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Unlocking the Mysteries of Rare Disease Drug Development: A Beginner's Guide for Clinical Pharmacologists

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ABSTRACT

Clinical pharmacologists face unique challenges when developing drugs for rare diseases. These conditions are characterized by small patient populations, diverse disease progression patterns, and a limited understanding of underlying pathophysiology. This tutorial serves as a comprehensive guide, offering practical insights and strategies to navigate its complexities. In this tutorial, we outline global regulatory incentives and resources available to support rare disease research, describe some considerations for designing a clinical development plan for rare diseases, and we highlight the role of biomarkers, real-world data, and modeling and simulations to navigate rare disease challenges. By leveraging these tools and understanding regulatory pathways, clinical pharmacologists can significantly contribute to advancing therapeutic options for rare diseases.

1 | Overview

The quest to develop drugs for rare diseases is akin to navigating uncharted territories. Rare diseases, often referred to as orphan diseases, affect a small fraction of the population, yet they collectively impact millions of lives worldwide. With over 10,000 rare diseases identified, the challenge lies not only in their rarity but also in their complexity and diversity. These conditions frequently have genetic origins, manifesting early in life and leading to significant health burdens [1].

Imagine a world where a diagnosis of a rare disease does not come with a sense of hopelessness. For many patients and their families, this is not yet a reality. The scarcity of patients makes it difficult to conduct traditional large-scale clinical trials (CTs), which are the cornerstone of demonstrating the efficacy and safety of new treatments. Additionally, the heterogeneity of rare diseases—each with its unique progression and symptoms—complicates the design and implementation of clinical studies. The limited understanding of the natural history and pathophysiology of these diseases further adds to the challenge, making it hard to identify appropriate endpoints and outcome measures [2].

Yet, the development of treatments for rare diseases is of paramount importance. For many rare conditions, there are no approved therapies, leaving patients with few or no options. The high unmet medical need in this area presents a significant opportunity for scientific and medical advancements. Moreover, breakthroughs in rare disease research often pave the way for understanding more common diseases, as the underlying mechanisms may be shared [3].

This tutorial aims to provide a practical guide for clinical pharmacologists new to the field of rare disease drug development. We delve into the clinical aspects of rare disease drug development,

exploring the various phases of development and the unique hurdles they present. Here, innovative strategies such as the use of real-world data (RWD) and real-world evidence (RWE) come into play. Furthermore, the tutorial covers tools and pathways that can accelerate rare disease drug development. Regulatory pathways, like the FDA's Accelerated Approval Program, offer mechanisms to expedite the approval process for therapies targeting rare diseases. Mechanistic models such as physiologically based pharmacokinetic (PBPK) modeling and quantitative systems pharmacology (QSP) are valuable tools in rare diseases to inform dosing strategies, optimize clinical trial designs, and build the evidence of effectiveness.

2 | Rare Diseases Definition and Epidemiology

The Global Genes Project estimates that approximately 300 million people worldwide are affected by a rare disease. A conservative, evidence-based estimate for the global population prevalence of rare diseases is 3.5%–5.9%, which equates to 263–446 million persons affected globally at any point in time [4].

Rare diseases are defined variably across different regions, typically affecting a small segment of the population (fewer than 1 in 2000 people in any WHO region) [5]. The classification of these diseases is primarily based on prevalence rates, which can differ markedly from one country to another and is shaped by legislative actions, as they are designed to encourage research and development in this field [6] (Table 1).

3 | Understanding the Barriers to Rare Disease Drug Development

While there are many incentives for rare disease research and development to ensure that patients suffering from these conditions receive the necessary attention and access to appropriate treatments, rare disease drug development has intrinsic challenges related to diagnosis and access to trial enrollment and eventually access to the health care system. These challenges are further described below.

3.1 | Diagnostic Odysseys

The concept of "zebra versus horse" is crucial in understanding the challenges of diagnosing rare diseases. Medical students are often taught, "When you hear hoofbeats, think horses, not zebras," meaning they should consider common diagnoses before rare ones. This principle, attributed to Dr. Theodore Woodward in the late 1940s, aims to prevent overdiagnosis of rare conditions [26]. However, this approach significantly impacts the diagnostic journey of patients with rare disease, often leading to prolonged and challenging "diagnostic odysseys". On average, it takes 4.7 years for patients to receive an accurate diagnosis [27]. This delay is primarily due to the low likelihood of disease occurrence and poor knowledge among patients and healthcare workers about typical signs and symptoms. Misdiagnosis is common, with a correct diagnosis made without expert help in only 21% of cases [28]. Specialized centers for rare diseases and advances in diagnostic techniques, such as whole-genome sequencing, are showing promise in shortening diagnostic odysseys and improving outcomes for patients with rare diseases.

3.2 | Barriers to Clinical Trials Participations

Access to CTs for patients, particularly those with rare diseases, is hindered by several significant barriers that contribute to inequitable participation. One of the primary challenges is the geographic concentration of clinical trial sites, which are often situated in urban areas with established healthcare infrastructure. This leaves rural and underserved communities with limited access to trials, making it difficult for patients to participate due to long travel distances. Many patients, especially those from underrepresented backgrounds, are reluctant to travel significant distances to trial sites, further exacerbating recruitment issues [29].

Operational barriers such as complex referral processes and inadequate support for navigating trial participation can also impede access. Many patients rely on their healthcare providers for information about available trials, but providers may lack awareness of current studies or may not prioritize discussing them due to perceived patient hesitations or logistical difficulties [30]. Additionally, financial constraints also play a critical role in limiting trial access. Patients from lower socioeconomic backgrounds often face wage losses when participating in trials, which can deter them from enrolling or lead them to drop out prematurely [31].

Lastly, the inclusion and exclusion criteria set for participants in CTs can sometimes be overly stringent, inadvertently excluding many potential participants. For instance, patients with certain chronic conditions may be disqualified from participating in CTs, which disproportionately affect minority populations who are more likely to have these conditions.

Addressing these barriers requires a multifaceted approach that includes increasing the number of trial sites in underserved areas, implementing decentralized aspects of the CTs, improving communication strategies to build trust and awareness among potential participants and revising some eligibility criteria to be more inclusive [32]. Table 2 presents several common inclusion and exclusion criteria related to clinical pharmacology that can be reassessed to enhance the recruitment and enrollment of patients with rare diseases in CTs. It is essential to recognize that this table offers general recommendations, and each case should ultimately be evaluated individually. The decision to relax specific criteria should be informed by an understanding of drug ADME (absorption, distribution, metabolism, and excretion) characteristics, the nature and steepness of the toxicity relationship observed in preclinical data, and the available clinical data that indicate the likely therapeutic window—the range of drug doses that achieves the desired effect without causing unacceptable side effects. This information aids in determining an acceptable level of uncertainty and appropriate strategies for relaxing certain inclusion/exclusion criteria. Additionally, it is crucial to consider how specific criteria impact recruitment rates. For instance, in pediatric rare diseases, organ impairment is relatively uncommon among younger patients, which suggests that relaxing certain criteria may not significantly affect

TABLE 1 | Rare disease definition in different countries and key initiatives to support rare disease research.

Country/region	Definition of rare disease	Incentives/resources	Description	Key features
United States	<200,000 individuals	Orphan Drug Act (ODA) [7]	Provides incentives for developing drugs for rare diseases, including tax credits, market exclusivity, and exemption from user fees	– 7years of market exclusivity – Tax credits for clinical trials – Exemption from user fees
		Rare Pediatric Disease Priority Review Voucher Program [8]	Grants priority review vouchers for drugs treating rare pediatric diseases, allowing expedited review for subsequent applications	– Accelerated review process – Encourages development of pediatric treatments
		Accelerating Rare disease Cures (ARC) Program [9]	Launched in 2022 to address complexities in rare disease drug development and increase treatment availability	– Promotes innovative trial designs – Engages with patients and stakeholders – Enhances regulatory understanding
		Orphan Products Grants Program [10]	Provides funding for clinical trials and natural history studies to support the development of medical products for rare diseases	– Financial support for research – Encourages innovation in treatment development
		Rare Neurodegenerative Disease Grants Program [11]	Awards grants for research and development of interventions targeting rare neurodegenerative diseases like ALS	– Focus on prevention, diagnosis, and treatment – Collaborative funding opportunities
		Humanitarian Use Device (HUD) Program [12]	Designates medical devices intended to treat or diagnose a rare disease affecting fewer than 8000 individuals in the US	– Streamlined approval process – Supports device innovation for rare conditions
		Rare Disease Innovation Hub [13]	Aims to enhance coordination between FDA centers and expedite the approval of rare disease drugs	– Single point of contact for stakeholders – Focus on innovative regulatory science
		Rare Disease Endpoint Advancement (RDEA) Pilot Program [14]	Supports the development of novel efficacy endpoints for drugs treating rare diseases	– Joint initiative between CBER and CDER – Focus on innovative endpoint development
		START Pilot Program [15]	A collaborative initiative to facilitate efficient development of therapies for rare diseases by providing FDA guidance on clinical study designs	– Early engagement with sponsors – Focus on high-quality data generation – Addresses product-specific development issues

(Continues)

TABLE 1 | (Continued)

Country/region	Definition of rare disease	Incentives/resources	Description	Key features
European Union	< 5 in 10,000 individuals	Orphan Medicinal Products (OMP) Regulation [16]	Provides a 10-year market exclusivity, protocol assistance from EMA, fee reductions, and EU-funded research for orphan drugs. Encourages member states to offer national incentives such as tax benefits	– Market exclusivity – Protocol assistance – Fee reductions for orphan drug applications
		European Reference Networks [17]	Virtual networks that connect specialized healthcare providers across the EU and Norway to address complex or rare diseases requiring highly specialized treatment	– Improve clinical care through guidelines and training – Involve patients and stakeholders – Conduct research and clinical trials – Enable cross-border collaboration using IT systems
United Kingdom	<1 in 2000	The UK Rare Disease Framework [18]	Supports rare disease treatments through funding, specialized services, and health technology assessments (HTA)	– Access to innovative treatments – Evaluation of cost-effectiveness through NICE
		Innovative Medicines Fund (IMF) [19]	Provides funding for promising medicines that are not yet approved, allowing patient access while further evidence is gathered	– Supports early access to treatments – Focus on high unmet medical needs
Canada	< 5 in 10,000 individuals	The National Strategy for Rare Diseases Strategy [20]	Aims to create a comprehensive framework for managing rare diseases, including financial incentives and support for research. Currently lacks formal orphan drug designation pathways	– Support patient outcomes and sustainability – Invest in innovation – Seek national consistency – Collect and use evidence
Australia	< 2000 individuals	Orphan Drug Program by TGA [21]	Streamlines the approval process for orphan drugs with fee waivers and expedited reviews. Encourages innovation in treatment development	– Fast-tracked approvals – Support for clinical trials in rare diseases
Japan	< 50,000 patients	The Orphan Product Development Support Program [22]	Provides incentives such as market exclusivity and grants for clinical trial costs for orphan drugs. Encourages early consultation with regulatory authorities	– 10 years of market exclusivity – Financial support for clinical trials
		Sakigake Designation System [23]	A unique initiative aimed at expediting the development of innovative medical products, including those for rare diseases. Allows faster review processes and provides additional support	– Priority review process – Enhanced consultation with regulatory bodies
Brazil	< 65 in 100,000 individuals	The Brazilian Rare Disease Law (Ordinance No. 199, issued on January 30, 2014) [24, 25]	Provides incentives such as tax exemptions, priority in public procurement, and expedited registration processes for orphan drugs. Encourages local production of rare disease treatments	– Tax benefits for manufacturers – Simplified regulatory processes

TABLE 2 | Patient eligibility criteria in clinical trials (inclusion/exclusion) that can be revised to maximize recruitment of rare disease patients in clinical trials.

Criterion	Suggestion	Reasoning
Organ impairment (renal and hepatic impairment)	In absence of urinary excretion data, you may consider including patients with mild renal impairment in the early phase clinical trials if there is assuring nonclinical toxicology data and if there is an adequate safety margins for the tested doses	Mild renal impairment is not expected to result in exposure more than 2-fold, which is acceptable for wide therapeutic range drugs [33]
	For drugs that are not predominantly cleared through kidney, consider including patients with mild and moderate renal impairment in the P2/P3. Inclusion of subjects with severe renal impairment can be considered based on availability and totality of evidence approach (based on Safety results from nonclinical programs, safety for earlier trials for high doses)	If drug is excreted unchanged with $<30\%$, mild and moderate renal impairment is expected to have <2-fold increase in drug exposures. This increase in exposure is considered clinically insignificant for drugs with clean clinical safety profile. It should be noted that, for orally administered drugs, it is important to understand that the fraction excreted unchanged may be underestimated Data from Drug–drug interaction and hepatic impairment can enabling inferring the expected impact of urea toxins on drug exposures and hence the need for dose adjustment in patients with severe renal impairment [33]
	For drugs that are predominately renally cleared, you might consider approaches such as PBPK model predictions of the impact of renal impairment on drug exposure and also consider sequential risk-based assessment with sequential enrollment of mild then moderate renally impaired subjects	Certain food (e.g., grapefruit) may have impact on CYP enzymes and transporters. Literature evidence regarding the strength of interaction may vary. PBPK modeling can enable reasonable predictions of drug exposures [33–35]
	For modalities with known excretion pathways that are not expected to be through the kidney (e.g., mAb, oligonucleotides, enzyme replacement therapy), excluding any subjects with organ impairment is not needed	These modalities are not expected to be renally cleared and therefore, no impact on PK. If there are no safety considerations or impact on response or pharmacodynamics expected, there is no need for restrictive criteria. Population PK/PD and exposure-response analysis can be used to further assess the impact of renal impairment on exposure and response [34]
	Consider including subjects with hepatic impairment for drugs that are cleared mainly through the kidney or for drugs with no expected metabolism through liver microsomes (e.g., mAb and oligonucleotides) or limited hepatic metabolism (i.e., fraction metabolized $<20\%$)	The drug exposure is unlikely to be affected by hepatic function [35, 36]

(Continues)

TABLE 2 | (Continued)

Criterion	Suggestion	Reasoning
Drug–drug interactions	Utilize endogenous biomarkers in early phase clinical studies to de-risk potential clinical drug–drug interaction	Endogenous biomarkers are increasingly used now to indicate whether a drug inhibits key transporters or enzymes, allowing for early identification of DDI risks without the need for extensive dedicated studies [37]. If there is not risk of drug–drug interaction, inclusion/exclusion criteria can be widened
	For drugs that are substrate for several enzymes or can impact many enzymes and transporters, consider a risk-based assessment strategy where close monitoring of subjects' safety during the clinical trials is performed Consider conducting epidemiological screening to assess the likelihood of coadministration of comedications that can result in a drug interaction and consider delaying the conduct of clinical DDI and update exclusion criteria if the likelihood of coadministration is low	If the interaction affects only a minor metabolic pathway, or affects a major one but metabolism can shift to unaffected pathways, drug levels may not change significantly [38]. However, for substrate drugs with a narrow therapeutic index, small changes in levels may be significant If the likelihood of coadministration with a certain substrates or perpetrators is low, consider conducting the DDI study post approval
	Utilize PBPK modeling to understand the potential for interaction	PBPK modeling can de-risk drug–drug interaction potential identified based on in vitro drug–drug interaction data [37] A typical washout of perpetrators is 5 half-lives for inhibitors and between 7 and 14 days or 5 half-lives of inducers (whichever is longer). However, PBPK modeling can enable assessment of the impact of a shorter washout period on the drug exposure. Consider a $\leq$2-fold change in drug exposure if wide therapeutic window is expected [37]
Food drug interactions	Leverage resources of food drug interaction database and literatures, and PBPK modeling approaches to make informed decisions about necessary food restrictions without imposing unnecessary limitations on participants [39–41]	The strength of the evidence regarding specific food drug interaction should be carefully assessed by assessing the literature. PBPK modeling can inform the level of impact of certain food on drug exposures. See for example [42, 43]

recruitment; thus, the type and timing of these assessments could be discussed with the regulators.

4 | Understanding the Global Support for Rare Disease Research and Development

In the US, the Orphan Drug Act (ODA) incentivizes the development of treatments for rare diseases by offering benefits such as tax credits, market exclusivity, and waivers for certain fees. Similarly, the FDA has established various initiatives like the Rare Pediatric Disease Priority Review Voucher Program and the Orphan Products Grants Program to facilitate research and expedite the approval process for orphan drugs. These programs are designed to enhance access to therapies for conditions affecting small patient populations (Table 1).

The Special Protocol Assessment (SPA) is a regulatory mechanism provided by the FDA in the United States, designed to facilitate the development of drugs intended for serious conditions, including rare diseases. The SPA allows sponsors to obtain FDA agreement on the design and size of CTs intended to support a marketing application, ensuring that the proposed studies will adequately address the regulatory requirements for efficacy and safety. While the SPA is particularly beneficial for rare diseases due to the challenges associated with small patient populations and unique disease characteristics, it is not exclusively limited to these conditions. The SPA can be utilized for any serious or life-threatening disease or condition, thereby extending its applicability beyond just rare diseases. In the context of rare diseases, the SPA can help streamline the development process by providing clarity on regulatory expectations early in the trial design phase. This is crucial since many rare diseases lack established treatment options and have complex biological underpinnings that can complicate CTs designs.

In 2018, the FDA took a significant step forward by establishing the Complex Innovative Trial Design Meeting Program. This program specifically addresses the need for innovative approaches in CTs, particularly when simulations are necessary to determine trial characteristics like power and Type I error. The program structure includes two meetings with regulatory staff, spaced approximately 120 days apart, allowing for thorough discussion and refinement of proposed designs.

In Europe, the Orphan Medicinal Products (OMP) Regulation provides a 10-year market exclusivity period and financial incentives to encourage drug development for rare diseases. The EMA also offers scientific advice to help developers navigate regulatory requirements effectively. Japan's Sakigake Designation System exemplifies an innovative approach that accelerates the development of breakthrough therapies through priority reviews and enhanced regulatory support.

Additionally, global initiatives such as the International Rare Disease Research Consortium (IRDiRC) promote collaboration among stakeholders to improve research outcomes and treatment accessibility. By leveraging these resources and understanding regulatory pathways, clinical pharmacologists can significantly contribute to advancing therapeutic options for rare diseases, ultimately improving patient care and outcomes.

Table 1 outlines various regulatory incentives and supporting resources available worldwide, highlighting key features that support drug development efforts in this critical area.

5 | Designing the Clinical Development Plan (CDP) for Rare Diseases

5.1 | Key Similarities and Differences of the Clinical Development Programs for RDs Versus Common Diseases

When designing CTs for RDs, drug developers must follow the same fundamental principles used in common disease trials—demonstrating both drug efficacy and safety [44]. However, the unique nature of rare diseases introduces several critical challenges that drug developers must carefully navigate. These challenges stem from inherent characteristics of rare diseases: limited patient populations, variable disease progression patterns, and often incomplete understanding of disease pathophysiology and natural history. Such factors create significant complexities in demonstrating efficacy and safety effectively. With lack of clinical study design precedence, drug developers frequently encounter difficulties with patient selection and recruitment, careful consideration of endpoint selection, assurance of adequate statistical power despite small populations, establishment of appropriate control groups, and selection of suitable biomarkers and outcome measurements.

A key distinction in rare disease trials is that they often cannot progress through the traditional Phase 1 to Phase 3 study sequence commonly used in drug development (Figure 1). For instance, conventional dose-finding studies, while standard in common disease trials, may be impractical in rare disease drug development. To address this seamless Phase 1/2 through Phase 3 designs are often considered for rare diseases to reduce development time, where rapid development is crucial due to the unmet medical need. In addition, while traditional approaches to demonstrate substantial evidence of effectiveness require at least two adequate and well-controlled CTs, there is a growing acceptance of using data from a single adequate controlled clinical trial and confirmatory evidence for rare diseases [45].

However, in many rare diseases, flexibility may further be needed, pushing drug developers and regulators to develop and accept alternative evidence generation strategies. These innovative approaches include translating preclinical data to clinical, leveraging biomarker data, real-world data, external control groups, Bayesian analysis, “n-of-1” clinical investigations, and master protocols—each offering unique strategies to address the limitations of conventional CTs and establish confirmatory evidence of effectiveness [46, 47]. It should be noted that such unconventional methodologies require explicit regulatory acceptance of its scientific rigor [48].

5.2 | The Clinical Pharmacology Landscape

A typical clinical pharmacology program follows a well-established pathway that builds evidence systematically. It

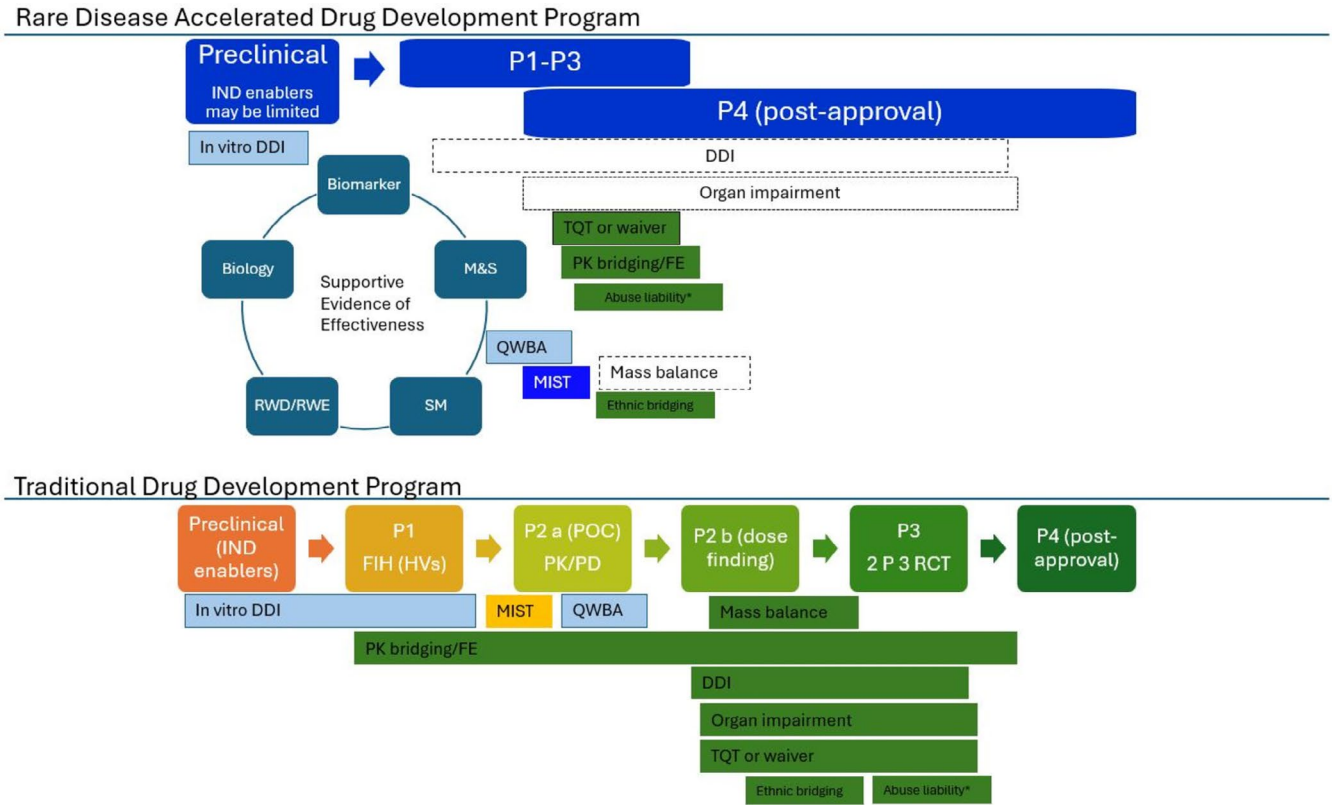

FIGURE 1 | Overview of traditional versus accelerated clinical drug development. Drug development programs typically follow different pathways depending on the therapeutic area and urgency of medical need. In traditional development programs, clinical studies progress sequentially through distinct phases, thus reducing the uncertainty in decision making. For rare diseases and other conditions warranting accelerated development, the program may be streamlined through various approaches. These include conducting seamless Phase 1 through Phase 3 studies in patients or beginning with a Phase 1 single ascending dose study in healthy volunteers, followed by multiple ascending doses in patients, leading into a combined Phase 2/3 pivotal efficacy study. In these accelerated programs, confirmatory evidence of effectiveness may be supplemented through additional sources such as biomarker data, real-world data, and modeling and simulation approaches. Because of the accelerated nature of the development, some of the clinical pharmacology studies may be deferred to after approval or waived. *As deemed necessary for drugs with central nervous system activity. DDI, Drug–drug interaction; FE, Food effect; FIH, First in human; HVs, Healthy volunteers; IND, Investigational new drug; M&S, Modeling and simulations; MIST, Metabolite in safety (using preclinical and clinical data); P1-4, Phase1 through 4 studies; POC, Proof of concept; QWAB, Quantitative Whole-Body Autoradiography (preclinical); RCT, Randomized controlled trial; RWD/E, Real world data/evidence; SM, Statistical methods (e.g., Bayesian analysis, external control and synthetic control arm synthesis); TQT, Thorough QT study.

usually starts with single and multiple ascending dose studies in healthy volunteers to establish drug safety and PK. This is followed by thorough QT studies, drug–drug interaction studies, special population studies (renal/hepatic impairment), food effect studies, and mass balance study. Large Phase 2 studies allow robust dose-ranging assessments, typically evaluating 3–4 dose levels in hundreds of patients. Population PK analyses are conducted with rich data from multiple studies. Exposure-response relationships for both efficacy and safety are characterized through dedicated studies with intensive PK/PD sampling [49].

However, the clinical pharmacology approach in rare diseases requires significant adaptation to meet the accelerated development timelines and the limitations in data [50]. The key is maintaining scientific rigor while being pragmatic and innovative in data collection and analysis approaches. This often requires early and frequent regulatory interaction to align on the development strategy and acceptance of alternative approaches to standard clinical pharmacology requirements. Some clinical pharmacology assessments such as clinical drug–drug interactions (DDIs) studies, organ impairment studies (particularly in severe renal and hepatic conditions), and QT liability assessments have been deferred to the post-marketing phase, provided the missing evaluations don't compromise the drug's safety and efficacy for most patients [51]. Indeed, FDA guidance for developing drugs for treatment of Duchenne Muscular Dystrophy (DMD) and Related dystrophinopathies indicates that regulatory agencies may delay or waive studies on the effects of renal or hepatic impairment if the drug's metabolic pathways and the charactrisitcs of the patient population, when considered together, suggest a low risk of clinically significant impacts on pharmacokinetics or pharmacodynamics [52]. Any remaining gaps can be addressed through postmarketing requirements or commitments.

But the role of clinical pharmacology in the clinical development plan for rare diseases extends beyond these typical clinical pharmacology studies. In rare disease trials, where complete data from Phase 1–3 studies may be limited, clinical pharmacology

clinical pharmacology plays a critical bridging role. It connects established knowledge with unknowns through sophisticated linking and modeling approaches. This is particularly crucial for rare diseases, where traditional data collection may be challenging [53–56]. Table 3 provides a step-by-step guide to the different types of modeling strategies in rare diseases.

6 | Specific Considerations for Clinical Trials in Rare Diseases

6.1 | Navigating Dose Selection With Limited Data

Effective dose selection is crucial for optimizing therapeutic outcomes, particularly in the context of rare diseases where clinical data may be limited. We recently published a review on getting the dose right for rare diseases, and we refer the reader to this comprehensive review [60]. Below is a summary of a few key points for dose selection in rare diseases:

- The foundation of effective dose selection in rare diseases begins with maximizing all available data, including preclinical and early clinical data, as well as alternative data sources. Natural history studies provide valuable insights into disease progression patterns, while real-world evidence can support dose refinement post-approval. In situations where data sources are very limited, including preclinical data, careful individual dose titration may be considered to ensure patient safety and treatment efficacy.
- Model-informed dosing selection integrates multiple data sources to optimize individual patient dosing. PBPK modeling enables accurate prediction of drug disposition in specific patient populations, while population PK/PD modeling accounts for critical inter- and intra-individual variability. QSP models provide deeper insights into target engagement and biological pathways. Disease progression modeling helps account for temporal changes in patient condition, while exposure-response modeling aids in identifying optimal therapeutic windows. Extrapolation from related diseases or adult populations can provide additional insights when direct data is limited.
- Adaptive trial design strategies offer powerful tools for optimizing dose selection in rare disease studies. Bayesian adaptive designs allow for flexible dose-finding approaches, while response-adaptive randomization helps optimize treatment allocation in small patient populations. Platform trials can evaluate multiple doses simultaneously, increasing efficiency. Adaptive sample size re-estimation based on interim analyses helps maintain study power while minimizing patient exposure to suboptimal doses.
- Biomarker-based approaches provide crucial insights for dose selection in rare diseases (refer to biomarker section later). Identifying and validating disease-specific biomarkers help guide dose selection and monitor treatment response. Pharmacodynamic biomarkers establish proof of mechanism, while Surrogate Endpoints (SEs) enable early efficacy assessment. Safety biomarkers help identify dose-limiting toxicities, particularly important in vulnerable rare disease populations. Genetic markers can aid in patient stratification, enabling more precise dosing approaches for specific patient subgroups.
- Dose individualizations are particularly critical in rare diseases, where patient heterogeneity can significantly impact drug response. Age-related differences in drug disposition must be carefully evaluated, especially in pediatric populations often affected by rare diseases. Organ dysfunction's impact on drug exposure requires careful assessment, as many rare diseases affect multiple organ systems. Genetic polymorphisms affecting drug metabolism and potential drug–drug interactions with concomitant medications need thorough evaluation. Disease severity variations must be accounted for in dosing strategies.
- Patient-centric approaches in dose selection have become increasingly important in rare disease drug development. Patient preferences regarding dosing regimen should be carefully considered, including the impact of dosing frequency on quality of life. The feasibility of home administration can significantly affect treatment accessibility and adherence. Patient-reported outcomes should be incorporated into dose optimization strategies, ensuring that dosing approaches align with patient needs and preferences. The impact of dose modifications on adherence must be carefully evaluated to ensure optimal treatment outcomes.

6.2 | Endpoints and Outcome Measures

Selecting appropriate endpoints to be evaluated represent one of the most challenging aspects of clinical trials disease. One of the challenges in endpoint selection is a limited understanding of the natural history of the disease. The clinical manifestations, characteristics of the patient populations and/or subpopulations, and rate of disease progression are oftentimes not clear or well-defined. In addition, there is heterogeneity in disease manifestations, making it challenging to identify an endpoint and to inform its response to treatment interventions. It is important to conduct a well-designed natural history study in the absence of investigational interventions to inform CT design, including endpoint selection.

In diseases where outcome measures have not been established, natural history studies can help identify relevant patient populations, biomarkers, and clinical outcomes of interest that are meaningful to patients and sensitive to changes in the context of CTs. Identification of these elements is critical to inform clinical trial design, maximize the chance of a successful trial, and improve the efficiency of a clinical development program. In certain situations, data from a natural history study may also be used as an external control for a single-arm interventional trial, provided that the patient populations are comparable, the outcomes are well defined, objectives (survival), and collected in a systematic manner, and the potential confounders/biases and missing data are minimized. The challenges in conducting natural history studies include recruiting and retaining representative patients, ensuring standardization of data/sample collection across clinical sites, maintaining/storing study data and samples, minimizing missing data, and documenting changes

TABLE 3 | The role of modeling and simulations in clinical development for rare diseases.

General overview		Case example in RD
a) Population PK/PD and exposure-response		
Example of applications	1. Selecting dosing regimens to be tested in clinical trials by utilizing approaches such as: a. Identifying factors influencing PK and guide dosage regimen to minimize variability in response, supported by E-R data b. Simulate expected drug exposure metrics (e.g., AUC, C_{max}, C_{min}, C_{avg}, etc.) for different doses or regimens to derive individual PK parameters or exposure metrics for use in evaluating exposure–response relationships 2. Informing trial designs to facilitate the reliable estimation of covariate effects through key strategies such as: a. Driving sample size and sampling scheme requirement b. Assessing covariate impact on PK parameters c. Predict sample size needed for specific subgroups (e.g., pediatric, geriatric, renal or hepatic impairment) d. Incorporating variability at individua and population levels e. Simulating various trial scenarios 3. Driving exposure metrics for conducting exposure response analysis	PopPK/PD model to support dose and regimen selection for asfotase alfa in the Hypophosphatasia (HPP) [57] Data collection: a. Data were pooled from 5 clinical trials involving 73 patients aged 1 day–66.8 years b. Data collection included sparse PK, PD (including but not limited to tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP), and immunogenicity data) Exploratory data analysis: Trends of the data vs. time Modeling: c. Develop Population PK and PK/PD models using NLME approach d. PopPK model: a linear two-compartment model was used to describe PK e. PD model: indirect response models were used to describe PD endpoints f. Exposure-response modeling between the estimated average asfotase alfa concentration at steady state (Cavg, ss) and multiple pharmacodynamic, radiological and clinical assessments: (plasma inorganic pyrophosphate or PPi and Pyridoxal-5′-phosphate or PLP), Radiographic Global Impression of Change (RGI-C) and Rickets severity scale (RSS), skeletal morphology and musculoskeletal function, 6-min walk test (6MWT), Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) and Modified Performance-Oriented Mobility Assessment—Gait subtest (MPOMA-G) g. Covariate analysis: Covariates were prespecified or explored to assess their influence on PK and PD Model evaluation: h. PopPK and PK/PD models were assessed using VPC Simulations: i. Dose-exposure-response relationships: simulations evaluated responses across dosing regimens (0.14–14 mg/kg/week) j. Responses plateaued at a dose of ~6 mg/kg/week k. The disease onset subtype (infantile or juvenile) did not influence the dose–response relationships for the endpoints evaluated l. The 6 mg/kg/week dose, representing the median dose administered across trials, was consistent with the findings from dose-exposure-response simulations m. Simulated PD responses were comparable between the 6 mg/kg/week regimens administered as 2 mg/kg three times weekly and 1 mg/kg six times weekly n. Safety assessment examined adverse event rates across exposure quartiles and found no exposure dependent safety concerns at the recommended doses Integration and decision making: o. Modeling and simulation analyses identified 6 mg/kg/week as the recommended dosage regimen This systematic approach ensured the robust evaluation of dose regimens, supporting clinical decisions for HPP treatment
Methodology	Empirical model (top-down) PopPK model is composed of 3 components: a. Structural models: to describe drug kinetics and response b. Stochastic models: capture variability c. Covariate models: incorporate demographic, intrinsic, and extrinsic factors	
Data needed for: a. Constructing the model b. Validating/evaluating the model	Data needed for constructing the model: Time-ordered information on dosing, concentration, biomarkers and PD endpoint, and covariates Validating/evaluating the model: a. Internal validation using data splitting into training and test dataset b. External validation using new dataset from another study c. Goodness-of-fit diagnostic plot: PRED vs. DV, PRED vs. WRES or CWRES, and time vs. WRES or CWRES d. Log-likelihood profiling e. Bootstrapping techniques Simulation-based diagnostics: VPC, NPC, NPDE, PPC plots	
Phase in which it is applied (preclinical, Phase 1 through 4)	Primarily used in Phase 1, 2, and 3 with limited application in preclinical and post-marketing trials	
Special population (pediatrics) [53]	PopPK supports the PIP by providing dosing recommendations, trial designs, and sparse sampling for pediatric studies	
Covariates, extrinsic, intrinsic factors	Extrinsic factors such as Treatment, Food, Concomitant medications, smoking and other environmental exposures Intrinsic physiological factors such as Age, Weight, Height, BMI, Biochemical information (protein and enzyme levels, organ functions measures such as eGFR or ALT, AST), Genetics polymorphism	
Software used	NONMEM, MonolixSuite, Phoenix NLME, and various R packages for modeling and simulations	

(Continues)

TABLE 3 | (Continued)

General overview		Case example in RD
b) PBPK		
Example of applications	1. Pediatrics (pPBPK) dose selection: to inform peds clinical studies and/or confirm dose in extrapolation study section in PIP and PSP 2. DDIs and dose modification: to predict drug exposure impacted by enzyme- or transporter-mediated DDIs 3. FIH dose projection: to predict PK in human based on preclinical exposure (IVIVE) 4. Maternal–fetal (m-f) to predict exposure to drugs throughout pregnancy. 5. Organ (HI& RI) impairment: to design HI and RI studies and/or support the inclusion of RI or HI patients in phase 2/3 clinical trials. 6. Food effect and ARA-DDIs 7. Formulation effect and bioequivalence	Sickle Cell Disease (SCD) Pediatrics PBPK (pPBPK) model for Voxelotor 1. Construct a PBPK modeling using in vitro and clinical data in adults (training set) 2. Verify the model in adults using independent clinical data set (testing set) 3. Refine the model in adults with SCD: account for disease-related changes (drug binding to hemoglobin to increases the protein's affinity for oxygen, adjust blood-plasma ratio) using clinical data set in patients (retrospective simulation) 4. Refine the model in adolescents (12–< 17 years) with SCD 5. Integrate age-related changes (allometry, maturation modifier on clearance, plasma protein binding and ontogeny changes for albumin that impacts drug binding and hematocrit changes that impacts blood exposure of the drug) based data in children and adolescents with SCD 6. Predict exposure and dose of voxelotor in younger ages (based on FDA's distinct categories for pediatric patient populations): a. Neonates—birth through 27 days, corrected for gestational age b. Infants—28 days–23 months c. Children—2–11 years d. Adolescents—12–< 17 years
Methodology • Empirical vs. mechanistic • Bottom-up vs. top-down	Mechanistic model (bottom-up) or semi-mechanistic (middle-out; to bridge any gaps in "system" parameters)	
Data needed for: • Constructing the model • Validating the model	For DDI application—construct substrate and perpetrator PBPK model using: In vitro and in silico human ADME data • Physicochemical: LogP, pKa • In vitro absorption: Peff, solubility, Distribution: B/P, Kp, Kd, $f_{u,p}$, • Metabolism and transport: Km, Vmax, Jmax, Clint DDI: Ki, Kinact, KI, Induction (EC50, Emax, and γ) In vivo human PK data (for validating the model) • Absorption and first pass metabolism: F=Fa.Fg.Fh, Ka • Elimination: CL, CLR • PK of metabolite(s) after parent drug administration • mass balance study, single-dose and multiple-dose ascending study data	
Phase in which it is applied (preclinical, Phase 1 through 4)	Preclinical to Phase 1, 2, and 3 (predicting the DDI potential based on PBPK modeling early in drug development can appropriately inform inclusion/exclusion criteria or dosing strategy for Phase 1/2/3 trials)	
Special population (pediatrics)	FDA request an initial PSP following the end of Phase 2 meeting whereas EMA require a PIP before a marketing authorization application, respectively	
Covariates, extrinsic, intrinsic factors	Extrinsic factors 1. Formulation(s) (solubility enhancers, amorphous, controlled release, long acting injectables, gastroretentive, etc.) 2. Concomitant medications (ARA/PPI, CYPs inhibitors/inducers, transporter) 3. Food (fasting, fed, HFB, LFB), pediatrics food (cow's milk and soy formula, human breast milk & formula milk, FaSSIF and FeSSIF) 4. Routes of administration (ocular, pulmonary, oral, subcutaneous, dermal) Intrinsic physiological factors 1. Age—pediatrics and geriatrics 2. Weight 3. Pregnancy 4. Genetics polymorphism (DGI) 5. Kidney impairment 6. Liver impairment 7. Other disease conditions (e.g., achlorhydria)	
Software used	GastroPlus, Simcyp, and PK-Sim (with defined "system" parameters) or other software that need qualification & validation	

(Continues)

TABLE 3 | (Continued)

General overview	Case example in RD
c) QSP modeling	
Example of applications	Target selection, MOA, target engagement, translational PK/PD, dose finding, support regulatory strategy
Methodology	Mechanistic (bottom-up), semi-mechanistic (middle out), multi-scale, multi-modal
Data needed	Animal and human data. Proteomic, metabolomic, biomarker, gene expression/RNA-seq, pharmacodynamic endpoints, clinical endpoints
Phases	Target identification to Phase 3. Distribution of applications weighted more heavily in pre-clinical to clinical proof of concept stage
Software used	Matlab, R, python, C/C++, QSP disease platforms, integrated PBPK-QSP models and platforms
Applications in rare diseases	Enzyme replacement therapy, gene therapy, gene editing, cell therapy, ADCs and bispecific

Pediatric extrapolation of Enzyme Replacement Therapy (ERT) for lysosomal storage disorder. In this case, QSP model enabled linking a specific (pathway based) biomarker to pharmacodynamic response (e.g., Sphingomyelin) as well as linking this biomarker to clinical endpoints of interest e.g., Spleen volume or DLCO (lung function) [58, 59]

Specific steps included:

1. Landscape of disease mechanisms and drug MOA
2. Scoping of mechanisms implicated in both adult and pediatric populations
3. Evaluating scope of available data
4. Linkage of mechanisms to clinical characteristics
5. Description of model structure and equations
6. Code development, implementation of model
7. Optimization of model to available data
8. Validation of model on independent datasets
9. Development of simulation scenarios and cohorts
10. Summarizing results and conclusions

While the steps appear linear, there is often iteration and cycling through steps to balance the level of detail in the model, available data, and fitness-for-purpose for intended application

in diagnostic criteria and standard of care. Additionally, two types of measures that can be used for assessing outcomes in CTs include clinical outcome assessments (COAs) and surrogate endpoints (SEs).

6.2.1 | Understanding Challenges in Clinical Outcome Assessments and Ways to Address Them

COAs are measures that describe or reflect how a patient functions, feels, or survives; they are direct measures of clinical benefit. The type of COA [i.e., patient reported outcome (PRO), observer reported outcome (ObsRO), clinician-reported outcome (ClinRo), and performance outcome (PerfO)] to be used and evaluated in CTs is driven by the concept of interest (COI) to be measured and the context in which it will be applied, that is, context of use (COU). The COI is the aspect of an individual's experience or clinical, biological, physical, or functional state that the assessment is intended to capture. The COU specifies the way COA scores will be used as the basis for an endpoint, including the purpose for their use in a drug development program [61].

When there are limited natural history data and wide variations in disease presentations and progressions, COIs are not completely apparent, making it challenging to select and develop COAs for endpoint measurement. To better understand the natural history and COIs and to construct an appropriate COA measurement strategy, it is important to collect information from multiple sources, including literature, clinical experts, and patient advocacy groups [62]. Input from patients and caregivers can also be obtained using qualitative interviews or surveys. However, due to the rarity of the disease, it may be difficult to recruit a representative sample of patients or caregivers for qualitative purposes [63].

The low prevalence and heterogeneity in the disease onset and symptoms in rare diseases often result in evaluations of patients from different age groups and geographic regions with various disease severity and/or progression in a single trial. This poses challenges not only in choosing the outcome to be assessed but also in defining the COU. A measurement strategy is to focus on common symptoms across patient subgroups and to include multiple types of COA instruments such as ObsRO and PerfO to measure outcomes across age groups [61]. Alternative COA approaches potentially addressing heterogenous manifestations may include the use of multiple endpoints (including multicomponent endpoints and composite endpoints) among others in rare disease CTs [64, 65]. The use of multiple endpoints with global hypothesis testing exemplifies such an approach to improve the power of the CTs to detect differences between treatment groups in heterogenous patient populations.

Many rare disease trials are conducted across the globe as patients are geographically dispersed, as mentioned previously. In this case, cultural relevance and appropriateness must be considered in the selection of COAs, and they can be examined through translatability assessment [62]. Rater training and calibration are important considerations in implementing the outcome measurement in rare disease trials, in which modified COAs or different rating scales for different age subgroups are used and/or evaluations are performed by multiple investigators across different sites and countries [63].

It is important that the COA instrument chosen for endpoint measurement is appropriate for the COI and COU and is fit-for-purpose i.e., the evidence supporting the instrument's content validity and reliability is sufficient to support its COU. Content validity refers to the adequacy with which a measure assesses the domain of interest, and reliability is the degree of consistency exhibited when a measurement is repeated under identical conditions [66]. Only a few disease-specific COA instruments are currently available and deemed sufficient for use in rare diseases. Given the extensive time to develop a new COA for use in rare disease populations, appropriate items that match the COI and the COU can be selected using existing item banks and COAs. Alternatively, existing COAs or items from existing banks/COAs can be modified and validated for the proposed COU [62].

6.2.1.1 | Using ObsRO as a Clinical Outcome Assessment (COAs) in Pruritus in Patients With all Forms of Progressive Familial Intrahepatic Cholestasis (PFIC). Odevixibat was developed to treat a rare liver condition called progressive familial intrahepatic cholestasis (PFIC), where patients experience severe, persistent itching (pruritus). Through reviewing medical literature and conducting interviews with patients, caregivers, and medical experts, it was confirmed that itching was the most important symptom to measure and itching severely impacted patients' quality of life, especially during nighttime. Based on this data, a single-item ObsRO was devised to measure the "Scratch" concept, where caregivers would observe and rate the severity of their patient's scratching twice daily. In the Phase 3 clinical trial, the scores from this ObsRO were used to define a positive pruritus assessment that was subsequently used in defining the primary efficacy endpoint, which was the proportion of positive pruritus assessments at the patient level over the 24-week treatment period [67].

6.2.2 | Understanding the Importance of SEs in Rare Diseases

SEs are endpoints that are used in CTs as a substitute for a direct measure of how a patient feels, functions, or survives; they are indirect measures of clinical benefit. They are often used when the direct measurement of a clinical outcome is impractical, time-consuming, or ethically challenging. These may include biomarker or intermediate clinical outcomes. From regulatory perspectives, a SE can be classified into the following:

- A validated SE is an endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the SE predicts a specific clinical benefit [68, 69]. A validated SE could be used to support traditional full approval.
- A reasonably likely SE (RLSE) is an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the SE is expected to be correlated with an endpoint intended to assess clinical benefit in CTs, but without sufficient clinical data to show that it is a validated SE [68, 70]. A RLSE could be used to support accelerated approval, which is a regulatory pathway offered by regulatory agencies, such as FDA, to expedite the approval of drugs for serious conditions that fill an unmet medical need based onSEs. A RLSE could be used as a basis for accelerated approval with the requirement of a postmarketing confirmatory trial to verify the clinical benefit. If the confirmatory trial shows that the drug actually provides a clinical benefit, traditional approval for the drug can be granted. On the other hand, if the confirmatory trial fails to demonstrate that the drug provides clinical benefit, there are regulatory procedures in place that could lead to removing the drug from the market [71].
- A candidate SE is an endpoint or biomarker still under evaluation for its ability to predict clinical benefit (BEST glossary).

7 | Some Important Tools and Strategies in Rare Disease Drug Development

7.1 | Utility of Biomarkers in Rare Disease Drug Development

Biomarkers, such as genetic mutations, protein expression levels, or specific disease-related molecules, can help identify patients who are more likely to respond to a particular treatment. Additionally, biomarkers can serve as objective measures to monitor disease progression and evaluate the effectiveness of experimental therapies. By leveraging biomarkers, researchers and clinicians can optimize drug development strategies, improve patient selection, dose selection, and accelerate the discovery of much-needed treatments for rare diseases.

The examples below highlight how biomarkers can be crucial in diagnosing, monitoring, and developing treatments for rare diseases, ultimately improving patient outcomes:

- The use of Fibroblast Growth Factor 23 (FGF23) in Tumor-induced Osteomalacia: Elevated levels of FGF23 (Fibroblast Growth Factor 23) are used as a biomarker to diagnose and monitor treatment response in patients with this rare condition, which causes weakened bones and severe pain [72].
- Using Cystatin C in Nephropathic Cystinosis: Cystatin C levels are used to assess kidney function in patients with nephropathic cystinosis, a rare genetic disorder that leads to the accumulation of cystine crystals in various organs, including the kidneys [73].
- Using Alpha-Galactosidase A in Fabry Disease: This enzyme deficiency is a biomarker for Fabry disease, a rare genetic disorder that leads to the buildup of a specific type of fat in the body's cells, causing pain, kidney failure, and heart issues [74].

In addition, biomarkers are increasingly being used as a RLSE (to support accelerated approval) or a validated SE (to support traditional full approval) in rare diseases to expedite the development of new treatments. For instance, in Duchenne muscular dystrophy (DMD), biomarkers such as microdystrophin or dystrophin expression have been utilized as RLSE to support accelerated approval [75, 76]. Another recent example is the use of NFL as a RLSE to support the accelerated approval of tofersen in superoxide dismutase 1 amyotrophic lateral sclerosis (SOD1 ALS) patients [77].

As discussed in the Endpoint and Outcome Measures Section, biomarkers as validated SE are endorsed when the biomarkers can substitute proxy measures used in CTs to predict clinical benefit or outcomes that are considered meaningful for patients. Use of biomarkers for traditional full approval requires a more extensive evaluation of both analytical and clinical validation. Clinical validation includes strong correlation with clinical outcome measures. While statistical correlations established through large interventional outcomes studies have frequently been used to develop predictive relationships, correlations alone do not provide predictive value for a biomarker that can be evaluated based on its biology. The biological bases of biomarkers and their relationship to the pathophysiology of disease represent a valuable and critical insight into predictive value. Mechanistic modeling tools such as Quantitative System Pharmacology (QSP) become important in this regard. Refer to the QSP modeling section for more details.

7.2 | Real-World Data and Evidence for Rare Diseases

As mentioned previously, a key reality in rare disease research and drug development is the limited availability of data. These limitaitons span multiple categories and impact all stages of drug development. This provides both a challenge and an opportunity for pharmaceutical sponsors to fill some of these data gaps, assuming the data in question is of sufficient density and quality and aligned with the proposed disease target. Also, due to the small numbers of people affected, there are unique challenges in understanding rare diseases and drug development for these conditions, including patient identification and recruitment, trial design, and costs. Natural history data and RWD play significant roles in defining and characterizing disease progression, final patient populations, novel biomarkers, genetic relationships, and treatment effects [78, 79].

7.2.1 | Types of RWD/RWE Used for Rare Disease Research

Real-world evidence (RWE) clinical evidence refers to the potential risks and benefits of medical products, derived from real-world data (RWD). RWD can include patient demographics, medical history, clinical outcomes, patient-reported experience measures, costs, and resource use. Different types of experimental and observational study designs can help generate RWE from RWD. The different types of RWE studies are often categorized as non-interventional (i.e., observational) studies and analyses that include registry, claims database, patient surveys, and abstraction analysis [80].

Sponsor companies often acquire such data either through service agreements or direct procurement of certain data types for targeted disease states from various vendors (refer for Table 4 for vendor examples). Of course, the format of the various RWD types is varied and unlikely to be structured or compliant with regulatory standards. This makes integration with traditional, structured, company-generated data a challenge.

7.2.2 | Integrating RWD and Modeling Approaches—General

Real-world data answers some regulatory questions, guides study designs, and enables drug differentiation. Integrating real-world evidence (RWE) with modeling can have many benefits for rare disease drug development, including improved and augmented CTs, earlier access to treatments, patient identification, a more informed disease progression model, and overall better decision making [78, 81–83]. With respect to improvements in CTs specifically, RWD and RWE can help by generating hypotheses, identifying patient baseline characteristics, and assessing trial feasibility. RWE can augment CTs by providing additional data on a drug candidate's safety and efficacy. For example, RWE can generate synthetic control groups for rare diseases as part of a clinical trial simulation exercise.

There is a natural symbiosis between data, models, and tools. While there is a hierarchy to these elements, they carry separate but related expectations with respect to quality, information value, and standardization that are needed for the integration of disparate data types so that the joined (integrated) data can be used with confidence and that the models and tools built from such data can be used with high fidelity. The addition of RWD types creates additional challenges to this process as the data types are often large, unstructured, and may not adhere to conventional or any data standards. In addition, the integration of RWD for the purpose of a control group in various clinical designs can create problems with balance, particularly when

TABLE 4 | Some external sources of RWD used to support rare disease drug development (often purchased or acquired by pharmaceutical sponsors).

Vendor (link)	Data type
Truveta (https://www.truveta.com/)	EHR data—including notes and images; linked with SDOH, mortality, and claims data for more than 120 million patients
Worldwide Clinical Trials (https://www.worldwide.com/)	Registries and NHS natural history studies; access to medical claims through Trinity Analytics; access to historical medical records
Komodo Health (https://www.komodohealth.com/)	Average 7+ years of patient journeys for more than 330 million unique US individuals
Castor (https://www.castoredc.com/)	Platform provides scalable technology for long-term data collection and analysis across diverse patient populations

Abbreviation: SDOH, Social Determinants of Health.

conditional probabilities are estimated from unbalanced designs, as could be derived from using RWD compared with CT data in rare disease patients. More experience and regulatory guidance is needed here as well.

7.2.3 | Overcoming Challenges of RWD for Rare Diseases

Most sponsors recognize the difficulty of generating enough data from their own development plans to support a regulatory filing for rare or ultra-rare disease indications. In addition, RWD sources for all 10,000 rare diseases simply do not exist. Even so, there are initiatives to promote collaboration and co-investment in rare disease R&D with the intention of both leveraging the available data and creating opportunities to collaborate on models and tools that improve the quality of the regulatory filings.

Two of the more recent and prominent efforts in the quest to leverage RWD for pediatric rare disease research and development are the rare disease cures accelerator, data analytics platform (RDCA-DAP) supported and governed by the Critical Path Institute and funded by the US FDA and the Ecosystem for Rapid adoption of modeling and simulation Methods (ERAMET) New Horizons Grant (HORIZON-HLTH-2023-IND-06-04) effort supported by the EU [84–86]. Both efforts emphasize maximizing available data to inform rare disease drug development, but both are beholden to various data generators to share this data and information to inform the greater rare disease ecosystem. Of note, in 2023, the US Food and Drug Administration (FDA) approved the first medication, called omaveloxolone, to treat Friedreich Ataxia (FA) in individuals 16 years of age or older [87]. This was done based on data shared via the C-Path RDCA-DAP platform. This product was also approved in Europe in Feb. 2024.

ERAMET's focus is to rethink the assessment and development of orphan and pediatric medicines with emphasis on integrating modeling and simulation methods alongside real-world data. The ERAMET project involves 17 partners from Belgium, Norway, the UK, Italy, Spain, France, and the Netherlands. They are working together over a period of 4 years. ERAMET intends to provide and implement a robust framework for the development and validation of mature modeling and simulation methods, specifically tailored to address regulatory needs in the development and assessment of orphan and pediatric medicines. It will establish a transparent ecosystem for drug development and assessment, facilitating the adoption of modeling and simulation (M&S) methods along with various data types, including real-world data such as registries and electronic healthcare data. One of the expected outcomes of the effort will be the development of models and tools supporting defined use cases that can likely be prequalified by the EMA for broader use supporting rare disease drug development.

8 | Modeling and Simulations

Modeling and simulation are particularly useful to drug developers because they enable drug developers to: support recommendations on dosing, the evidence for safety and efficacy in addition to certain clinical study design features such as sample sizes, sampling schemes, and patient and endpoint selection. Furthermore, it allows developers the ability to test critical assumptions linked to various drug development milestones as well as critical design constructs [77]. These are essential for rare disease drug development given the paucity of data available in target populations and the reliance on extrapolation of assumptions from mainstream diseases and populations [78, 79].

Population pharmacokinetic/pharmacodynamic (PK/PD) modeling and exposure-response analyses are now universally adopted by companies developing drugs for rare diseases [53]. Complementing these analyses, physiologically based pharmacokinetic (PBPK) modeling predicts how drugs are absorbed, distributed, metabolized, and excreted across different tissues and organs. PBPK models are particularly valuable for understanding the impact of patient-specific factors like kidney and liver function, potential drug interactions, and age on drug exposure. While the adoption of PK/PD and PBPK modeling is widespread, QSP is a more recent addition to the modeling toolkit that has seen increasing uptake in recent years.

Quantitative systems pharmacology is a mechanistic modeling approach that has been applied across a wide spectrum of diseases to advance and prioritize data-driven hypotheses on investigational compounds' mechanisms of action, de-risk the translational parameters for compounds going into the clinic and through proof of concept (POC), as well as inform and advance the design of combination therapies, to name a few (Figure 2) [88–93]. Systems approaches have had a long and rich history and impact in life sciences and medicine and reflect the true system-wide nature of healthy and disease physiology across biological scales. With the advancement of modern measurement technology, the ability to probe and generate data and derive knowledge across these biological scales to further sharpen our understanding of disease has significantly increased. This has improved the ability to develop innovative interventions and led to important innovative medicines that have enhanced health span or increased life span.

In the context of the broad spectrum of rare diseases, including inborn errors of metabolism (IEMs) as well as complex diseases with a polygenic role in the etiology of disease, QSP has played a unique role in advancing our understanding of disease or investigational compounds against unmet medical needs [94–97]. In the case of both IEM and complex rare disease cases, the size of the patient population often translates to and necessitates more agile and well-informed trials to maximize the utility of the generated data toward testing the underlying hypothesis. In the case of IEMs, where known genetic causes of disease and associated pathways are implicated, the use of mechanism-based approaches such as QSP is critical for representing this knowledge in a quantifiable and computable model. This allows for a QSP-based simulation-driven approach to optimizing drug and trial attributes to maximize the probability of success of drug trials and accelerate the approval of innovative medicines. Table 3c provides an overview and specific example for the application of QSP modeling in some IEMs [58, 59].

While the application of QSP in IEMs has benefited from knowledge of genetic causes of disease and associated pathways, more complex rare diseases with a polygenic risk profile and heterogeneous phenotypes represent a different opportunity space.

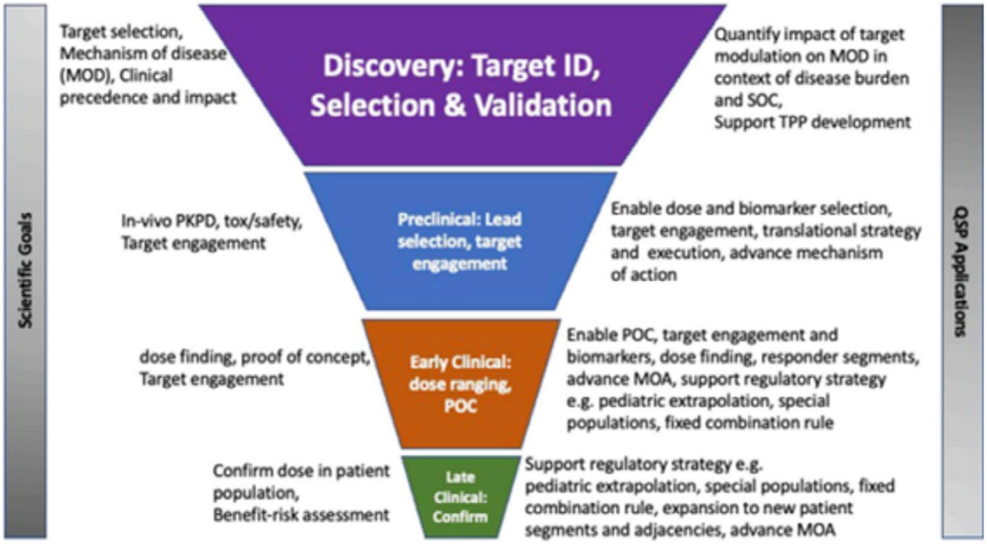

FIGURE 2 | Application of QSP model in drug discovery and development stages. Graphical illustration of the role of translational QSP modeling in drug development decision making from target identification to late clinical development.

One example in this area is Amyotrophic lateral sclerosis (ALS), where much progress remains toward elucidating underlying genetic causes of disease and characterizing patient phenotypes. Identification and targeting of specific genetically defined segments like SOD-1 have enabled and propelled the development of medicines for ALS. A QSP model for SOD-1 ALS was developed and utilized to simulate and optimize the treatment regimen for Tofersen [98]. More broadly, the applications of QSP for complex rare diseases are wide-ranging and also include advancing mechanisms of disease and enabling a range of activities along the translational path toward clinical POC. Examples of these applications include advancement of a biomarker and target engagement strategy, as well as identification and selection of treatment responders for advancement to later stage trials.

The human genome project has catalyzed progress in genetics and genomics. Coupled with continued advancement in computational technology and biological measurements, we are ushering in an era of P4 medicine, namely predictive, preventive, personalized, and participatory [99]. Systems medicine plays a foundational role in advancing and implementing this era of P4 medicine by bridging the increasing body of data we have across biological scales with systems thinking and approaches to push the boundaries of disease understanding and development of innovative medicines [100]. Systems biology and pharmacology (QSP) are indispensable tools in this systems toolbox for both the researcher and drug developer to reap the benefits of these technologies towards accelerating and enhancing the drug development engine [101]. As highlighted in this tutorial, there is much momentum to build upon, leveraging and building on the catalogue of successful QSP case studies to advance the development of novel drugs for rare diseases.

9 | Key Take Home Messages and Future Direction

This tutorial is meant to serve as an introductory guide for those who are novices to the field. Designing CTs for rare diseases involves several unique challenges beyond the fundamental principles that apply to common diseases. Collaboration between multiple subject matter experts, including biostatisticians, clinicians, and clinical pharmacologists, is instrumental in optimizing trial design and execution. The recently introduced ICH M15 guideline provides an excellent framework for fostering such collaborations, including early interactions with regulatory authorities [102]. This guideline emphasizes the importance of cross-functional teams in developing and validating biomarkers, determining appropriate sample sizes, and designing efficient trials. Furthermore, strategic partnerships between academic institutions, industry partners, and regulators can enhance the overall quality and efficiency of CTs. These partnerships can facilitate knowledge transfer, promote scientific innovation, and optimize patient recruitment and retention strategies. Moreover, the ICH M15 guideline provides a standardized approach and language for MIDD, serving the harmonization of regulatory standards across regions, reducing duplication, and fostering shared assessments among agencies.

General guiding principles to design a clinical development program for rare disease can be as follows:

1. Adhering to Fundamental Principles: the primary focus of any clinical trial, including those for rare diseases, is to demonstrate the drug's efficacy and safety.
2. Recognizing Challenges in Rare Diseases: rare diseases have smaller patient populations, which complicates patient recruitment and selection. The progression of rare diseases can be unpredictable, adding complexity to the trial design. A limited comprehension of disease pathophysiology and natural history makes it harder to design effective trials.
3. Addressing Patient Selection and Recruitment: Develop targeted recruitment strategies, collaborate with patient advocacy groups, rethink patients' inclusion/exclusion criteria to maximize recruitment, and use global trial sites to increase participant numbers.
4. Identifying and Selecting Endpoints: Carefully choose clinically meaningful endpoints that reflect the patient population and the disease characteristics.

5. Ensuring Statistical Power: Utilize adaptive trial designs and Bayesian statistical methods to enhance statistical power despite small sample sizes.
6. Establishing Control Groups: Consider external controls, patient registries, and/or RWD when traditional control groups are not feasible.
7. Selecting Biomarkers and Outcome Measurements: Select biomarkers and outcomes that are relevant and sensitive to changes in the disease condition.
8. Rare disease trials may not follow traditional Phase 1 to Phase 3 progression. Use clinical pharmacology to bridge data gaps and inform labeling, especially important for rare diseases. Tools such as PBPK and QSP models and real-world data and evidence are particularly useful for rare diseases.
9. Use available regulatory resources: There are multiple mechanisms via which drug developers can consult the FDA starting from early stages of drug development, including regarding the adequacy of the clinical pharmacology program, use of MIDD, and align on study designs.

It is important to note that we did not cover some aspects that require tutorials each on their own. Novel modalities in rare diseases and the use of artificial intelligence/machine learning (AI/ML) to repurpose existing drugs are transforming the landscape of rare disease treatment. The emerging field of digital twins, which creates virtual representations of individual patients by integrating real-time data with mechanistic models, holds immense promise for personalizing treatments. Similarly, end-to-end modeling approaches that connect early bench research through clinical development to commercial forecasting represent an important frontier that deserves dedicated attention.

Additionally, digital health solutions are revolutionizing rare disease management by creating unprecedented opportunities for patient care and data collection. Remote monitoring technologies, including wearables and connected devices, enable continuous tracking of patient symptoms and vital signs, reducing the burden of frequent clinic visits while providing real-time health insights to healthcare providers. Digital biomarkers, derived from these monitoring tools, offer objective measures of disease progression and treatment response, particularly valuable in rare diseases where traditional endpoints may be challenging to assess. Tracking disease progression through digital tools allows for more precise documentation of the natural history of rare diseases, capturing subtle changes that might be missed in traditional clinical settings. Together, these digital health solutions are transforming rare disease care by enabling more personalized, data-driven approaches while simultaneously building a deeper understanding of these conditions through continuous, real-world evidence generation. However, these are beyond the scope of this introductory tutorial and are not covered here.

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A.I. tools such as ChatGPT were used to improve the readability.

Conflicts of Interest

Mariam A. Ahmed is an employee of Takeda and has received salaries and stocks. Bilal AbuAsal is an employee of Boehringer Ingelheim and has received salaries and stocks. Jeffrey S. Barrett is an employee of Aridhia Bioinformatics and has received salaries and stocks. Karim Azer is an employee of Novartis and has received salaries and stocks. Elizabeth Shang is an employee of Merck & Co and has received salaries and stocks. Noha Rayad is an employee of AstraZeneca and has received salaries and stocks. All other authors declared no Conflicts of Interest for this work.

Disclaimer

The opinions expressed are the employees' own and not those of their respective organization.

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