICER of CFTR was $950217 per QALY, which is not cost-effective
Kazi (2020)	US	ATTR-CM wild-type or variant and heart failure Patients range in age from 18 to 90 years old.	Markov model	Cost-Effectiveness Analysis	Tafamidis versus ATTR-CM usual treatment.	QALY	Direct Medical Cost	Healthcare	Tafamidis cost-effective at $100,000/QALY
Giudice (2019)	Italy	Patients with a TBSA concentration of 14–22% and an intermediate-deep thermal burn	Retro spective	Cost-Consequences Analysis	NexoBridâ versus standard of care (Burn debridement with eschar removal).	The length of stay in the ICU/SICU and the need for escharotomy and autograft surgeries	Direct Medical Cost	Patient	NXB's average savings was 5350 euros
Galan (2021)	Spain	Transthyretin (TTR) amyloid polyneuropathy patients	Cohort	Cost-Consequences Analysis	Inotersen versus patisiran versus tafamidis.	Patient burden and costs compared	Direct Medical Cost Indirect Cost	Patient	The annual cost per patient receiving tafamidis treatment was 137,954€; inotersen treatment was 308,358€, and patisiran treatment was 458,771€.
Hagendijk, (2020)	Nether lands	The advanced neuroendocrine tumor patients	Markov model	Cost-effectiveness Analysis	At a high dose, octreotide long-acting release (O-LAR) was compared to O-LAR 60 mg every 28 days.	QALY	Direct Medical Cost	Healthcare	ICER with LO treatment were €19,000 per QALY to €53,500 per QALY

of 2.5 years was utilized in studies by Jalali *et al*., (2020)and Kazi *et al*., (2020), shorter time horizons of 1 year were used by Giudice *et al.* (2017); Marita *et al.* (2019) and Galan *et al.* (2021). Hagendijk *et al.* (2021) used the 28-day longest time horizon in their research. 3) Economic evaluation. The majority of the publications under evaluation performed cost-effectiveness studies to evaluate the efficacy of orphan pharmaceuticals in comparison to the standard of care or the absence of an orphan drug (Hagendijk *et al*., 2021; Jalali *et al*., 2020; Kazi *et al*., 2020; Wherry *et al*., 2020). A cost-repercussions analysis was used in studies by Giudice and colleagues in 2019 (Giudice *et al*., 2017) and Galan and colleagues in 2021 (Galan *et al*., 2021) to evaluate the costs, consequences, and clinical outcomes related to the use of orphan medications. 4) Intervention. In the investigations, almost all orphan medicines were assessed as potential therapeutic choices in comparison to the gold standard of care. In these investigations, the orphan medication was not administered to the comparator or control group. Galan *et al*. contrasted three potential therapies in 2021 (Galan *et al*., 2021) (based on the disease burden experienced by inpatients and the cost of care. For the treatment of rare diseases, all of the orphan drugs evaluated had received approval from the Food and Drug Administration (FDA) (Giudice *et al*., 2017; Kazi *et al*., 2020; Marita *et al*., 2019; Wherry *et al*., 2020) or other regulatory bodies, such as the European Medicines Agency (Galan *et al*., 2021). In this study, the economics of orphan medications such as nusinersen, verotigene neparvovec, ivacaftor, NexoBridTM, inotersen, patisiran, tafamidis, and octreotide were assessed. 5) Type of cost and perspective. The examined publications include a variety of charges and viewpoints, including both direct and indirect medical expenditures. However, in the work by Wherry *et al*. in 2020, patients with cystic fibrosis, a condition that falls within the category of chronic uncommon diseases, had their lifetime expenditures used to determine the Incremental Cost-Effectiveness Ratio (ICER). In this research, the emphasis was on direct medical expenses since they sought to evaluate the cost of care during the use of orphan medications, which is intimately related to the intervention. Prioritizing healthcare policies and initiatives requires measuring the financial and healthcare costs of diseases in society (Davari *et al*., 2019). 6) Economic evaluation results. Almost all investigations (Giudice *et al*., 2017; Hagendijk *et al*., 2021; Jalali *et al*., 2020; Kazi *et al*., 2020; Zimmermann *et al*., 2019) showed that orphan medications were more cost-effective than their comparators. However, only Wherry in 2020 (Wherry *et al*., 2020), discovered that ivacaftor was not cost-effective when used in conjunction with supportive treatment to treat cystic fibrosis patients who had the G551D mutation. In a subsequent study by Galan (Galan *et al*., 2021) that contrasted the prices of inotersen, patisiran, and tafamidis, it was discovered that the latter was the most affordable option for individuals with Transthyretin Amyloid Cardiomyopathy. The cost-effectiveness ratio for tafamidis was also determined to be $100,000 per Quality-Adjusted Life Year (QALY) (Kazi *et al*., 2020).

Rare diseases impose a significant clinical and economic burden on patients and healthcare systems, risking the inability to meet patients' needs and hindering equal access to treatment (Cannizzo *et al*., 2018). Historically, the development of commercial medications has failed to address the requirements of people with rare diseases. To incentivize the development of drugs for rare diseases that would otherwise be uneconomical, numerous jurisdictions have enacted orphan drug legislation. For instance, the only expected expenses associated with expanding the indication of sildenafil to treat pulmonary artery hypertension and chronic thromboembolic pulmonary hypertension are the costs of performing clinical trials and marketing (Gupta *et al*., 2015; Simoens *et al*., 2011).

However, due to the small market size, these medications are often quite expensive. Orphan drugs are rarely cost-effective, leading to restrictions in funding and patient access. Conversely, these constraints may not align with societal expectations (Drummond *et al*., 2007). Some authorities have implemented rigorous negotiations to balance multiple competing societal objectives, such as promoting innovation, facilitating access to medicines, and ensuring affordability (Panteli

et al., 2016; Simoens *et al*., 2022).

The additional time that caregivers spend providing care implies a loss of annual output. In a recent study that utilized the human resource method for economic evaluation, it was revealed that when a lifetime horizon was considered, high costs resulted in significantly higher indirect costs. Additionally, Dussen *et al.* (2014) examined lost output due to absenteeism and lost production resulting from early retirement while estimating indirect costs using caregivers' actual wages, in comparison to our method of calculating indirect costs using caregivers' actual income. About 10.6 percent of the direct costs were attributed to expenses such as lodging, transportation, food, and other items, indicating a significant burden associated with access to medical services (Pearson *et al*., 2018; Qi *et al*., 2021). Pharmaceutical, inpatient, and outpatient treatments were all included in the direct healthcare costs. The majority of the resources needed by individuals with uncommon diseases are covered by pharmaceutical costs. Recent research indicates that drugs have accounted for roughly 90% of rare disease healthcare costs (HsuI *et al*., 2018). Even though outpatients represent a far larger population than inpatients admitted for the treatment of a rare condition, the average cost per person for inpatients is roughly ten times that of outpatients (Cai *et al*., 2019). A cost analysis study is required to provide policymakers and hospital administrators with valuable information to enhance hospital services and manage resources effectively (Dianingati *et al*., 2019). Measuring the economic cost of illness can offer policymakers better insights for developing more targeted interventions for rare diseases at different levels of the healthcare system (Jo, 2014) While some orphan drugs are subject to specific conditions, not all orphan drugs are. There are various instances when the small number of patients treated with an orphan drug and its limited economic viability can be called into question (Simoens, 2011). Financial consequences associated with rare diseases encompass both direct expenditures, which encompass medical and nonmedical expenses, as well as indirect costs. The financial burden associated with specific rare diseases can amount to millions of dollars each year, primarily due to various cost factors such as hospitalizations, emergency visits, medications, dental health services, palliative care, outpatient visits, insurance expenses and reimbursement, rehabilitation care, home health care, assistive devices, social services, and the provision of caregiver (Angelis *et al*., 2015; Chiu *et al*., 2018; Friedlander *et al*., 2019). The economic burden of a disease comprises three types of costs: direct costs, indirect costs, and intangible costs. (Mursinto & Kusumawardani, 2016). The majority of costs are accounted for by direct costs (Péntek *et al*., 2016). Among these, the direct medical cost of rare diseases (RD) contributes to nearly half of the total burden (45%), followed by indirect costs due to the loss of productivity (44%), non-medical costs (7%), and uninsured healthcare costs (4%) (Yang *et al*., 2022). Direct costs include direct medical costs such as drug costs, medical device costs, treatment costs, medical treatment costs, costs associated with supporting examinations like laboratory tests, CT scans, and physiotherapy costs, as well as other direct costs of treatment (direct non-medical costs) such as hospitalization costs, administrative costs, and transportation costs. Indirect costs encompass expenses that cannot be directly attributed to a product or service, such as administration, promotion, security, etc. Four articles calculated direct medical expenses, one article calculated both direct and indirect costs, one article only considered direct costs and one article focused solely on lifetime costs, as per the seven articles reviewed. In addition to the direct medical costs associated with RD, there are significant indirect costs related to productivity losses, non-medical expenses like spending on home or motor vehicle modifications, and certain healthcare costs not covered by insurance. Many people with RDs have high medical needs that lead to missed work, early retirement, and reliance on caregivers for activities of daily living (Yang *et al*., 2022). The annual cost ranges from £726 to £378,000, with a median value of £31,012. According to the data, 24% of drugs have an annual cost below £10,000, 58% fall within the price range of £10,000 to £100,000, and the remaining 18% have an annual cost equal to or exceeding £100,000 (Onakpoya *et al*., 2015).

Compared to some studies, one of the factors most directly or indirectly affecting the ultimate price of medicines is the anticipated financial impact of the new treatment on pharmaceutical spending (Jommi *et al*., 2021; Korchagina *et al*., 2017; Villa *et al*., 2019).

To quantify the effectiveness of an intervention, commonly used health outcome measures such as the QALY are employed. Generic health outcome measures, like the QALY, serve as tools to express an intervention's effectiveness (Blonda *et al*., 2021). The QALY indicator has been considered valuable for assessing both the quantity and quality of life and for comparing diseases, including informal care or mental health care for conditions that are difficult to measure. However, the primary advantage of the QALY approach lies in its ability to guide decisions based on predefined thresholds for "acceptable" and "unacceptable" costs per QALY (Beresniak & Dupont, 2016). The QALY is a statistic derived from an economic model that combines the number of years gained from treatment with the patient's health-related quality of life. In the context of conventional cost-effectiveness analysis (CEA), the metric used is the incremental cost per quality-adjusted life-year (QALY) gained, also known as the incremental cost-effectiveness ratio (ICER). The incremental cost-utility ratio values shift from positive to dominant (lower incremental costs and larger QALYs gained) or decrease when the societal perspective is taken into consideration (Aranda-Reneo *et al*., 2021). Can the consideration of societal costs change the recommendations of economic evaluations in the field of rare diseases? This is the subject of an empirical analysis. A Norwegian study investigated whether society preferred to prioritize the treatment of rare diseases and accept orphan medications with higher ICERs (Desser *et al*., 2010).

To make a decision, this metric is compared to a predetermined or revealed willingness-to-pay threshold (Postma *et al*., 2022). Besides QALY, numerous outcomes resulting from the usage of orphan medications in uncommon diseases have been studied, including ICU/SICU length of stay and the necessity for procedures, as well as patient burden and expenses. The efficacy of a program is evaluated from multiple perspectives, including those of society, the healthcare system, and the patient.

The economic evaluation component included in the Health Technology Assessment (HTA) serves as the central element in the assessment process, providing valuable insights to inform decisions regarding resource allocation (Jönsson, 2009). HTA can assist health systems in making more efficient use of their limited resources, thereby maximizing population health outcomes within a budget constraint (Teerawattananon *et al*., 2021). The perspective of economic evaluation should be carefully determined at the beginning of the study. Typically, there are multiple perspectives, including patients, the health system, payers, and society. Measuring costs and consequences is essential for identifying multiple perspectives. Since HTA is always used to determine reimbursement, the payer perspective is very common, but it may not convey the entire cost picture. The societal perspective encompasses healthcare, non-health, productivity, intangible costs, and more, and it presents difficulties in study design, data acquisition, and analysis protocol (Chen, 2022). The application of a societal perspective is highly recommended for conducting economic evaluations in the field of public health (Café *et al*., 2019). This approach is beneficial as it encompasses and considers multiple perspectives, providing a comprehensive analysis. Health economic evaluations that have been conducted with a limited perspective, focusing only on direct costs in the analysis, may exhibit bias and have the potential to substantially underestimate the actual societal benefits of the interventions. Moreover, the absence of a societal perspective can lead to suboptimal allocation of resources, resulting in a decrease in overall societal welfare and potential losses (Café *et al*., 2019; Fakhri *et al*., 2017).

The majority of research in this review concluded that using orphan medicines was cost-effective. Eighty-five percent of orphan drugs showed significant clinical effects. Orphan medications are more likely to be considered cost-effective (and reimbursed if applicable) (Postma *et al*., 2022). Orphan drugs often offer larger health gains than non-orphan

drugs, but due to their substantially higher costs, they tend to be less cost-effective than non-orphan drugs (Chambers *et al*., 2020). The absence of high-quality cost and outcome data is a major limitation in rare disease research.

Conclusion

In summary, the economic evaluation considered all aspects of the intervention, identifying the potential to select a more cost-effective and efficient choice to reduce patient burdens. Adding a new intervention or program typically proves to be more cost-effective.

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