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Translational Pharmacoeconomics in Rare Diseases: Integrating Clinical, Economic, and Social Value in Health Decision-Making

Gustavo Moretta [1,2,*], Rosana Chaud [3], Valery Tancon Guillén [1], Eliana Mateus [4], José Parodi García [1] and Ricardo Fujita Alarcón [1]

[1] Universidad San Martín de Porres, Faculty of Medicine, Peru
[2] Silher Corporación, Peru
[3] Fondo Intangible de Seguridad Social, SIS Peru
[4] Universidad Nacional de Colombia
* Correspondence: Gmorettap@usmp.pe

Abstract

Rare diseases pose a growing challenge for health systems due to the combination of high clinical need, limited evidence, and elevated costs. This article analyzes the intersection between translational medicine and pharmacoeconomics, identifying a structural gap between the clinical value of innovations and traditional economic evaluation frameworks. Drawing on a narrative review of the literature—in which 240 scientific articles were identified and the 30 most methodologically and thematically relevant were selected through systematic screening by title, abstract, and full-text relevance—and a comparative analysis of frameworks in Europe, the United States, and Latin America, we propose the concept of *translational pharmacoeconomics* as an integrative framework that explicitly incorporates clinical, economic, and social dimensions of value into health decision-making. This approach has direct implications for the design of more equitable, adaptive, and sustainable health policies, particularly in contexts of evidence scarcity and unmet clinical need.

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1. Introduction

Rare diseases, defined across health systems as conditions affecting a small proportion of the population, collectively represent a global health challenge of significant magnitude. It is estimated that more than 300 million people worldwide live with one of the more than 7,000 identified rare diseases, many of them chronic, progressive, and potentially life-threatening (World Health Organization, 2023).

Over recent decades, the development of therapies for rare diseases—commonly referred to as orphan drugs—has accelerated substantially, driven primarily by advances in molecular biology and translational medicine. This phenomenon has been especially pronounced in regions such as the United States and Europe, where specific regulatory frameworks—including the Orphan Drug Act in the U.S. and the European Medicines Agency (EMA) orphan drug regulation—have incentivized innovation in this field (FDA, 2022; European Medicines Agency, 2023).

In the United States, the orphan drug access model is strongly market-oriented, characterized by rapid regulatory approval and broad availability, although frequently accompanied by elevated prices that generate tensions around system sustainability and equitable access (FDA, 2022). In contrast, European countries have developed more structured health technology assessment (HTA) systems, in which bodies such as NICE in the United Kingdom apply cost-effectiveness criteria while

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progressively incorporating disease-specific modifiers—such as severity and unmet medical need—for rare conditions (NICE, 2022).

Even within these consolidated systems, orphan drugs present significant challenges due to limited clinical evidence, uncertainty about long-term outcomes, and high associated costs. These difficulties are amplified in Latin America, where health systems often face budgetary constraints, institutional fragmentation, and the absence of robust HTA frameworks, generating substantial inequities in access to innovative therapies (Pichon-Riviere et al., 2019).

Within this heterogeneous global context, conventional pharmacoeconomic approaches—particularly cost-effectiveness analysis (CEA) and cost-utility analysis (CUA)—rely on the estimation of the incremental cost-effectiveness ratio (ICER). While these tools have been widely adopted as a standard for efficient resource allocation, they present significant limitations in the context of rare diseases, where evidence scarcity, surrogate endpoints, and elevated structural uncertainty are the norm (Drummond et al., 2015).

As a consequence, traditional economic evaluation models may systematically underestimate the value of interventions in rare diseases by failing to adequately capture dimensions such as disease severity, unmet medical need, and broader social impact. This misalignment has generated a growing debate around the relevance of classical HTA frameworks and the need to incorporate more flexible, adaptive, and equity-sensitive approaches across different health contexts (OECD, 2018; NICE, 2022).

Translational medicine has simultaneously transformed the development of novel therapies by enabling faster transitions from molecular discovery to clinical application. However, this accelerated process frequently occurs in evidence-scarce environments, where available clinical data at the time of regulatory approval are limited. As a result, the final phases of the translational continuum—particularly those related to value assessment and health system implementation—are characterized by elevated uncertainty and methodological constraints (Woolf, 2008).

Together, these elements reveal a critical gap between the clinical value generated through translational research and the economic frameworks used to evaluate it—a gap that manifests differently depending on the health system context. The objective of this review is to analyze the limitations of conventional pharmacoeconomic approaches in rare diseases and to propose a conceptual framework grounded in translational medicine that enables a more comprehensive assessment of health value.

2. Translational Medicine in Rare Diseases: Dynamics and Regional Differences

Translational medicine has consolidated as a central axis in the development of innovative therapies, particularly for rare diseases, where advances in molecular biology, genetics, and omics technologies have enabled the identification of specific pathophysiological mechanisms and the development of targeted interventions. This approach seeks to shorten the distance between scientific discovery and clinical application, commonly structured as a continuum spanning from basic research (T0) to health system implementation and population impact assessment (T4) (Woolf, 2008).

In the context of rare diseases, this translational process displays distinctive characteristics. Unlike other therapeutic areas, clinical development is typically conducted with small patient populations, adaptive designs, and the frequent use of surrogate endpoints. This gives rise to what has been termed an *"evidence-scarce environment"*, in which regulatory and clinical decisions must be made under high levels of uncertainty (Facey et al., 2015).

In the United States, the translational ecosystem is highly developed and characterized by strong integration among basic research, the pharmaceutical industry, and regulatory agencies. The FDA has implemented mechanisms such as accelerated approval and special designations for orphan drugs, facilitating faster transitions from research to market access—even with limited clinical evidence (FDA, 2022).

In Europe, while translational development is also robust, there is a greater articulation with HTA systems. The EMA has promoted adaptive approval mechanisms and real-world evidence generation; however, effective patient access subsequently depends on national HTA evaluations,

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which introduces an additional layer of validation and implementation delays (European Medicines Agency, 2023). The EU established a comprehensive framework for orphan medicines through Regulation (EC) No 141/2000, providing incentives including protocol assistance, regulatory fee reductions, and ten years of market exclusivity—a framework that has proven largely successful, with more than 2,000 designations granted and over 100 medicines authorized since its inception (European Medicines Agency, 2023).

In contrast, Latin America faces significant structural limitations in translational medicine. Basic research and clinical development capacity remain constrained, and dependence on evidence generated in other contexts is high. Health system fragmentation and the absence of local evidence-generation mechanisms hinder the effective incorporation of therapeutic innovations into clinical practice. This produces what we term an *"expanded translational gap"*—a dual distance not only between laboratory and patient, but also between geographic regions in terms of access and implementation capacity (Pichon-Riviere et al., 2019).

Another critical element is the compression of the translational cycle. Technological advances allow for accelerated therapy development, but this acceleration is not always accompanied by equivalent maturation of clinical evidence. As a result, the final phases of the translational continuum—particularly those related to value assessment, financing, and access—become critical junctures where uncertainty accumulates and is transferred to decision-makers (Facey et al., 2015).

In this scenario, translational medicine in rare diseases represents not only a scientific challenge, but also a methodological and systemic one. Heterogeneity in evidence generation, dependence on limited data, and regional differences in implementation capacity configure an environment in which the assessment of intervention value requires more flexible and integrated approaches.

3. Limitations of Conventional Pharmacoeconomic Approaches in Rare Diseases

Pharmacoeconomics has consolidated as a central tool in health technology assessment, particularly through CEA and CUA methodologies. These approaches aim to maximize efficiency in the allocation of health resources by comparing costs and health benefits expressed through the ICER (Drummond et al., 2015).

However, in the context of rare diseases, these approaches present structural limitations that compromise their applicability and validity. Clinical trials in rare diseases typically involve small sample sizes, non-comparative designs, and frequent use of surrogate endpoints, introducing high degrees of uncertainty into effectiveness estimates (Facey et al., 2015).

This uncertainty translates into what the literature has defined as *"structural uncertainty"*—uncertainty that cannot be resolved through statistical analysis alone, but derives from limitations inherent to study design and incomplete knowledge of the natural history of the disease (Grimm et al., 2020). Economic models therefore require long-term extrapolations that amplify result variability and reduce the robustness of estimates.

Orphan drugs typically present significantly elevated costs due to reduced market size, research and development expenditures, and the absence of economies of scale. This leads to ICERs that frequently exceed conventional cost-effectiveness thresholds applied by HTA agencies, generating systemic barriers to financing (Schuller et al., 2015).

Another critical limitation is the limited capacity of conventional models to capture relevant dimensions of health value. In rare diseases, disease severity, absence of therapeutic alternatives, caregiver burden, and social impact acquire central relevance—yet these are typically not adequately reflected in models based exclusively on QALYs (Lakdawalla et al., 2018).

These limitations have been recognized by various regulatory agencies. NICE has introduced specific modifiers for Highly Specialised Technologies (HST), allowing greater flexibility in ICER interpretation based on severity and rarity of the condition (NICE, 2022). International organizations have similarly noted the need to adapt economic evaluation frameworks for contexts of high uncertainty and unmet clinical need (OECD, 2018).

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In Latin America, these limitations are exacerbated by additional constraints—including the absence of local data, limited technical capacity in economic modeling, and the lack of standardized HTA processes across most countries. This generates a dual burden: the uncertainty inherent to rare diseases, plus contextual uncertainty derived from heterogeneous and fragmented health systems. This regional dimension warrants explicit consideration in any equity-sensitive evaluation framework (Pichon-Riviere et al., 2019).

Together, these findings suggest that traditional pharmacoeconomic approaches present significant limitations in rare diseases that are not only technical but also conceptual—failing to incorporate key dimensions of health value. This underscores the need to evolve toward more comprehensive models capable of integrating uncertainty, equity, and social value into health decision-making.

4. The Critical Gap Between Translational Value and Economic Evaluation Frameworks

The advances of translational medicine have enabled the development of highly specific therapies for rare diseases—many grounded in well-characterized molecular mechanisms with the potential to modify the natural course of illness. Yet this scientific progress has not been accompanied by an equivalent evolution in the economic evaluation frameworks used for health decision-making.

In practice, a structural misalignment exists between the clinical value generated by these innovations and the instruments employed to assess them within health systems. While translational medicine operates in an environment of accelerated innovation and emerging evidence, traditional pharmacoeconomics rests on assumptions of robust evidence, comparability, and stability that are rarely met in the context of rare diseases (Facey et al., 2015).

Beyond its technical dimensions, this gap reflects a deeper conceptual tension. Traditional evaluation frameworks are designed to maximize aggregate efficiency, whereas rare diseases demand the explicit incorporation of equity, severity, and social value. The consequence is a decision-making paradox: populations with the greatest disease burden and fewest therapeutic alternatives face the highest access barriers. This distributive injustice has been extensively discussed in the health economics literature (Nord et al., 1999), and its persistence suggests that technical refinements to ICER-based models—without structural reform—are insufficient.

This gap manifests heterogeneously across regions. In Europe, HTA systems have begun incorporating rare disease modifiers, but implementation varies considerably across member states, generating disparities in treatment access (NICE, 2022). In the United States, the absence of a centralized evaluation framework produces rapid innovation availability alongside significant tensions around pricing and equity of access (ICER Institute, 2023). In Latin America, the gap widens further due to structural constraints: limited local data, restricted economic modeling capacity, and significant budgetary limitations—barriers that are contextual, not merely methodological (Pichon-Riviere et al., 2019).

In aggregate, this critical gap demonstrates the need to evolve toward more comprehensive evaluation approaches capable of reconciling the clinical value generated by translational medicine with health decision-making processes—the foundation for the integrative framework proposed in the following section.

5. Toward Translational Pharmacoeconomics: Implications for Health Decision-Making

5.1. Conceptual Definition

Translational pharmacoeconomics is defined as an integrative model that extends conventional economic evaluation frameworks by explicitly incorporating not only efficiency metrics, but also clinical, social, and contextual dimensions of health value. Unlike traditional approaches centered on

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the ICER, this model recognizes that decisions in rare diseases occur in environments of limited evidence and high unmet clinical need, where efficiency maximization cannot serve as the sole decision criterion (Lakdawalla et al., 2018).

From a health policy perspective, this shift implies a transition from purely technical decision models toward deliberative models in which multiple dimensions of value are explicitly considered. These include: disease severity, absence of therapeutic alternatives, magnitude of clinical benefit, uncertainty associated with the evidence base, and the social impact on patients and caregivers.

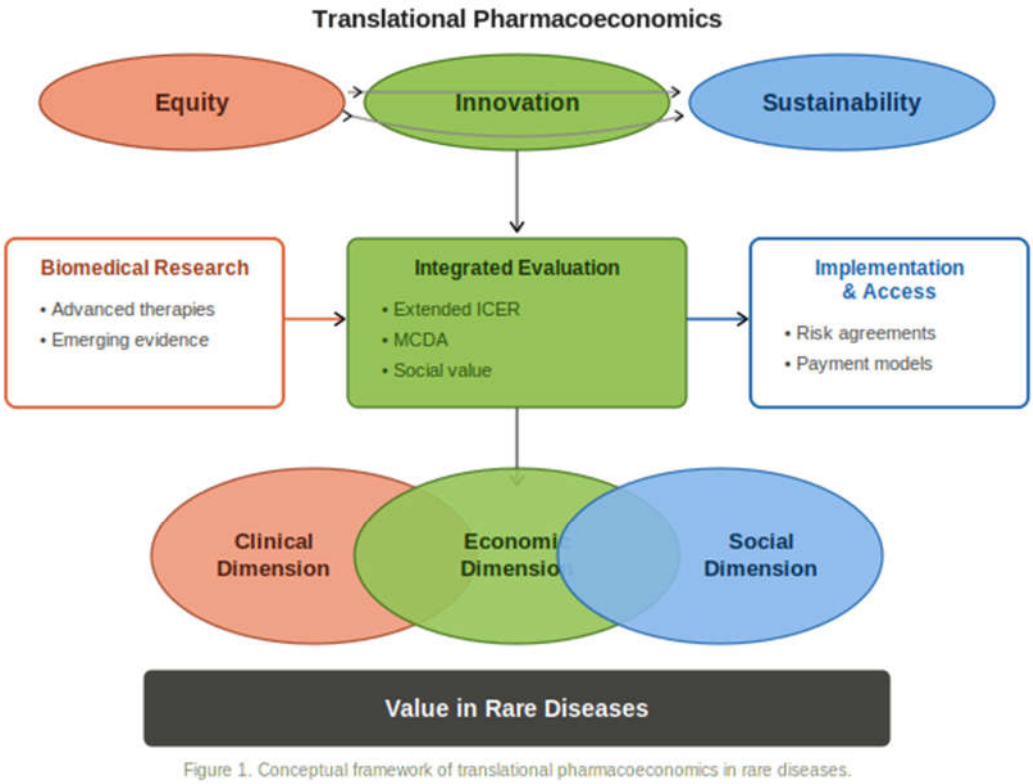

Figure 1. Conceptual framework of translational pharmacoeconomics in rare diseases.

Figure 1. Conceptual framework of translational pharmacoeconomics in rare diseases. The model integrates equity, innovation, and sustainability through an integrated evaluation process connecting biomedical research with health system implementation, incorporating clinical, economic, and social dimensions of value.

5.2. Methodological Tools

Multi-criteria decision analysis (MCDA) enables the structured integration of multiple value dimensions, facilitating transparent deliberative processes that go beyond ICER-based comparisons (Marsh et al., 2016). MCDA is particularly relevant for rare diseases because it can formally weight criteria such as severity, innovation, and equity alongside cost-effectiveness, making value trade-offs explicit for decision-makers rather than implicit.

Real-world evidence (RWE) is essential for reducing post-approval uncertainty and adjusting financing decisions based on outcomes observed in routine clinical practice (Facey et al., 2015). In contexts where pre-approval clinical trial data are necessarily limited—due to small patient populations and adaptive study designs—RWE provides a critical mechanism for progressive evidence generation and iterative decision refinement.

5.3. Adaptive Financing Mechanisms

From a public policy standpoint, this framework also requires the development of adaptive financing mechanisms. Risk-sharing agreements, outcomes-based payment schemes, and deferred

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payment models for high-cost therapies—particularly gene therapies—allow health systems to manage uncertainty and distribute financial risk between payers and manufacturers (OECD, 2018).

Concrete examples illustrate the practical applicability of these mechanisms: the managed entry agreements negotiated for Luxturna (voretigene neparvovec) in several European countries, and the outcomes-based financing arrangements established for Zolgensma (onasemnogene abeparvovec) in Italy and Germany, represent early applications of risk-sharing principles in high-cost, evidence-limited contexts. Their replication in Latin America requires substantial institutional strengthening but demonstrates operational viability in higher-income settings.

5.4. Regional Implications

In Europe, this approach has begun to materialize through mechanisms such as NICE's Highly Specialised Technologies programme and initiatives such as ORPH-VAL, which proposed multi-criteria frameworks integrating clinical, economic, and social elements in rare disease value assessment (NICE, 2022; Annemans et al., 2017).

In Latin America, the implementation of translational pharmacoeconomics represents both a necessity and an opportunity. Given the combination of budgetary constraints and high unmet disease burden, health systems require decision frameworks that prioritize interventions not solely on efficiency grounds, but also on their social and clinical impact. This requires strengthening institutional HTA capacities and developing regionally adapted financing mechanisms—a process that implies international cooperation, data-sharing infrastructure, and sustained political commitment (Pichon-Riviere et al., 2019).

Translational pharmacoeconomics does not propose replacing existing frameworks but extending them. The ICER and traditional metrics remain useful tools; however, they must be interpreted within a broader framework that incorporates additional dimensions of value. This shift is not only methodological but also normative—recognizing that health decisions are, ultimately, social decisions reflecting collective values.

6. Conclusions

Rare diseases require a paradigm shift in economic evaluation. Traditional models are insufficient for capturing their complexity, given the structural mismatch between accelerated translational innovation and frameworks designed for evidence-rich environments. Translational pharmacoeconomics provides an integrative approach that explicitly incorporates equity, sustainability, and clinical value into health decision-making—a more appropriate framework for the unique challenges posed by orphan drugs and the populations who depend on them.

The evidence synthesized in this review supports three priority recommendations: (1) **Harmonization of policies and international collaboration**—particularly through joint HTA mechanisms and coordinated data-sharing between regions; (2) **Innovative financing and reimbursement models**—including risk-sharing agreements, outcomes-based payment, and deferred financing adapted to regional contexts; and (3) **Strengthening translational research infrastructure**—especially in Latin America, where the expanded translational gap amplifies existing inequities in access.

Health systems that fail to adapt their evaluation frameworks to the unique characteristics of rare diseases will continue to produce distributively unjust outcomes—denying access to high-value therapies precisely to those with the greatest clinical need. In their totality, decisions in this domain must be understood as social decisions reflecting collective values regarding equity, innovation, and solidarity.

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Study Limitations: This study has several limitations that should be acknowledged. As a narrative review, it is inherently subject to selection bias in the identification and weighting of evidence. The selection of 30 primary studies from a broader pool of 240 articles was based on thematic and methodological relevance criteria, but was not performed through systematic review methodology; accordingly, conclusions should be interpreted as conceptual and framework-oriented rather than as the product of a systematic evidence synthesis. Additionally, the heterogeneity of health systems across the regions analyzed limits direct comparability and the generalizability of specific policy recommendations. Future research should include systematic reviews and primary empirical studies validating the translational pharmacoeconomics framework in specific health system contexts.

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