UNIVERSITY OF SÃO PAULO
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Criteria adopted in different models of public healthcare systems for the evaluation of reimbursement recommendations of orphan drugs: a scoping review

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LIST OF ABBREVIATIONS

ASMR *Amélioration du Service Médical Rendu* (Improvement of the Medical Service Rendered)

DOI Digital Object Identifier

EMA European Medicines Agency

HTA Health Technology Assessment

ICER Incremental Cost-Effectiveness Ratio

INAHTA International Network of Agencies for Health Technology Assessment

JBI Joanna Briggs Institute

LSDP Life Saving Drugs Program

LILACS Latin American and Caribbean Health Sciences Literature

NHI National Health Insurance

NHS National Health System

PCC Population, Concept and Context

PHI Private Health Insurance

PRISMA-ScR Preferred Reporting Items for Systematic Reviews and Meta-Analyses - extension for Scoping Reviews

QALY Quality-Adjusted Life-Year

SMR *Service Médical Rendu* (Medical Service Rendered

SHI Social Health Insurance

WHO World Health Organization

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ABSTRACT

Background: Access to drugs for rare diseases constitutes a challenge to healthcare systems, especially those with public funding. The difficulty of conducting robust clinical trials limits the quality of evidence and elevates the cost of development, later translated into the drug's prices. Thus, it is necessary for the Health Technology Assessment (HTA) agencies to have differentiated criteria for the evaluation of reimbursement recommendations when dealing with such drugs.

Objective: To identify and summarize the specific criteria used when evaluating reimbursement recommendations for orphan drugs that are adopted by HTA agencies in countries with different models of public healthcare systems.

Methods: A comprehensive literature search was performed on the databases PubMed, LILACS, Scopus and Embase up until March of 2022. We included any publication type (opinion articles, commentaries, editorials, original articles and reviews) that addressed the criteria used by HTA agencies in countries with public healthcare systems when evaluating reimbursement recommendations for orphan drugs.

Results: This scoping review summarizes the identified criteria for 18 countries and ranks them within three models of healthcare systems (NHS, NHI and SHI). We identified that NHS countries, such as the UK, Sweden, and Italy, lean towards innovation, the collection of real-world data, and the impact on organizational aspects of the system. Meanwhile, SHI countries, such as Germany, France and the Netherlands, often employ budget ceilings and expedited evaluation processes. All models shared concern over unmet need and disease nature. The 16 included studies range from 2015 to 2022 and the majority consists of reviews of HTA reports and original articles.

Conclusion: This review provides a good basis for the understanding of each model's classification and general tendencies when creating differentiated criteria to accommodate and compensate for the lack of evidence and investment around rare diseases.

Keywords: rare diseases, orphan drugs, Health Technology Assessment.

1. INTRODUCTION

Currently, there's no universally accepted definition for rare diseases and the prevalence threshold varies across countries[1]. According to the World Health Organization (WHO), a disease is considered rare once its prevalence in a given population is lower than 65 for every 100.000 habitants. While these diseases are individually rare, collectively they affect 1 person out of every 15 in the world, coming up to 400 million total. There are around 5,000 to 8,000 known rare diseases[2].

The population affected by rare diseases is distributed along different regions, making epidemiologic data scarce and disjointing scientific knowledge. Therefore, the causes, physiopathology, and progression of such diseases are often poorly understood[2]. In addition, diagnosing can be challenging due to the heterogeneous clinical presentation of many rare diseases and the difficulty of interpreting complex diagnostic algorithms. And so, there can be a serious delay until the correct diagnosis or even an incorrect one, which leads to inadequate treatment[3].

Around 70% of known rare diseases bore genetic origin and present themselves as potentially fatal chronic conditions with degenerative aspects[4]. Thus, it is necessary to have drugs designed to soften the symptoms, prolong life, and enhance the quality of life. These drugs are known as "orphan drugs". According to Jarosławski et al.[5], the term references how pharmaceutical companies used to ignore researching rare diseases, due to the high risk of failure involved in working with a reduced number of patients. This complicates the conduction of clinical trials, while also diminishing the prospect of the return on investments. Consequently, these drugs turn remarkably expensive and with weak evidence of effectiveness and safety[3, 6]. Currently, pro-orphan drug policies, such as extended market exclusivity and expedited approvals, help to secure profits and ensure the industry interest in developing orphan drugs[5].

Rare disease patients' access to orphan drugs is a complex process, determined by factors such as policy incentives to research, regulatory approval, market availability, health technology assessment results, and reimbursement processes[7, 8]. Granted the increasing pressure over

governments' health budgets, this access can be particularly problematic in countries with universal healthcare systems, since purchasing too many expensive orphan drugs will inevitably bring about budget cuts in other areas, as to provide financial sustainability[9].

In this context, it is fundamental to identify and make explicit fair, consistent, and equitable criteria for orphan drug reimbursement. In public healthcare systems, decision-making processes for technology incorporation are usually carried out by Health Technology Assessment (HTA) agencies. While conventional HTA processes are important to improve the efficiency and effectiveness of healthcare, they have been considered insufficient to capture the social demands of rare disease patients[10]. Hence, the need for differentiated criteria for orphan drugs that seek to balance treatment's added value given the uncertainty of clinical evidence and the incremental cost-effectiveness ratio that are much higher than traditional willingness-to-pay thresholds [3].

Previous reviews that sought information about HTA criteria specific to rare diseases generally created panoramic cuts of a single region of (assumed) similar countries, forfeiting a global view[11, 12, 13, 14]. In addition, such studies included European countries with different healthcare system models and left unexplored how these differences impact the way HTA agencies conduct reimbursement recommendations. To our knowledge, there are currently no broader reviews that go beyond the European continent and address models of public healthcare systems.

2. OBJECTIVE

In order to fill this gap, this study aimed to identify and summarize the specific criteria used when evaluating reimbursement recommendations for orphan drugs that are adopted by HTA agencies in countries with different models of public healthcare systems.

3. MATERIALS AND METHODS

To guide the conduct of this scoping review, we followed the Joanna Briggs Institute (JBI) manual[15] as well as the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist[16]. The search strategy, eligibility criteria and method of analysis for this review were specified in advance and documented in a protocol available upon request from the corresponding author.

3.1. Research Question

The research question to be answered in this scoping review was: What are the HTA criteria used for reimbursement recommendations for orphan drugs in countries with different models of public health systems? This question was elaborated based on the PCC elements: Population (rare diseases), Concept (specific/differentiated criteria for orphan drug evaluation) and Context (HTA agencies of countries with public healthcare systems).

3.2. Search Strategy

A comprehensive literature search was conducted to identify relevant studies in the Medline (via PubMed), LILACS (Latin American and Caribbean Health Sciences Literature), Scopus, and Embase databases until March 2022. A complementary search was performed on Google Scholar for the first 305 results, to identify non-indexed studies. The reference lists of included studies were also screened for potentially interesting studies. The complete search strategies for each database are presented in Appendix 1.

3.3. Inclusion Criteria

There is much debate over the definitions of healthcare system models due to their complexity. To help summarize it, we assumed four core models in various degrees of implementation around the world, mostly distinguished by how they are financed, who provides the services, and what level of integration is between the two, as follows[17]:

- National Health System (NHS or Beveridge model): financed through general taxation, that is, each and every tax charged in the country has a portion directed to it. This way, the state becomes the single-payer. Service providers are almost exclusively comprised of public facilities and state employees, fully integrated with the system. The United Kingdom is the most recognized for this model's implementation.

- Social Health Insurance (SHI or Bismark model): financed through a dedicated payroll tax on workers' salary. Depending on the country, these funds can be collected by single or multiple entities (federal or regional government or even sectorial insurance companies under the umbrella of a public or quasi-public organization), which form the system's payers. Service providers are a mixture of public and private facilities (not-for-profit or for-profit), usually without much integration. Germany is the greatest example of this model's application.

- National Health Insurance (NHI): financed through general taxation or payroll tax, but making the state the single-payer regardless. Service providers are mixed and not integrated. Non-integration often means providers are free to compete with each other by offering better deals to the payer state. That's how both Canada and Australia operate.

- Private Health Insurance (PHI, often called the Out-of-Pocket model): financed and provided entirely through private initiative, ranging from the individual to the corporate level. The United States is in the vanguard of this model's implementation.

The present study focuses on countries with public healthcare (NHS, SHI, or NHI) whose HTA agencies are members of the International Network of Agencies for Health Technology Assessment (INAHTA)[18]. We did this to highlight our focus on centralized, national organizations that are willing to openly share their data. Countries were selected arbitrarily to showcase a

diverse range of healthcare system models and contexts, thus including: Argentina, Australia, Brazil, Canada, Finland, France, Germany, Ireland, Italy, Malaysia, Netherlands, Poland, Russia, South Korea, Spain, Sweden, Switzerland, Uruguay, and the United Kingdom (treated as the separate jurisdictions of England, Northern Ireland, Scotland, and Wales). The information for classification into the different models of health systems was obtained from previous literature[17, 19, 20, 21, 22].

This scoping review included any publication type (opinion articles, commentaries, editorials, original articles, and reviews) so long as it addressed the criteria used by HTA agencies when evaluating reimbursement recommendations for orphan drugs. The selection was limited to English, Portuguese, and Spanish languages.

Articles that covered HTA criteria for other diseases (such as neglected diseases) or for non-selected countries as well as articles that the full text could not be retrieved, conference abstracts, thesis, and dissertations were excluded.

3.4. Study Selection

The studies retrieved from the databases were allocated into the Rayyan platform[23], a specialized tool for systematic reviews, to exclude duplicate files, analyze the titles and abstracts of the articles, and analyze complete articles whose abstracts were previously selected. Two researchers (A.F. and L.V.B.) independently screened the titles and abstracts (stage 1) and full texts (stage 2). Any disagreements were resolved by reaching a consensus in both stages.

3.5. Data Extraction

A spreadsheet in Microsoft Excel® was filled independently by two reviewers (A.F. and L.V.B.) to extract the following data: authors, publication year, countries and their respective HTA agency, definition of rare disease, and identified assessment criteria for orphan drugs. Any disagreements were resolved by consensus through discussion.

4. RESULTS

The electronic search identified 1,481 records, 347 being identified as duplicates and removed. Of the 1,134 remaining articles, 81 were selected for full-text reading. After analyzing them and their reference lists, a total of 16 studies[7, 12, 14, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36] were included in this review (Figure 1). Information on the reasoning for the exclusion of the articles are presented in Appendix 2.

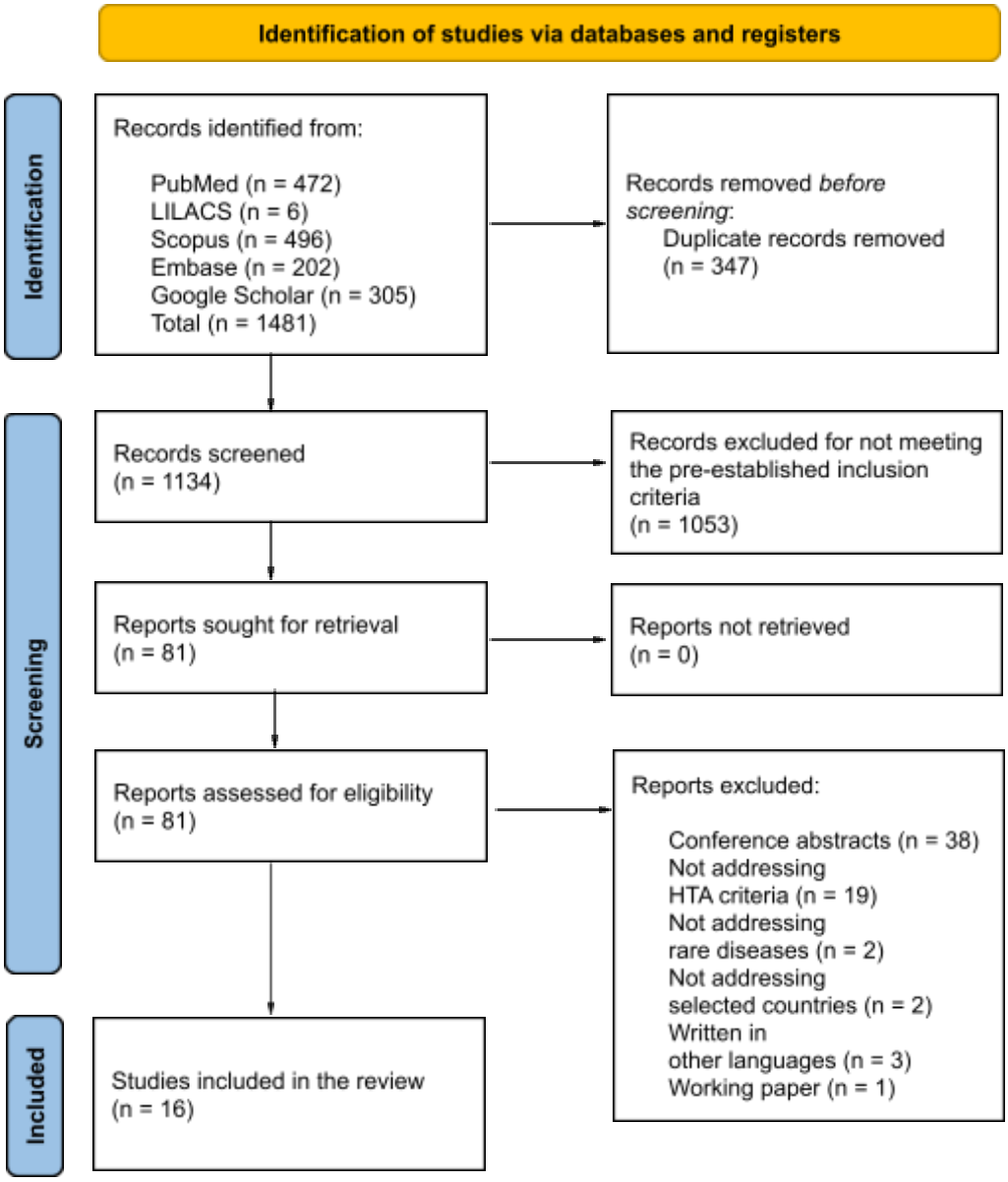

Figure 1. PRISMA flowchart of the review process.

The characteristics of included studies are displayed in Table 1. These studies were published recently, ranging from 2015 to 2022, half of from 2018[26, 30, 33, 36] to 2020[7, 14, 24, 25]. The top observed countries were England (n = 12, 75.00%)[7, 12, 14, 27, 28, 29, 30, 31, 32, 34, 35, 36], Scotland (n = 11, 68.75%)[7, 12, 14, 27, 28, 29, 30, 31, 32, 35, 36], France (n = 10, 62.50%)[7, 12, 27, 28, 14, 29, 30, 31, 35, 36], Germany (n = 8, 50.00%)[7, 12, 14, 25, 30, 31, 35, 36], Sweden (n = 8, 50.00%)[12, 14, 27, 28, 29, 30, 31, 35], and the Netherlands (n = 8, 50.00%)[7, 12, 14, 25, 30, 31, 32, 35]. The majority of the studies based their findings on reviewing HTA reports (n = 7, 43.75%)[24, 26, 28, 29, 32, 34, 35], followed by original articles (n = 4, 25.00%)[14, 27, 30, 36], where the authors made direct contact with experts and workers from the HTA agencies. While all studies related to rare diseases, the distinction of ultra-rare diseases was only addressed in 6 studies[14, 31, 32, 33, 35, 36], constituting 37.50% of the total included.

Table 2 presents a summary of HTA criteria for rare diseases for each country. Unfortunately, no information of interest could be found for Argentina, Malaysia, Northern Ireland, and Uruguay. The most unique appraisal process identified was that of England, counting with a dedicated committee and set of values[14]. In contrast, the least differentiated approach was that of Russia, with reimbursement relegated to a federal drug list covering only 24 rare diseases and depending on regional budgets[7]. The majority of countries conform to the European Medicines Agency (EMA) definition of rare diseases[7, 12, 14, 24, 25, 26, 31, 33, 36], based on the prevalence of up to 50 patients for every 100,000 individuals. This value was standardized for the sake of better comparing countries and unifying findings.

In Table 3, the keywords for identified criteria are ranked in decreasing order of how many countries with the same healthcare system model adopt them. Unmet need[14, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36] and the disease nature[7, 12, 14, 24, 27, 28, 29, 30, 31, 32, 35, 36] are both featured among the top 5 terms for all models, followed by safety net programs[26, 31, 36] (with the exception of the NHI column).

Each model presented either unique or particularly more valued criteria. For the NHS model, that would be innovation[7, 14, 27, 28, 29, 33, 35], as in, promoting and rewarding pharmaceutical companies for technological innovation in orphan drugs development through approval and reimbursement.

For the NHI model, more emphasis was placed on conditional economic analyses[24, 31], that is, the exemption from presenting certain types of economic analyses during the evaluation by the HTA agency if some attributes are met. The included articles go into more detail about each country's legislature over such attributes, the evaluation process, and the financial thresholds involved.

Finally, for the SHI model, mentions of expedited process[7, 14, 28, 29, 31, 35] were often present. In other words, countries following the Bismark model tend to prioritize the assessment of orphan drugs or those which fulfill criteria deemed important.

Table 1. General characteristics from the included studies (n = 16).

Characteristics	**n**	**%**	**References**
Publication year			
2015	1	6.25	31
2016	1	6.25	28
2017	2	12.50	27, 29
2018	4	25.00	26, 30, 33, 36
2020	4	25.00	7, 14, 24, 25
2021	3	18.75	12, 34, 35
2022	1	6.25	32
Countries analyzed			
Australia	4	25.00	25, 26, 31, 36
Brazil	1	6.25	34
Canada	5	31.25	14, 24, 25, 26, 36
England	12	75.00	7, 12, 14, 27, 28, 29, 30, 31, 32, 34, 35, 36
Finland	2	12.50	14, 31
France	10	62.50	7, 12, 14, 27, 28, 29, 30, 31, 35, 36
Germany	8	50.00	7, 12, 14, 25, 30, 31, 35, 36
Ireland	3	18.75	12, 14, 31
Italy	2	12.50	14, 31
Netherlands	8	50.00	7, 12, 14, 25, 30, 31, 32, 35
Poland	3	18.75	7, 12, 14
Russia	1	6.25	7
Scotland	11	68.75	7, 12, 14, 25, 27, 28, 29, 31, 32, 35, 36
South Korea	1	6.25	31
Spain	1	6.25	31

Characteristics	n	%	References
Sweden	8	50.00	12, 14, 27, 28, 29, 30, 31, 35
Switzerland	2	12.50	14, 31
Wales	3	18.75	12, 30, 33
Publication type			
Book Chapter	1	6.25	33
Original article	4	25.00	14, 27, 30, 36
Narrative review	1	6.25	31
Review of HTA reports	7	43.75	24, 26, 28, 29, 32, 34, 35
Systematic Review	3	18.75	7, 12, 25
Condition analyzed			
Rare disease	16	100.00	7, 12, 14, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36
Ultra-rare disease	6	37.50	14, 31, 32, 33, 35, 36

Table 2. HTA criteria adopted by each country.

Country	HTA agency	Healthcare system model	Disease definition*	Adopted criteria
Australia	PBAC	NHI	50	The standard HTA process gives the possibility of risk sharing on the condition that real-world evidence will be collected; Submitters can opt in a supplementary process if four factors apply: unmet need; severe, progressive and life-threatening disease; low number of patients; evidence of clinical improvement; Has a safety net program, exclusive to drugs that got rejected based on cost-effectiveness, that considers disease burden, is flexible with evidence requirements, has no ICER threshold and allows patient participation.
Brazil	CONITEC	NHS	65	Employs standard HTA process for orphan drugs, however it considers unmet need.
Canada	CADTH	NHI	50	The standard HTA process has the possibility of price negotiation and patient participation, considers the unmet need and disease burden and makes optional some of the economic analyses.
England	NICE	NHS	50	Orphan drugs pass through the Highly Specialized Technology (HST) appraisal process, a unique assessment framework that considers unmet need, the nature of the condition (rarity and severity), life-extending and end-of-life properties, the impact of the disease on caregivers' quality of life, other benefits beyond health, innovation and impact on organizational aspects of the NHS; QALY is weighted if ICER surpasses £100,000/QALY or there's strong evidence of significant QALY gains over alternatives;

Country	HTA agency	Healthcare system model	Disease definition*	Adopted criteria
				Accepts uncertainty of both clinical and economical evidence; Offers conditional approvals to mitigate high ICER values, as well as a budget ceiling of £20M over 3 years before reassessing the drug and renegotiating prices; Opened to patient participation through the Public Involvement Program (PIP); Has a safety net program that also follows the HST framework, but offers the possibility of risk sharing and re-evaluation after real-world evidence is collected.
Finland	FinCCHTA	NHS	50	Has a safety net program for temporary reimbursement, requiring safety, clinical effectiveness and comparative economic analyses.
France	HAS	SHI	50	All drugs are judged solely based on therapeutic benefit, calculated to render three levels of reimbursement (SMR) and five levels of therapeutic improvement in comparison to alternatives (ASMR), which guides coverage rate and price negotiations, respectively; Orphan drugs can have their assessment put forward in line if they score an ASMR level of I to III (high degree of innovation); During standard HTA process, there's no ICER threshold and economic analyses are not required if the budget impact is kept below €20M/year; Considers unmet need, disease nature, quality of life improvements, additional benefits and the impact on organizational aspects; Accepts uncertainty of clinical and economic evidence; Allows conditional approvals for the collection of real-world data;

Country	HTA agency	Healthcare system model	Disease definition*	Adopted criteria
				Opened to patient participation through the committee's direct invitation; Has a safety net program for cases of unmet need, where economic analyses are exempted.
Germany	G-BA	SHI	50	Common drugs are evaluated by the IQWiG agency. However, orphan drugs cases are relayed to the G-BA in an expedited process; Evidentiary requirements are lowered, additional benefits are considered proven by default and there's the possibility of conditional approvals; During the HTA process, economic analyses are not required if the annual budget impact is kept below €50M. If not, a cost-benefit analysis is employed. After the first year of reimbursement, prices are renegotiated based on a complete economic analysis and the real-world effectiveness data; Has a safety net program that considers disease severity and unmet need, doesn't require economic analyses and encourages patient participation.
Ireland	HIQA	NHS	50	Has a safety net program with standard HTA process requirements; Has a Rare Diseases Technology Review Committee that provides input after the standard HTA process, to pressure for a review or price renegotiation, in order to guarantee reimbursement.
Italy	AGENAS	NHS	50	Orphan drugs can be enrolled in an expedited HTA process, even before market authorization. This process counts with a unique

Country	HTA agency	Healthcare system model	Disease definition*	Adopted criteria
				reimbursement fund, gives preference to innovative technologies and can allow for conditional approvals, provided that the manufacturer brings new cost-effectiveness or added benefit data for the agreed re-assessment; All drugs with market authorization are reimbursed by the healthcare system. The costs are balanced by restricting distribution to specific centers, professionals or patients; Has a safety net program that exempts budget impact analysis and also cost-effectiveness analysis in case of unmet need.
Netherlands	ZiN	SHI	50	Preference is given to drugs assessing unmet need and life-threatening conditions, skipping them ahead in line for evaluation; All drugs with market authorization are exempted from HTA processing as long as the annual cost per patient is lower than €25k or the total annual budget impact is lower than €2.5M; During standard HTA process, economic analysis is not required if the budget impact is kept below €50M/year or below €10M/patient in a year or in case of unmet need; The ICER threshold is linked to disease severity; Allows for evidence uncertainty and conditional approvals; Has a safety net program with lenient evidence requirements and no economic analysis whatsoever, as well as no ICER threshold in case of unmet need.
Poland	AOTMiT	SHI	50	Standard HTA evaluation is given to orphan drugs, but they can be reimbursed through drug programs.

Country	HTA agency	Healthcare system model	Disease definition*	Adopted criteria
Russia	CHQAC	SHI	10	No differentiated HTA evaluation is given to orphan drugs, but some are covered by specialized lists in certain regions of the country.
Scotland	SMC	NHS	50	Like all nations under the United Kingdom, follows the prerogative of Britain's NICE up to a point and then adds to it with its own policies; Considers unmet need, disease rarity, quality of life improvements for both patients and caregivers, life-extending and end-of-life properties and organizational benefits; Accepts uncertainty of evidence and higher cost/QALY and ICER threshold, as long as conditions are applied to the approval; Offers the possibility of risk sharing and a temporary approval for the collection of real-world data; Opened to patient participation through the Patient And Clinician Engagement (PACE) and Patient And Public Involvement Group (PAPIG) program.
South Korea	NECA	NHI	Not determined by prevalence	Employs standard HTA process that removes the requirement for economic analysis in cases of unmet need.
Spain	AETS	NHS	Not determined by prevalence	Has a safety net program that considers unmet need and doesn't require economic evaluation.

Country	HTA agency	Healthcare system model	Disease definition*	Adopted criteria
Sweden	TLV	NHS	50	Considers unmet need, nature and severity of the condition, quality of life improvement, technological innovation and the impact on organizational aspects; Accepts uncertainty of clinical evidence and offers flexible ICER thresholds, despite increasing scientific and methodological demands in accordance with high asking prices; Offers the possibility of temporary approval, to gather real-world evidence.
Switzerland	SFOPH	SHI	50	Considers unmet need and life-threatening risk to accelerate evaluation; No ICER threshold in general; Has a safety net program with standard HTA process requirements.
Wales	AWMSG	NHS	50	Orphan drugs pass through the Highly Specialized Technology (HST) appraisal process, a unique assessment framework that considers unmet need, the nature of the condition (rarity and severity), the impact of the disease on caregivers' quality of life, other benefits beyond health, innovation and impact on organizational aspects of the NHS; QALY is weighted if ICER surpasses £100,000/QALY or there's strong evidence of significant QALY gains over alternatives; Opened to patient participation through the Clinician And Patient Involvement Group (CAPIG), after initial reproval.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SMR, *service médical rendu* (medical service rendered); ASMR, *amélioration du service médical rendu* (improvement of the medical service rendered).

*Disease definition by prevalence, standardized as less or equal to for every 100,000 people.

Table 3. Ranking of HTA criteria adopted in selected countries according to the healthcare system model.

NHS (Beveridge)	NHI	SHI (Bismark)
unmet need[14, 27, 28, 29, 31, 32, 33, 34, 35, 36]	unmet need[24, 25, 26, 31, 36]	disease nature[7,12, 14, 27, 28, 29, 30, 31, 32, 35]
safety net program [31]	conditional economic analyses[24, 31]	expedited process[7, 14, 28, 29, 31, 35]
conditional approval[14, 29, 31, 35]	disease nature[24, 26, 36]	safety net program[31]
disease nature[12, 14, 28, 29, 35, 36]	patient participation[24, 31]	unmet need[14, 27, 28, 29, 31, 36]
innovation[7, 14, 27, 28, 29, 33, 35]	conditional ICER threshold[31]	budget ceiling[7, 12, 30, 31, 35, 36]
real-world data collection[14, 29, 31]	flexible evidence requirement[31]	conditional approval[14, 29, 31]
additional benefit[12, 14, 28, 30, 33, 35, 36]	price negotiation[24, 26, 36]	conditional economic analyses[7,12, 31, 36]
flexible evidence requirement [14, 27, 28, 29, 31, 35]	real-world data collection[25]	conditional ICER threshold[12, 28, 31]
impact on caregivers' quality of life[12, 28, 29, 30, 33]	risk sharing[25]	flexible evidence requirement[7, 14, 28]
impact on organizational aspects[14, 28, 29, 30, 32, 33, 34, 35, 36]	safety net program[26, 31, 36]	additional benefit[14, 36]
patient participation[7, 14, 28, 31, 32, 33, 35, 36]		drug program[7]
conditional ICER thresholds[12, 28, 29, 31]		patient participation[31]
life-extending and end-of-life qualities[28, 29]		price negotiation[7, 28]
price negotiation[7, 14]		real-world data collection[7, 31, 36]
quality of life improvement[12, 28, 30, 33, 34]		impact on organizational aspects[28, 29, 35]
risk sharing[31]		quality of life improvement[28, 29]
weighted QALY[12, 30]		
budget ceiling[30]		
conditional economic analyses[31]		
expedited process[14]		

5. DISCUSSION

To our knowledge, this is the first review to analyze different healthcare system models and explore how these differences impact the way HTA agencies conduct reimbursement recommendations when evaluating orphan drugs for rare diseases. This scoping review identified 16 studies addressing the criteria adopted by HTA agencies in 18 countries with public healthcare systems of different models (NHS, SHI, and NHI). Here we summarized our findings for each country and model, highlighting the NHS tendency towards general health promotion, the SHI focus on economic aspects, and the shared concern with patients' health needs.

The missing data from Argentina, Uruguay, and Malaysia were due to a lack of studies that met our inclusion criteria. On the other hand, the case of Northern Ireland is different. As the study by Czech et al.[7] pointed out, the UK's NICE, based in England, evaluates new drugs and relays its recommendation or not to the other three countries (Scotland, Northern Ireland, and Wales), where each then can re-evaluate through their own HTA agency, adding steps or reworking the entire process. For that purpose, Wales has the AWMSG agency and Scotland has the SMC, respectively. But as ours and Czech et al.[7] findings suggest, Northern Ireland's Department of Health doesn't seem to add differentiated criteria when re-assessing orphan drugs, thus barring it from being mentioned in this study.

When first starting this review, we anticipated finding economic criteria as the most prevalent in both the discussions around the theme and the assessment processes of HTA agencies. Fortunately, the data collected did not show this. While there is a hefty interest by the healthcare systems toward costs, the prominence of the terms unmet need[14, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36] and disease nature[7, 12, 14, 24, 27, 28, 29, 30, 31, 32, 35, 36] in all three models suggests a greater focus on contextualizing the living conditions of rare disease patients and the system's duty to provide for them.

In this study, there is a lack of representation for the NHI model. Of the 18 analyzed countries, only three adopt this model of healthcare[17]: Australia, Canada, and South Korea. Despite this, mentions of the Australian Life Saving Drugs Program (LSDP[26, 31, 36]), a safety net program, were present in all but one of the articles featuring the country. Since the program deals exclusively with the re-evaluation of drugs that were rejected based on poor cost-effectiveness analyses[26, 31, 36], it is the main avenue for orphan drugs reimbursement in the country.

This showcases an interesting approach to orphan drugs evaluation. We observed that a proper differentiated evaluation can occur: after the agency's rejection, such as safety net programs[31]; at the same time as non-orphan drugs, no matter if the process is separated, partially separated, or adapted[14]; or before non-orphan drugs, that is, through an expedited process[7, 14, 28, 29, 31, 35].

Of the nine featured countries following the NHS model, only Italy utilizes an expedited process[14] with unique funds for orphan drugs. However, out of the six countries with SHI model, four adopt this criteria[7, 14, 28, 29, 31, 35]: France, Germany, the Netherlands, and Switzerland. Poland and Russia are exceptions. Our data reveals that SHI systems also have a tendency towards implementing budget ceilings[7, 12, 30, 31, 35, 36], that is, if the drug reimbursement annual cost to the system does not reach a certain value, its evaluation by the HTA agency is met with no requirements for economic analyses, or even a complete exemption from being evaluated in the first place (as Netherlands does[7]). Both criteria are in line with the value that the SHI model confers to individual's rights[10], to not only guarantee access to medicine, but if possible, multiple choices of drugs.

In contrast, NHS systems aspire for efficiency[10], to be the single-payer and single provider, strengthening the ties between the government, the healthcare system, and the health facilities and its staff. With this proximity, the system inherits the state's purchasing power as well as its need to spend public funding efficiently. As such, economic criteria are shown more prominently as conditional approvals[14, 29, 31, 35], price negotiations[7, 14], risk sharing[31] contracts, but especially, by demanding real-world data collection[14, 29, 31] before extending a drug's reimbursement within the system. Along with considerations of

innovation[7, 14, 27, 28, 29, 33, 35], the impact on caregivers' quality of life[12, 28, 29, 30, 33] and the impact on organizational aspects[14, 28, 29, 30, 32, 33, 34, 35, 36] (such as the training of medical staff to administer the newly approved drug or the purchase of new equipment to properly monitor the new treatment), these are all NHS prevalent criteria that indicate a wider, more general view of a country's long-term welfare granted by the model implementation.

At last, while not exceedingly prevalent in any of the models, patient participation[7, 14, 24, 28, 31, 32, 33, 35, 36] was present nonetheless. Special recognition should be given to the UK's initiative in implementing it as proper programs, with submission formularies and a designated place on the evaluation process, instead of infrequent requests from either the orphan drug manufacturers or the HTA evaluation committee. We consider patient participation[7, 14, 24, 28, 31, 32, 33, 35, 36] as immensely important to help highlight key quality of life improvements[12, 28, 29, 30, 33, 34] and other additional benefits[12, 14, 28, 30, 33, 35, 36] during the evaluation.

This study has some limitations. It is possible that articles not indexed in the searched databases or not written in Portuguese, Spanish, or English were missed. More importantly, the selection of countries based on INAHTA membership, while advantageous in some regards, is to be noted as a limitation, for cutting shorter the amount of possible data that could have been of interest. There is also the matter of classifying the countries under the three models. For that purpose, we followed the definitions presented in Cuadrado et al.[17], Alfaro et al.[19], Serapioni et al.[20], Rosengren et al.[21], and Rotaru et al.[22] However, as acknowledged earlier, there is much debate over the models' descriptions and the countries' assortment within them. Therefore, our results would've varied if following different classifications.

6. CONCLUSION

This scoping review covered the different approaches used by 18 countries with public healthcare when assessing orphan drugs reimbursement recommendations. When comparing criteria, it is important to contextualize them into the healthcare system models adopted, their different ways of securing funding and providing services, as well as the level of integration

between the two. We hope this review provides a good basis for the understanding of each model's classification and general tendencies when creating differentiated criteria to accommodate and compensate for the lack of evidence and investment related to the rare diseases.

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8. APPENDICES

Appendix 1. Search strategy by database.

Database	Search strategy
Medline (via PubMed)	#1 “Rare Diseases”[Mesh] OR (Disease, Rare) OR (Rare Disease) OR (Orphan Diseases) OR (Disease, Orphan) OR (Orphan Disease) OR (Rare Condition) OR (Rare Conditions) OR (Rare Disorder) OR (Rare Disorders) OR (Ultrarare Disease) OR (Ultrarare Diseases) OR (Ultra-rare Disease) OR (Ultra-rare Diseases) OR (Very Rare Disease) OR (Very Rare Disease) OR (Orphan Drug) OR (Orphan Drugs) OR (Drugs, Orphan) OR (Drug, Orphan) OR (Orphan Medicine) OR (Orphan Medicines) OR (Orphan Medicinal Product) OR (Orphan Pharmaceuticals) #2 (Social Value Arguments) OR (Value Assessment) OR (Value Judgment) OR (Value Drivers) OR (Framework) OR (Evaluation Criteria) OR (Health Technology Assessment Criteria) OR (Decision Making Criteria) OR (Decision Making) OR (Decision Factors) OR (Decision) OR (Coverage Decisions) #3 “Technology Assessment, Biomedical”[Mesh] OR (Biomedical Technology Assessment) OR (Assessment, Health Technology) OR (Assessments, Health Technology) OR (Health Technology Assessment) OR (Health Technology Assessments) OR (Technology Assessments, Health) OR (Assessment, Biomedical Technology) OR (Assessments, Biomedical Technology) OR (Biomedical Technology Assessments) OR (Technology Assessments, Biomedical) OR (Technology Assessment) OR (Assessment, Technology) OR (Assessments, Technology) OR (Technology Assessments) OR (HTA) #1 AND #2 AND #3
LILACS	((MH:Rare Diseases) OR (Disease, Rare) OR (Rare Disease) OR (Orphan Diseases) OR (Disease, Orphan) OR (Orphan Disease) OR (Rare Condition) OR (Rare Conditions) OR (Rare Disorder) OR (Rare Disorders) OR (Ultrarare Disease) OR (Ultrarare Diseases) OR (Ultra-rare Disease) OR (Ultra-rare Diseases) OR (Very Rare Disease) OR (Very Rare Disease) OR (Orphan Drug) OR (Orphan Drugs) OR (Drugs, Orphan) OR (Drug, Orphan) OR (Orphan Medicine) OR (Orphan Medicines) OR (Orphan Medicinal Product) OR (Orphan Pharmaceuticals)) AND ((Social Value Arguments) OR (Value Assessment) OR (Value Judgment) OR (Value Drivers) OR (Framework) OR (Evaluation Criteria) OR (Health Technology Assessment Criteria) OR (Decision Making Criteria) OR (Decision Making) OR (Decision Factors) OR (Decision) OR (Coverage Decisions)) AND ((MH:Technology Assessment, Biomedical) OR (Biomedical Technology Assessment) OR (Assessment, Health Technology) OR (Assessments, Health Technology) OR (Health Technology Assessment) OR (Health Technology Assessments) OR (Technology Assessments, Health) OR (Assessment, Biomedical Technology) OR (Assessments, Biomedical Technology) OR

	(Biomedical Technology Assessments) OR (Technology Assessments, Biomedical) OR (Technology Assessment) OR (Assessment, Technology) OR (Assessments, Technology) OR (Technology Assessments) OR (HTA))
Scopus	(TITLE-ABS-KEY(Rare Diseases) OR TITLE-ABS-KEY(Disease, Rare) OR TITLE-ABS-KEY(Rare Disease) OR TITLE-ABS-KEY(Orphan Diseases) OR TITLE-ABS-KEY(Disease, Orphan) OR TITLE-ABS-KEY(Orphan Disease) OR TITLE-ABS-KEY(Rare Condition) OR TITLE-ABS-KEY(Rare Conditions) OR TITLE-ABS-KEY(Rare Disorder) OR TITLE-ABS-KEY(Rare Disorders) OR TITLE-ABS-KEY(Ultrarare Disease) OR TITLE-ABS-KEY(Ultrarare Diseases) OR TITLE-ABS-KEY(Ultra-rare Disease) OR TITLE-ABS-KEY(Ultra-rare Diseases) OR TITLE-ABS-KEY(Very Rare Disease) OR TITLE-ABS-KEY(Very Rare Disease) OR TITLE-ABS-KEY(Orphan Drug) OR TITLE-ABS-KEY(Orphan Drugs) OR TITLE-ABS-KEY(Drugs, Orphan) OR TITLE-ABS-KEY(Drug, Orphan) OR TITLE-ABS-KEY(Orphan Medicine) OR TITLE-ABS-KEY(Orphan Medicines) OR TITLE-ABS-KEY(Orphan Medicinal Product) OR TITLE-ABS-KEY(Orphan Pharmaceuticals)) AND (TITLE-ABS-KEY(Social Value Arguments) OR TITLE-ABS-KEY(Value Assessment) OR TITLE-ABS-KEY(Value Judgment) OR TITLE-ABS-KEY(Value Drivers) OR TITLE-ABS-KEY(Framework) OR TITLE-ABS-KEY(Evaluation Criteria) OR TITLE-ABS-KEY(Health Technology Assessment Criteria) OR TITLE-ABS-KEY(Decision Making Criteria) OR TITLE-ABS-KEY(Decision Making) OR TITLE-ABS-KEY(Decision Factors) OR TITLE-ABS-KEY(Decision) OR TITLE-ABS-KEY(Coverage Decisions)) AND (TITLE-ABS-KEY(Technology Assessment, Biomedical) OR TITLE-ABS-KEY(Biomedical Technology Assessment) OR TITLE-ABS-KEY(Assessment, Health Technology) OR TITLE-ABS-KEY(Assessments, Health Technology) OR TITLE-ABS-KEY(Health Technology Assessment) OR TITLE-ABS-KEY(Health Technology Assessments) OR TITLE-ABS-KEY(Technology Assessments, Health) OR TITLE-ABS-KEY(Assessment, Biomedical Technology) OR TITLE-ABS-KEY(Assessments, Biomedical Technology) OR TITLE-ABS-KEY(Biomedical Technology Assessments) OR TITLE-ABS-KEY(Technology Assessments, Biomedical) OR TITLE-ABS-KEY(Technology Assessment) OR TITLE-ABS-KEY(Assessment, Technology) OR TITLE-ABS-KEY(Assessments, Technology) OR TITLE-ABS-KEY(Technology Assessments) OR TITLE-ABS-KEY(HTA))
Embase	#1 'Rare Disease'/exp OR 'Rare Diseases' OR 'Orphan Diseases' OR 'Disease, Orphan' OR 'Orphan Disease' OR 'Rare Condition' OR 'Rare Conditions' OR 'Rare Disorder' OR 'Rare Disorders' OR 'Ultrarare Disease' OR 'Ultrarare Diseases' OR 'Ultra-rare Disease' OR 'Ultra-rare Diseases' OR 'Very Rare Disease' OR 'Very Rare Disease' OR 'Orphan Drug'/exp OR 'Orphan Drugs' OR 'Drugs, Orphan' OR

	'Drug, Orphan' OR 'Orphan Medicine' OR 'Orphan Medicines' OR 'Orphan Medicinal Product' OR 'Orphan Pharmaceuticals' #2 'Social Value Arguments' OR 'Value Assessment' OR 'Value Judgment' OR 'Value Drivers' OR 'Framework'/exp OR 'Evaluation Criteria' OR 'Health Technology Assessment Criteria' OR 'Decision Making Criteria' OR 'Decision Making'/exp OR 'Decision Factors' OR 'Decision'/exp OR 'Coverage Decisions' #3 'Biomedical Technology Assessment'/exp OR 'Assessment, Health Technology' OR 'Assessments, Health Technology' OR 'Health Technology Assessment' OR 'Health Technology Assessments' OR 'Technology Assessments, Health' OR 'Assessment, Biomedical Technology' OR 'Assessments, Biomedical Technology' OR 'Biomedical Technology Assessments' OR 'Technology Assessments, Biomedical' OR 'Technology Assessment' OR 'Assessment, Technology' OR 'Assessments, Technology' OR 'Technology Assessments' OR 'HTA' #1 AND #2 AND #3
Google Scholar	((Rare Diseases) OR (Rare Disease) OR (Orphan Diseases) OR (Orphan Disease) OR (Rare Condition) OR (Rare Conditions) OR (Rare Disorder) OR (Rare Disorders) OR (Ultrarare Disease) OR (Ultrarare Diseases) OR (Ultra-rare Disease) OR (Ultra-rare Diseases) OR (Very Rare Disease) OR (Very Rare Disease) OR (Orphan Drug) OR (Orphan Drugs) OR (Orphan Medicine) OR (Orphan Medicines) OR (Orphan Medicinal Product) OR (Orphan Pharmaceuticals)) AND ((Social Value Arguments) OR (Value Assessment) OR (Value Judgment) OR (Value Drivers) OR (Framework) OR (Evaluation Criteria) OR (Health Technology Assessment Criteria) OR (Decision Making Criteria) OR (Decision Making) OR (Decision Factors) OR (Decision) OR (Coverage Decisions)) AND ((Biomedical Technology Assessment) OR (Health Technology Assessment) OR (Health Technology Assessments) OR (Biomedical Technology Assessments) OR (Technology Assessment) OR (Technology Assessments) OR (HTA))

Appendix 2. List of excluded studies and exclusion reasoning (n = 65)

Reason for Exclusion	**Authors and publication year**	**Title**	**Reference**
Conference abstracts	Akbraian, E.; Allen, N.; Schmitz, S. (2020)	Patient Centricity in HTA: Fact or Fable	Value in Health 2020;23(Supplement 2):S681 doi: 10.1016/j.jval.2020.08.1684
	Akehurst, R. L. *et al*. (2019)	SPECIALISED HEALTH TECHNOLOGY ASSESSMENT PROCESSES FOR VERY RARE DISEASES: PAST, PRESENT AND FUTURE	Value in Health 2019;22(Supplement 3):S728 doi: 10.1016/j.jval.2019.09.1732
	Akesson, C. *et al*. (2019)	UNDERSTANDING THE ROLE OF REAL-WORLD EVIDENCE IN HEALTH TECHNOLOGY ASSESSMENT FOR ORPHAN DRUGS	Value in Health 2019;22(Supplement 3):S862 doi: 10.1016/j.jval.2019.09.2446
	Boers, T. V. *et al*. (2019)	COMPARATIVE ASSESSMENT OF HTA OUTCOMES IN BRAZIL, CANADA AND THE UNITED KINGDOM	Value in Health Regional Issues 2019;19(Supplement):S57 doi: 10.1016/j.vhri.2019.08.325
	Brown, R. J.; Ioannou, P.; Cadwell, K. (2019)	A REVIEW OF SIX YEARS OF THE NICE HIGHLY SPECIALISED TECHNOLOGY (HST) PROGRAMME	Value in Health 2019;22(Supplement 3):S860 doi: 10.1016/j.jval.2019.09.2435

	Bustamante, M. M. D.; Yang, E.; Anderson, K. (2020)	EVALUATING THE HTA IMPACT OF REAL-WORLDEVIDENCE FROM FORMAL ORPHAN DRUG REGISTRIES	Value in Health 2020;23(Supplement 1):S347 doi: 10.1016/j.jval.2020.04.1320
	Caban, A. *et al*. (2016)	Access to orphan drugs in Poland-is change in health technology assessment approach required?	Value in Health 2016;19(7):A442-A443 doi: 10.1016/j.jval.2016.09.559
	Corless, S.; O'Brien, S. (2022)	Pharmacoeconomic Evaluation Criteria for Highly Specialised Technologies, and Subsequent Recommendations: A Comparison of NICE UK and the NCPE Ireland	Value in Health 2022;25(1 - Supplement):S188 doi: 10.1016/j.jval.2021.11.914
	Dusza, M. *et al*. (2019)	ULTRA-ORPHAN MEDICINAL PRODUCTS ASSESSMENT: COMPARISON OF THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE) AND THE INSTITUTE OF CLINICAL AND ECONOMIC REVIEW (ICER) HTA FRAMEWORKS	Value in Health 2019;22(Supplement 3):S859 doi: 10.1016/j.jval.2019.09.2428
	Facey, K. (2021)	Appraisal Framework suitable for Rare Disease Treatments	IMPACT HTA WP10
	Gosain, S. *et al*. (2018)	COMPARISON OF PHARMACOECONOMIC (PE) EVALUATIONS FOR DRUGS FOR RARE DISEASES (DRDS) EVALUATED BY CADTH AND NICE	Value in Health 2018;21(Supplement 3):S465 doi: 10.1016/j.jval.2018.09.2741

	Gosain, S. *et al*. (2014)	Consideration for rare diseases in drug reimbursement decision-making	Value in Health 2014;17(3):A236 doi: 10.1016/j.jval.2014.03.1378
	Harrison, K.; O'Rourke, D.; Jonsson, P. (2022)	Above and Beyond: Assessing the Nature and Impact of Additional Considerations Above Clinical and Cost Effectiveness by 8 HTA Agencies for a Rare Disease Area	Value in Health 2022;25(1 - Supplement):S172 doi: 10.1016/j.jval.2021.11.836
	Heyes, A. E. *et al*. (2018)	HTA AND REIMBURSEMENT CONSIDERATIONS FOR RARE DISEASES IN EUROPEAN MARKETS: WHAT ARE THE IMPLICATIONS FOR MANUFACTURERS?	Value in Health 2018;21(Supplement 3):S468 doi: 10.1016/j.jval.2018.09.2758
	Kerr, A. *et al*. (2014)	A comparison of international health technology assessment systems-does the perfect system exist?	Value in Health 2014;17(7):A441 doi: 10.1016/j.jval.2014.08.1157
	Korchagina, D. *et al*. (2016)	Elements of orphan drugs value	Value in Health 2016;19(7):A600-A601 doi: 10.1016/j.jval.2016.09.1463
	Korchagina, D. *et al*. (2014)	Health Technology Assessment, Price and Reimbursement Review for Orphan Drugs In France	Value Health 2014;17(7):A540 doi: 10.1016/j.jval.2014.08.1734
	Korchagina, D. *et al*. (2014)	Comparative analysis of HTA decisions, price and reimbursement level of orphan drugs in France and Italy	Value in Health 2014;17(7):A539-A540 doi: 10.1016/j.jval.2014.08.1732

	Lockhart, C. M.; Hansen, R. N. (2016)	Value assessment of orphan drugs for treatment of rare diseases: A systematic review	Value in Health 2016;19(3):A79 doi: 10.1016/j.jval.2016.03.652
	Morawski, J. *et al*. (2014)	Reimbursement trends and evidence requirements for ultra-orphan therapies across Europe: Optimising market access in increasingly challenging markets	Value in Health 2014;17(7):A431 doi: 10.1016/j.jval.2014.08.1097
	Nemeth, B.; Piniazhko, O. (2016)	Mcda application in central and eastern Europe: Selection of the most important criteria based on examples	Value in Health 2016;19(7):A471 doi: 10.1016/j.jval.2016.09.723
	Nicod, E. (2014)	To what extent do disease and treatment characteristics influence HTA-based recommendations for a sample of orphan drugs in three countries, and could these indicate whether orphan drugs have a “special status”?	Value in Health 2014;17(7):A540 doi: 10.1016/j.jval.2014.08.1736
	Nicod, E. (2014)	Why are there differences in HTA recommendations across countries? A systematic comparison of HTA decision processes for a sample of orphan drugs in four countries	Value in Health 2014;17(7):A540 doi: 10.1016/j.jval.2014.08.1737
	Nicod, E. *et al*. (2016)	Dealing with uncertainty and accounting for social value judgments in value assessments for orphan drugs: Qualitative evidence from four european countries	Value in Health 2016;19(3):A4-A5 pui: L72310700

	Nicod, E.; Kanavos, P. (2014)	Value Assessments for Orphan Drugs: Mixed Methods to Systematically Compare HTA Decision-Making Processes in Four Countries	NA
	Nicod, E.; Kanavos, P. (2013)	Inter-country variability in coverage decisions for orphan drugs: Criteria driving HTA recommendations in six countries	Value in Health 2013;16(3):A3 doi: 10.1016/j.jval.2013.03.019
	Scholten, J. *et al*. (2014)	National rare disease strategies: The current state for orphan drug market access in European union (EU) member states	Value in Health 2014;17(7):A418 doi: 10.1016/j.jval.2014.08.1016
	Shih, A. Y. *et al*. (2013)	Clinical and economic evidence thresholds for orphan drugs: Are requirements for favorable health technology assessment and reimbursement on the rise?	Value in Health 2013;16(3):A108 doi: 10.1016/j.jval.2013.03.512
	Skora, K. *et al*. (2017)	The practice of decision-making of public health authorities in poland on reimbursement of orphan drugs	Value in Health 2017;20(9):A564 doi: 10.1016/j.jval.2017.08.938
	Stefanov, R.; Raycheva, R. (2017)	Health technology assessment and rare disease decision making: Focus on orphan drugs	International Journal of Technology Assessment in Health Care 2017;33(Supplement 1):186-187 doi: 10.1017/S0266462317003518

	Stevenson, A. *et al*. (2018)	NICE: A MULTIPROGRAM HTA ORGANIZATION TO SUIT ALL?	Value in Health 2018;21(Supplement 3):S205-S206 doi: 10.1016/j.jval.2018.09.1218
	Tavella, F. *et al*. (2014)	Health Technology Assessment, Price and Reimbursement Review for Orphan Drugs In Italy	Value Health 2014;17(7):A540 doi: 10.1016/j.jval.2014.08.1733
	Taylor, C. B. *et al*. (2016)	Developing HTA guidelines for rare disease therapies - an industry perspective	Value in Health 2016;19(7):A819 doi: 10.1016/j.jval.2016.08.662
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*Titles as shown translated on search databases.

Assinaturas	
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