Title: Making Orphan Drugs and Services Available and Accessible for People Who Live with Rare Diseases: what has been done? A Systematic Scoping Review

Hesam Ghiasvand[a], Maxwell S. Barnish[b], Tayebeh Moradi[c], Elham Nikram[b] and Seyran Naghdi[d]

a. Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

b. Peninsula Technology Assessment Group (PenTAG), University of Exeter, Exeter UK

c. Department of Health Services Management, School of Health Management and Information Sciences, Iran University of Medical Sciences, Tehran, Iran

d. Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK

Abstract:

Objectives: Rare diseases are recognized as non-prevalent health disorders. Availability, accessibility, and affordability of Orphan Drugs (ODs), alongside genetic testing, are the major contributors to ensuring no patient is excluded by the health system. Therefore, making ODs available and accessible has been a challenge even for high-income nations. This review aims to summarize the evidence on the availability and accessibility of orphan drugs and other required resources for managing rare diseases.

Methods: The Joanna Briggs Institute scoping review method was used as the analytical framework. We searched Medline, and Embase through Ovid, and Web of Science. We used Guilford et al. [18] definition and classification of accessibility and its dimensions to synthesize the evidence.

Results: The majority of the final included evidence is about the financial, and then availability and physical accessibility to ODs. Furthermore, almost all the evidence comes from high-income countries.

Conclusion: The principal hurdles to the availability and accessibility of ODs and other related services are very high prices, lack of a legal framework, and budgetary impact on public funding. A lack of reimbursement mechanisms and lower availability of other resources are among other problems.

Keywords: Rare diseases, Orphan drugs, Availability, Accessibility, Systematic scoping review

1. Introduction

Rare diseases (RDs) are health problems and disorders that are characterized by their low prevalence in the population. There is no global consensus on definition of RDs. In the European Union (EU), health problems and disorders that affect no more than 5 in 10,000 people are defined as RDs, whereas in the United States (USA), conditions affecting fewer than 200,000 people overall are defined as RDs. Although there is no global consensus on the definition of RDs, by taking a rule of thumb, an approximate prevalence of 650 to 1000 per million population might be a commonly accepted threshold in this regard[1-3].

The Orphan Drugs (ODs) law in the USA introduced in 1983 is recognized as the first legislative and official governmental action to address the barriers facing pharmaceutical companies for investment in RDs. This was followed by other regions and countries around the world, as Japan passed the same law in 1993; whereas for the EU, it was in 2000[4].

Enacting these laws was a turning point in the management of RDs. Many countries launched their initiatives to increase public awareness about RDs, and the needs of PWLRDs. There have also been actions to incentivize pharmaceutical companies to be a part of the problem-solving agenda for RDs. Developing financing and reimbursement mechanisms, in addition to a shift from conventional economic evaluation methods as a part of health technology assessment (HTA) to more flexible and equity-oriented criteria, are among the actions that have been taken as a part of governmental commitments to making treatments for RDs available and accessible for People Who Live with Rare Diseases (PWLRDs). For instance, Medicare and Medicaid in the US and universal or near-universal insurance coverage in Japan and the EU reimburse the high cost of treatment of RDs[3].

There remain challenges due to the absence of legal and policy frameworks in many countries. These include the inadequacy of funding and low motivation of payers (especially insurers) to

reimburse expensive drugs[5]. In the US, spending on ODs increased from 4% to 10% from 1997 to 2017, which equates to $43 billion in 2017[6]. Approximately 7000 RDs affect approximately 20-30 million people in the USA; however, treatments are only available for 5% of them. As estimated in 2017, 449 ODs have been approved by the Food and Drug Administration (FDA)[7-9].

The situation is more problematic in developing countries, especially those not considered high-income nations. For instance, in China, it was found that if health insurers implement a 5% co-payment for PWLRDs, only three generic ODs would be affordable among middle-income patients. In China, more than 100 commercial insurers actively cover health costs. however, only approximately 5-10 ODs are reimbursed under these schemes[10, 11]. Financial coverage was granted for 20 RDs under the different available protection schemes in Chile in 2019. In Chile, the lack of professional genetic counselling is the main problem for the accessibility of ODs and services for PWLRDs[12].

A review of high-income European countries shows that in Belgium, approximately 78 ODs were available and accessible by the end of 2016, while in France, essential services and products may be reimbursed, including off-label products. In Germany and the Netherlands ODs are fully reimbursed. In Italy, ODs are provided by the NHS following the same coverage for all other medicinal products. In Romania, some genetic tests are provided to patients free of charge[13].

As access to ODs and services is an important factor in managing RDs and there is a need to know what has been done in this vital aspect of equity, this systematic scoping review aimed to summarize the evidence through a structured approach on availability and accessibility to ODs and services to manage RDs around the world.

2. Methods

The Joanna Briggs Institute (JBI) scoping review method was followed as the framework[14]. The JBI guidance explicitly provides a guideline for a systematic approach to all type of knowledge synthesis. That makes all the reviews to be conducted in a rigorous, transparent and trustworthy manner. The JBI framework includes all the aspect of a review process including identifying the research question, identifying relevant studies, study selection, charting the data, collating, summarizing and reporting the results and possibly consultation. Based on this guidance, to answer a specific question (or series of questions) all the reviews begin with the development of an a-priori protocol with inclusion and exclusion criteria that relate clearly to the objective and review question.

A comprehensive systematic scoping review was performed to summarize the evidence on the availability and accessibility of orphan drugs and other required resources for managing rare diseases, and provide a picture of where we are now? A standardised protocol was used for this review, but the protocol was not registered.

2.1. Identifying the research question

In the first stage of this review, the research question was identified based on the PCC (Population, Concept, and Context) elements. For the present research question, the population was all patients who live with rare diseases (PWLRDs); the concept was accessibility and availability either broadly understood or in their composite dimensions, including physical, financial, and acceptability), and the context was all health systems in which rare diseases and orphan drugs are managed.

2.2. Identifying relevant studies

Medline, EMBASE (both Ovid) and Web of Science were searched in June 2021. Initially we explored the Medical Subject Heading (MeSH) thesaurus through OVID for “rare diseases”, "orphan drugs”, “orphan diseases”, and “accessibility”. Then, an appropriate search strategy

was generated from the combination of different vocabularies for these terms and was adapted for each database. For this purpose, all related studies from 1983 (As the first act on ODs was passed in 1983 in the USA) to the search date were retrieved through the exact research strategy (Table 1). The search identified studies published in the English language.

Table 1. Search strategy and filters applied

2.3. Study selection

The selection of relevant studies was carried out according to the JBI approach, Figure 1. Two members of the research team performed this step independently, and any discrepancies were addressed by consensus or by conferring with a third reviewer. Studies on the following topics were eligible for inclusion: policies, plans, acts, legislations, incentives and encouraging actions, financing and reimbursement mechanisms, private/commercial or compulsory/public insurers, charities, and public population initiatives, and benefits packages to ensure the accessibility of ODs and services for PWLRDs were included. Studies not on PWLRDs (for instance: studies on carers/parents of PWLRDs) were excluded. Letters to the editor, commentaries, non-systematic narrative reviews, suggestions, perspectives, calls for national or global actions, and case reports were also excluded. We used quality assessment tools developed by Joanna Briggs Institute for qualitative, cross-sectional, and systematic reviews[15-17].

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the scoping review process

2.4. Charting the data

Data from included studies were independently charted by two independent reviewers. Any discrepancies were resolved by consensus or by discussing with a third reviewer. Standardised data extraction forms were used and can be found in Additional file (1) in the appendix. Data

extracted included study characteristics (authors, year of publication, country, objective, study design, subjects/participants, data collection method, data analysis methods), study results, and study authors' conclusions, can be found in Additional file (1) in the appendix.

2.5. Collating, summarizing, and reporting the results

In this final stage of the analysis process, Guilford et al.'s access to health care services concepts[18] were used to synthesise the results. This framework defines access as a complex concept that needs to be considered not only in terms of the availability of resources and facilities. A such, Guilford et al [18] proposed three dimensions of access: physical accessibility, financial accessibility (affordability), and acceptability of the services by the population of interest. In light of this definition, included studies were sorted into four groups:

- Studies on the availability and physical accessibility of ODs or services for RDs;
- Studies on the financial accessibility (affordability) of ODs or services for RDs;
- Studies on the acceptability of ODs or services for RDs;
- Studies on developing the capacity for making ODs or services accessible for RDs

In addition, results from the included studies were tabulated in terms of the design, country, year of publication, tier of study regarding accessibility dimension, study level (regional, national, international) as well as study outcomes of interest (legislation, drug market regulation, developing/investing in capacity, accessibility of ODs, affordability of ODs, availability of resources, ethical issues, economic evaluation/HTA considerations, patients' or their representatives' voice, equity/equality in utilizing the ODs). After this, considering the accessibility concept from Guilford et al. [18], a narrative description of the results of the evidence for each category of accessibility was used. As no studies has assessed the acceptability of ODs or services for PWLRDs, no analysis was conducted for this domain.

3. Results

In this scoping review, the search identified 1582 studies. Following the critical appraisal process, 38 studies were eligible for inclusion.

3.1. Study profile

Table 2 shows the characteristics of the included studies.

Table 2. Study characteristics

As shown in Table 2, most of the studies were cross-sectional and comparative. Most evidence comes from high-income countries, so studies from the USA, Canada, Belgium, and Spain constitute slightly more than 50% of the evidence. Almost all of the studies were conducted in the period 2016 to 2020, and the majority were conducted at the national level. The financial accessibility or affordability of ODs or RD services forms 47% of the outcomes of interest among studies, followed by availability and physical accessibility.

A summary of the studies based on the four dimensions of accessibility is provided below:

3.1.1. Availability & physical accessibility

14 studies addressed this dimension:

- Roll (2012)[19] in Germany concluded that the density of physicians, especially cardiologists/algologists, has a significant negative association (p=0.0097) with delays in diagnosing Marfan syndrome.
- Lexchin (2020)[20] in Canada emphasized the necessity of adopting a different policy than Australia to provide faster access to ODs.
- Blankart et al. (2011)[21], through their comparative study of 11 countries, concluded that the speed of the authorization process (the time between application and market authorization) was the fastest in the US, with an average of 362 days, followed by the EU (394 days).

- Baran-Kooiker et al. (2018)[22] highlighted the variation in the number of registry centres for RDs between the Netherlands, Poland, and Russia and the important role of a high number of these centres in identifying PWLRDs and then having a health technology assessment facility in place for assessing the ODs.
- Kamusheva et al. (2018)[23] discussed the availability of developed pharmacoeconomic guidelines with or without specific reimbursement requirements for orphan medicinal products in several Central and Eastern European countries (CEECs). They concluded that some CEECs require comprehensive structures to facilitate reimbursement decisions on ODs.
- Meng et al. (2019)[24] found a need for legal changes for availability: free active helplines to assist PWLRDs and their families regarding their health, psychological, and social needs.
- Yan et al. (2020) [25] in China stated that the socioeconomic dimension of difficulties in accessing a definitive diagnosis of rare diseases should be addressed, especially the uneven distribution of high-quality healthcare and disadvantaged patients.
- Merker et al. (2018)[26] in the US found that the median driving distance to the nearest network clinic was 51.3 miles for patients with neurofibromatosis (NF).
- Lichtenberg (2013)[27] found that in the USA, potential years of life lost to rare diseases before age 65 (PYLL65) declined at an average annual rate of 3.3% and that, in the absence of lagged new drug approvals, PYLL65 would have increased at a rate of 0.9%.
- Herder et al.'s (2016)[28] found that regulatory access to US-approved orphan drugs in Canada increased to 74% between 1997 and 2012. However, temporal access to orphan drugs is slower in Canada.

- Hyry et al. (2015)[29] demonstrated that legal and ethical arguments could be applied to encourage manufacturers to offer therapies. For example, a French program expedited treatment for more than 20,000 (orphan and non-orphan) patients over a period of three years.
- Bourdoncle et al. (2019)[30] argued that the median period between granting European marketing authorization and publication of the reimbursement decision was 360 days. The broadest availability—through community pharmacies—was guaranteed in only 31.1% of cases. Prescriptions were mainly restricted either to hospital-based doctors or to specialists.
- Koçkaya et al. (2021)[31] found that of the 105 rare drugs on the European Medical Agency (EMA) list, 34 were inaccessible in Turkey. Of the 71 available drugs, 23 (32%) were licensed and 48 (68%) were unlicensed in Turkey.
- Mestre-Ferrándiz et al. (2020)[32] discussed the EMA's approval of 100 orphan medicines (with a designation of 31/12/2017) between 2002 and 2017. Eighty-six have a national code (NC) assigned by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Fifty-four were launched in Spain (representing 54% of the full sample; 63% with NC). For the 53 orphan drugs with launch dates in Spain, the median time between receiving NC and its launch was 13.4 months (standard deviation: 17.0; minimum: 2.1; maximum: 91.7). The median time is 12.4 months and 14.0 months for those medicines launched in Spain.

3.1.2. Financial accessibility (affordability)

Tackling financial barriers to achieving ODs and services for PWLRDs has been investigated in 18 studies as follows:

- Denis et al. (2010)[33], in their comparative study, found that treatment is free of charge at point of use in Sweden and the UK but has a fixed price in Belgium, France, Italy, and the Netherlands. The reimbursement is provided by the NHS in Italy and the UK but in Belgium, Sweden, France, and the Netherlands by social insurance. Except for Belgium, in the other countries, the reimbursement is based on cost-effectiveness analyses; however, reimbursement is also based on the budget impact in all countries except Sweden.
- Pejcic et al. (2018)[34], in their comparison of Balkan countries, found that Greece had the highest number of reimbursed orphan drugs (n = 45). Not a single orphan drug was reimbursed in Montenegro. By February 1, 2017, the mean access delay for these 29 therapies was 788 days, ranging from 49 days for Ocaliva® to 2994 days for Ceplene®.
- Kanters et al. (2018)[35] concluded that there were large differences in patient access to ultra-orphan drugs among countries in terms of pricing and reimbursement mechanisms.
- Zelei et al. (2016)[36] found that due to external price referencing of pharmaceuticals, the relative budget impact of orphan drugs is expected to be higher in CEE than in Western European (WE) countries unless accessibility of patients continues to be more limited in more economically disadvantaged European regions.
- Yehia et al. (2020)[9] in the USA found that ODs with annual costs of $50,000 or more had twice the odds of having prior authorization requirements compared with less expensive ones for fee-for-service mechanisms within Medicare Part D.
- Chambers et al. (2019)[6] concluded that in the USA different private health plans across the country are less likely to restrict ODs than non-ODs.

- DuPont et al. (2010)[37] concluded that in Belgium, twenty-two of 25 (88%) submissions for orphan drugs were approved for reimbursement compared to 74 of the 117 (63%) non-orphan innovative medicines.
- Chua and Conti (2018)[38] concluded that in the USA, out-of-pocket spending on orphan drugs may have risen since 2014, potentially exacerbating access barriers among patients undergoing treatment for rare diseases with few therapeutic alternatives.
- Chambers et al. (2019)[6], using multivariate regression, found that several drug-related factors were associated with less restrictive coverage, including indications for orphan diseases or paediatric populations, an absence of safety warnings, time on the market, lack of alternatives, and expedited FDA review.
- Lee et al. (2020)[39] found that in South Korea, as many orphan drugs have not yet been deemed reimbursable after approval, a reimbursement policy should be established that considers the characteristics of orphan drugs.
- Robinson et al. (2014)[7] concluded that in the USA, select drugs identified as the only FDA-approved product indicated for a certain rare disease achieved relatively robust coverage (at least 65% of plans) but often included some form of utilization management.
- Kuester et al. (2019)[40] in the USA demonstrated that families with a child with a rare disease remained with their commercial health insurer longer than families who did not have a child with a rare disease.
- Lopata et al. (2021)[41] in the USA found that cost considerations are prominent factors in determining whether orphan drugs will be covered under the pharmacy or medical benefit and how providers will acquire orphan drugs.

- Gammie et al. (2015)[42], in a comparative study, concluded that access to orphan drugs depends on an individual country's pricing and reimbursement policies, which vary widely between countries. High prices and insufficient evidence often prevent orphan drugs from meeting the traditional health technology assessment criteria, especially regarding cost-effectiveness, which may restrict access.
- McCormick et al. (2018)[43] found that over time, there has been an increase in common drug review (CDR)-positive recommendation rates for orphan drugs, although most are conditional on a price reduction. It is unclear whether this change in CDR recommendations will impact equitable and timely access to orphan drugs across Canada.
- Gong et al. (2016)[10] in China found that within a periodic treatment course, the average treatment cost of 23 orphan drugs is approximately 4,843.5 USD, which equates to 505.6 days of per capita net income for an urban resident with a middle income (187.4 days for a high-income urban resident) or 1,582.8 days of income for a rural resident with a middle income (657.2 days for a high-income rural resident).
- Min et al. (2019)[44] in China found that healthcare insurance is an effective safeguard for patients with rare diseases; however, affordable and accessible treatment is still lacking for such patients.
- McGuire (2019)[45] in Canada concluded that the social resource allocation in an affluent context like Canada indicates that theorizing about health care access must go beyond the simplistic premise of "health care for all." There are deep questions to be explored about the different visions of accessibility, value, and belonging of people those who work within and on the health care system in various modalities.

3.1.3. Studies on building capacity for making ODs or services accessible

This category of evidence explores the studies that have been performed to seek the opinions, thoughts, and ideas of experts, and the public, on making ODs or services available, along with physical and financial access. They may have insightful implications for policymakers to design and implement appropriate policies, regulations, and plans for ODs.

- Torrent-Farnell et al. (2018)[46] suggested developing a roadmap for making ODs accessible in Spain that requires networks and establishing a dialogue among stakeholders. The European recommendations could be introduced at both the national and regional levels .
- Bae et al. (2020)[47] concluded that, although people in the South Korea advocate for the idea that rare diseases should have an allocated budget, they don't perceive rare diseases are as important as more common diseases.
- Bourke et al. (2018)[48] concluded that the UK general public does not value rarity as a sufficient reason to justify special consideration for additional NHS funding of orphan drugs.
- Leandro et al. (2014)[49] concluded that there is a general lack of knowledge about the selection of patient cases that should be sent for genetic counselling or molecular testing of HFE-HH by Portuguese physicians (especially by general practitioners). The lack of family-based screening may indirectly compromise the efficiency of disease prevention in terms of early diagnosis and treatment.
- Berdud et al. (2020)[50] concluded that the NICE incremental Cost-Effectiveness Threshold (CET) (£20 K per QALY) is an anchor for developing the ODs. They estimated the adjusted reasonable CET for orphan drugs to be £39.1 K per QALY at the rare diseases population cut-off and £78.3 K per QALY at the orphan population midpoint. For ultra-orphan drugs, the adjusted CET was £937.1 K.

- Picavet et al. (2012)[51] concluded that it is important to reduce country-dependent inequalities in patient access to orphan drugs. Therefore, they advocate regulating the compassionate use of orphan drugs at the European level. Negotiations with pharmaceutical companies and access to unauthorized drugs would still be facilitated.

3.2. Narrative synthesis

This section narratively synthesises the findings of the review in five parts: the descriptive findings, the findings of physical accessibility and availability of ODs, the findings of financial accessibility of ODs, findings of acceptability of ODs, and findings of developing the capacity for availability and financial accessibility of ODs, moving away from the particularities of individual studies as listed above and towards generalities across studies.

3.2.1. Descriptive findings

Availability and accessibility to ODs and services for PWLRDs need to be a part of tackling the health inequalities agenda, not only in low- and middle-income countries but also in high-income countries. Tracing the clues shows that despite the well-established agenda, policies, and plans for health equity, the problems of availability of resources, accessibility and utilization of ODs, and services for PWLRDs are apparent. The history of considering the equity concerns about the ODS suggests that there have been serious considerations about availability and accessibility since 2005.

Also, the evidence base focuses mainly on high-income countries. This might highlight the lack of priority of the issue among middle- and low-income countries, although China could be an exception in this regard. It seems there is a marked difference between high- and middle-income-countries. One potential reason for this could be lower economic and political capacity in middle-income countries. On the other hand, public campaign groups and networks (e.g., charities) are probably faced with more limitations in developing countries than high income

countries. Among other reasons could be differences in political will and inclination to hear the voices of PWLRDs and their households. However, what is evident is the considerable difference between countries.

3.2.2. Physical accessibility or availability

The lack of an adequate supply of resources, particularly genetic and biotechnological advanced technologies, and the high costs of drugs and therapeutic interventions are central barriers to access to services. Pharmaceutical companies have less motivation to invest in expensive drugs with limited market potential. Moreover, clinical laboratories require high-tech equipment to diagnose RDs[52, 53]. This barrier goes beyond availability and physical accessibility of resources, as a lack suitable skilled (sub) specialists human resources compounds the problem for RDs. This could be alleviated with in-time detection and prescription of treatment regimens without delay[19].

Alongside these barriers, certain issues are receiving insufficient attention in terms of making ODs and services accessible for PWLRDs. Lack of a comprehensive registry for identifying and enrolling the patients and a lack of legislation for mobilizing social, community, and public capacities to come together to address the problem are among the more tractable issues[36, 51]. Government commitment through developing national strategies and policies plays a crucial role in this field. Developing national documents for RDs with a holistic approach that includes all stakeholders and then recruits actors has not yet become a policy agenda for many countries[54]. Even after developing the concept of universal health coverage (UHC) by the World Health Organization (WHO) and World Bank (WB) and a global effort to implement it, the issue of RDs and the necessity of making ODs and services accessible for PWLRDs have not received priority.

3.2.3. The financial accessibility or affordability of ODs

The problem of the unaffordability of ODs and related services for RDs is another common barrier for all countries. Highly expensive drugs for rare and ultra-rare diseases are a major challenge for all governments. There is no globally accepted definition of ultra-rare diseases, however, a prevalence of less than 1 per 50,000 persons (or fewer than 20 patients in a population of 1 million) has been cited by NICE in England [55-57]. This definition has been cited in the other studies [58,59]. Developing appropriate financing and reimbursement mechanisms requires a collective contribution from different stakeholders, including governments, charities, community-based organisations, pharmaceutical companies, and private insurers. There is no doubt if sustainable financial resources for providing ODs and services to PWLRDs are to be achieved, the government through its general budgets or a specifically allocated health budget must play the central role. However, at the same time, the government needs contributions from charities, communities, and the pharmaceutical industry. This could be achieved in part by the government incentivizing charities or pharmaceutical companies to address some of the issues[36, 60]. Tax exemptions and promoting the reputation of charities and pharmaceutical companies are among the positive actions that a government could undertake. In the case of low-income countries that are dependent on the import of ODs, governments face additional challenges relating to exchange rate changes and compensating importers for losses. Therefore, for such countries, governments need to formulate clear exchange policies.

Central to the reimbursement policy for ODs is how to pay for ODs and services for PWLRDs. Challenges include deciding the ceiling for payments, issues around co-payments, deciding how payments should be made and whether this should involve third parties and defining rules about who can prescribe and distribute the ODs. Countries differ in the approaches they take, and no one approach appears clearly superior. Indeed, it seems to depend on the nation's

macroeconomic condition and its government's capacity for control and monitoring of both supply and demand sides[42, 61, 62].

Nevertheless, adequate financial protection against the catastrophic and impoverishing impacts of RDs does not seem to be achieved in many countries. In terms of financing RDs, ethical considerations[10] are a key consideration. As the public budget is constrained on one side and there are plenty of unmet common health needs on the other side, allocating a highly constrained budget to a small part of the population may appear illogical. This ethical dilemma has been approached in different ways. For many policymakers, the focus should be on prevention and intensification of pre-birth screening and genetic testing. Therefore, they consider that the budget should be focused on this important aspect. Other countries have adopted a multicriteria health technology assessment approach to assess the value of such drugs and services for RDs. Indeed, they believe that equity-oriented considerations should have more weight than purely economic considerations. Therefore, they believe in developing multidimensional decision-making criteria to design a benefits package for RDs.

3.2.4. Acceptability of ODs

The acceptability of services as a component of accessibility was not covered in the included studies. RDs not only cause physical conditions, but also have important mental and social adverse effects. Due to resource and time pressures facing patients' households it is important to design services packages considering what is individually, culturally, and socially most appropriate. However, as stated, this dimension is often overlooked and deserves further attention. From a health economic view of point, performing discrete choice experiments that stem from the patient-centred care concept could be used to develop guidelines and protocols for PWLRDs by health systems.

3.2.5. Research of developing the capacity of accessibility of ODs

These efforts can make an important contribution to awareness, attitude, and also behaviours of the public and policymakers about access to ODs. This encompasses a range of topics regarding making ODs available, accessible, and affordable through an evidence-informed approach. For instance, exploring the views of the public about the financing of ODs and reimbursement is of such importance that policymakers also consider these aspects and have prepared convincing answers to stakeholders. Similarly, the translation of such knowledge to practice and the policy agenda is of considerable importance, although there are challenges with such evidence potentially being of limited interest to policy-makers in low-income countries.

5. Discussion

The present work presents a scoping review investigating what has been done to make ODs and services accessible for PWLRDs. Progress has been noted in many countries, but the extent of prioritisation afforded to ODs compared to more common diseases was shown to differ substantially between contexts. A series of barriers to improving access to ODs were identified. The principal hurdles to the availability and accessibility of ODs and other related services are very high prices, lack of a legal framework, and budgetary impact on public funding. A lack of reimbursement mechanisms and lower availability of other resources are among other problems.

The present study used a scoping review approach in order to systematically assess what evidence has been published that can address the research question. The review was conducted using standardised JBI[14] methods to minimise subjectivity and reviewer bias. Additionally, screening, data extraction and analysis procedures were conducted independently by two reviewers for this same reason. Scoping reviews are still considered an emerging methodology[63] and further methodological advancements are likely to emerge in the field in

the coming years. As scoping reviews do not undertake a risk of bias assessment[63], they cannot offer assurance of the quality of the evidence underpinning the findings and therefore serve to explore and seek to stimulate advances in the current state of the evidence, rather than offer absolutely definitive conclusions for practice. Understanding the exploratory nature of scoping reviews is essential to recognising their value and using their findings appropriately[64]. Only English language articles were eligible. This restriction was required for practical and logistical reasons. No studies assessed the acceptability of ODs or services for PWLRDs, so no analysis could be conducted on these aspects. Available evidence was not equally distributed across levels of economic development and the vast majority of evidence came from high-income countries. Studies were, however, generally fairly recent and many were cross-nationally comparative, offering valuable broader insight.

The present work benefits from considering countries across a range of levels of economic development. It was found across the identified evidence base that the extent of progress towards access to ODs and the barriers identified differed according to economic context. Country-specific studies may generate findings that reflect the particularities of the particular country and are not generalisable across contexts. For example, a study in Chile[12] identified a lack of professional genetic counselling to be the key barrier to accessibility of ODs and services for PWLRDs, a finding that was not replicated in the wider international evidence base. Therefore, international reviews such as the present work are better placed to capture generalities that transcend particular contexts, while valuing the insights offered by specific contexts and particularities relating to specific health and political systems and levels of economic development. A prior review using different methods offers valuable insights into the availability of ODs[13] but was limited to eight European countries at relatively high levels of economic development and did not explore in detail factors underlying differential access to ODs.

It is important to recognise that scoping reviews are not designed to identify mechanisms. Furthermore, it is important to be cautious regarding the implications of the findings[63], given the purpose of scoping reviews[64]. From an exploratory perspective, the present work emphasises the importance of governmental investment in ODs, either from central or more specific funds. Key areas that emerged in the analysis included political will, resources, access to specialist medical personnel, lack of registry data, affordability of ODs, cultural factors affecting how prioritising RDs would be perceived and the need for capacity building. Across studies, it was notable that settings differed in how they approached the prioritisation of RDs versus more common diseases. This may reflect different values that are being used to inform the prioritisation decision. After all, health care decision making and health technology assessment are values-based systems[65-66] and the values underpinning these can differ, including equity, procedural justice and market-based values. The concept of cost-effectiveness is central to many healthcare systems where there is a finite budget to allocate. Cost-effectiveness seeks to make best use of the available resources. If cost-effectiveness is measured purely in terms of for example an Incremental Cost Effectiveness Ratio (ICER)[67], as commonly used in decision making, the cost-effectiveness is typically poorer in RDs than more common diseases. Therefore, in some health systems, such as NICE, there are specific initiatives such as the Highly Specialised Technologies stream to appraise treatments for RDs where it is recognised that the clinical evidence may not be as extensive and where the ICER threshold is higher, indicating a tolerance of poorer cost-effectiveness. Prioritising ODs can be controversial[10, 42], as it entails prioritising expensive often less cost-effective treatments affecting a smaller number of people with severe RDs over people with more common conditions, due to the opportunity cost intrinsic in a health system with finite resources. Unless RDs are prioritised, in a system focused on cost-effectiveness, access to ODs is likely to be restricted.

The key unanswered questions include: i) the acceptability of ODs or services for PWLRDs, which were not addressed by any included studies, ii) a more definitive assessment of the mechanisms by which observed patterns of findings and effects may operate, iii) further assessment of the country- and health-system level factors such as political will, advocacy and inertia that may affect the generation and uptake of policy programmes designed to improve access to ODs and associated services, and iv) assessment of implementation science approaches to seek to address some of these barriers. The above could be considered to be priorities for future research. Realist methods[68] could be a valuable approach for the more detailed assessment of mechanistic factors.

6. Conclusion

Access in its different dimensions is an important driver for effective and efficient management of RDs and ODs. The issue of tackling accessibility barriers has been in the sight of policymakers for the past three decades. Almost all the evidence is from high-income countries. The main issue is associated with the more expensive ODs and diagnostic modalities for RDs, leading to financial accessibility to be of great importance for countries. In settings where resources for more prevalent diseases are limited, there has been insufficient resource to ensure access to treatments for PWLRDs. Therefore, these countries should adopt a supportive approach aligned with the World Health Organization's Universal Health Coverage framework to ensure no patients are excluded from the health care system even if they have a rare condition. Indeed, the most convincing way from the perspective of policymakers to make ODs accessible is stipulating UHC, rather than the logic that is used to finance and reimburse the prevalent diseases. Moreover, expanding global networks and campaigning for support for RDs and ODs can lead to improvements in awareness, attitudes, and behaviours by the public and policymakers in the short- and long-term.

List of Abbreviations

RDs: Rare Diseases

ODs: Orphan Drugs

PWLRDs: People Who Live with Rare Diseases

USA: United States of America

EU: European Union

CEECs: Central East European Countries

FDA: Food and Drug Administration

DCR: Drug Committee Review

NHS: National Health Services

UHC: Universal Health Coverage

WHO: World Health Organization

WB: World Bank

UK: United Kingdom

USD: United States Dollar

EMA: European Medical Agency

NC: National Code

AEMPS: Agencia Espanola de Medicamentos y Productos Sanitarios

PYLL: Potential Years of Life Lost

WE: Western European

PRISMA: Preferred Reporting Items Standard for Systematic Review and Meta-Analysis

MeSH: Medical Subject Heading

HTA: Health Technology Assessment

NICE: National Institute for Health and Care Excellence

QALYs: Quality Adjusted Life Years

CET: Cost-Effectiveness Threshold

R&D: Research and Development

Availability of data and materials: The present work is a systematic review and as such, all data are publicly available through the cited data sources.

Declaration of interest: The authors declare that they have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Authors' contributions: SN and HG initiated, conceptualized, and designed the study. SN performed the searches and drafted the initial version of the manuscript. HG, SN and TM all made equal contributions to the primary and critical appraisal of the retrieved records and finalizing of the manuscript. MSB contributed to the further interpretation of data, revised the manuscript for important scientific content and edited the manuscript for clarity and quality of English language. EN contributed to editing the methodology section and added definitions for some of the terminology. All authors take appropriate responsibility for the work undertaken and approve the manuscript for submission.

Funding: This paper was not funded.

References:

1. Rodwell, C. Aymé S. Rare disease policies to improve care for patients in Europe. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease1852(10), 2329-35 (2015).

2. Fagnan DE, Yang NN, Mckew JC, et al. Financing translation: Analysis of the NCATS rare-diseases portfolio. Science Translational Medicine 7(276), 276ps3 (2015).

3. Liu, BC, He L, He G, et al. A cross-national comparative study of orphan drug policies in the United States, the European Union, and Japan: towards a made-in-China orphan drug policy. Journal of Public Health Policy31(4),407-1 (2010).

4. Bagley N, Berger B, Chandra A, et al. The Orphan Drug Act at 35: observations and an outlook for the twenty-first century. Innovation Policy and the Economy19(1),97-137 (2019). ** This is a key work for understanding the policy context behind orphan drugs

5. Lucas, F. Improving market access to rare disease therapies: a worldwide perspective with recommendations to the industry. Medicine Access@ Point of Care2, 2399202618810121 (2018). ** This is a key work for understanding the global perspective on improving access to rare disease therapies

6. Chambers JD, Panzar AD, Kim DD, et al. Variation in US private health plans' coverage of orphan drugs. American Journal of Managed Care25(10), 508-12 (2019).

7. RobinsonSW, Brantley K, Liow C, et al. An early examination of access to select orphan drugs treating rare diseases in health insurance exchange plans. Journal of Managed Care Pharmacy, 20(10),997-1004 (2014).

8. Putkowski, S. The National Organization for Rare Disorders (NORD) Providing advocacy for people with rare disorders. NASN School Nurse 25(1),38-41 (2010).

9. Yehia F, Segal JB, Anderson GF. Predictors of orphan drug coverage restrictions in Medicare, Part D. American Journal of Managed Care26(9),e289-e94 (2020).

10. Gong S, Wang Y, Pan X, et al. The availability and affordability of orphan drugs for rare diseases in China. Orphanet Journal of Rare Diseases 11(1),1-12 (2016).

11. ChengA,Xie Z. Challenges in orphan drug development and regulatory policy in China. Orphanet Journal of Rare Diseases12(1),1-8 (2017).

12. Encina G, Castillo-Laborde C, Lecaros JA, et al. Rare diseases in Chile: challenges and recommendations in universal health coverage context. Orphanet Journal of Rare Diseases14(1),1-8 (2019).

13. Cannizzo S, Lorenzoni V, Palla I, et al. Rare diseases under different levels of economic analysis: current activities, challenges and perspectives. RMD Open4(Suppl 1), e000794 (2018).

14. Peters MDJ, Godfrey C, McInerney P, Munn Z, et al. Scoping Reviews (2020 version), in: JBI Manual for Evidence Synthesis, Munn Z, Aromataris E, Editors. JBI (2020). ** This is the key work explaining the JBI method that underpins the synthesis.

15. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk in: JBI Manual for Evidence Synthesis, Munn Z, Aromataris E, Editors. JBI (2020).

16. Lockwood, C., Z. Munn, K. Porritt. Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation. JBI Evidence Implementation13(3),179-87 (2015).

17. Aromataris, E., Fernandez, R., Godfrey, C.M., et al. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. JBI Evidence Implementation13(3),132-40 (2015).

18. Gulliford M, Figueroa-Munoz J, Morgan M, et al. What does 'access to health care' mean? Journal of Health Services Research & Policy7(3),186-8 (2002). ** This provides the key definition and classification of accessibility and its dimensions

19. Roll K. The influence of regional health care structures on delay in diagnosis of rare diseases: the case of Marfan Syndrome. Health Policy105(2-3),119-27 (2012).

20. Lexchin J,Moroz N Does an orphan drug policy make a difference in access? A comparison of Canada and Australia. International Journal of Health Services50(2),166-72 (2020).

21. Blankart CR,Stargardt T, Schreyögg J. Availability of and access to orphan drugs. Pharmacoeconomics,29(1), 63-82 (2011).

22. Baran-Kooiker A,Czech M, Kooiker C. Multi-criteria decision analysis (MCDA) models in health technology assessment of orphan drugs—a systematic literature review. Next steps in methodology development? Frontiers in Public Health 6, 287 (2018)

23. KamushevaM, Manova M, Savova AT, et al. Comparative analysis of legislative requirements about patients' access to biotechnological drugs for rare diseases in Central and Eastern European Countries. Frontiers in Pharmacology 9,795 (2018).

24. Joldic M, Todorovic J, Terzic-Supic Z. The needs of patients with rare disease in Serbia. Why do we need national strategy for rare disease? Health & Social Care in the Community27(5), e861-e70 (2019).

25. Yan X,He S, Dong D. Determining how far an adult rare disease patient needs to travel for a definitive diagnosis: a cross-sectional examination of the 2018 national rare disease survey in China. International Journal of Environmental Research and Public Health17(5), 1757 (2020).

26. MerkerVL, Dai A, Radtke HB, et al. Increasing access to specialty care for rare diseases: a case study using a foundation sponsored clinic network for patients with neurofibromatosis 1, neurofibromatosis 2, and schwannomatosis. BMC Health Services Research18(1),1-9 (2018).

27. Lichtenberg FR. The impact of new (orphan) drug approvals on premature mortality from rare diseases in the United States and France, 1999–2007. European Journal of Health Economics14(1),41-56 (2013).

28. Herder M, Krahn TM. Some numbers behind Canada's decision to adopt an orphan drug policy: US orphan drug approvals in Canada, 1997–2012. Healthcare Policy11(4),70 (2016).

29. Hyry H, Manuel J,Cox MT, et al. Compassionate use of orphan drugs. Orphanet Journal of Rare Diseases 10, 100 (2015).

30. Bourdoncle M, Juillard-Condat B, Taboulet F. Patient access to orphan drugs in France. Orphanet Journal of Rare Diseases14(1),1-9 (2019).

31. Koçkaya G, Atalay S, Oğuzhan G, et al. Analysis of patient access to orphan drugs in Turkey. Orphanet Journal of Rare Diseases 16(1), 1-8 (2021).

32. Mestre-Ferrándiz J, Iniesta M, Trapero-Bertran M, et al. Analysis of the evolution in the access to orphan medicines in Spain. Gaceta Sanitaria 34(2),141-9 (2019).

33. Denis A, Mergaert L, Fostier C, et al. A comparative study of European rare disease and orphan drug markets. Health Policy 97(2-3),173-9 (2010).

34. PejcicAV, Iskrov G, Jakovljevic MM, et al. Access to orphan drugs–comparison across Balkan countries. Health Policy122(6),,583-9 (2018).

35. Kanters, TA, Redekop WK, Hakkaart L. International differences in patient access to ultra-orphan drugs. Health Policy and Technology7(1),.57-64 (2018)

36. Zelei T, Molnár MJ, Szegedi M, et al. Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries. Orphanet Journal of Rare Diseases,11(1),1-11 (2016).

37. Dupont AG, Van Wilder PB. Access to orphan drugs despite poor quality of clinical evidence. British Journal of Clinical Pharmacology71(4),488-96 (2011).

38. Chua, K.-P., Conti RM. Out-of-pocket spending on orphan drug prescriptions among commercially insured adults in 2014. Journal of General Internal Medicine34(3),338-40 (2019).

39. Lee SH, Yoo SL, Bang JS, et al. Patient accessibility and budget impact of orphan drugs in South Korea: long-term and real-world data analysis (2007–2019). International Journal of Environmental Research and Public Health17(9),2991 (2020).

40. KuesterMK, Jackson EA, Runyan BM, et al. The effect of a pediatric rare disease on subscriber retention rates for commercial health insurers in the United States. Journal of Managed Care & Specialty Pharmacy25(2),186-95 (2019).

41. Lopata E, Terrone C, Gopalan A, et al. Meeting the affordability challenges posed by orphan drugs: a survey of payers, providers, and employers. Journal of Managed Care & Specialty Pharmacy27(6),706-13 (2021).

42. Gammie T, Lu CY, Babar ZUD. Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. PloS One10(10),e0140002 (2015).

43. McCormick JI, Berescu LD, Tadros N. Common drug review recommendations for orphan drugs in Canada: basis of recommendations and comparison with similar reviews in Quebec, Australia, Scotland and New Zealand. Orphanet Journal of Rare Diseases13(1),1-12 (2018).

44. Min R, Zhang X, Fang P, et al. Health service security of patients with 8 certain rare diseases: evidence from China's national system for health service utilization of patients with healthcare insurance. Orphanet Journal of Rare Diseases 14(1),1-18 (2019).

45. McGuire M. Paces of costly care: rare disease drug access in Canada. MedicalAnthropology39(4),319-32 (2020).

46. Pontes C, Fontanet JM, Vives R, et al. Evidence supporting regulatory-decision making on orphan medicinal products authorisation in Europe: methodological uncertainties. Orphanet Journal of Rare Diseases13(1),1-15 (2018).

47. Bae EY, Lim MK, Lee B, et al. Who should be given priority for public funding? Health Policy124(10), 1108-14 (2020).

48. Bourke SM, Plumpton CO, Hughes DA. Societal preferences for funding orphan drugs in the United Kingdom: an application of person trade-off and discrete choice experiment methods. Value in Health21(5),538-46 (2018).

49. Leandro B, Paneque M, Sequeiros J, et al. Insufficient referral for genetic counseling in the management of hereditary haemochromatosis in Portugal: a study of perceptions of health professionals requesting HFE genotyping. Journal of Genetic Counseling23(5), 770-7 (2014).

50. Berdud M, Drummond M, Towse A. Establishing a reasonable price for an orphan drug. Cost Effectiveness and Resource Allocation18(1),1-18 (2020).

51. Picavet, E, D. Cassiman, S. Simoens. Evaluating and improving orphan drug regulations in Europe: a Delphi policy study. Health Policy108(1),1-9 (2012).

52. Pohjola, P., Hedley V, Bushby K, et al. Challenges raised by cross-border testing of rare diseases in the European union. European Journal of Human Genetics24(11),1547-52 (2016).

53. Wouters OJ,McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA, 323(9),844-53 (2020).

54. Dharssi S, Wong-Rieger D, Harold M, et al. Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet Journal of Rare Diseases12(1), 1-13 (2017).

55. National Institute for Health and Clinical Excellence. NICE Citizens Council Report Ultra Orphan Drugs. London, NICE (2004).

56. Huges DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? Quarterly Journal of Medicine 98,829–36 (2005).

57. National Institute for Health and Clinical Excellence. Appraising Orphan Drugs. London, NICE(2008).

58. Sardella M, Belcher G. Pharmacovigilance of medicines for rare and ultrarare diseases, Therapeutic Advances in Drug Safety, 9(11), 631–8 (2018).

59. Harari S, Humbert M. Ultra-rare disease: an European perspective. European Respiratory Review29, 200195 (2020).

60. Czech M, Baran-Kooiker A, Atikeler K,et al. A review of rare disease policies and orphan drug reimbursement systems in 12 Eurasian countries. Frontiers in Public Health7,416 (2020).

61. Kawalec P, Sagan A, Pilc A. The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe. Orphanet Journal of Rare Diseases11(1),1-11 (2016).

62. Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. Intractable & Rare Diseases Research7(4), 213-22 (2018).

63. Khalil H, Peters MDJ, Tricco AC, et al. Conducting high quality scoping reviews - challenges and solutions. Journal of Clinical Epidemiology130,.156-60 (2021).

64. Tricco AC, Lillie W, Zarin KK, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Annals of Internal Medicine169,467-73 (2018).

65. Lehoux P,Blume S. Technology assessment and the sociopolitics of health technologies. Journal of Health Politics, Policy and Law25,1083-118 (2001).

66. Ten Have, H. Ethical perspectives on health technology assessment. International Journal of Technology Assessment in Health Care20(1), 1-6 (2004).

67. Bambha K Kim WR. Cost-effectiveness analysis and incremental cost-effectiveness ratios: uses and pitfalls. European Journal of Gastroenterology and Hepatology16 (6),519-26 (2004).

68. Pawson R, Greenhalgh T, Harvey G, et al. Realist review – a new method of systematic review designed for complex policy interventions. Journal of Health Services Research and Policy10(S1),21–34 (2005).

Table 1. Search strategy and filters applied

Identifying relevant studies
Databases: MedLine, EMBASE through OVID, and Web of Science (1983- 2021)
Limits: Only English language
Date: Up to 30/06/2021
Search strategy schematic form: #1 rare diseases OR orphan drugs #2 health services accessibility #3 health care access #1 AND #2 #1 AND #3

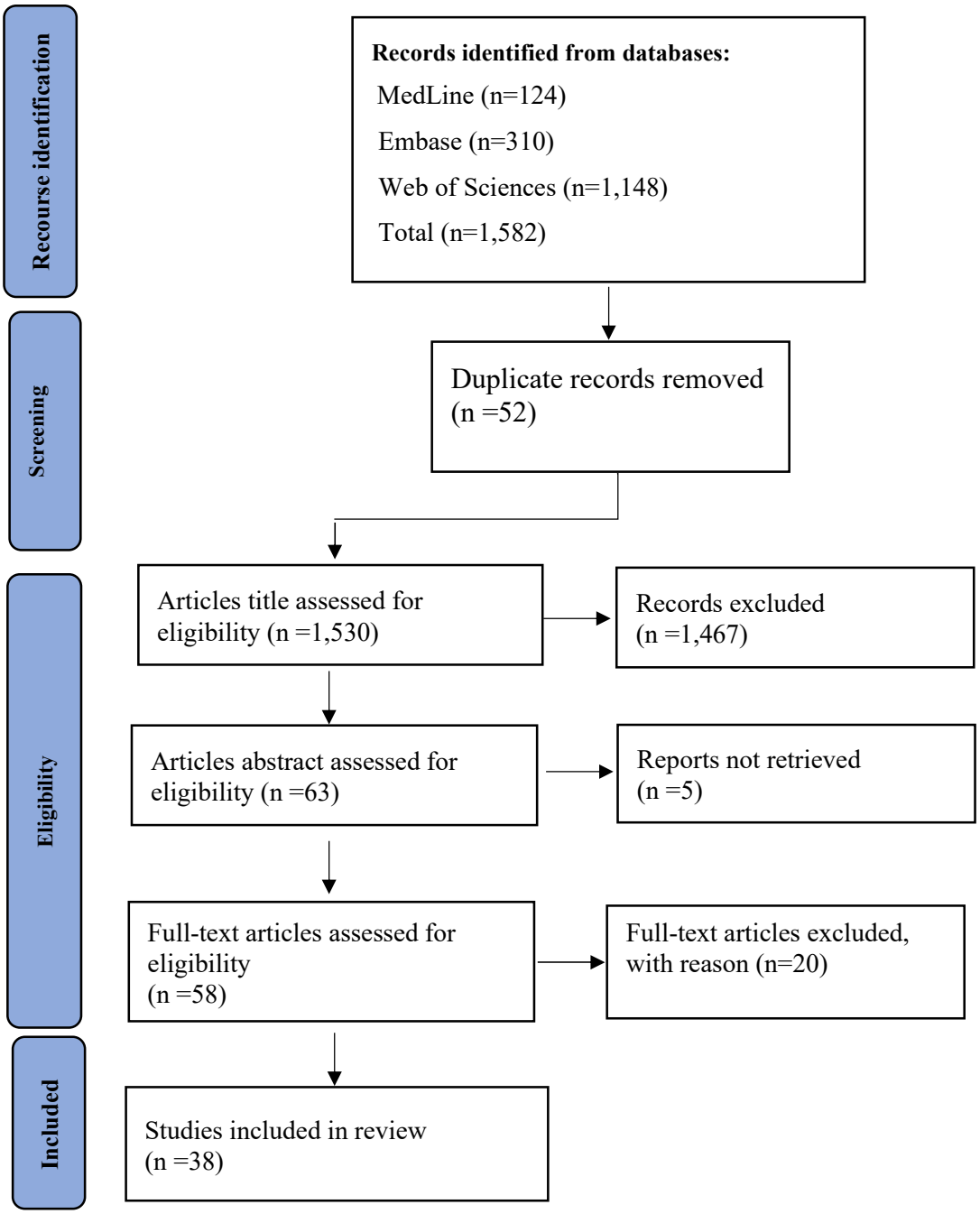

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the scoping review process

Table 2. Study characteristics

Characteristic	Frequency (%)
Study design:	
• Cross-sectional	17 (45)
• Comparative	10 (26)
• Qualitative	3 (8)
• Review	2 (5)
• Longitudinal	2 (5)
• (Review+ Qualitative)	1 (3)
• Cohort	1 (3)
• Health Economics	2 (5)
Country:	
• USA	9 (24)
• Canada	4 (11)
• China	3 (8)
• Spain	3 (8)
• Belgium	3 (8)
• UK	3 (8)
• Serbia	2 (5)
• South Korea	2 (5)
• Germany	2 (5)
• Netherlands	1 (3)
• Hungary	1 (3)
• Poland	1(3)
• New Zealand	1 (3)
• Portugal	1 (3)
• France	1 (3)
• Turkey	1 (3)
Year of Publication:	
• 1983-2005	2 (5)
• 2006-2021	36(95)
Dimension of Accessibility:	
• Availability & Physical accessibility	14 (37)
• Financial accessibility	18 (47)
• Acceptability	0.00 (0)
• Capacity Building on ODs Accessibility (e.g., research studies)	6 (16)
Study Scale:	
• Regional/Provincial	3 (8)
• National	21 (55)
• International	14 (37)
Countries by Income:	
• Upper Middle Income	3 (20)
• High Income	13 (80)

OD = orphan drug, UK = United Kingdom, USA = United States of America.