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### Health Policy Analysis

## Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review With Content Analysis



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### ABSTRACT

**Objectives:** Three hundred million people living with rare diseases worldwide are disproportionately deprived of in-time diagnosis and treatment compared with other patients. This review provides an overview of global policies that optimize development, licensing, pricing, and reimbursement of orphan drugs.

**Methods:** Pharmaceutical legislation and policies related to access and regulation of orphan drugs were examined from 194 World Health Organization member countries and 6 areas. Orphan drug policies (ODPs) were identified through internet search, emails to national pharmacovigilance centers, and systematic academic literature search. Texts from selected publications were extracted for content analysis.

**Results:** One hundred seventy-two drug regulation documents and 77 academic publications from 162 countries/areas were included. Ninety-two of 200 countries/areas (46.0%) had documentation on ODPs. Thirty-four subthemes from content analysis were categorized into 6 policy themes, namely, orphan drug designation, marketing authorization, safety and efficacy requirements, price regulation, incentives that encourage market availability, and incentives that encourage research and development. Countries/areas with ODPs were statistically wealthier (gross national income per capita = \$10 875 vs \$3950,  $P < .001$ ). Country/area income was also positively correlated with the scope of the respective ODP (correlation coefficient = 0.57,  $P < .001$ ).

**Conclusions:** Globally, the number of countries with an ODP has grown rapidly since 2013. Nevertheless, disparities in geographical distribution and income levels affect the establishment of ODPs. Furthermore, identified policy gaps in price regulation, incentives that encourage market availability, and incentives that encourage research and development should be addressed to improve access to available and affordable orphan drugs.

**Keywords:** drug regulatory, health equity, orphan drug policy, rare diseases, treatment access.

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### Introduction

An *orphan drug* can be defined as any medicinal product intended for a rare disease or a disease with no existing satisfactory method of diagnosis, prevention, or treatment.<sup>1,2</sup> Accounting for the varying terminologies and definitions across nations and organizations, rare diseases are typically defined as conditions with limited treatment alternatives, with an average prevalence of fewer than 40 to 50 cases per 100 000 population or that affect a small number of patients compared with the total population.<sup>3</sup> Although individually rare, these diseases collectively affect 300 million patients worldwide, half of whom are children, with 30%

likely to die by age 5.<sup>4</sup> With over 7000 types identified worldwide, rare diseases are also termed “significant minorities.”<sup>5,6</sup> Many people living with rare diseases experience barriers to accessing timely care. The low prevalence of rare diseases often deters industries from developing novel drugs, because the substantial investment required is rarely recoverable based on limited patient numbers. These medicinal products are therefore “orphaned” as sponsors are hesitant to develop them under usual marketing conditions. Worldwide, less than one-tenth of patients with rare diseases have received disease-specific treatment.<sup>7</sup>

Policy frameworks that optimize the research and development, licensing, pricing, and reimbursement processes of orphan drugs are impactful means of addressing the unmet medical needs

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of patients with rare diseases. The Orphan Drug Act, enacted by the Food and Drug Administration (FDA) of the United States in 1983, was the first legislation to regulate orphan drugs and offered financial and regulatory incentives to companies that developed and registered orphan drugs.<sup>8</sup> From 1983 to 2009, over 2000 orphan drug applications were submitted to the FDA, with the approval of approximately 350 orphan drugs for over 420 indications compared to only 34 drugs eligible for approval between 1967 and 1983.<sup>9,10</sup> Since then, more authorities have set up orphan drug legislation for their jurisdictions, including the European Union, Singapore, Japan, Australia, South Korea, and Taiwan. In recent years, increasing numbers of non-high-income countries have included orphan drug policy (ODP) development in their policy agenda.<sup>11</sup>

Several articles reviewed country-specific orphan drug and rare disease policies, which were limited by the scope of selected countries or were restricted to English peer-reviewed journal articles.<sup>11-13</sup> Current development of ODP on a global scale remains unclear for several reasons. Firstly, most policy documents were published through governmental channels and were not reported in journal articles. Secondly, these documents may not be electronically accessible to the public. Thirdly, ODP may not be available as a separate document but could be embedded within a wider piece of legislation, making it difficult for academic search engines to identify. Finally, these documents are likely to be written in the local language of the countries/areas of interest. This study aims to provide an up-to-date global overview of ODP in the era of innovative medicine and to reflect associated changes in drug regulation policy.

## Methods

Establishment and scope of ODP were examined from 194 World Health Organization (WHO) member countries and 6 nonmember areas (Hong Kong, Kosovo, Macau, Palestine, Sahrawi Republic, and Taiwan) with independent drug regulatory authorities.<sup>14</sup> An ODP is defined as any “formal decision or a plan of action that has been taken by, or has involved, a state organisation”<sup>15</sup> related to the access and regulation of orphan drugs, in the form of pharmaceutical legislation, regulation, or policies. Other terminologies, including “access,”<sup>16,17</sup> “availability,”<sup>16</sup> “reimbursement,”<sup>18</sup> “marketing authorization,”<sup>19</sup> and “regulation,” used in this review, are defined in [Table 1](#).

### Government Information Source

Governmental policy documents on drug regulation were searched, reviewed, and retrieved through (1) a standardized internet search by keywords (see [Appendix 1](#) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>), (2) scanning websites of drug regulatory authorities (DRAs) of each country/area, and (3) direct emails to DRAs to verify the information from the internet. Emails were sent to national pharmacovigilance centers participating in the WHO Programme for International Drug Monitoring, assisted by the program coordinating office at WHO headquarters and the network of the International Society of Pharmacovigilance, to confirm the latest country-specific ODP status and to request official documents mentioning existing ODP that were not publicly accessible at the time of this study. Policy document collection ended on July 31, 2019.

### Academic Information Source

A systematic review of academic literature was performed to ensure comprehensive reporting and to complement the

information from government documentation. Searched databases include PubMed, EMBASE, Web of Science, and the Cochrane Library. The academic literature was searched following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and updated to July 31, 2019.<sup>20</sup> The search strategy include the keywords (“orphan” or “high cost” or “rare diseases”) and (“drugs” or “medicines” or “pharmaceuticals”) and (“legislation” or “regulation” or “policy”) in any field (see [Appendix 1](#) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>). An additional manual search was conducted based on the reference lists of included articles.

### Eligibility Criteria and Publication Selection

All government documentation that described any policies, legislation, or regulation related to orphan medicine and drugs developed to diagnose, prevent, or treat rare diseases was screened and selected. Policies implemented by nongovernmental entities were excluded. For academic literature, all peer-reviewed drug policy research, including systematic reviews, comparative analyses, policy analyses, and original studies with mixed methods that focused on ODP, were included. Reference lists of included studies were searched and reviewed manually with additional literature added. All government documents and academic articles were screened, selected, reviewed, and cross-checked independently. Discrepancies in publication selection were settled during consensus meetings.

### Data Extraction

Information on the establishment of the DRA (existence, name, and website) and status of ODP for each country/area was extracted from included documentation and publications. Country/area names and geographical areas were documented according to the WHO member country list.<sup>14</sup> Country/area income (gross national income per capita) and income level (high income, upper-middle income, lower-middle income, and low income) were documented according to the World Bank Report in 2019.<sup>21,22</sup> Absence of ODP was confirmed if no evidence was found after thorough perusal of regulation documents and academic literature. Orphan drug policy establishment was determined as unknown if the country's drug regulation documents were not available from the DRA website, internet search, email correspondence, or academic literature. Non-English documents were translated into English for data extraction and analyses.

### Data Synthesis and Content Analysis

Themes and subthemes of orphan drug policy were pre-identified based on 2 previous studies (see [Appendix 2](#) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>).<sup>11,23</sup> Relevant texts from included documents and publications were extracted and categorized accordingly by A.Y.L.C. Additional themes/subthemes were generated for texts that could not be categorized under the preidentified themes/subthemes. V.K.Y.C. and M.G. crosschecked the data extraction spreadsheet and categorization by reviewing each governmental publication and academic publication, respectively. Consensus meetings were held with A.Y.L.C., V.K.Y.C., M.G., and senior author X.L. to confirm theme and subtheme categorization.

### Statistical Analysis and Data Visualization

The scope of the established ODP was calculated using the percentage of subthemes addressed in the policy documents of each country/area over the total number of subthemes identified globally. A heat map was used to illustrate the level of ODP

**Table 1.** Definitions of terminologies.

Terms	Definitions
Access	Ability or potential to receive appropriate treatment, if needed, to achieve best possible outcome. It is measured in physical accessibility, affordability, and acceptability, but not merely the adequate supply of treatment.
Availability	Adequacy of supply for required treatment or presence of policy
Reimbursement	Rational decision and amount that payers are willing to pay and cover services and medications on behalf of end users
Marketing authorization	Issuance of approval status by a competent drug regulatory authority for marketing or free product distribution after comprehensive scientific evaluation
Regulation	Policy set by a statutory body to exert control in accordance with higher legislative framework

development. The income difference between countries/areas with and without an established ODP was tested using the Mann-Whitney U Test. The correlation between country incomes and the scope of ODP subthemes was analyzed using the Spearman correlation. We used R Foundation for Statistical Computing version 3.6.0 (Vienna, Austria) and ggplot2 for data analysis and visualization.

## Results

### Evidence From Government Documents and Academic Literature

A total of 172 drug regulation documents from 162 of the 200 countries/areas were found and read in full (see Appendix 3 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>). The remaining 38 countries had no identifiable drug regulation documents owing to a lack of an identifiable DRA (n = 7), a lack of identifiable DRA websites (n = 9), inaccessible DRA websites (n = 4), or DRA websites without identifiable drug regulation documents (n = 18).

A total of 77 academic publications were included in our narrative synthesis based on eligibility criteria (see Appendix 4 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>). Of the 68 countries/areas discussed in academic literature, 42 were reported to have an existing ODP while 26 had no identified ODP despite reporting significant unmet needs. Academic interest in ODP is growing globally over the years (see Appendix 5 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>). Although the Orphan Drug Act was established in 1983, only 6 countries had made contributions to the academic literature concerning ODP until 2000. Following the establishment of the EU Orphan Medicine Regulation in 2000, discussions around ODP surged between 2006 and 2010, and 2014 and 2018, respectively.

### Establishment of ODP by Country

Orphan drug policies were identified under a range of descriptive terms for statutory or regulatory instruments such as acts, decrees, guidelines, ordinances, or policies, each corresponding to the respective countries'/areas' legal structures, enforced by DRAs. We identified 92 countries/areas (92/200, 46.0%) with legislation, regulations, or policies that facilitated patient access to orphan drugs (Fig. 1). Europe was identified as having the highest ODP establishment rate (42 of 54, 77.8%), with Africa having the lowest (6 of 47, 12.8%).

Between 2013 and 2019, ODP establishment increased gradually in non-high-income countries/areas (Fig. 2). Of the 37 countries/areas with an established ODP since 2013, 20 (54.1%) were of low- or

lower-middle-income, and 10 (27.0%) were of upper-middle-income. Nonetheless, at the time of this study, countries/areas with an ODP were statistically wealthier (gross national income per capita = \$10 875 vs \$3950,  $P < .001$ ). Orphan drug policies were established in only 19.4% of the 31 low-income countries/areas; indicating a considerable policy gap in these countries/areas.

### Characteristics of Global ODP

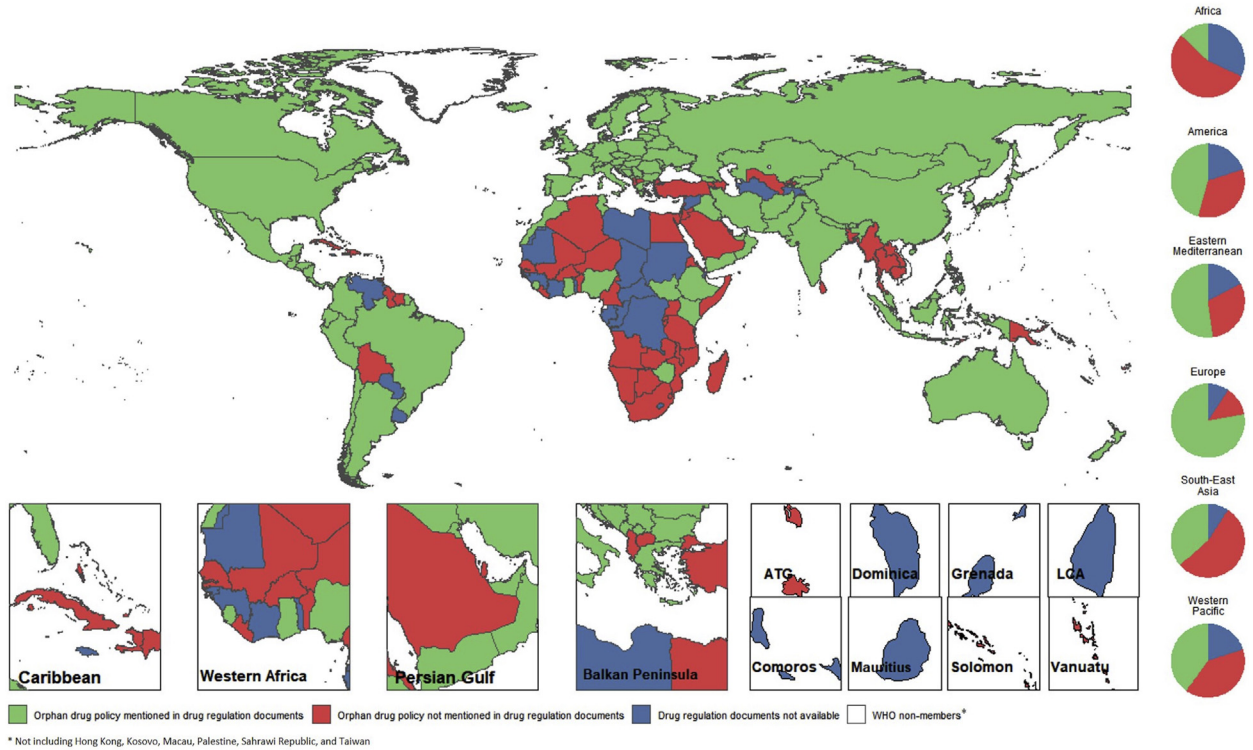
Content analysis of extracted texts from governmental and academic sources yielded 34 subthemes, which were categorized into 6 themes, namely, orphan drug designation, marketing authorization, safety and efficacy requirements, price regulation, incentives that encourage market availability, and incentives that encourage research and development (Table 2). Themes and subthemes of ODP by country/area are summarized in Table 2 and in Appendix 6 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.06.020>. The number of countries/areas with policy themes are presented with quotes to illustrate each theme in Table 3. High-income countries comprised a greater proportion with an established ODP and a broader scope of ODP themes/subthemes (Fig. 3). Spearman correlation showed that country/area income was positively correlated with policy scope (correlation coefficient = 0.57,  $P < .001$ ).

### Identified Themes in ODP

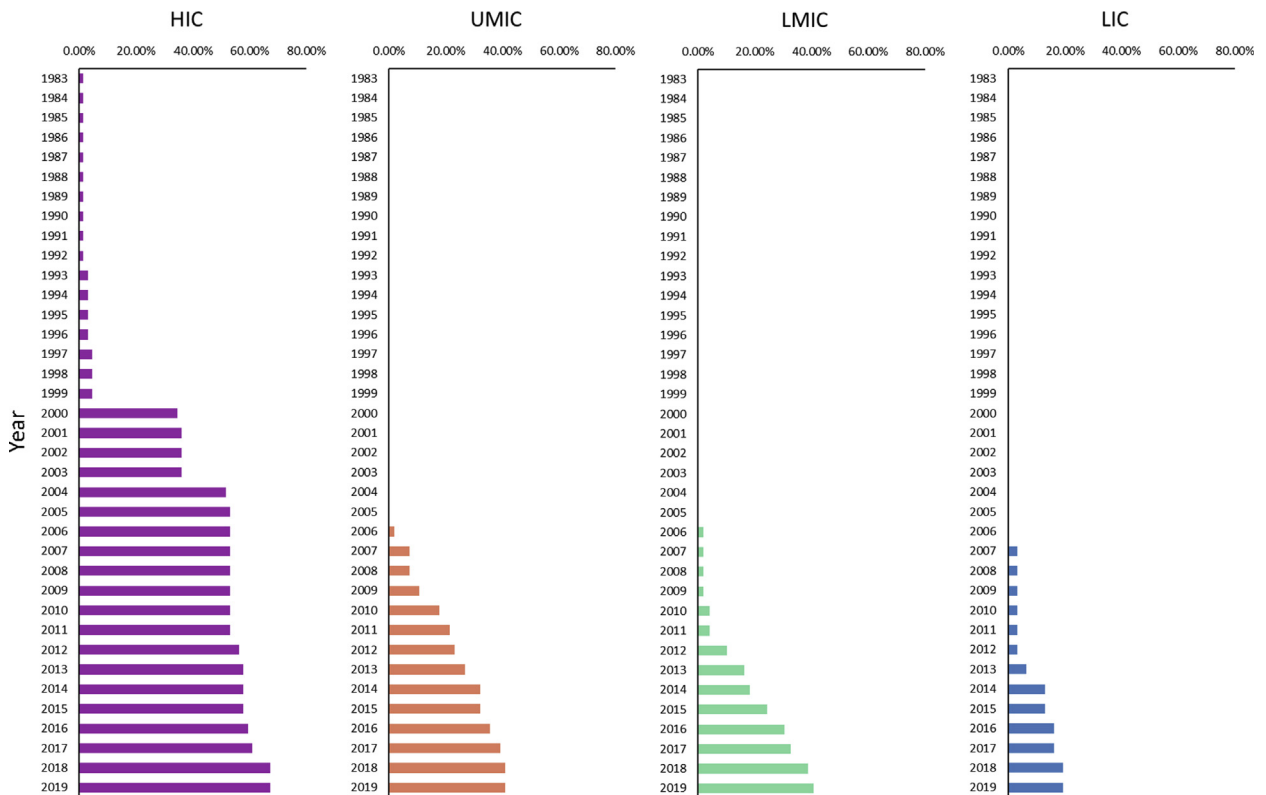
Orphan drug designation was the most frequent theme identified. This refers to the special status granted by a DRA that qualifies a medicinal product for exclusive development and marketing conditions. Orphan drugs are often defined as drugs intended for the treatment, diagnosis, prophylaxis, or rehabilitation of rare diseases. When defining rare diseases, most countries/areas adhered to the European Union definition of low prevalence (0.05%), whereas others followed the number of prevalent cases, such as Australia (<2000), South Korea (<20 000), and the United States (<200 000). Countries/areas such as Chile, Kenya, Peru, and Singapore required the disease severity to be "life threatening" and "severely- or 'chronically-' debilitating." Orphan drugs are also defined by their availability as pharmaceutical products or active ingredients not developed, imported, or registered owing to low commercial returns and unfavorable marketing conditions. Countries/areas such as China and Vietnam acknowledged orphan drug designation from referenced competent authorities.

Marketing authorization refers to the marketing permit or license granted for an orphan drug before importation or supply in the form of samples (paid or free), wholesale, or retail. The validity of such permits range from 12 months to 5 years. Thirteen countries/areas exempted orphan drugs from drug registration on essential medicines lists, drug registries, product licences, or serial

**Figure 1.** Geographical distribution of orphan drug policy establishment.



**Figure 2.** Cumulative percentage of countries with an established orphan drug policy, by income level.



HIC indicates high-income countries; LIC, low-income countries; LMIC, lower-middle income countries; UMIC, upper-middle-income countries.

**Table 2.** Themes and subthemes of orphan drug policy in the content analysis.

Theme	Subtheme
Orphan drug designation	Definition of rare diseases
	Designation or official list of rare diseases
	Definition of orphan drugs
	Designation or official list of orphan drugs
	Criteria and procedures for orphan drug designation
Marketing authorization	Designation committee
	Provisions for marketing authorization
	Criteria for obtaining marketing authorization
	Validity duration of marketing authorization
	Priority/expedited/accelerated/fast-track approval
	Reference to overseas orphan drug approval
Safety and efficacy requirements	Premarketing authorization access
	Proof of efficacy/safety/cost-effectiveness
	Clinical trial authorization/exemption
	Health technology assessment criteria
	Definition/requirements of sponsor or applicant
	Pharmacovigilance requirement/adverse event monitoring
	Recall of products
Price regulation	Provisions and guidelines for price regulation
	Mode of price regulation
	Managed entry agreements
	Exemption from price regulation
	Maximum retail price
Incentives that encourage market availability	Payer subsidies/reimbursement/funding/copayment
	Financial assistance for cross-border health access
	Compassionate use
	Tax credits or exemptions
	Fee refund/reduction/waiver
	Sponsor/applicant reimbursement
Incentives that encourage research and development	Patent protection/market exclusivity/monopolization
	Funding for research/development/clinical trials
	Protocol assistance
	Scientific advice/consultation
	National plan or strategy

and quality control. Forty-three countries/areas had provision for priority review, expedited registration, or fast-track approval for orphan drugs. Timelines for authorization decisions ranged from 5 days to 12 months. The fastest approval time was identified in Costa Rica (5 days), followed by Chile and the United Arab Emirates (both 20 days). In countries such as Kazakhstan and Panama, fast-track approval was identified without a specified timeline.

Owing to limited uptake, comprehensive proof of quality, safety, and efficacy of candidate orphan drugs may not be readily available. To ensure high regulatory standards, drug regulations in Kazakhstan require applicants to conduct a specific study program whereby findings form the basis for benefit-risk ratio evaluation. In Brazil, where complete clinical development of orphan drugs is not available, clinical reports containing efficacy data based on Brazilian or international references, *in vivo* and *in vitro* studies, or relative bioequivalence studies using international comparator

medicines are accepted as proof of efficacy. Risk minimization plans, pharmacovigilance plans, and updated reports of the orphan drug from drug commercialized countries were considered acceptable proof of safety.

To mitigate steep costs and low commercial interests, some countries/areas provide incentives to encourage orphan drug research and development. In the United States, clinical research that evaluated the safety and efficacy of orphan drugs was funded through the Orphan Products Clinical Trials Grants Programme by the FDA and the Orphan Products Research Project Grant by the National Institutes of Health. Patent protection in the form of market exclusivity was provided for each orphan drug with duration ranging from 5 years (Australia), 7 years (United States), 8 years, or 8.5 years for pediatric orphan drugs (Canada) to 10 years (European Union, Japan, Taiwan). Provision for scientific advice or consultation concerning the design and implementation

**Table 3.** Summary of orphan drug policy themes coverage.

Themes (number of countries/areas)	Quotations to illustrate the themes
Orphan drug designation (82 of 92, 89.1%)	Definition of rare diseases: "rare disease or condition' means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." (United States)
	Designation of rare diseases: "The DOH, upon recommendation of the RDTWG, shall have the authority to designate any disease that is recognized to rarely afflict the population of the country as a rare disease." (The Philippines)
	Criteria and procedures for orphan drug designation: "Article 3 Criteria for designation 1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition ... Article 5 Procedure for designation and removal from the register 1. "In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorization is made ..." (European Union)
	Marketing authorization (78 of 92, 84.8%)
Marketing authorization (78 of 92, 84.8%)	Provisions for marketing authorization: "Pharmaceutical products intended both for the Kenya market as well as products intended for export will be registered with the Pharmacy and Poisons Board. The following criteria will be used in the registration: ... (4) Unique characteristic of the drug product such as life-saving and orphan drugs. Orphan drugs are products for rare conditions for which the small size of the local market would make registration otherwise commercially unattractive." (Kenya)
	Validity duration of marketing authorization: "The retention of the listed product in the register of listed products will be for a duration of 12 (twelve) months and is renewable subject to review at the end of the retention period." (Sierra Leone)
	Priority/expedited/accelerated/fast-track approval: "Applications under this category shall have a decision made within three (3) months of submission." (Ghana)
Safety and efficacy requirements (44 of 92, 47.8%)	Reference to overseas orphan drug approval: "to prioritize the registration for circulation and grant of import permits for rare drugs and vaccines which have been assessed for prequalification by the World Health Organization" (Vietnam)
	Pre marketing authorization access: "A Marketing Authorization shall not be required for, as follows: 5.1. a magistral preparation and a galenic product; 5.2. an orphan medicinal product; ..." (Kosovo)
	Clinical trial authorization/exemption "CDSCO may relax such requirement of local Phase IV clinical trial, where the new drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug." (India)
	Health technology assessment criteria "We only consider drugs for very rare conditions. The majority of our topics are identified by the National Institute for Health Research Innovation Observatory. They aim to notify the Department of Health and Social Care of key, new and emerging healthcare technologies that might need to be referred to NICE against the following timeframes: new drugs, in development, at 20 months to marketing authorisation new indications, at 15 months to marketing authorisation." (United Kingdom)
Safety and efficacy requirements (44 of 92, 47.8%)	Definition/requirements of sponsor or applicant: "Positive decision on state registration of orphan drugs can be made if the Applicant assumes obligation to: (1) carry out a specific study program within a specified time period, the results of which will be the basis for re-evaluation of the 'benefit-risk' ratio; (2) to ensure application of the medicinal drug under strict medical supervision; (3) immediately inform the governmental body of any adverse effects emerging due to the orphan drug application and measures taken..." (Kazakhstan)

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Table 3. Continued

Themes (number of countries/areas)	Quotations to illustrate the themes
	<p>Pharmacovigilance requirement/adverse event monitoring:            "... surveillance activities and monitoring of quality, safety, and efficacy will be implemented within six months after the product is registered. Surveillance procedures and requirements are as follows:            a) The product registration holder must report any adverse reactions involving orphan product to NPRA (...)            b) Periodic Safety Updates Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) must be submitted to NPRA for orphan products in the category of new chemical entities/new products and biologics every 6 months for the first 2 years and once a year for the following 3 years.            c) Products will be sampled and tested to ensure that it complies to the established standards and specifications. Actions will be taken against products that do not comply to the established standards." (Malaysia)</p>
Price regulation (21 of 92, 22.8%)	<p>Mode of price regulation:            "The Economic Committee for Health Products of the Ministry of Health negotiates the price of an orphan drug with the pharmaceutical company, taking into account the improvement in clinical added value of the drug; prices of drugs serving the same therapeutic purpose; sales volumes; conditions of use; and prices in Ireland, Italy, Portugal, Spain and the European Union. The Ministry of Health decides on reimbursement taking into account the clinical added value of the drug and the improvement in the clinical added value of the drug as compared to existing therapies." (France)</p>
	<p>Managed entry agreements            "After a negative advice, companies may enter into negotiations for managed entry agreements (in which for example, the pharmaceutical company refunds a predefined percentage of the price for every unit sold) as defined by the Royal Decree of December 21th, 2001" (Belgium)</p>
	<p>Exemption from price regulation            "(5) Maximum increase on hardship cases (except for orphan drugs, lower priced drugs &amp; intravenous infusions) shall be 8% per annum of the existing approved MRPOf the respective drug. In case of lower priced drugs, increase shall not exceed 25 paisa per tablet/capsule/respule/caplet/patch/5ml of syrup, suspension and elixir." (Pakistan)</p>
	<p>Maximum retail price            "Zur Wahrung des finanziellen Gleichgewichts des Systems der sozialen Sicherheit darf einem ozialversicherungsträger für eine Arzneispezialität dieses Bereiches höchstens der ermittelte EU-Durchschnittspreis verrechnet werden." (Austria)</p>
Incentives that encourage market availability (43 of 92, 46.7%)	<p>Financial assistance for cross-border health access            "Rare disease patients or their legal guardians may apply to the central competent authority by submitting an application form, together with certificates, care plans and relevant documents issued by a medical care or research institution specified in Article 10; after review and approval by the Review Committee, the central competent authority may provide subsidies for patients to travel overseas and participate in international medical cooperation projects." (Taiwan)</p>
	<p>Tax credits or exemptions            "SEC. 44H. CLINICAL TESTING EXPENSES FOR CERTAIN DRUGS FOR RARE DISEASES OR CONDITIONS. (a) GENERAL RULE.-There shall be allowed as a credit against the tax imposed by this chapter for the taxable year an amount equal to 50 percent of the qualified clinical testing expenses for the taxable year..." (United States)</p>
	<p>Fee refund/reduction/waiver            "The Secretary must waive the following fees: (a) a fee that would have been payable, but for this subregulation, as part of an application under subsection 22C(1) of the Act relating to a medicine that is a designated orphan drug; (b) a fee that would have been payable, but for this subregulation, as part of an application under subsection 22E(3) of the Act relating to a medicine that is a designated orphan drug; (c) a fee that would have been payable, but for this subregulation, as part of the registration of a designated orphan drug; (d) a fee that would have been payable, but for this subregulation, for applying for a therapeutic goods (priority applicant) determination in relation to a medicine that is a designated orphan drug." (Australia)</p>
	<p>Sponsor/applicant reimbursement            "There is a special fund (part of the Croatian Health Insurance Fund [CHIF]) for orphan drugs.. Orphan drugs included in the essential list of drugs of the CHIF are completely reimbursed, while those included in the additional list are partially reimbursed." (Croatia)</p>

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**Table 3.** Continued

Themes (number of countries/areas)	Quotations to illustrate the themes
Incentives that encourage research and development (44 of 92, 47.8%)	Patent protection/market exclusivity/monopolization “SEC. 527. (a) Except as provided in subsection (b), if the Secretary- (1) approves an application filed pursuant to section 505(b), or (2) issues a license under section 351 of the Public Health Service Act for a drug designated under section 526 for a rare disease or condition and for which a United States Letter of Patent may not be issued, the Secretary may not approve another application under section 505(b) or issue another license under section 351 of the Public Health Service Act for such drug for such disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license. Section 505(c)(2) does not apply to the refusal to approve an application under the preceding sentence.” (United States)
	Funding for research/development/clinical trials “SEC. 5. (a) The Secretary may make grants to and enter into contracts with public and private entities and individuals to assist in defraying the costs of qualified clinical testing expenses incurred in connection with the development of drugs for rare diseases and conditions.” (United States)
	Scientific advice/consultation “There are particular challenges associated with designing and conducting trials in populations with rare diseases. We encourage sponsors to request regulatory advice from Health Canada before filing their applications. This advice can take a few different forms depending on the nature of the question. In some cases a teleconference or email is sufficient. In other cases an in-person meeting may be appropriate for a more detailed discussion.” (Canada)

CDSCO indicates Central Drugs Standard Control Organisation; DOH, Department of Health; MRP, maximum retail price; NICE, National Institute for Health and Care Excellence; NPRA, National Pharmaceutical Regulatory Agency; RDTWG, Rare Diseases Technical Working Group.

of orphan drug trials was identified from European Union member-states and 6 other countries/areas.

Incentives to encourage the market availability of orphan drugs were also identified. China offers tax reductions to reduce value-added tax during the purchasing process of orphan drugs. Patients with rare diseases are able to obtain drugs free or at low prices from government or nongovernment organization subsidies in Colombia and Peru. In Canada and China, orphan drugs can be imported through the Special Access Programme or pathways for orphan drugs that are “highly urgently needed in clinical care,” respectively, which enables sales of drugs that would not otherwise be sold or distributed in the country. Similarly, in the Philippines, named-patient programs allow the importation of orphan drugs via a compassionate special permit before product registration. European Union member-states and Taiwan have policies that assist patients in accessing cross-border healthcare.

Price regulation was the least common theme of all identified ODPs. Various modes of price regulation such as maximum retail price or price ceiling and price negotiation were identified. In Bahrain, ODP mechanisms followed that of either innovator drugs or generic drugs depending on the novelty of the active ingredient. In Austria, orphan drugs are regulated to ensure that the maximum ex-factory price would not exceed the European Union average price. Similarly, in Pakistan orphan drugs are exempt from the maximum price increase (8% per annum of the existing approved maximum retail price of the respective drug) fixed by the government. Prices in other countries such as Japan, Austria, Germany, and Belgium are determined from negotiation between governmental agencies and pharmaceutical companies.

## Discussion

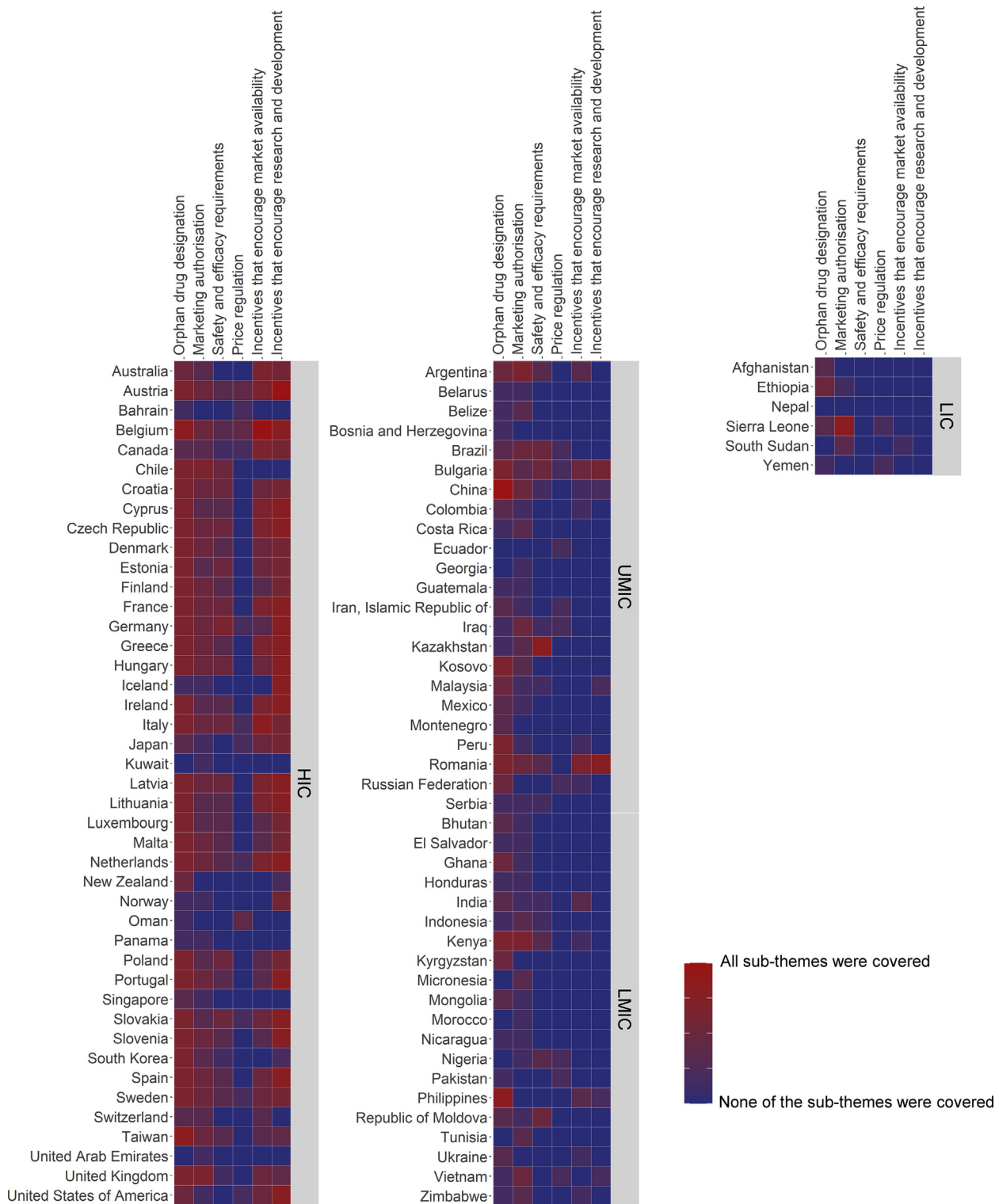
Our study presents an overview of global ODP from 194 WHO member countries and 6 nonmember areas. This includes

countries/areas that were not examined previously, especially those that are non-English speaking and non-high income.<sup>11-13</sup> Compared with the 2015 review,<sup>11</sup> our findings illustrate major differences in ODP globally. Ninety-two countries/areas with an ODP were identified, with a notable increase in ODP establishment in non-high-income countries/areas. In particular, the world's top 2 populous countries, China and India, recently established an ODP. Our findings demonstrate disparities in ODP establishment and ODP scope by geographical distribution and country/area income level. This underscores the unmet needs in orphan drug access caused by a lack of an ODP establishment or gaps in policy scope. Before this review, the global ODP landscape lacked clarity; therefore, the additional knowledge from countries/areas with similar cultural, economic, health, and political realities will be beneficial to policy makers. This will support proposals to improve the current ODP, or lack thereof, in their own jurisdiction. Similarly, this will help patient organizations to advocate for achievable and realistic ODP changes based on experiences of countries/areas with similar backgrounds. Finally, this provides a foundation for future global-scale ODP research, such as cost-effectiveness, quality improvement, and participatory action studies, that will be inclusive of countries/areas whose ODP establishment is recent. Because each country/area's health system operates under unique local setting, cross-comparisons of ODP should not be made without considering underlying cultural, economic, health, and political factors. Moreover, although commonly applied to rare diseases, orphan drug designation may also be granted to medicinal products for nonrare diseases with limited treatment options. For instance, alectinib and certinib were approved for orphan drug status in the United States to treat ALK+ non-small cell lung cancer, an orphan subset of a nonrare condition.<sup>24</sup> Thus, comprehensive contextual understanding must be sought when interpreting the policy content of each country/area.

Characterized by small patient populations, the free-market competition of orphan drugs is inherently distorted. Other



**Figure 3.** Orphan drug policy scope, by income level.



HIC indicates high-income countries; LIC, low-income countries; LMIC, lower-middle income countries; UMIC, upper-middle-income countries.

factors contributing to orphan drug market failures include monopolization, steep research and developmental costs, asymmetrical knowledge on rare diseases, and inelasticity of patient demands owing to life-threatening consequences in the absence of timely drug access.<sup>25,26</sup> A robust ODP is critical to correct these market failures that render conventional regulatory mechanisms ineffective. Even with existing ODP frameworks, within-framework policy gaps might lead to unintended perverse effects when availability and affordability of orphan drugs are not matched. Although policy content may vary according to local circumstances, holistic ODP covering different themes should be in place to outline the regulatory standards that each jurisdiction is obliged to achieve to ensure fair treatment access for patients with rare diseases. According to our findings, ODPs from high-income countries/areas generally attain a wide scope on all policy themes except for price regulation. This partially explains the perpetual rise in orphan drug prices. Meanwhile, in non-high-income countries/areas, incentives that encourage research and development, incentives that encourage market availability, and price regulation were underrepresented. Driven by a lack of attractive benefits, pharmaceutical companies may be less motivated to research and develop orphan drugs, which may deter market entrants owing to reduced potential return on investment. This could explain the lack of availability of orphan drugs in non-high-income countries/areas. Indeed, Picavet et al<sup>27</sup> found that sales and volume uptake of orphan drugs were greater in EU countries with higher gross domestic product, while Szedegi et al<sup>28</sup> found a greater absolute expenditure and proportion of gross domestic product allocated to orphan drugs. Orphan drug availability was low in non-high-income European Union countries, where budget confinement could exclude non-cost-effective medications.<sup>27,29</sup> Despite differences in country income, external price referencing systems gave rise to similar drug prices in both high- and low-income countries, making them less affordable in low-income countries on account of their ability to pay.<sup>28,30</sup> As such, orphan drug access is more commonly observed in higher-income countries owing to clearer reimbursement frameworks, affordable population risk-sharing, and a more favorable maximum negotiated price.<sup>29</sup>

To ensure orphan drug availability and affordability, price negotiation is a common strategy practiced by high-income countries/areas to moderate changes in equilibrium price and quantity. In particular, Germany relies on a mandatory price negotiation mechanism that subjects orphan drugs to cost-benefit analyses. Nevertheless, such governmental-industry negotiation is often criticized as a “black box” that overlooks patient involvement where transparent consensus among patients, practitioners, and health technology assessment bodies are vital.<sup>31,32</sup> In Belgium, marketing authorization applicants/holders may negotiate a managed entry agreement (MEA) if the final decision on the previous drug reimbursement request was negative or was not made within the period specified by the law.<sup>33</sup> MEAs are contractual agreements between marketing authorization holders and payers when price and reimbursement cannot be decisively concluded owing to uncertainties in the clinical effectiveness and budgetary impact of the drug.<sup>34</sup> Currently, mechanisms such as various forms of MEAs, pay-for-performance, risk-sharing models, and patient access schemes with conditions for medication-use monitoring, outcome measurements, and real-world data collection are being tested.<sup>35</sup> To accommodate the dynamic nature of orphan drug developmental life cycles, adaptive pricing mechanisms should be adopted. Pricing should be iterative based on the strength of efficacy and safety evidence, and ranges of indications through indication value-based or multiple-indication pricing.<sup>31</sup> As such, orphan drug prices can be readjusted based on the updated efficacy and safety evidence or

when approved for a wider range of indications such as nonrare diseases in the future.<sup>31</sup> In The Netherlands, a conditional reimbursement trajectory was introduced requiring authorized drugs to be reevaluated every 4 years.

Alternative policy frameworks that may facilitate orphan drug access exist; however, their nonspecificity place them outside the scope of this review. First, patients may continue to access orphan drugs via non-orphan-drug-specific policies and ad hoc requests. Some countries/areas have pathways that facilitate access to broader special drugs, including orphan drugs. Examples include Armenia (low demand but vital drugs), Brunei (drugs intended to treat serious or life-threatening conditions), Hong Kong and Turkey (named-patient basis), and Saudi Arabia (drugs addressed unmet medical needs). Yet, patients with rare diseases and foreign orphan drug suppliers may be required to navigate myriad time-consuming procedures to access orphan drugs if pathways are non-orphan drug-specific or if requests are processed on an ad hoc basis. Secondly, where resources are scarce, orphan drugs are unlikely to be accessible without appropriate policies. To facilitate timely patient access to orphan drugs, countries/areas may consider leveraging the WHO prequalification approval and parallel or twinned approval with the help of foreign competent authorities to uphold regulatory standards.<sup>36</sup> Countries/areas may subsidize patients' cross-border health treatment if the required treatment and expertise present too many barriers to import. Third, 7 countries/areas in our studies had no identifiable DRAs. Stepwise efforts should be made to assist these countries in setting up and strengthening the DRA. Regional ODP frameworks in the European Union and Central America are useful examples of how neighboring countries with similar rare disease epidemiology and patient needs can converge regulatory efforts for orphan drugs. Existing frameworks can be extended while designing specifications that incorporate their unique cultural, economic, health, and political backgrounds.

The methodology of our review was designed to overcome the limitations faced by previous reviews. First, previous reviews were limited to a selection of countries determined by authors based on geographical and socioeconomic diversity, and confined to publication and reporting biases.<sup>11-13</sup> In this study, we sought to obtain information from all countries by meticulously searching for evidence from direct governmental sources and systematic academic literature searches. Second, previous studies were limited to English publications, discounting the representativeness of the qualitative synthesis, particularly in many low- and middle-income countries/areas. To maximize the completeness of our narrative synthesis, non-English documents were translated to identify policies. One limitation of our study is that this review only examined ODP in 6 non-WHO member areas. Other non-WHO member-countries/areas with DRAs may be missed. Additionally, state- or province-level governmental evidence was not assessed, therefore within-country variations in policy development were not considered. Lastly, 33.1% (54 of 163) of drug regulation documents required translation to English, which could potentially incur minor inaccuracies during interpretation. Collaboration with experts from various countries and international organizations has helped to mitigate the last limitation.

Current ODP implementation is limited by a lack of robust evidence. Of note, landmark trials for orphan drugs are subject to single-arm, open-label study design with small sample sizes and inadequate long-term outcome assessment.<sup>37</sup> Uncertainties remain in the effectiveness and safety of orphan drugs in real-world settings. Therefore, future research that aims to establish rare disease registries, unbiased from industry influence, is important to collect reliable longitudinal data for the post-marketing effectiveness and safety evaluation of orphan drugs.<sup>38</sup>

Innovative solutions such as mining big data for adverse event information and the role of social media in pharmacovigilance should be explored.<sup>39</sup> Meanwhile, the impact of established ODP on patient access to treatment and patient outcomes requires comprehensive, rigorous evaluation.

## Conclusions

While observing the global growth of ODP establishment, drug authorities should be prepared to develop or refine current policies to optimize patient access to orphan drugs. In particular, policy improvements in the thematic areas of price regulation, incentives that encourage market availability, and incentives that encourage research and development are recommended to ensure affordability for payers with sufficient returns for manufacturers. Case practices and the results of policy implementation from countries/areas with ODPs will benefit those seeking to develop their own policies.

## Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2020.06.020>.

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