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Methods and criteria for the assessment of orphan drugs: a scoping review

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Abstract

Objectives: This study aimed to identify different criteria for priority setting of rare diseases to help policy makers in making evidence-informed decisions.

Methods: A scoping review was conducted to comprehensively examine the existing various methods and criteria for prioritizing orphan drugs and rare diseases. We performed searching in Scopus, PubMed, Embase, and websites of health technology assessment (HTA) agencies, 2000–21, and data were extracted.

Results: From the 1,580 identified publications, eleven articles were included. Multicriteria decision analysis was the most frequent method (seven out of eleven studies) used for priority setting. The extracted criteria for priority setting of orphan products were analyzed based on six main categories as follows: health outcomes and clinical implications (six subsets which showed clinical implications), economic aspects (four subsets that indicated the economic effects of orphan drugs and rare diseases), disease and population characteristics (six subsets that included the characteristics of the rare diseases), therapeutic alternatives and uniqueness of orphan technologies (two subsets which discussed the alternatives and uniqueness of orphan technologies), evidence (three subsets which regarded the quality and availability of evidence), and other criteria (three subsets dealing with social and organizational criteria). Cost-effectiveness, budget impact, and disease severity were the most frequent criteria in the studies.

Conclusions: Because of the high price of orphan drugs and limitations of using HTA for reimbursement of them, it is critical to explore them by precise technical methods like multiple criteria decision making in priority setting.

A rare disease is a disease which affects a small number of people in a population as compared with other prevalent diseases (1). In other words, a rare disease is a medical condition which has low prevalence, is life-threatening or chronically debilitating, and has different definitions from one country to another (2). Examples of rare diseases include genetic diseases, rare cancers, infectious tropical diseases, and degenerative diseases (3;4). For example, the National Organization for Rare Diseases has defined them as diseases affecting fewer than 200,000 individuals, or approximately sixty per 100,000 population (4). However, the European Union (EU) has defined the condition as affecting no more than five in 10,000 people. Totally, it is estimated that there are 6,000–8,000 rare diseases in the world affecting approximately 6–8 percent of the world's population (1;3).

Today, approvals of orphan drugs such as biopharmaceutical products for patients with serious, disabling, and fatal diseases have provided new chances for the patients (4). Following these achievements, the market for orphan drugs is expanding. In 2015, worldwide sales of orphan drugs reached USD 100 billion, but the market is expected to amount more than USD 200 billion by 2022. It is estimated that, by 2022, one-fifth of all prescription drug sales will be related to orphan drugs. Furthermore, the average annual cost for orphan drugs is calculated to be five times greater than that for nonorphan medications (USD140,443 vs. USD27,756, respectively) (4).

There is a lot of debate in different countries over the financial support of orphan drugs. These debates include the allocation of governmental subsidies for orphan drug development such as providing tax incentives and clinical development costs as well as extending patent protections (4). There is evidence of a societal impulse to prioritize treatment for conditions that are severe or

genetic based, and those which affect very young people (4). On the other hand, health system policy makers in the world must deal with the conflict generated by competing increasing demands and insufficient resources for providing orphan drugs and their financial protection in their own countries. Orphan drugs may be costly to develop, but the target population is very small, and the need to recoup (R&D) "research and development" costs is often reflected in high prices (5).

Although the availability and affordability of orphan drugs have high priority for policy makers in all countries, such policies are sometimes destined to fail or are limited because of cost-effectiveness (CE). Because of that, prioritization for rare diseases drugs is becoming very important in order to ensure maximum efficacy and effectiveness with limited resources. There is no definite way to prioritize orphan drugs. Different methods are used to do so, including CE analysis and multicriteria decision analysis (MCDA). However, the common characteristics in all these methods (mostly related to MCDA) are their needs for the criteria for prioritization that could lead to maximum efficacy and effectiveness of health interventions (6). Regarding all the aforementioned reasons, this study aimed to identify the methods and criteria for prioritizing rare diseases and orphan drugs. The results of this study can help make evidence-informed policies for rare diseases in many countries in various aspects. These aspects can include prioritizing these diseases for ensuring availability and affordability of their treatment in the form of benefit packages or subsidies, provide scientific accountability evidence for community, plan to manufacture and produce drugs, and finally choose the appropriate solution to supply drugs and treatment for rare disease.

Methods

The scoping review was conducted because we wanted to identify knowledge gaps and scope a body of literature about various methods and criteria for prioritizing orphan drugs and rare diseases. For this purpose, we used the five stages of Arksey and O'Malley's framework, as described below, for scoping the review (7):

Identifying the Initial Research Questions

According to the purpose of this study, we put the following items on the agenda:

What are the methods for prioritizing orphan drugs and rare diseases?

Which criteria were selected for prioritizing orphan drugs and rare diseases?

Identifying Relevant Studies

We performed comprehensive literature searching in the major databases, including Scopus, PubMed, Embase, and the websites of health technology assessment (HTA) agencies (like EUnetHTA, CADTH, and NICE) from 1 Jan 2000 to 1 Jan 2021, for English and Persian language articles in all types of research. Aiming to search the abovementioned databases, a search strategy appropriate to each database regarding MeSH guidelines was used with the following keywords: "orphan drugs," "orphan disease," "drug costs," "prioritize," "budgeting," "economics," and "health policy" (Supplementary Table 1). We also searched across the websites of governments and organizations and Google for data in gray literature to obtain possible related evidence.

Study Selection

The conducted searches included only the studies which could provide information about prioritizing orphan drugs or diseases (the papers with type of original or review with explicit method section). The titles and abstracts of the articles which were found were checked out by two researchers in parallel and any disagreements were resolved by mutual consent. The abstracts were reviewed and the studies without an explicit methods section were excluded. Full texts of the remaining articles were reviewed for inclusion. In addition, references in the selected articles were further searched for additional articles.

Data Charting and Collation

In this part, the data were extracted from the articles according to the developed framework based on the questions and the dimensions of the studies and then presented in excel sheets. The framework combined the general specifications of the articles, such as the title, year, authors, country, and method for prioritizing orphan drugs or diseases as well as the criteria for prioritizing.

Summarizing and Reporting Findings

In the final step, to ensure the accuracy of data extraction and literature analysis, we used text search in MAXQDA software (8) to determine categories and subsets for priority setting.

The findings of the selected studies were synthesized using a directed approach of qualitative content analysis known as deductive category formulation (9). In this study, the researchers were interested in better understanding of the methods and criteria currently used for priority setting of orphan drugs and rare diseases, and research questions were used to find differences and similarities in different studies to formulate categories. Two researchers independently produced the intially identified categories. Then, the researchers shared their drafted analyses and interpretations and had a meeting to discuss the identified categories. We classified all categories into subsets according to the general commonalities among them.

Results

Study Selection

Thousand five hundred and eighty articles were found in the initial search. After reviewing titles and abstracts, we excluded sixteen duplicates and a further 1,472 papers which did not refer to orphan drugs or rare diseases or were otherwise not relevant. We reviewed the full text of the remaining ninety-two papers and found eleven relevant papers to include in our review. This process was carried out in accordance with the PRISMA statement and is summarized in Figure 1 (10).

Characteristics of Studies

All identified studies were published between 2015 and 2019. Contexts included fourteen different countries (see Table 1),

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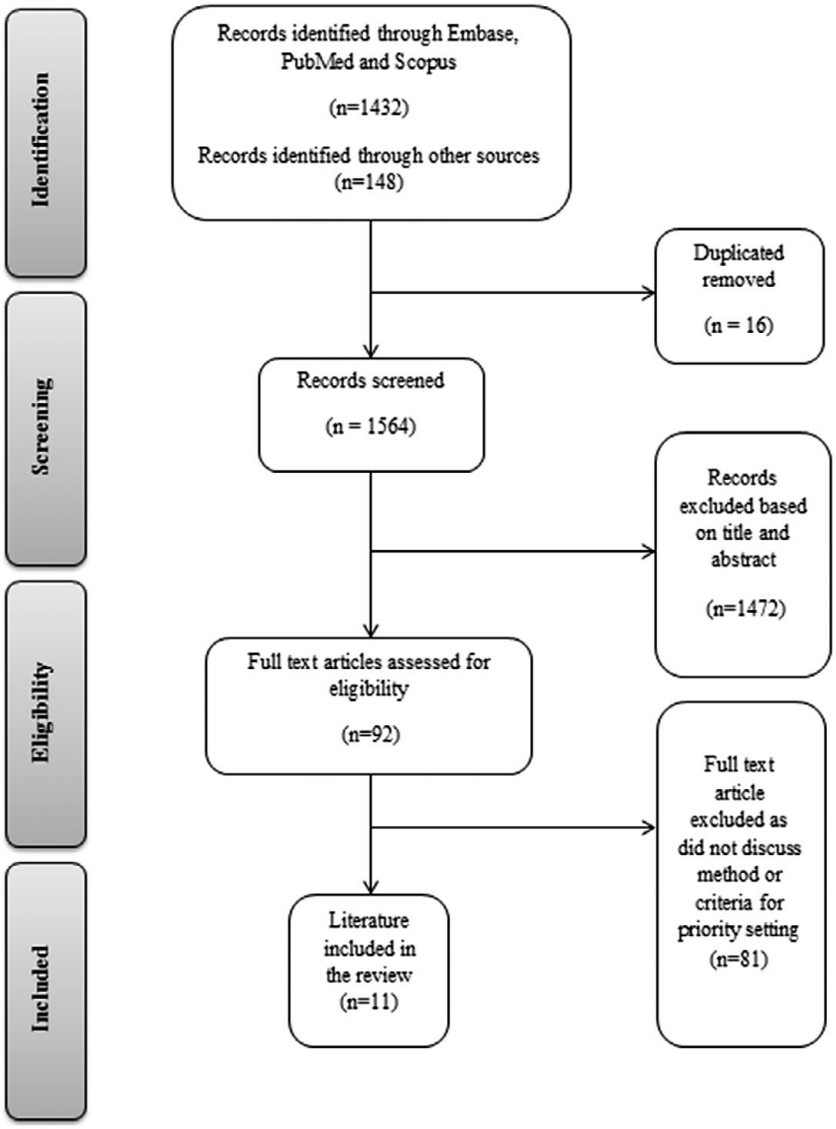

Figure 1. Article screening process (PRISMA 2018 flow diagram).

Central and Eastern European countries, and Europe as a whole (4–6;11–16).

Methods of Assessment

Two main methods for assessment of orphan drugs and rare diseases were identified. This review included three review articles that were assessed for the valuation criteria of orphan medicines in different countries. Six tested the criteria for priority setting of orphan drugs qualitatively. In the qualitative studies, the researchers employed "qualitative MCDA or discrete choice model" to score and rank the criteria (17). Two studies used mixed methods where CE analysis was compared to MCDA (Table 2). As we can see, MCDA was the most frequent method (seven out of eleven studies) for priority setting of orphan drugs and rare disease. In all seven studies, the main criteria were extracted and prioritized according to the MCDA method based on the opinion of experts, and in two of them, scenarios were designed based on the importance of different criteria.

Criteria for Assessment

Criteria for priority setting of orphan drugs and rare diseases were analyzed in six main domains as follows: health outcomes and clinical implications, economic aspects, disease and population characteristics, therapeutic alternatives and uniqueness of orphan technologies, quality and availability of evidence, and other social and organizational criteria. Figure 2 shows the frequency of each criterion in the reviewed literature and as we can see CE, budget impact and disease severity were mentioned most frequently (see Figure 2). In the next part, the subsets of each domain are explained comprehensively.

Health Outcomes and Clinical Implications

Health Benefits. Three studies addressed health benefits of policy making for orphan drugs. "Impact on the patient, job and family," "health and social effects," "impact on the provision of care services," "capacity related to the benefits of treatment," and "improvement health" were the main proxy attributes which

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Table 1. Frequency of Included Papers[CMT5] on the Base of Country

The countries	Studies
United Kingdom (UK)	Ollendorf et al. (4) Lopez-Bastida et al. (5) Lasalvia et al. (6) Nicod (11)
Scotland	Nicod (11)
Sweden	Ollendorf et al. (4) Nicod (11)
France	Ollendorf et al. (4) Nicod (11)
Canada	Ollendorf et al. (4) Lasalvia et al. (6) Short et al. (12)
Netherlands	Ollendorf et al. (4) Friedmann et al. (13)
Germany	Ollendorf et al. (4) Lopez-Bastida et al. (5)
Poland	Lasalvia et al. (6) Kolasa et al. (14) Kolasa et al. (15)
Spain	Lopez-Bastida et al. (5) Lasalvia et al. (6) Guarga et al. (16)
Belgium	Lasalvia et al. (6)
Colombia	Lasalvia et al. (6)
Italy	Lopez-Bastida et al. (5) Lasalvia et al. (6)
Norway	Lasalvia et al. (6)
Bulgaria	Lasalvia et al. (6)

reflected health benefits (4;5;11). The term "improvement health" is related to the patient's feeling in the treatment process on the EQ-5D scale (5).

Clinical Benefits. Clinical benefits were determined in orphan drugs policy making as attributes like "clinical uncertainty," "clinical evidence," and "clinical effectiveness and efficacy" (8;13–15). Clinical evidence was defined as the best available scientific information to guide decision making about clinical management (14).

Efficacy/Effectiveness. "Comparative efficacy" was the most frequent attribute in the included studies for the evaluation of policy making for orphan drugs and three papers mentioned this attribute (7;10;11). This attribute was the most quantitative attribute regarding the orphan drugs policy making (7).

Safety. Safety was one of the important attributes mentioned by six included studies. The main terms which were defined for safety in the included studies were "safety and tolerability," "drug safety considerations," "the level of treatment safety," "safety and side effects," "level of side effects," and "drug safety" (5;7;8;11–13). Given the shortage of data on safety aspects of orphan drugs, discussions between experts will have a great value for determining safety status (13).

Quality of Life. In Eastern and Central European countries, the "quality of life lost without treatment" was one of the important attributes for policy making of orphan drugs (11). Priority setting of rare diseases could be performed by QALYs via disease states (11).

The Level of Uncertainty in Effectiveness. "The degree of uncertainty about the effectiveness of the drug" for orphan drugs policy making was defined via attributes like clinical benefit, study design, comparator, population and generalizability, sample size, and safety (9). This attribute can be categorized into three levels: "immature but promising data," "appropriate surrogate endpoints," and "robust clinical endpoints" (9).

Economics Aspects

Cost-Effectiveness. The most frequent main attribute mentioned in seven papers was "cost-effectiveness." Considerations regarding the methods of incremental cost-effectiveness ratio (ICER) calculations for adapting the orphan drugs policy making context and determining the accurate threshold for it were the major discussions in the papers (4;5;10–14). According to the Ollendorf et al. (4) study, for England and Wales, Sweden, and the Netherlands, the CE thresholds were Pound Sterling 100,000, 35,000–100,000, and EURO 80,000 per QALY, respectively. ICER in MCDA context based on the Friedmann et al. (13) study (as trade-off criteria of decision matrix) was categorized into three groups, ICER below EURO 24,000, ICER in the range between 24,000 and EURO 48,000, and ICER above EURO 48,000.

Costs. Four papers mentioned "cost" via proxy attributes like "cost data," "treatment costs," and "costs of drugs for rare patients (nonmedical and medical)" (5;12;14;17). This term refers to the resources which must be allocated to treatment (5). Lopez-Bastida et al. (5) suggested that where information was lacking about nonmedical costs for rare diseases, it could be excluded from policy making.

Budget Impact. After CE, "budget impact" was the most frequent attribute among the economic factors, and five papers mentioned this attribute (4;10–13). According to the Ollendorf et al. (4) study, for England and Wales, France, and Germany, budget impact thresholds were Pound Sterling 20, EURO 30, and EURO 50 Million per year, respectively. Total costs of insurance coverage of orphan drugs in the first two years in the MCDA context based on the Friedmann et al. (13) study (as trade-off criteria of decision matrix) were categorized into three groups: budget savings or positive budget impact "below EURO 1.2 Million," "in the range between EURO 1.2 and 2.4 Million," and "above EURO 2.4 Million."

Opportunity Cost and Financial Affordability. This attribute was mentioned in only one study as a factor related to economic aspects of orphan drugs policy making (8).

Disease and Population Characteristics

Disease Severity. Disease severity was used to refer to the pretreatment health state of patients, the more severe the disease, the greater the impact on society, especially on patients and caregivers. Most of the rare diseases can cause morbidity, disability, reduced quality of life, and shorter life expectancy. A large part of these conditions begins during childhood and many of them lead to major disability. Generic health-related quality of life or disease-specific quality of life tools can help to measure this criterion (1). In the study of the evaluation of orphan drugs in the MCDA framework, the severity of the disease was a high relevance criterion in all studies (2). In Poland, in order to evaluate priority of fifty-four

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Table 2. Extraction Data from Full Text

No.	References	Title	Criteria	Subcriteria	Results	Method
1	Nicod (11)	Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries	Clinical uncertainties	Clinical benefit	Reasons for cross-country differences included heterogeneity in the evidence appraised, in the interpretation of the same evidence, and in the different ways of dealing with the same uncertainty. These may have been influenced by agency-specific evidentiary, risk and value preferences, or stakeholder input.	Mixed methods were used to systematically examine the HTA decision processes for individual drugs and countries on the basis of a validated methodological framework
				Study design		
				Comparator		
				Population and generalizability		
				Sample size		
				Safety		
			disease	Disease nature affecting the patient		
				Unmet need		
				Rarity, orphan status, small patient population		
				Issues around current treatment alternatives		
				Complex pathway, no best practices or advances		
				National priority		
			Treatment	Clinical benefit and type of benefit		
				Innovative nature of the benefit		
				Indirect benefits from the treatment		
				Adverse events manageable/ nonsignificant		
2	Short et al. (12)	A National Approach to Reimbursement Decision-Making on Drugs for rare diseases in Canada? Insights from across the ponds	Policy elements	Eligibility/scope	Almost all countries have multiple mechanisms through which coverage for Drugs for Rare Diseases (DRD). Countries have not created separate centralized review processes for DRDs; Instead, they have modified components of existing mechanisms and added safety nets.	Systematic review of policies and processes
				Patient population		
				Clinical evidence		
				Cost data		
				Cost-effectiveness		
				Patient input		
				Review/decision-making participation		
				Decision options Decision factors		
				Transparency		

(*Continued*)

Table 2. (*Continued*)

No.	References	Title	Criteria	Subcriteria	Results	Method
3	Ollendorf et al. (4)	Evaluating and valuing drugs for rare conditions: no easy answers		Patient/carer/family impact	As the evaluation of orphan drugs is not simple, assessors of evidence must determine whether different standards should be used to determine the net health benefit of a rare-disease intervention; Decision makers must decide whether and how to allow contextual factors to accompany more traditional methods of evidence synthesis and economic evaluation; and above all, societies must choose how far they are willing to go to tip the scales toward equity and away from equality.	Overview of the societal, ethical, and coverage/reimbursement of novel treatments for rare diseases
				Benefits other than health/ social		
				Impact on care delivery/ training		
				Human dignity principle		
				Needs-solidarity principle		
				Cost-effectiveness principle		
				Plausibility of treatment effects		
				Feasibility of randomized study		
				No treatment alternatives		
				Life-threatening		
				Feasibility (budget impact)		
				Disease burden		
				Medical necessity		
				BI (Budget Impact) threshold		
				Budget impact assessment		
				C-E threshold		
				Allows for QALY “weighting” when QALY gain exceeds 10 yr		
4	Lasalvia et al. (6)	International experiences in multicriteria decision analysis (MCDA) for evaluating orphan drugs		Rarity of the disease	The framework of MCDA considers characteristics of orphan diseases and their clinical and economic impact. At the same time, it must be accompanied by qualitative processes for incorporating societal values in criteria weighting and constructing decision rules.	A scoping review was conducted in order to characterize MCDA frameworks for assessing OD (Orphan Drugs)
				Complexity in production		
				Severity of the disease		
				Alternatives available/ Unsatisfied needs/ Availability of therapeutic		
				Budget impact		
				Comparative efficacy		
				Innovation/research level		
				Safety/Tolerability		
				Burden of disease		
				Use for a single indication		
				Cost-effectiveness		

(*Continued*)

Table 2. (*Continued*)

No.	References	Title	Criteria	Subcriteria	Results	Method
5	Kolas et al. (14)	Revealed preferences towards the appraisal of orphan drugs in Poland—multi criteria decision analysis		Indication uniqueness	The MCDA matrix consisted of thirteen criteria, of which clinical evidence, cost of therapy, and safety considerations were the main contributors.	The MCDA analysis was performed utilizing validated ZR × MCDA tool
				Disease rarity		
				Disease severity		
				Advancement of technology		
				Manufacturing technology		
				Therapeutic alternative		
				Scientific evidence for clinical efficiency		
				Benefits from use of medicine (safety aspects)		
				Cost-effectiveness analysis		
				Budget impact analysis		
				Therapy cost		
				HTA recommendations issued elsewhere		
				Rationalization analysis		
6	Zelei et al. (19)	Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries	Disease-related factors	Prevalence (rarity) of disease	The presentation of good clinical evidence, budget impact, equity principles based on disease prevalence and nonavailability of alternative treatment options seems to play key roles in reimbursement decisions.	Systematic review on the evaluation criteria of orphan medicines
				Severity of disease		
				Identifiability of the patients of treatment		
				Loss of QALYs without treatment		
				Unmet medical need		
				Clinical heterogeneity of the disease		
			Treatment-related factors	Evidence of treatment efficacy or effectiveness		
				Capacity to benefit from the treatment		
				Treatment is curative or delays progression or alleviates symptoms		
				Safety profile of treatment		
				Innovative profile of treatment		
				Manufacturing complexity		

(*Continued*)

Table 2. (*Continued*)

No.	References	Title	Criteria	Subcriteria	Results	Method
			Economic factors	Cost-effectiveness Budget impact		
				Number of indications		
				Potential for off-label use		
			Societal factors	Societal impact of treatment		
				Equity in access to treatment		
				Legal considerations		
7	López-Bastida et al. (5)	Using a stated preference discrete choice experiment to assess societal value from the perspective of decision makers in Europe. Does it work for rare diseases		Severity of the disease	In the five-country model (UK, France, Germany, Italy, and Spain), relative preference for attributes like treatment costs, improved health, value for money, and the availability of treatment options attracted the most attention.	A discrete choice experiments (DCE) was used on a convenience sample of participants from five European countries to explore their preferences in distinct healthcare scenarios involving orphan drugs
				Improvement in health		
				Waiting times		
				Availability of other treatments		
				Side effects		
				Value for money		
				Beginning of life		
				Cost of treatment		
8	Guarga et al. (16)	Implementing reflective multicriteria decision analysis (MCDA) to assess orphan drugs value in the Catalan Health Service (CatSalut)	Disease Impact	Disease severity	The final framework was composed of ten quantitative criteria (Core Model) and four qualitative criteria (Contextual Tool), the most important criteria were “disease severity”, “unmet need”, “comparative effectiveness” and “comparative safety / tolerability”.	Qualitative and quantitative MCDA were tested. A staged approach was used with the following main steps: selection and structuration of quantitative criteria (Core Model) and qualitative criteria (Contextual Tool), framework scoring and assessment of three orphan drug case studies
				Unmet needs		
			Comparative outcomes of orphan drugs	Improvement of efficacy/ effectiveness		
				Improvement of safety/ Tolerability		
				Improvement of patient perceived health/PRO (Patient-Reported Outcome)		
				Type of therapeutic benefit		
			Economic consequences of intervention	Annual patient cost of treatment		
				Other medical costs		
			Knowledge about intervention	Quality of evidence		
				Expert consensus/clinical practice guidelines		
			Normative contextual criteria	Population priorities and access (principle of equity)		
				Common goal and specific interests		
			Feasibility contextual criteria	System capacity and appropriate use of orphan drugs		

(*Continued*)

Table 2. (*Continued*)

No.	References	Title	Criteria	Subcriteria	Results	Method
9	Schey et al. (18)	Multi-criteria decision analysis (MCDA): testing a proposed MCDA framework for orphan drugs		Rarity	Scenario testing to measure the impact of weighting the criteria differently showed slight difference in the ranking of the drugs. The clinical/economic experts put more weight on efficacy, whereas the patient advocates weighed treatment efficacy and impact on daily lives equally. Linear model, suggests a good correlation between the average annual cost per patient and each drug's aggregate score.	MCDA framework was developed using the nine criteria by using the suggested numerical scoring system on a scale of one to three for each criterion to test three scenarios
				Level of research undertaken		
				Level of uncertainty of effectiveness		
				Manufacturing complexity		
				Follow-up measures		
				Disease severity		
				Available alternatives/Unmet needs		
				Treatment impact on disease		
				Unique indication or no		
10	Kolasa et al. (14)	Potential impact of the implementation of multiple-criteria decision analysis (MCDA) on the Polish pricing and reimbursement process of orphan drugs		Indication uniqueness	The MCDA approach may lead to different outcomes compared to a traditional HTA process. Improving the list of decision criteria leads to a closer look at a given health technology. Discussing the overall appropriateness of adapting the MCDA approach can help transparent and equitable resource allocation in the healthcare sector.	A four step approach should include: systematic review to select, establishment of database of orphan drugs, categorization of health technology appraisals and MCDA appraisal carried out, comparison of outcomes from traditional HTA and MCDA outcomes.
				Disease rarity		
				Disease severity		
				Advancement of technology		
				Manufacturing technology complexity		
				Therapeutic alternative (unmet medical need)		
				Scientific evidence for clinical efficiency (level of uncertainty)		
				Benefits from use of medicine (safety and adverse effects)		
				Cost-effectiveness		
				Budget impact (in €)		
11	Friedmann et al. (13)	Using MCDA to appraise orphan drugs: a systematic review	Disease-specific criteria	Disease severity	MCDA is increasingly used in the assessment of orphan drugs. It has proven to help make reimbursement decisions for orphan drugs. However, more research needs to be done on its application.	Overview of the existing evidence regarding the use of MCDA in the appraisal of orphan drugs worldwide
				Disease burden		
				Disease rarity		
				Disease social impact on patient and Carer's daily life		
			Intervention related criteria	Clinical effectiveness and efficacy		
				Safety		
				Cost-effectiveness		
				Quality of evidence		
				Type of preventive benefit		

(*Continued*)

Table 2. (*Continued*)

No.	References	Title	Criteria	Subcriteria	Results	Method
				The existence of alternatives Unmet needs		
				Comparative patient-perceived outcomes		
				Budget impact		
				Health benefits		
				Advancement of technology		
				Manufacturing complexity		
				Uniqueness		
				Level of uncertainty of effectiveness		
				Level of research undertaken		
				Life-saving		
				Social impact of treatment on patient and carers' daily lives		
				Annual costs of drugs Per person		
			Criteria related to the specific context	Expert consensus/Clinical practice guidelines		
				Size of affected population		
				Mandate and scope of healthcare system		
				Population priorities and access		
				Common goals and specific interests		
				Environmental impact		
				Opportunity costs and affordability		
				System capacity and appropriate use of intervention		
				Political/Historical/Cultural context		
				Vulnerable groups		

Abbreviations: BI, budget impact; DCE, discrete choice experiments; DRD, drugs for rare diseases; MCDA, multicriteria decision analysis; OD, orphan drugs; PRO, patient-reported outcome.

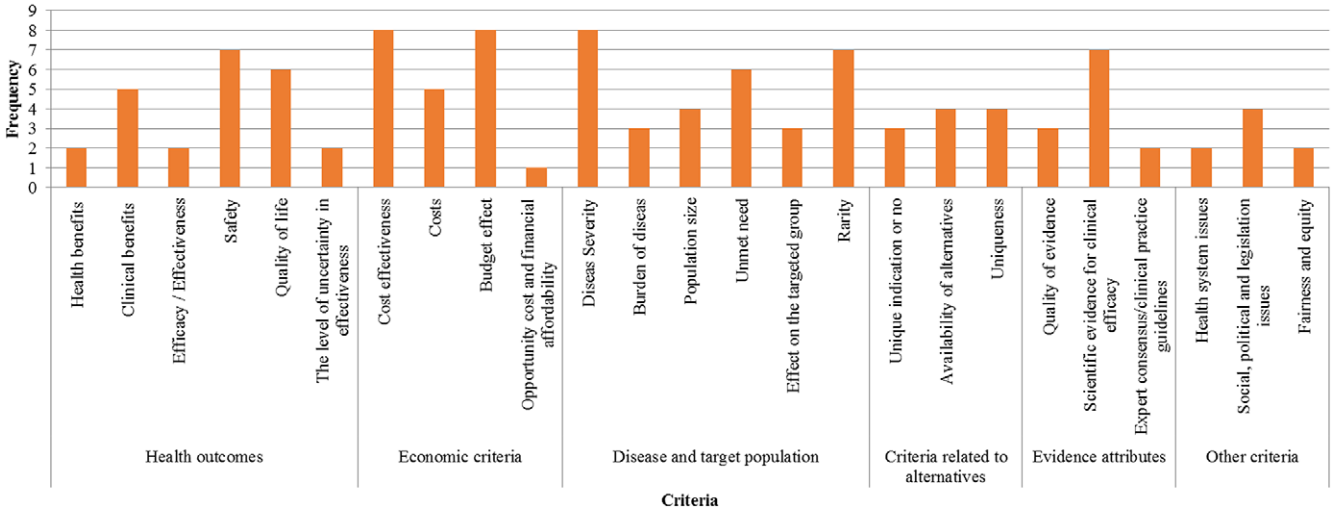

Figure 2. Frequency of each criterion in the literature.

orphan drugs in comparison with each other, the disease severity was used in an MCDA framework (3).

Disease Burden. The burden of disease, including the prevalence, incidence, life years adjusted based on the disease, predicted health years, economic burden, and other indices related to the burden of disease, was defined as a criterion for priority setting (4). In several studies, disease burden was one of the criteria used to evaluate orphan drugs (2;5).

Population Size. The number of eligible patients is another factor influencing the decision-making process in the field of orphan drugs. In evaluating ten orphan drugs, the criterion of disease population size was used together with other criteria in four European countries (6). Also, in a study performed in Canada, the population size was used in decision making in the field of rare disease drugs (7).

Disease Effects. This criterion expresses the effects that the disease has on the patient. In a study prioritizing ten orphan drugs in four countries (England, Scotland, Sweden, and France in 2016), the effects of the disease on the patient were considered as one of the evaluation criteria (6).

Disease Rarity. The rarity of the disease by itself as single attribute is not enough to measure value of orphan products; however, the rarer the disease, the more complex its assessment in terms of research and development because evidence is harder to generate (2). To use this criterion in priority setting, different studies defined rarity based on the prevalence of disease in a certain population. For example, in a European study which evaluated six orphan drugs in the MCDA framework, disease rarity was considered at three levels: (i) 1: 2.000–1: 20.000, (ii) 1: 20.000–1: 200.000, and (iii) less than 1: 200.000 (8). In Poland, to evaluate twenty-seven orphan drugs in comparison with each other in an MCDA framework, disease rarity was studied at three levels: (i) prevalence less than 0.5 per 10,000, (ii) prevalence in the range of 0.5–1 per 10,000, and (iii) prevalence more than 1 per 10,000 (9).

Unmet Needs. Unmet needs may be recognized when current interventions have serious limitations on efficacy, safety, tolerability, and impact on quality of life. It is highly relevant for orphan diseases, where important therapeutic limitations persist and there are few interventions focused on a specific condition (2). Unmet medical needs in Poland were studied at three levels: (i) no comparable alternative available, (ii) second-line treatment available, and (iii) at least one comparable alternative available (9). The unmet need was one of the criteria used in the evaluation of orphan drugs in the MCDA framework in the Netherlands (10). In Spain and Central and Eastern European countries, unmet needs were used as a measure of the value of orphan drugs (11;12).

Therapeutic Alternatives and Uniqueness of Orphan Technologies

D.1 Availability of Alternative Technology. Absence of therapeutic alternatives represents a predominant difficulty for orphan diseases (2). In a study in Central and Eastern European countries, the availability of alternative technology in the evaluation of orphan drugs was considered (12). This criterion was used to assess a set of orphan drugs in different studies, especially those conducted under the MCDA framework (1;2;6).

Uniqueness. Uniqueness was one of the criteria mentioned in the studies on the evaluation of orphan drugs in the MCDA framework (5;10). To evaluate twenty-seven pairs of drugs in Poland using the MCDA framework, uniqueness was used at three levels: (i) one unique indication, (ii) more than one orphan indication, and (iii) one or more indications for common diseases (9).

To evaluate six orphan drugs in the MCDA framework in a study in Europe, this criterion was defined at three levels: (i) existing orphan or nonorphan indication for the same molecule, (ii) potential for multiple indications, and (iii) unique indication or no. In Poland, this criterion was also used in the MCDA framework to test fifty-four pairs of orphan drugs (3).

Quality and Availability of Evidence

Quality of Evidence. Although decision making about orphan drugs and diseases based on particular features like their scarcity and high prices leads to high ICER and budget impacts, their assessment according to HTA criteria can be a challenge (16). So, the quality of evidence, such as the level and the number of studies undertaken and the relevancy, is an important criterion that can contribute to making more accurate decisions (6;13;18).

Scientific Evidence for Clinical Efficiency. In our reviewed papers, six pointed to this criterion as an important factor for priority

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setting (4;12–15;19). The quality and quantity of the scientific evidence are limited due to low power from small populations, limited time horizons, and limited diagnostic capacities. It is therefore difficult to confirm the added value of the drug and uncertainty about the efficiency and safety increases. One article, however, mentions that it is possible to undertake an acceptable clinical trial with a small patient population by undertaking sequential, three-stage, or adaptive designs rather than traditional clinical trials (19).

Expert Consensus/Clinical Practice Guidelines. Expert consensus refers to the ideas and opinions of an expert panel about the priorities of orphan drugs and diseases. These documents are not evidence-based clinical practice guidelines. Because of the limitations in scientific evidence of orphan drugs and diseases which use expert consensus or clinical practice guidelines, European countries have started considering practical criteria for better judgments in decision making such as ensuring an adequate, transparent assessment process and providing a consistent decision support tool for policymaking (13;16).

Other Social and Organizational Criteria

F.1 Health System Issues. Capacity management in health systems is about the organizational responses to existing demands given limited resources. Due to the scarcity of rare diseases (in form of individual diseases) and the high price of orphan drugs, one of the criteria that was considered in priority setting of orphan drugs and rare diseases in the literature was the system's capacity and its appropriate use of orphan drugs based on the context of each country (13;16).

Social, Political, and Legislative Issues. The social impact of rare diseases and orphan drugs, such as the indirect costs imposed on families and caregivers, has been included in MCDA approaches but was often ignored in other HTA approaches (4;19). Because the formal approaches designed for decision making about common health services are problematic in the assessment of orphan drugs, there are other criteria which are considered under MCDA frameworks, especially in European countries: developed national priority, political context, and government legislation that determine governments' strategies about priority of orphan drugs and rare diseases to reduce the burden of diseases and catastrophic costs (11;13).

Fairness and Equity. Equity issues of orphan drugs and rare diseases due to the nature of these diseases (low patient population, high costs, and low health gain) are highly important. Since the ICERs of these treatments are so high and the amounts of health resources are limited, most of them would not fall under standard thresholds of CE. It has been suggested that patients with rare diseases have a human right to treatment raising issues of equity in terms of access to orphan drugs (19). Therefore, this criterion has been mentioned as a one of the contextual criteria in new methods of priority setting in determining a social value for orphan drugs (13;16;19).

Discussion

In the era of growth in the development and use of orphan drugs to treat rare diseases, understanding the methods and criteria in priority setting of rare diseases and orphan drugs for policy making such as financing, legislation, and regulation is so important. The review of priority setting literature for orphan drugs and rare diseases showed that setting of criteria is the first and most important step and the rest of the prioritization process is based on these criteria. According to the conducted scoping review, there were numerous studies discussing both methods and criteria for priority setting of orphan drugs and rare diseases. Some studies, especially from European countries, have used various methods such as the MCDA and discrete choice experiment to appraise orphan drugs but the interest in MCDA for comparing cases by using multiple scoring and direct weighting was more frequent (11;18;19). Since there is no consistent framework for decision making and prioritizing these drugs, some studies have attempted to demonstrate the benefits of having a unique framework like Evidence and Value: Impact on Decision-Making (EVIDEM) or to incorporate HTA and MCDA as a new method (13).

In terms of "health outcomes and clinical implications," the most frequent attributes in the reviewed studies were identified as safety, clinical benefits or effects, health benefits or effects, efficacy/effectiveness, and the quality of life and uncertainty about efficacy, respectively, and the maximum frequency was related to "safety." Our results can be compared with research performed by Friedman et al. (13) who suggested some attributes related to health outcomes for policy making of orphan drugs. These attributes were as follows: "clinical effectiveness," "effectiveness,", and "safety," this research focused on the using of MCDA for appraisal orphan drugs but our research was more comprehensive and considered all methods and criteria for assessment and appraisal of orphan drugs with more details, both of studies acknowledged on safety and effectiveness as the most important attributes related to the health outcomes.

In the section of "economic factors," the attributes with the highest frequency in the included studies were CE, budget impact, costs, and opportunity cost and affordability, respectively. "Cost-effectiveness" and "budget effect" have the maximum frequency in this theme. Friedman et al. (13) suggested the CE as the most important of criteria related to "economic factors," however our research found "budget impact" and "cost-effectiveness" as the most important criteria in this regards.

According to the studies concerning "disease and population characteristics," "disease severity," "population size," "rarity of the disease," and "unmet needs" are important factors that are considered in making decisions and the maximum frequency was related to "disease severity." It is better to measure the rarity of the disease according to the prevalence in a certain population (2;8;9). Our research and Friedman et al. found "disease severity" as the most important criteria related to "disease and population characteristics."

In terms of treatment alternatives, "the availability and uniqueness of treatment" is one of the important factors that should be considered in making decisions. Depending on the number of alternatives available and the quality of their treatment, degrees of uniqueness can be determined at several levels. Friedman et al. did not give enough attention to this kind of criteria; our research expressed more details about "the availability and uniqueness of treatment."

As mentioned in the results section, according to the small size of population, the difficulty to confirm the added value, the limited time horizon, and the limited diagnostic capacities, the power of scientific evidence is limited for orphan drugs and rare diseases, which finally means inability to reach a consensus (13). Therefore, if the scientific evidence for clinical efficacy and the quality of evidence in this area are increased, expert consensus can be reached more easily and clinical practice guidelines can be developed.

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We should consider that the assessment of these criteria depended on the decision method which applied. This point is important because it impacts on the final decisions. As a result, identifying explicit criteria and methods for an adequate evaluation of orphan drugs and rare diseases improves accessibility and affordability of these kinds of medications. As a whole, this study contributes to a better understanding of the methods and the attributing criteria for complex decision making regarding orphan drugs and rare diseases. Since the price of orphan products is so high and its validation and appraisal for reimbursement and coverage are not compatible based on the traditional HTA, it is critical to explore the issue in precise technical methods which consider multiple criteria in priority setting. However, these criteria can lead to different priorities in different countries in accordance with contextual frameworks which show country-specific preferences (20).

Therefore, we suggest that these criteria be used for developing a robust framework for orphan drugs policy making, as is the case for MCDA and Accountability for Reasonableness (A4R) (21) which have been discussed in the global literature for general priority setting of health care in the recent years to cope with these complexities. Similar to our results, Friedman et al. found that MCDA has great capacity to be used for orphan drugs reimbursement policy making.

Limitations

In this review, access to the full text of some papers was limited. Hence, we excluded them accordingly. As we performed a scoping review rather than a systematic review, our work did not include a quality review of the identified articles.

Conclusion

Orphan drugs are often costly and traditional methods of HTA are not appropriate for making reimbursement decisions. Alternative methods such as MCDA and A4R may be appropriate in priority setting. Future research in these methods would be beneficial.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S0266462322000393.

Conflicts of Interest. The authors declare that they have no conflict of interest.

References

1. **Richter T**, **Nestler-Parr S**, **Babela R**, et al (2015) Rare disease terminology and definitions—A systematic global review: Report of the ISPOR rare disease special interest group. *Value Health* **18**, 906–914.
2. **Pearson I**, **Rothwell B**, **Olaye A**, **Knight C** (2018) Economic modeling considerations for rare diseases. *Value Health* **21**, 515–524.
3. **Gammie T**, **Lu CY**, **Babar ZU-D** (2015) Access to orphan drugs: A comprehensive review of legislations, regulations and policies in 35 countries. *PLoS One* **10**, e0140002.
4. **Ollendorf DA**, **Chapman RH**, **Pearson SD** (2018) Evaluating and valuing drugs for rare conditions: No easy answers. *Value Health* **21**, 547–552.
5. **Lopez-Bastida J**, **Ramos-Goni J**, **Aranda-Reneo I**, et al (2019) Using a stated preference discrete choice experiment to assess societal value from the perspective of decision-makers in Europe. Does it work for rare diseases? *Health Policy* **123**, 152–158.
6. **Lasalvia P**, **Prieto-Pinto L**, **Moreno M**, et al (2019) International experiences in multicriteria decision analysis (MCDA) for evaluating orphan drugs: A scoping review. *Expert Rev Pharmacoecon Outcomes Res* **19**, 409–420.
7. **Arksey H**, **O'Malley L** (2005) Scoping studies: Towards a methodological framework. *Int J Soc Res Methodol* **8**, 19–32.
8. **Software V** (2018) MAXQDA.
9. **Hsieh H-F**, **Shannon SE** (2005) Three approaches to qualitative content analysis. *Qual Health Res* **15**, 1277–1288.
10. **Tricco AC**, **Lillie E**, **Zarin W**, et al (2018) PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* **7**, 467–473.
11. **Nicod E** (2017) Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries. *Eur J Health Econ* **18**, 715–730.
12. **Short H**, **Stafinski T**, **Menon D** (2015) A national approach to reimbursement decision-making on drugs for rare diseases in Canada? Insights from across the ponds. *Health Policy* **10**, 24.
13. **Friedmann C**, **Levy P**, **Hensel P**, **Hiligsmann M** (2018) Using multicriteria decision analysis to appraise orphan drugs: A systematic review. *Expert Rev Pharmacoecon Outcomes Res* **18**, 135–146.
14. **Kolasa K**, **Zwolinski KM**, **Zah V**, **Kaló Z**, **Lewandowski T** (2018) Revealed preferences towards the appraisal of orphan drugs in Poland-multi criteria decision analysis. *Orphanet J Rare Dis* **13**, 1–14.
15. **Kolasa K**, **Zwolinski KM**, **Kalo Z**, **Hermanowski T** (2016) Potential impact of the implementation of multiple-criteria decision analysis (MCDA) on the polish pricing and reimbursement process of orphan drugs. *Orphanet J Rare Dis* **11**, 1–12.
16. **Guarga L**, **Badia X**, **Obach M**, et al (2019) Implementing reflective multicriteria decision analysis (MCDA) to assess orphan drugs value in the Catalan Health Service (CatSalut). *Orphanet J Rare Dis* **14**, 1–9.
17. **Baltussen R**, **Marsh K**, **Thokala P**, et al (2019) Multicriteria decision analysis to support health technology assessment agencies: Benefits, limitations, and the way forward. *Value Health* **22**, 1283–1288.
18. **Schey C**, **Krabbe P**, **Postma M**, **Connolly M** (2017) Multi-criteria decision analysis (MCDA): Testing a proposed MCDA framework for orphan drugs. *Orphanet J Rare Dis* **12**, 1–9.
19. **Zelei T**, **Molnár MJ**, **Szegedi M**, **Kaló Z** (2016) Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries. *Orphanet J Rare Dis* **11**, 72.
20. **Onakpoya IJ**, **Spencer EA**, **Thompson MJ**, **Heneghan CJ** (2015) Effectiveness, safety and costs of orphan drugs: An evidence-based review. *BMJ Open* **5**, e007199.
21. **Daniels N** (2018) Combining A4R and MCDA in priority setting for health. *Cost Eff Resour Alloc* **16**, 51. https://doi.org/10.1186/s12962-018-0124-9.

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