

Reimagining rare disease policies through a global lens

COMMUNICATION | EDITORIAL | INVITED CONTRIBUTION | **PERSPECTIVE** | REPORT | REVIEW

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ABSTRACT

An estimated 400 million individuals suffer from rare diseases globally. Tackling rare diseases has historically posed difficulties, including the lack of knowledge about their underlying causes, lack of resources for patients, and fundamental inefficiencies at multiple stages along the pipeline, from basic science discovery to clinical translation and diagnosis. The development of rare disorder therapeutics, often termed orphan drugs, faces a unique set of challenges in clinical trials: difficulties in recruiting patients, difficulties in following conventional clinical trial structure, as well as financial barriers for drug approval. Here, I argue for the creation of an international organisation for rare diseases to coordinate a shared global patient registry and standard for orphan drug approval. An initiative of such nature, with representation from experts and organisations in the science, medicine, and patient-support industries will assist in overcoming the present challenges, whilst accelerating progress and improving the experience during treatment of patients with rare disorders.

SCIENCE \Rightarrow POLICY

Rare diseases altogether cause a large financial burden and personal suffering on an unignorable portion of the population. Yet, our lack of understanding of these diseases and the scarcity of patients present unmet challenges to developing and validating new therapies. I argue that the rare disease community can benefit greatly from an international organisation that coordinates databases, patients, and new research globally.

Keywords Rare diseases · Orphan drugs · International organisations · Science policy · Grants

Introduction

By definition, rare diseases individually affect a small proportion of the population, and this has partly contributed to the historical lack of attention directed towards this field. Yet, rare disorders collectively affect roughly 260 to 400 million patients globally [1]. There are approximately 6,800 known rare disorders, affecting 25

million people in the U.S. alone, and nearly 30 million people in Europe [2]. For a significant part of history, patients of rare diseases were left helpless, without treatment options, due to a systemic flaw that prevents significant drug discovery for rare diseases.

In 1983, significant progress began with the United States leading the way by introducing the landmark Orphan Drug Act (ODA). The ODA

clarifies the definition of rare disorders (or “orphan diseases”) in the U.S. by defining rare diseases as those affecting less than 200,000 Americans [3]. The act also incentivises the industry to develop orphan drugs by: providing seven-year market exclusivity for such drugs; lowering development costs through tax benefits, grants, and application fee waivers; and allowing fast-track development and approval [4].

In other countries, legislation for rare diseases vary in the specific programmes introduced. Japan established the National Programme on Rare and Intractable Diseases in 1972. In the early- to mid-2010s, several Latin American nations such as Argentina, Brazil, and Chile introduced national laws or ordinances for rare diseases [5]. Notably, the introduction of Law 26,689 in Argentina in 2011 established prevalence criteria for rare diseases and mandated patient and data registries as well as new programmes to improve diagnosis and care for rare diseases.

In addition, there are programmes that operate at an international level. In 2009, a collaborative effort between the European Commission and the National Institutes of Health in the United States led to the establishment of the International Rare Disease Research Consortium (IRDiRC)—which unites other national and international, for-profit, non-profit and governmental organisations for greater collaboration to advance rare disease research. [6].

Current Challenges

While the introduction of legislation such as the Orphan Drug Act has opened doors to new opportunities to develop therapies for rare diseases (pharmaceutical, surgical, radiation, physical, mental health support therapies or otherwise), many challenges remain. Broadly, the problems tend to aggregate at three nodes along the pipeline from research to clinical translation:

1. lack of access to information for patients;
2. barriers against clinical trials for orphan drugs; and
3. unreliable data on rare disease prevalence.

Improvements are possible with policy and structural changes regulating research grants and clinical trial design.

The scarcity of patients with specific rare diseases, or subtypes of rare disorders, significantly impairs the ability to recruit sufficient pools of patients for clinical trials. Consequently, the low availability of patients hinders the success and efficacy of clinical trials. First, small sample sizes hinder the ability for physicians to draw definitive conclusions from trials about the efficacy of the drugs under examination. Moreover, logistical and policy regulations further limit studies to small geographic regions, exacerbating the problem of patient scarcity and further reducing the scientific weight of the published results from randomised controlled trials.

From a clinical perspective, when it comes to rare diseases, there are two key problems. The first relates to negative patient outcomes resulting from slow or inaccurate patient diagnosis. According to European and trans-Atlantic surveys, first-line physicians lacking familiarity with rare diseases are often unclear about the presenting symptoms, so that they misdiagnose the patient with a more familiar ailment and implement an incorrect treatment, potentially allowing the disease to progress to a more advanced stage [2]. The second relates to a lack of understanding about disease progression, complicating the determination of the appropriate clinical trial endpoints validating orphan drugs. In such cases, molecular biomarkers may be the necessary alternative [7]. Our most recent understanding of rare disease manifestations and relevant biomarkers must be made readily available for researchers and physicians across the globe, to not only optimise diagnosis, but standardise the endpoints for clinical trials conducted in different countries.

To further complicate the problem, the prevalence of many rare disorders is ill-researched, leading to an inaccurate (often overestimated) understanding of the patient population size for a specific rare disorder. This can lead to a lack of return on investments that companies have devoted towards validating therapies for specific diseases, thus making them less likely to do so again in the future. The overestimation of rare disease prevalence has been attributed most commonly to the fact that studies regarding prevalence are

done regionally, and often, only using hospital data [7].

Some of the most valuable metrics in assessing the state of rare disease diagnosis, treatment, and care are the feedback and reflections from patients. A survey conducted in both the U.S. and the U.K. examined the quality of patient care for a wide range of rare disease [8]. Dishearteningly, the survey found that around half of the rare disease patients receive conflicting information from different healthcare providers, with patients receiving on average two to three misdiagnoses. Furthermore, it takes on average seven to eight years for patients with rare diseases to receive a proper diagnosis [8]. These results altogether suggest an urgent need to reconsider the manner in which diagnostic criteria are organised for healthcare professionals.

Policy Recommendations

Most challenges that remain today with rare disease policies can be addressed by a global effort to unify policies for patients in areas of advocacy, diagnosis, basic research, new drug development, and clinical trials. These international efforts can be accomplished through current organisations such as the International Rare Disease Research Consortium (IRDiRC).

Such an organisation would be led by a cohort of leaders from the clinical, industrial, and academic fronts of rare disease research. Through this organisation, a shared patient registry can be established. This allows clinicians from one nation to gain access to rare disease patient records from another region or country, who would otherwise not have been able to enrol in trials or receive a similar level of healthcare. These patients can then be recruited by more clinical trials, thereby benefitting both the study and the patients, while pushing progress on therapeutic development. The sharing of patient registries and other databases can also increase the accuracies of the estimated prevalence for many rare disorders, thus better informing the design of clinical trials.

The committees within these existing international organisations for rare diseases should also work to standardise the requirements for the ap-

proval of orphan drugs. By doing so, each approved orphan drug designation would have a greater geographical impact, serving more patients than they do under the current model, with an added financial incentive to companies involved in development.

Furthermore, the proposed global organisation for rare diseases should include representation from patient advocacy groups to strengthen the communication between patients, physicians, and governments. By facilitating patient-doctor communication and promoting patient recruitment, patient advocacy groups play a large role in the success of clinical trials [9, 10]. This collaboration can solidify our understanding of disease manifestation and lead to a more robust diagnosis protocol, which can then be standardised across countries and communicated to patient groups in different regions.

Affecting hundreds of millions of patients, rare diseases altogether impose a large family and financial burden. It is therefore in the best interest of the global community to agree on a new unifying strategy that maximises the efficiency of our time and efforts in combating rare disorders.

Suggested Further Study

Above, I argue that many of the current problems can be addressed by the transnational sharing of resources such as patient registries and databases; by further promoting patient representation at the global level; and by establishing an internationally consistent standard for the approval of orphan drugs. This piece serves as a call to action for further studies on the feasibility of these undertakings and the most appropriate funding and administrative strategies that should be employed to overcome these challenges. For instance, in creating a globally accessible pool of rare disease patients for clinical trials, a series of other needs arise that require further funding. The travel expenses of the patient as they participate in clinical trials away from home will cumulate to a significant sum that calls for additional support from governmental and non-profit organisations. To meet these financial needs, difficult questions must be answered regarding the sources of this funding, and the ethics behind each.

Furthermore, the three major challenges mentioned above can be most efficiently tackled by an international organisation for rare diseases. Practically, it is most efficient to call on current international rare disease organisations that can expand their role and carry out these projects. However, the determination of which international organisation is most suitable to take on this role requires further evaluation of their missions, sources of funding, and governmental structures. I argue that the IRDiRC is the most suitable on the basis of its focus on coordinating research and diagnostic goals across national governments and non-governmental organisations (NGOs). Currently, the IRDiRC is funded by the European Union through the European Joint Programme on Rare Disease [11]. It is conceivable that this funding scheme can be expanded to include the World Health Organisation (WHO), U.S. government, and NGOs that share a specific interest in supporting clinical and research progress.

With further evaluation and careful implementation, these measures can strengthen the ties within the global community of rare disease patients, researchers, and physicians, and further accelerate the progress towards successful treatment of rare disorders.

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Conflict of interest The Author declares no conflict of interest.