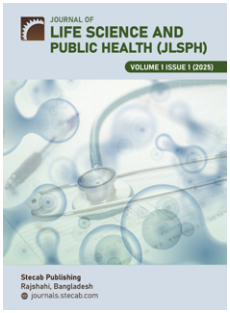

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Review Article

Orphan Drug Development for Rare Diseases: Therapeutic Challenges, Translational Strategies, and Global Health Equity

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ABSTRACT

Orphan drug development for rare diseases presents unique challenges that require targeted scientific, economic, and policy-based responses. With over 300 million individuals globally affected by rare diseases, the need for effective therapies is urgent. However, development is hindered by limited biological understanding, small patient populations, and difficulties in clinical trial recruitment. High research and development costs and inconsistent market incentives further discourage investment, especially in low- and middle-income countries (LMICs). Ethical concerns around access and affordability deepen disparities. To address these issues, legislative measures such as the U.S. Orphan Drug Act and similar policies in the EU and Japan offer benefits like market exclusivity and expedited regulatory review. Advances in genomic sequencing, artificial intelligence, and real-world data are enhancing diagnostics and drug discovery. Collaborative research models, adaptive trial designs, and decentralized clinical trials improve feasibility and inclusivity. Equity-driven frameworks such as tiered pricing and support for local manufacturing are critical to expanding access in LMICs.This article examines the interconnected challenges of orphan drug development and outlines evidence-based strategies to improve therapeutic innovation and global access. A coordinated, multisectoral effort is essential to ensure that the benefits of precision medicine and translational research extend beyond high-income countries and contribute to global health equity.

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1. INTRODUCTION

More than 7,000 rare diseases — defined in the United States as those that affect fewer than 200,000 people, and in the European Union have a prevalence of less than 1 in 2,000 people — together represent a substantial, though often overlooked, global health burden. Although rare, the combined burden is significant with a global prevalence of at least 300 million people. Many of these conditions are chronic, progressive, life-threatening disorders for which there is no cure and are commonly not diagnosed until very late in the disease process. (Iyer *et al.*, 2025).

Development of orphan drugs, medicinal products designed to treat rare diseases, has traditionally not been a priority for the pharmaceutical industry, given the lack of commercial market. Thus, patients and their families are frequently plagued by late diagnoses, few available treatments and significant financial burden. These challenges are particularly problematic in low- and middle-income countries (LMICs) where healthcare systems are likely to be poorly prepared to manage the heterogeneity and complexity associated with RDs, thus contributing to the existing global health inequities. (Chung *et al.*, 2022).

Challenges notwithstanding in this regard, studies of rare diseases are coming to be appreciated exactly for their broader scientific impact(Elechi *et al.*, 2025). Unraveling mysteries of rare diseases has yielded clues about more common disorders and has pushed the development of genetic and precision medicine technologies. However, there are still unaddressed aspects in the development, financing and accessibility at different economic and regulatory levels of the orphan drugs. (Ko, 2024).

This article aims to fill this gap by providing an overview of the present orphan drug development landscape. The article examines the barriers to scientific, economic, regulatory, and ethical progress, and new approaches that are arising to address them. Particular focus is on the differences between high-income and LMIC contexts to identify a path towards more equitable and more sustainable solutions in rare disease therapeutics. The purpose of this broad review is to contribute to a more inclusive, globally-sensitive model for orphan drug development (Ko, 2024).

2. LITERATURE REVIEW

2.1. Challenges in orphan drug development

2.1.1. Scientific and clinical barriers

The development of orphan drugs is frequently first impeded by substantial clinical and scientific constraints. Because rare disease patient groups are typically tiny, it is challenging to get solid biological data, which makes it challenging to completely comprehend disease mechanisms or pinpoint potential treatment targets. Many times, the disease's natural history is not well described, which makes it difficult to create validated outcome measures or useful clinical trial endpoints (Yoo, 2024). Moreover, the absence of dependable animal models further complicates preclinical research. The basic biomarkers required for diagnosis, illness monitoring, and medication response evaluation are absent in many rare disorders. Research in its early stages is significantly at risk due to this scientific ambiguity. Another challenge is finding patients for clinical studies. Multinational, multicenter investigations, which are expensive, logistically challenging, and frequently impractical in areas with inadequate diagnostic infrastructure, are required due to the worldwide dispersion of patients (Domínguez-Oliva *et al.*, 2023).

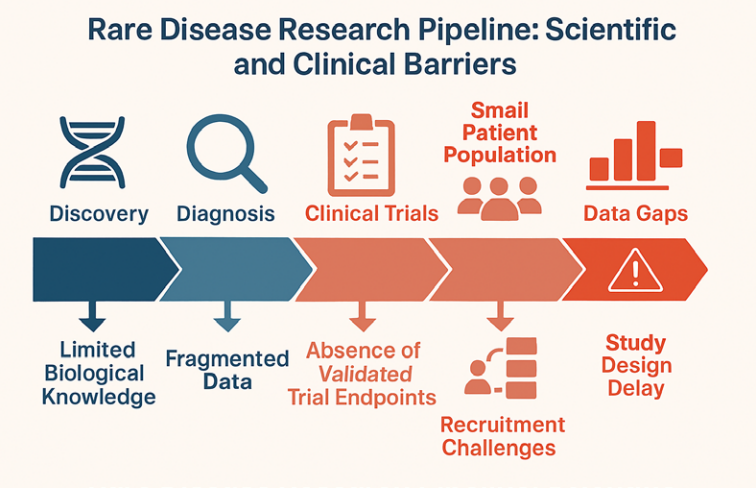

Figure 1. The rare disease research pipeline is often constrained by limited biological knowledge, fragmented patient data, and the absence of validated trial endpoints. These challenges slow therapeutic discovery and complicate study designs.

2.1.2. Economic and commercial hurdles

From a commercial standpoint, the economic paradigm for orphan drug research is essentially restricted. The high expenses of medication discovery, preclinical validation, and clinical trials are difficult to justify given the tiny market size and low revenue potential. Companies confront unpredictable routes to market access even if scientific achievement is attained since pricing and reimbursement policies differ greatly between jurisdictions and might not sufficiently incentivize innovation (Althobaiti *et al.*, 2023).

Significant market entry threats are another issue that pharmaceutical companies must deal with. There is no assurance of regulatory approval or commercial acceptance, and investing in orphan medications comes with significant upfront costs and lengthy timescales. Additionally, after approval, investor trust may be damaged by pricing pressures and public scrutiny, especially about expensive medications. The lack of trustworthy reimbursement and procurement systems in LMICs discourages corporate participation even more (Aartsma-Rus *et al.*, 2021).

2.1.3. Ethical and access issues

The development of orphan drugs presents a complex ethical environment. High-income nations and LMICs have glaringly different access to diagnosis and treatment, with the former suffering from inadequate healthcare infrastructure, low awareness, and delayed diagnosis. In environments with limited resources, access to novel treatments is slowed down by regulatory obstacles and inadequate harmonization (Adachi *et al.*, 2023).

A more profound ethical issue is when profit is put before of patient needs. The exorbitant price of many orphan medications presents challenging issues about justice and affordability in global health. Although businesses may use R&D expenditure to support price, this frequently results in limited access for the same patients these treatments are meant to help. In addition to scientific advancement, moral clarity, and legislative reform are necessary to address these disparities (Risse *et al.*, 2024).

2.2. Incentives for orphan drug development

2.2.1. Regulatory incentives

Orphan drug development has changed significantly as a result of regulatory regimes. Enacted in 1983 to encourage pharmaceutical companies to invest in therapies for rare diseases that previously had low financial returns, the U.S. Orphan Drug Act is a seminal policy. More than 600 orphan medications have been approved since the law's inception, compared to less than ten in the ten years before (Gabay, 2019). This accomplishment served as inspiration for the global adoption of comparable frameworks. By introducing the orphan legislation in 2000, the European Union provided a number of advantages, including as reduced fees, a ten-year market exclusivity period, and scientific advice from the European Medicines Agency (EMA). These advantages are reflected in Japan's regulatory framework, which also helps businesses by providing subsidies and expedited approvals. As global momentum grows, orphan drug rules have also been implemented in South Korea, Australia, and Canada (Aartsma-Rus *et al.*, 2021).

These frameworks all share regulatory incentives, including as fee exemptions, accelerated regulatory processes, seven to ten years of market exclusivity, and protocol support. These steps offer a more predictable route from bench to bedside and drastically lower entry barriers for developers, particularly small and mid-sized biotechnology companies (Ayati *et al.*, 2021).

2.2.2. Financial and commercial incentives

A variety of financial incentives have been created to lower the economic risk of developing orphan drugs in addition to regulatory support. In the United States, businesses can access federal research funds through the FDA's Orphan Products Clinical Trials funds Program and get tax credits that cover up to 25% of qualified clinical trial expenses (FDA Orphan Products Clinical Trial Grants: Assessment of Outcomes and Impact on Rare Disease Product Development - PubMed, n.d.).

The Priority Review Voucher (PRV) scheme, which provides a transferable voucher upon approval of medications for specific rare pediatric or tropical conditions, is one of the most profitable mechanisms. These vouchers, which can occasionally bring in hundreds of millions of dollars, can be offered to other businesses looking for accelerated FDA approval (Olliaro & Torreele, 2024).

Additionally, models of venture philanthropy and public-private partnerships (PPPs) have surfaced to stimulate early-stage research. These collaborations share risk, pool resources, and frequently prioritize unmet medical needs over short-term profit, making them critical contributors to the orphan drug pipeline (Rodrigues, 2023).

2.2.3. Global policy and advocacy support

The landscape of orphan drugs is being shaped more and more by advocacy networks and international health organizations. In a move toward broader inclusion in global health agendas, the World Health Organization (WHO) has started adding medicines for uncommon diseases to its Essential Medicines List (Costa *et al.*, 2024).

Rare illness action plans, which include registries, diagnostic programs, and specialized financing sources, are being adopted by national governments. These regulations assist establish national research priorities, enhance early diagnosis, and make epidemiological monitoring easier (Boulanger *et al.*, 2020).

Equally significant are patient advocacy groups and non-governmental organizations (NGOs), which offer vital assistance through active participation in policy lobbying, fundraising, and awareness campaigns. In LMICs, where institutional neglect of rare diseases continues and grassroots mobilization frequently serves as the impetus for legislative change, their activities are particularly crucial (Patterson *et al.*, 2023).

2.3. Emerging strategies and innovations

2.3.1. Advances in technology

Recent developments in technology are revolutionizing the field of rare diseases by facilitating quicker diagnosis and more accurate treatment targeting. The diagnostic procedure has been transformed by genomic sequencing, specifically whole-exome and whole-genome sequencing, which is especially useful for illnesses with a genetic basis. These techniques not only speed up clinical decision-making but also uncover new pharmacological targets, opening the door for customized therapies. Diagnostic yields in undiagnosed patients can exceed 30–40% (Ngoumou & Feudjio, 2024).

In uncommon diseases where de novo drug discovery is still expensive and time-consuming, artificial intelligence (AI) and machine learning (ML) are becoming increasingly effective methods for repurposing existing medications. Preclinical timescales can be greatly shortened by using AI platforms

to evaluate complicated biological datasets, find candidate compounds, and model therapeutic effects in silico (Visan & Negut, 2024).

Furthermore, continuous monitoring of uncommon illnesses outside of clinical settings is now possible because to real-world data (RWD) gathered from wearable technology and electronic health records. By offering more detailed phenotypic data, these techniques improve clinical trial design, improve longitudinal illness tracking, and offer real-time insights into therapy When combined, these tools provide a more patient-centered, dynamic approach to managing uncommon diseases efficacy (Ming *et al.*, 2020).

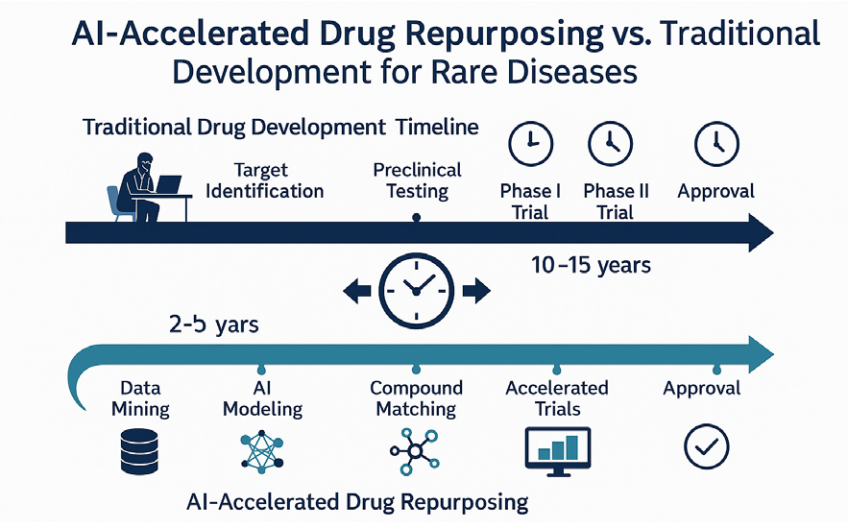

Figure 2. Artificial intelligence platforms are streamlining rare disease drug discovery by enabling rapid identification of candidate molecules and simulating therapeutic responses, thereby reducing time and cost.

2.3.2. New models of drug development

Because uncommon diseases are fragmented and resource-constrained, traditional drug development approaches are not well suited for them. As a result, cooperative consortia like E-Rare and the International Rare Diseases Research Consortium (IRDiRC) have formed, uniting patient organizations, industry, and academia to spur innovation through shared data and pooled funding (Austin *et al.*, 2018).

Open-source projects and pre-competitive research platforms are becoming more popular, enabling stakeholders to work together on early-stage research without being influenced by the commercial world. These models encourage openness, cut down on redundancy, and establish a common platform for businesses to build intellectual assets (Junaid *et al.*, 2022).

To address the difficulties associated with small patient cohorts, novel trial designs such as umbrella trials, adaptive trials, and basket trials are also being used. These designs enable simultaneous testing of several medicines across various mutations or illness categories, as well as flexible adjustments based on interim findings. This method preserves scientific rigor while increasing trial efficiency (Renfro & Sargent, 2017).

2.3.3. LMIC-focused strategies

Addressing uncommon diseases in low- and middle-income countries (LMICs) requires specific policies that focus affordability, accessibility, and local capacity-building. Cost-effective diagnostic technologies, such as point-of-care genetic testing, can drastically shorten diagnostic delays. Furthermore, decentralized clinical trials—which employ telemedicine, mobile health units, and regional hubs—enable greater involvement while reducing the need for centralized infrastructure (Fuhrer *et al.*, 2024).

Efforts to encourage technology transfer and local manufacture, such as voluntary patent pooling, can reduce reliance on high-cost imports. Finally, investments in regulatory harmonization, data systems, and rare disease registries are critical to providing a conducive climate for long-term research, development, and equitable access (Medicines Patent Pool, 2025).

2.4. Case studies

2.4.1. Successful orphan drug examples

The therapy of Spinal Muscular Atrophy (SMA), a rare neuromuscular condition that mostly affects newborns and young children, has seen two of the most important advances in orphan drug research (Crisafulli *et al.*, 2023).

In 2016, Biogen's spinraza (nusinersen) became the first SMA treatment to receive FDA approval. As an antisense oligonucleotide, it increases the production of survival motor neuron (SMN) protein, which is lacking in SMA patients, by altering the splicing of the SMN2 gene. Clinical studies demonstrated that Spinraza, particularly in infantile-onset SMA, changed the normal course of the disease, increased survival, and markedly improved motor function. The drug's approval promoted greater investment in the research and confirmed the promise of molecular precision medicines in rare diseases (Neil & Bisaccia, 2019).

Novartis created Zolgensma, a single-dose gene therapy that uses an adeno-associated viral vector to deliver a functional copy of the SMN1 gene. With its FDA approval in 2019, Zolgensma offers a long-term, potentially curative, and revolutionary

intervention. However, there was a lot of debate around its price, which exceeded $2 million per dose. Although high-income countries' insurance have offered coverage, LMICs still cannot access the therapy to a great extent. This case raises important issues regarding worldwide access, pricing transparency, and the viability of gene therapy models in public health systems. It also serves as an example of the ongoing conflict between innovation and equity (Mahajan, 2019).

2.4.2. National policy approaches

There are significant variances in national policy responses to rare diseases, which are a reflection of variations in political will, economic ability, and healthcare infrastructure.

A long-awaited step toward systematizing support for patients with uncommon disorders was India's National Policy for uncommon Diseases (2021). The policy offers a structure for national centers of excellence, diagnostic, and treatment funding. Additionally, it describes a crowdsourcing platform to help patients who need costly treatments (Vinekar & Jayadev, 2022).

The program has been criticized, nevertheless, because of its limited coverage of diseases, unclear timetables, and insufficient funding, especially when it comes to expensive orphan medications. Many patients continue to experience limited access to treatment and delays in diagnosis due to varied implementation across jurisdictions (Shafie *et al.*, 2020).

On the other hand, by incorporating uncommon diseases within their universal health care (UHC) plans, nations like Thailand and Brazil have achieved noteworthy progress. Protocols for the identification and treatment of particular rare diseases are part of Brazil's Unified Health System (SUS), which is backed by a legal framework that guarantees access as a fundamental right. With the help of foreign funders and local manufacturers, Thailand has also used its UHC platform to promote screening and subsidized treatment for several uncommon diseases (Gilardino *et al.*, 2022).

These instances demonstrate that, with robust legal and advocacy frameworks, state-led rare disease care is feasible even in middle-income environments.

In the meanwhile, strong policy environments support rare diseases in the US and the EU. These areas are now world leaders in the development and accessibility of orphan drugs thanks to centralized regulatory frameworks, consistent government financing, and significant civil society involvement. Both the U.S. Orphan Drug Act and the European Medicines Agency's orphan drug legislation are industry standards that have supported hundreds of approvals and act as models for developing nations (Patterson *et al.*, 2023).

2.4.3. International partnerships

Cross-border collaboration has emerged as an important pillar in resolving the complex problems faced by rare diseases, particularly given their low prevalence and dispersed patient populations. Rare Diseases International (RDI), the National Organization for Rare Disorders (NORD), and EURORDIS (Rare Diseases Europe) are three major international organizations that bring together patients, researchers, and policymakers. These platforms advocate for consistent regulations, provide access to diagnostics and therapies, and make it easier to share research data and clinical best practices across borders (Krishnaraj & Rajasimha, 2024).

Partnerships in therapeutic research and diagnostics are also becoming more popular because to initiatives like the Global Antibiotic Research and research Partnership (GARDP), the Drugs for Neglected Diseases initiative (DNDi), and the Foundation for Innovative New Diagnostics (FIND). These organizations are currently working in rare illness areas where there are little financial incentives, notwithstanding their initial focus on neglected infectious diseases. Their initiatives to provide low-cost, LMIC-appropriate solutions—such as diagnostic platforms and repurposing off-patent drugs—emphasize the importance of non-profit innovation methods in advancing global health equity (Iskandar *et al.*, 2022).

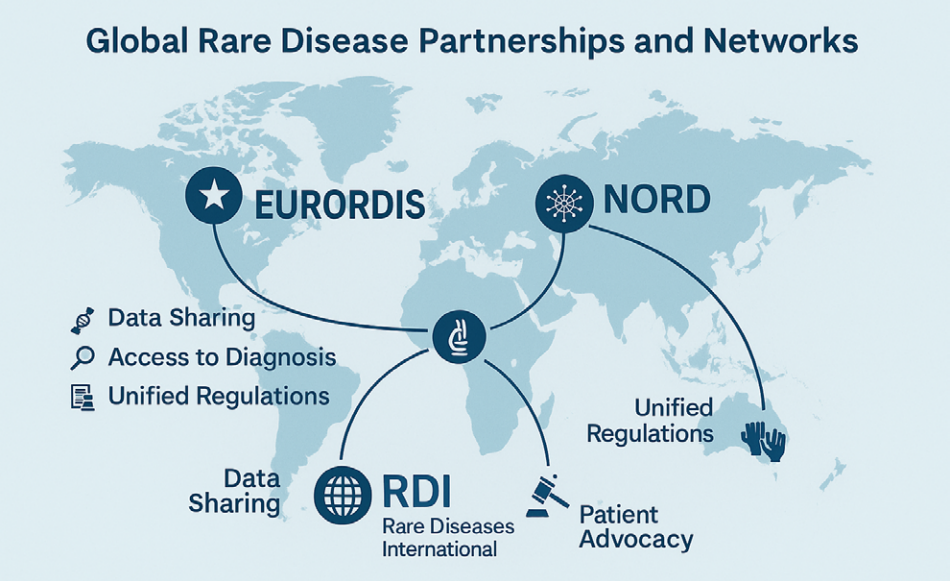

Figure 3. Global alliances among patient groups, researchers, and policymakers are driving harmonization of orphan drug regulations and facilitating knowledge-sharing across borders.

3. METHODOLOGY

This study employed a structured narrative review methodology to examine the challenges, incentives, and innovations in orphan drug development for rare diseases. The objective was to synthesize multidisciplinary evidence spanning scientific, economic, regulatory, ethical, and access-related dimensions, with particular focus on implications for low- and middle-income countries (LMICs).

3.1. Literature search strategy

A comprehensive literature search was conducted across three major electronic databases: PubMed, Scopus, and Google Scholar. The search included English-language publications from 2017 to 2025. Search terms and Boolean combinations included:

- "orphan drugs" OR "rare diseases"
- AND "drug development" OR "therapeutics" OR "precision medicine"
- AND "regulatory incentives" OR "public-private partnerships"
- AND "low- and middle-income countries (LMICs)" OR "access to medicines"

Additional relevant articles and policy reports were identified through backward citation tracking of key references.

3.2. Inclusion and exclusion criteria

3.2.1. Inclusion criteria

- Peer-reviewed research articles, review papers, and policy reports
- Publications presenting empirical data or structured analyses on orphan drug development
- Studies addressing scientific, economic, regulatory, or ethical aspects
- Articles discussing technological advances, clinical strategies, or access issues related to LMICs

3.2.2. Exclusion criteria

- Non-English publications
- Editorials, opinion pieces, or commentaries lacking empirical analysis
- Articles unrelated to orphan drug development or rare disease policy

3.3. Data extraction and synthesis

Information from eligible sources was extracted and thematically categorized into five key domains:

i. Scientific and clinical challenges
ii. Economic and commercial barriers
iii. Regulatory and financial incentives
iv. Emerging technological and strategic innovations
v. Equity-focused approaches, with emphasis on LMIC contexts

Findings were analyzed to identify recurring themes, knowledge gaps, and policy implications. Where applicable, real-world case studies were integrated to illustrate challenges and solutions.

3.4. Validation and triangulation

Data accuracy was validated by cross-referencing findings with guidelines from authoritative organizations such as the World Health Organization (WHO), U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and leading rare disease advocacy groups.

3.5. Ethical considerations

As a literature-based review, the study did not involve human or animal subjects and thus required no formal ethical approval.

4. RESULTS AND DISCUSSION

4.1. Future outlook

The future of orphan drug development is at the crossroads of innovation, regulatory reform, and global health justice. One critical requirement is policy consistency among regulatory agencies. Disparate definitions, approval routes, and incentives continue to divide the global environment, impeding cross-border collaboration and delaying access in underprivileged areas. Efforts to unify regulatory standards and speed up approvals—particularly for LMICs—are gaining pace through organizations such as the WHO's International Council for Harmonisation and regional initiatives in Asia and Africa(Ko, 2024).

Ensuring equity of access remains a tough problem. Emerging concepts for tiered pricing schemes based on country income levels may help to close the affordability gap. Simultaneously, by supporting local innovation ecosystems and implementing smart intellectual property (IP) reforms, LMICs may be able to develop and produce rare illness medicines autonomously.

Precision medicine and personalized therapies represent a paradigm shift away from one-size-fits-all treatments and toward interventions based on genotype, phenotype, or molecular signatures (Abubakar *et al.*, 2022).

While promising, these medicines raise ethical concerns about fair access, particularly in settings with poor genetic infrastructure or health-data privacy regulations.

Finally, long-term sustainability will necessitate novel financing approaches. Models such as subscription-based access, outcomes-based pricing, and risk-sharing agreements are being investigated to reconcile the high upfront costs of orphan medications with health-care system viability. As research progresses, the challenge will be to integrate these achievements into inclusive, resilient health systems that benefit both rare illness patients and broader public health goals (Al-kfairy *et al.*, 2024).

Table 1. Key challenges and corresponding solutions in orphan drug development

Challenge Area	Specific Challenges	Proposed Solutions / Strategies
Scientific & Clinical (Ayati *et al.*, 2021)	Limited understanding of rare disease biology- Small patient populations- Lack of validated trial endpoints	Investment in genomics, disease modeling, and biomarkers- Use of real-world data and AI to optimize trial design
Economic & Commercial (Lawal *et al.*, 2025)	High R&D costs with limited return- Investor hesitation due to small markets	Tax credits, R&D grants (e.g., FDA programs)- Public-private partnerships and venture philanthropy models
Regulatory (Okafor *et al.*, 2025)	Complex, non-harmonized approval processes- Long timelines	Accelerated approval pathways (e.g., Orphan Drug Act, EMA support)- Global policy harmonization efforts
Ethical & Access (Al-kfairy *et al.*, 2024)	High treatment costs- Limited availability in LMICs	Tiered pricing models- Local manufacturing, technology transfer, and voluntary licensing
Infrastructure in LMICs (Lawal *et al.*, 2025)	Weak diagnostic systems- Scarce clinical trial infrastructure	Point-of-care genetic diagnostics- Decentralized clinical trials using telemedicine and regional hubs
Fragmented Research Landscape (Ayomide *et al.*, 2024)	Siloed data and duplicated efforts	Collaborative consortia (e.g., IRDiRC, E-Rare)- Open-source platforms and data sharing initiatives

To synthesize the key findings of this review and facilitate practical interpretation, Table 1 provides a concise overview of the major challenges identified in orphan drug development and highlights corresponding solutions or strategic responses discussed throughout this review.

5. CONCLUSIONS

There has been great progress in the development of orphan drugs for rare diseases, but there are still substantial disparities and inequalities in access to timely and affordable medicines—in particular, in low- and middle-income countries (LMICs). But to address these we need more than scientific advances; we need coordinated action across research, policy, and finance.

For investigators, it is important to focus attention to collaborative efforts in data sharing, identify and in some instances validate biomarkers and clinical endpoints, and to use efficient designs for adaptive trials when dealing with rare conditions. Cross-national research consortia and open-source platforms should be extended to minimize duplication and catalyse discovery.

Funders and industry stakeholders also need to finance a portfolio of innovative financing models like risk sharing and tiered pricing and partnership models between the public and the private sector that de-risk early-stage development and ensure long-term affordability. Aiding local R&D ecosystems and manufacturing capacity in LMICs may also enhance access and resilience.

Policy makers seek for regulatory alignment between regions, incorporation of rare diseases strategies into national health plans and responsiveness in pricing and reimbursement mechanisms – to accommodate both public health and sustainability. The reinforcement of both rare disease registries and diagnostic programs, and health coverage with universal policies will be necessary for diminishing these access differences.

The future of orphan drug in this development paradigm is systems that are scientifically advanced and ethical based and with a global inclusivity. A coordinated, equity-based approach can guarantee that advances in rare disease therapeutics reach all populations regardless of geography or income.

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