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Rare Diseases and the Unseen Burden: A Patient-Centered Perspective

Jeroze Dalal

GlaxoSmithKline Pharmaceuticals, Head of Clinical Operations, Governance & Risk Management, Chief Patient Organization, GlaxoSmithKline Pharmaceuticals, Mumbai, India

ABSTRACT

Background: Rare diseases affect millions worldwide and pose substantial challenges to patients, healthcare providers, and researchers. Definitions of rarity vary geographically, complicating coordinated global responses. Patients often face prolonged diagnostic delays, limited treatment options, and significant social barriers.

Main Body: This perspective explores the multi-dimensional burden faced by rare disease patients, highlighting key issues such as diagnostic odysseys marked by misdiagnoses and emotional distress. Treatment availability is constrained by high costs and lack of approved therapies, especially in low- and middle-income countries. Clinical trials, central to advancing therapies, remain difficult to access for many due to geographic and logistical barriers. Decentralized Clinical Trials (DCTs) emerge as a promising innovation, leveraging telemedicine and remote monitoring to increase inclusivity and trial participation. Beyond medical challenges, patients and caregivers experience social isolation, stigma, and significant psychosocial strain. Addressing these gaps requires coordinated efforts to raise awareness, improve healthcare infrastructure, foster patient-centric and decentralized research models, and implement supportive policies promoting equitable access to care.

Conclusion: The rare disease community urgently needs integrated action combining early diagnosis, expanded therapeutic research, inclusive clinical trial designs, and social support mechanisms. Amplifying patient voices and fostering partnerships in research and policy are critical to developing effective, meaningful solutions. This comprehensive approach promises to transform the rare disease landscape, ensuring no patient remains unseen or underserved.

***Corresponding author**

Jeroze Dalal, GlaxoSmithKline Pharmaceuticals, Head of Clinical Operations, Governance & Risk Management, Chief Patient Organization, GlaxoSmithKline Pharmaceuticals, Mumbai, India.

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Abbreviations

DEI: Diversity Equity and Inclusion

DCTs: Decentralized Clinical Trials

Background

Rare diseases collectively affect an estimated 350 million individuals worldwide, yet patients with these conditions often face significant challenges including delayed diagnosis, limited therapeutic options, and inadequate social support. Definitions of what constitutes a rare disease vary by region, complicating efforts for coordinated global policy and research. Despite advances in genomics and personalized medicine, the scarcity of high-quality clinical practice guidelines and limited research investment continue to hinder improvements in care. A systematic literature search across major databases and resources reveals persistent barriers in diagnosis, treatment accessibility, and clinical trial inclusion for rare disease patients. The issue under discussion is the urgent need for multidimensional strategies that integrate enhanced awareness, innovative trial models such as decentralized clinical trials, equitable health policies, and patient-centered approaches. This perspective aims to synthesize current knowledge, highlight gaps, and propose actions to transform rare disease care and research landscapes.

Introduction

Rare diseases collectively affect millions worldwide, but individual conditions remain uncommon and often neglected. Despite advances in genetics and personalized medicine, patients continue to experience diagnostic delays, limited treatment options, and fragmented care. This review examines these barriers and highlights innovations in research and care models to improve outcomes.

Rare diseases present one of the most profound paradoxes in global health. Defined variably across regions—fewer than 1 in 2,000 people in Europe, fewer than 200,000 individuals in the U.S., and fewer than 1 in 10,000 in Japan—they are "rare" individually but collectively affect an estimated 350 million people worldwide [1-3]. Despite this considerable burden, patients with rare diseases remain among the most underserved, facing barriers at every step of their journey. My professional experiences, coupled with direct patient interactions, have revealed recurring challenges that demand urgent and coordinated action.

Defining "Rare": A Matter of Geography

The definition of a rare disease is not universal and varies across geographies. In the United States, a rare disease is defined as one affecting fewer than 200,000 individuals; in Europe, fewer than 1 in 2,000 people; and in Japan, fewer than 1 in 10,000 [4-5]. These thresholds mean some conditions may be considered "rare" in one region but not in another.

Leprosy illustrates this paradox. In the United States and Europe, it would qualify as a rare disease due to its extremely low prevalence. However, in countries such as India, Brazil, and Indonesia, leprosy remains relatively common, with over 200,000 new cases reported worldwide each year [6-7]. Thus, while globally "rare" in numbers, leprosy continues to pose a significant public health challenge in endemic regions. This highlights the importance of contextualizing rarity not only by prevalence but also by its burden of social and health systems.

The Diagnostic Odyssey

The journey to a diagnosis is often long and arduous, with patients enduring years of consultations, repeated investigations, and misdiagnoses before finally receiving an accurate diagnosis. Some are told their symptoms are psychological, leading to frustration and mistrust of healthcare systems [8-9].

For example, a young woman with Cushing's disease and a teenager with Wilson's Disease both faced delayed recognition despite debilitating symptoms [10]. These cases underscore the urgent need for greater awareness and timely access to specialized testing.

Limited Treatment Options and High Costs

After diagnosis, treatment options for many rare diseases remain limited or non-existent. Where therapies exist—often costly orphan drugs—they are inaccessible to most patients in low- and middle-income countries. Families face impossible choices between financial hardship and foregoing potentially lifesaving treatments [11-12]. For diseases like Duchenne Muscular Dystrophy or Wilson's Disease, available treatments are not curative and require lifelong adherence, further adding to economic and emotional strain.

Clinical Trials: A Narrow Pathway

Clinical trials often offer the only hope for patients with rare diseases. Yet, trial options are limited due to small patient numbers and scientific complexity, often concentrated in specific regions. This creates a situation where geography determines opportunity: a patient in Boston may have a chance to participate in a clinical trial, while a patient in Mumbai or Lagos may have none [13-15]. This geographic disparity excludes many from accessing innovative therapies. Decentralized Clinical Trials (DCTs), leveraging telemedicine and home-based interventions, represent promising solutions to broaden participation and democratize access for globally dispersed rare disease patients [16].

The Role of Decentralized Clinical Trials

Decentralized Clinical Trials (DCTs) leverage digital technologies, telemedicine, and local healthcare resources to conduct clinical research activities closer to or within patients' homes. This approach addresses key challenges inherent in rare disease trials, such as small and geographically dispersed patient populations and mobility limitations [17-20].

Key Benefits Include

Broader Access and Inclusion: DCTs dissolve geographic and socioeconomic barriers by enabling remote participation. This is vital for rare diseases where patients are widely scattered and often live far from specialized centers, especially in low- and middle-income countries like India. It enhances recruitment equity and trial diversity by including underserved populations [19].

Reduced Patient Burden: By minimizing travel requirements and allowing flexible scheduling, DCTs decrease logistical, financial, and emotional burdens on patients and caregivers, fostering higher enrollment and retention rates. This is particularly important for chronic, debilitating rare diseases that limit mobility[17].

Improved Data Quality and Real-World Insight: Continuous remote monitoring using wearable devices and digital patient-reported outcomes supports richer, more accurate data collection. This can capture real-world disease manifestations and treatment effects better than intermittent clinic visits [18].

Faster, Efficient Enrollment: Virtual trial sites can tap into larger pools of rare disease populations irrespective of location, accelerating enrollment timelines critical for rare disease studies [13]. This also accelerates event monitoring and safety reporting.

Empowered Patient Engagement: DCT models promote patient-centricity by enhancing convenience and communication, fostering trust and ongoing participation throughout the trial [21].

While challenges such as digital literacy, data security, and local infrastructure remain, DCTs offer a patient-friendly, scientifically robust path forward that aligns with global regulatory trends and the needs of diverse rare disease populations.

Psychosocial and Social Burden

Beyond medical hurdles, rare disease patients and their families face profound psychosocial challenges. The rarity of their condition often isolates them socially, as few around them understand their struggles. Mental health concerns—depression, anxiety, and chronic stress—are common yet under-recognized [16].

Families frequently become full-time caregivers, managing both the clinical and emotional toll. I recall a boy with Duchenne Muscular Dystrophy who faced exclusion at school due to mobility challenges. His parents alternated between advocating for his education and managing his medical care, leaving little space for their own lives. The teenager with Wilson's Disease similarly struggled to maintain friendships, as his neurological symptoms were misinterpreted as behavioral issues. Such examples highlight the need for holistic support—spanning education, employment, and social integration [17].

Limitations in Research and Policy

Despite advances in genomics and personalized medicine, investment in rare disease research remains disproportionately low. Commercial incentives for pharmaceutical companies are limited, and public funding is often insufficient [18,19]. Regulatory frameworks, though evolving, are still not agile enough to support adaptive trial designs or cross-border collaboration, both of which are essential for rare disease studies.

Insurance coverage for such conditions is almost nonexistent in many countries, meaning the financial burden falls directly on patients and families, who often must make out-of-pocket payments for lifelong treatment. This not only deepens inequity but also forces families into catastrophic health expenditure, adding a social and economic dimension to the burden of rare diseases [18].

Policy inattention worsens these gaps. National health systems often overlook rare diseases, leaving patient groups to advocate for recognition, registries, reimbursement, and financial support. The absence of coordinated international policy frameworks further marginalizes these patients [19].

The Way Forward: Listening to Patients

Addressing rare diseases requires a multi-pronged approach. Improving awareness among frontline providers can reduce diagnostic delays. Greater investment in research—both public and private—is needed to expand therapeutic options. Policies must ensure

affordability and equitable access, including innovative financing models for orphan drugs [18].

Equally important is expanding clinical trial access. By embracing decentralized and hybrid models, the research community can ensure that patients, regardless of geography, are not denied participation. For rare diseases, every patient counts, and every data point is precious [13].

Efforts must also be made to provide employment opportunities for patients living with rare diseases, recognizing their abilities and contributions. Embedding this within the spirit of Diversity, Equity, and Inclusion (DEI) will help reduce stigma, foster independence, and improve quality of life beyond medical care.

Finally, we must elevate the voices of patients. Their lived experiences provide essential insights into unmet needs, meaningful endpoints, and acceptable risk–benefit balances. Inclusion of patients as partners, not just participants, in research, policy, and healthcare delivery will ensure that solutions are relevant and impactful

Conclusion

Addressing the complex challenges of rare diseases requires a holistic, multi-pronged approach that spans awareness, research, policy, clinical care, and social support. Enhancing education among frontline healthcare providers is essential to reduce the diagnostic delays that many patients endure, thereby enabling earlier intervention and better outcomes [18]. Equally critical is the need for substantial investments from both public and private sectors to expand therapeutic options, coupled with policies that ensure affordable and equitable access through innovative financing models for orphan drugs [18].

Expanding clinical trial access by embracing decentralized and hybrid trial models is a transformative opportunity to include patients globally, overcoming geographical and socioeconomic barriers. In rare diseases, where patient populations are small and data limited, inclusive enrollment is vital to accelerate advances in diagnosis and treatment [13].

Beyond clinical interventions, creating and supporting employment opportunities highlights the importance of recognizing the abilities and contributions of people living with rare diseases. Embedding this within Diversity, Equity, and Inclusion (DEI) initiatives can reduce stigma, foster independence, and improve quality of life. Finally, centering the voices of patients and actively engaging them as partners in research, policy-making, and healthcare delivery provides invaluable insights that shape relevant, patient-centered, and effective solutions [20,21].

Together, these integrated efforts can transform the rare disease landscape, ensuring patients are empowered, supported, and fully included in the global health ecosystem, which is a vital step toward equity and improved health outcomes for this underserved population.

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