Innovations and Best Practices for Therapeutic Development in Pediatric Rare Diseases: A Model-Informed Drug Development Perspective

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Emerging innovations in pediatric rare diseases are offering up the opportunity to fundamentally change the way therapeutic development in pediatric rare diseases is enabled, largely through the application of model-informed drug development (MIDD). Pediatric rare diseases, often characterized by small patient populations, patient heterogeneity that is compounded by differences in adult and pediatric diseases, and limited development options, pose significant challenges in drug development. The ICH E11(R1) addendum particularly calls out the value of modeling and simulation and other statistical approaches in extrapolation and filling the gaps in knowledge and/or reducing uncertainties. Therefore, MIDD provides a powerful solution by enabling more efficient, data-driven decision-making, reducing the need for large, costly trials while ensuring that clinical endpoints are both relevant and feasible. MIDD approaches have been able to extrapolate the treatment responses from adults to pediatrics, making decisions around the viability of targets and dose selection simpler. In this whitepaper, we build on our previous results by critically examining the role of biomarkers and surrogate endpoints, statistical innovations, and modeling and simulation best practices as they apply to pediatric rare diseases therapeutic development. We posit that the effective integration of digital biomarkers, patient-reported outcomes, and quality of life methodologies into the development of therapies for pediatric rare diseases will catalyze a significant shift towards more personalized, patient-centered approaches in this vulnerable population.

Pediatric rare diseases continue to remain an underrepresented and understudied vulnerable population in clinical trials. The drug development landscape for these diseases is rapidly evolving, driven by advances in quantitative methods, regulatory frameworks, and patient-at-center efforts. However, significant barriers remain in translating discoveries into accessible, effective therapies for children with rare diseases. The unmet need for treatments for pediatric rare diseases is striking. Children with rare diseases may face delayed diagnoses, incorrect or missed diagnoses, and inadequate care due to off-label use, to an extent greater than adult rare diseases. Many children with rare diseases are left without treatment options, leading to diminished quality of life, physical disability, and, in some cases, premature death. The regulatory environment for pediatric rare diseases has also evolved, with regulators increasingly recognizing the need for specialized approaches to ensure that children with these diseases have access to effective treatments. In the United States, the Food and Drug Administration's (FDA) flagship regulatory mechanisms to accelerate the approval of drugs for rare diseases, including the Orphan Drug Designation, Breakthrough Therapy Designation, and Priority Review pathways, have been actively pursued by drug developers. Subsequently, the Guidance to Industry on FDARA Implementation gives clarity on pediatric investigations of molecular targeted drugs for rare cancers.[1] The very recent announcement of the US FDA setting up a rare diseases innovation hub and its strategic priorities (https://www.fda.gov/industry/medical-roducts-rare-diseases-and-conditions/fda-rare-disease-innovation-hub) is one example of the several regulatory frameworks being developed to ease the uncertainty of drug development in this segment. At the core of this discussion lies the construct of model-informed drug development as a principal integrative science. These regulatory mechanisms, combined with greater applications of MIDD particularly to substantiate the evidence of effectiveness thresholds for approval, have contributed to an increase in the number of approved treatments for pediatric rare diseases in recent years. Despite these advancements, there is a dire need for an increased rate of approval of medicines for rare pediatric indications. A look at the orphan drug designation database (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm) reveals that only 55 products have been approved between 1983 and 2025, at the time of writing this paper.

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In this whitepaper, we focus our expertise on areas of immediate impact using the emerging innovations in drug development science. Our prior work identified key areas of focus within the pharmaceutical industry,[2] as they relate to biomarkers and surrogate endpoints, innovations in advanced statistics, and model-informed drug development tools. In this whitepaper, we have examined some of the areas where MIDD tools have facilitated decision making in greater depth and propose some areas for further discussion and engagement. We also highlight two key case studies, both focusing on the strength and rigor of extrapolation for pediatric diseases based on limited adult data.

BIOMARKERS AND SURROGATE ENDPOINTS

The landscape of therapeutic development for pediatric rare diseases is evolving as pharmaceutical enterprises continue to place emphasis on patient-centered approaches. This is particularly the case in biomarkers and surrogate endpoints, with emerging emphasis on digital biomarkers, patient-reported outcomes (PROs), and quality of life (QoL) methodologies. As these newer avenues begin to take shape and play a key role in drug development, more emphasis has been given to biomarker qualification and validation. The complexity of the disease manifestations, particularly as it relates to adult and pediatric disease heterogeneity, creates an opportunity for more integrated methodologies paving the way for more personalized, real-time, and relevant endpoints in clinical trials and therapeutic interventions.

Digital biomarkers

Digital biomarkers are generally defined as objective, quantifiable physiological and behavioral data collected through digital technologies such as wearable devices, mobile apps, and sensors. The US FDA actually phrase these tools as a digital health technology (DHT) and defines them as a "system that uses computing platforms, connectivity, software, and/or sensors, for health care and related uses" in their December 2023 Guidance for Industry on DHT for Remote Data Acquisition in Clinical Investigations.[3] These biomarkers offer the potential for a significant advantage in rare pediatric diseases by providing continuous, real-time insights into the patient's health status, which can be particularly important for monitoring conditions that are difficult to assess in a clinical setting. Unlike traditional biomarkers, which often require invasive or one-time measurements, digital biomarkers allow for ongoing monitoring, capturing the dynamic nature of diseases that more dynamically change over time.

In the context of pediatric rare diseases, digital biomarkers are being increasingly considered in drug development. The first and most notable endpoint is the stride velocity 95th centile (SV95C) which was qualified as a primary endpoint by the European Medicines Agency (EMA) in trials for Duchenne muscular dystrophy.[4] However, the long lead times for the regulatory qualification of such measures as primary endpoints in pediatric rare diseases have been a constraint that must be overcome.[4]

There are examples of digital biomarkers in other rare indications mainly in adult development programs. Alexion and AstraZeneca have reported the development of digital biomarkers in debilitating rare neurological conditions, including neuromyelitis optica spectrum disorder. This rare autoimmune disorder is characterized by fluctuations in neurological symptoms leading to impaired mobility. Their collaboration with Ad Scientiam, a mobile technology company, emphasizes the generation of real-world patient-generated data by leading the development and clinical validation of potential new platform tools such as the NMOSDCoPilot.[5] Koneska (https://www.koneksahealth.com) indicates on their website the availability of a digital biomarker in Fabry disease. Another example is the Kinesia ONE™ motor assessment system for monitoring motor symptoms (https://www.glneurotech.com). These emerging applications of digital biomarkers in adult rare programs hopefully translate to successful pediatric applications.

PROs

PROs refers to a patient's health status directly from the patient. They are reported without interpretation by healthcare providers. PROs are gaining traction in drug development because they will provide direct insights into how a patient feels and functions in a clinical trial context, leading to understanding important disease specific measures. While the role of the PRO is not yet fully understood within early clinical trials, recent efforts such as FDA's Project Optimus (https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus) have resulted in a more patient-oriented measure of outcomes to better understand and facilitate dose optimization. In pediatric populations, however, PROs are likely to be challenging to collect, as younger children may not be able to articulate their symptoms clearly or are likely to misstated. To better understand their disease status, a modified outcome based on caregiver or parent input will be needed. PRO data are most commonly collected using questionnaires and interviews. PROs are supported by major Western regulatory agencies[6,7] in clinical development, and increasingly, drug developers are trying to incorporate PROs in rare disease drug development programs. While the use of PROs in rare pediatric trials is only just beginning, there are several other examples in common diseases that have successfully used PROs, including the NIH's PRO Measurement Information System (PROMIS) and EORTC's QLQ-C30 in oncology and HOOS-PS for hip osteoarthritis. When searched on clinicaltrials.gov, PRO and rare diseases search term, the authors found 19 entries, indicating much lower involvement.

A similar terminology, and often used interchangeably as PRO, is the QoL methodology. QoLs are used to assess the overall well-being of patients, considering their physical, emotional, and social aspects of health. In pediatric rare diseases, QoL has a significant impact on a child's overall functioning, independence, and ability to participate in school and social activities. Incorporating QoL assessments into clinical trials can help generate supportive data on the viability of the investigative treatments.

STATISTICAL AND DEVELOPMENT CONSIDERATIONS

Platform trials

Platform trials are a subset of master protocol designs[8] that enable the study of multiple drugs in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform based on a decision algorithm. Because of their flexibility, platform trials can learn from smaller patient populations:

this makes them particularly useful and relevant for rare diseases. **Figure 1** shows an illustration of how such a trial can be conceptualized. In this representation, a single comparator or standard of care is one of the study treatments, but there can be several investigational therapies. Staged progression can be designed with interim checks, and at each check, any one or more investigative therapies can be terminated or added.

Platform trials are generally regarded as an innovative approach to address clinical valuation of early-stage candidates, regardless of modality as the evidence evolves. As a type of randomized clinical trial design construct in which multiple interventions are evaluated concurrently against a common control group allowing new interventions to be added and the control group to be updated throughout the trial, they provide a dynamic and efficient mechanism to compare and potentially discriminate new treatment candidates. Their recent use in the evaluation of new therapies for COVID-19 has spurred new interest in the approach. Platform trials can be a superior design compared to a basic 2-arm clinical design when multiple therapies need investigation as it requires only a single control group. This results in the fact that platform trials can be conducted with fewer enrolled patients than a set of potentially redundant control groups in a series of separate 2-arm trials. This in turn allows for results to be published sooner for time-sensitive diseases, and for fewer patients to be exposed to the risks of a clinical trial.[9] Platform trials may be appropriate for phase II-IV trials.[8,10] Likewise for rare disease patients, there is a real opportunity to better leverage the small patient population and to maximize the information value of the few viable drug candidates.

The U.S. National Institutes of Health (NIH) has implemented policies that require the sharing of data from any NIH-funded clinical trial, and both the NIH and the National Library of Medicine released strategic plans that emphasize FAIR (findable, accessible, interoperable, and reusable) data-sharing standards for all funded studies.[11] Despite the potential for greater discovery and transparency and the added ethical benefits of sharing clinical trial data, barriers to sharing and accessing clinical trial data persist. One such barrier is the wide variability in information provision across clinical trial data-sharing platforms, complicating the ability of users to choose a technology platform that suits their data-sharing or access needs. Other challenges include technical barriers to entry such as lack of technical skills and digitization of traditional data and record-keeping.[12] This often leads to debating costs and benefits of a make or-buy decision, and the long-term implications of operational and maintenance requirements on sustainability and adoption.[13] Part of the challenge is identifying appropriate technologies that can scale and adapt to growing demand and future trends, while still balancing the necessary protection of IP with collaboration and data access.

As platform trials also facilitate collaboration to a greater degree than usually exists, it is critical that stakeholders overcome intellectual property concerns and develop agreements that recognize shared interests and still serve the common good. Recently, the use of a digital research environment (DRE) to facilitate platform trials has been proposed.[14] In addition to the operational efficiency and security benefits, a big advantage of this approach is that trial sponsors can collaborate at a level of detail that they determine appropriate, starting small and building as confidence and trust grow.

The difficulty for the sponsors to recruit enough patients in confirmatory trials in rare pediatric diseases is also a concern for the Regulators. FDA edited in 2017 a draft guidance on a collaborative approach for Gaucher disease[15]; in this guidance is provided an outline protocol is provided for a double-blind, controlled, randomized, multi-center, multi-arm, multi-company noninferiority or superiority trial to evaluate the efficacy and safety of various drugs vs. enzyme replacement therapy. Sharing the placebo arm for all the investigational drugs enables reducing the number of patients in the control group and then the total sample size.

While multi-company designs face practical challenges (communication, IP rights, resources), platform trials offer a more flexible alternative. These allow sequential drug entry/exit, with Bayesian metrics, such as the probability of treatment conditional on the trial data, guiding trial decisions and efficacy assessments.

Digital twins

In engineering, digital twins refer to a probabilistic simulation of a complex system that uses the best available data, sensors, and models to mirror the behavior of its corresponding twin.[16] In clinical trials, they are virtual patient replicas that simulate disease progression without treatment, particularly valuable for rare pediatric diseases where control groups are difficult to establish. While widespread applications are rare, a good example of the application of digital twins is the work by Kaddi et al in leveraging a quantitative systems pharmacology (QSP)-based "digital twin" approach to compare the efficacy of avalglucosidase alfa vs. the standard of

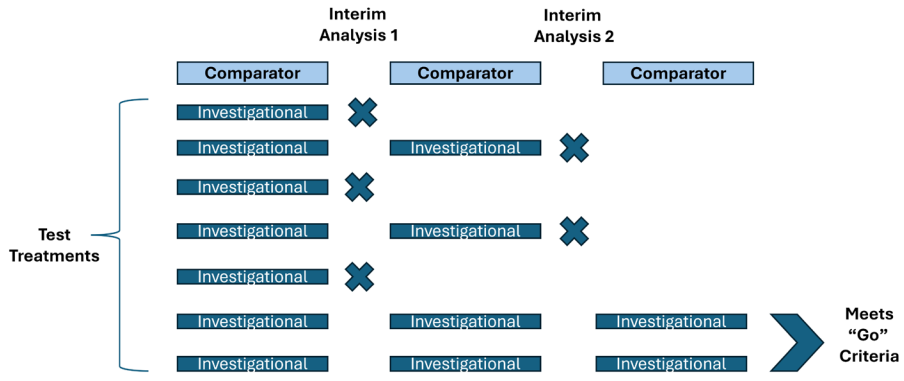

Figure 1 Illustration of a platform clinical trial.

care in a virtual population of severe infantile-onset Pompe disease patients. With their work, they were able to confirm that the increased urine Hex4 reduction after avalglucosidase alfa treatment was due to higher tissue glycogen clearance.[31]

External control arms offer an alternative by using historical trial data or real-world evidence, with comparisons made through causal inference methods. The two approaches, external control arm and digital twin approach, are compared in **Table 1**. In the subsequent sections, a more structural basis for these approaches is presented.

Developing a predictive model. The predictive models are trained on patient's data obtained from past trials, or possibly using Real World Evidence data when appropriate or possible. To be eligible for the simulation of a Digital twin arm, the candidate model should be developed under the highest quality standards such as those mentioned in TRIPOD guidance.[17] This means that information related to data source, predictors assessed, missing data handling, and model performance must be provided.

A digital twin's predictive model must accurately simulate both individual patient trajectories and population-level outcome distributions across all timepoints. Digital twins can be simulated using any robust predictive model. While both regression and machine learning models are viable, simpler regression models are often preferred for smaller datasets to avoid overfitting. Regardless of model choice, using regularization techniques (like lasso, elastic net, or dropout for neural networks) is recommended.

To fully qualify the model, evidence of the accuracy of predictions must be provided at both the population and individual levels. At the population level, distribution characteristics such as mean, median, standard deviation, q_5, and q_{95} quantile must be computed by simulations and compared to the corresponding model-free empirical parameters and their confidence intervals. At the individual level, calibration metrics quantifying to which extent observed and predicted values agree must be provided. For this purpose, calibration plots can be provided, and calibration slopes can be computed.[18]

Models must demonstrate predictive accuracy through internal and external validation on independent test data. For smaller datasets, and when no independent test database is available, the use of advanced internal validation methods like K-fold or bootstrap validation is recommended.[18]

Analyzing a study with a digital twin. Analyzing a trial using a digital twin approach must be conducted in the following way:

- Simulate the data of the primary endpoint according to the control arm predictive model. If the data are longitudinal: all intermediate time points must be simulated as well as drop-out time (or censoring time if the primary endpoint is a time to event)
- Analyze the data composed of the investigational drug arm data and simulated data, as control, according to the analysis plan as in any standard clinical trial.

Model uncertainty could be accounted for by simulating multiple control arm replicates, each using different parameter values, like multiple imputation techniques for missing data, and then combining the estimates in accounting for inflated uncertainty.

The process can be summarized as follows, assuming K replicates: For each replicate arm replicate $k, k \in 1, \ldots, K$

1. Generate model parameters Φ_k within uncertainty bounds (such as normal approximations, using Fisher information matrix in maximum likelihood estimation, or from posterior distribution in Bayesian framework)
   - Use Φ_k to simulate control arm data $\vec{Z}_{\mathbf{k}}$
   - Analyze data $\left(\vec{\mathbf{Y}}; \vec{Z}_{\mathbf{k}}\right)$ to estimate parameter of interest $\grave{\theta}_k$
2. Combine estimates $\grave{\theta}_k$ for final estimate and inference, $\grave{\theta} := \frac{1}{K}\sum_{k=1}^{K}\grave{\theta}_k$, and consider inflated variance estimate: $\widehat{var}\left(\grave{\theta}\right) = \frac{1}{K}\sum_{k=1}^{K}\widehat{var}\left(\grave{\theta}_k\right) + \frac{1}{K}\sum_{k=1}^{K}\left(\grave{\theta} - \grave{\theta}_k\right)^2$

N of 1 trials

Another type of clinical trial design that is an up-and-coming option is an N of 1 trial. As more rare disease therapies are based on precision and personalized medicine approach, particularly gene therapies, which is addressing a particular genetic variant, and

Table 1 Comparisons between external control arm and digital twin approach

	External control arm	Digital twin
Required data	• Historical RCT or RWE data • Selecting only patients meeting planned study I/E criteria	• Historical RCT or RWE data • Potentially completed by study summary results data • Patients from training database do not need to meet I/E criteria
Methodology	Causal inference methods to estimate average treatment effect (ATE): based on matching or weighting (IPTW estimator)	• Control arm data of the primary endpoint are simulated. • Including intermediate timepoints if the data are longitudinal. • Could be necessary to simulate drop-out mechanism
Assumptions	Causal inference assumptions in potential outcome framework, such as: • Unconfoundness: $Y^{(0)}, Y^{(1)} \perp A \mid X$ • Positivity: $0 < PS(X) < 1$ where $PS(X) := \mathbb{P}(A = 1 \mid X)$	Prediction model is properly qualified: in particular in the subset of patients that satisfy the I/E criteria of the study

hence serving as a corrector therapy, such trials can be very informative. These N-of-1 trials are meant for individualized therapy where there is much difficulty recruiting patients in any given genetic variant and thus could find utility for ultra rare diseases. These N of 1 trials can also be customized as a series of crossover assessments longitudinally in a single person or a group of trial participants. Regulatory agencies have increasingly accepted these designs as evidenced by the December 2023 guidance for industry "Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-considerations-development-drugs-and-biological-products) calling out these N of 1 trials in its innovative designs section V. B.3.

MODELING AND SIMULATION

Our prior work[2] has revealed that pediatric drug development has been supported by modeling and simulation in nearly all companies. They play an integral role in leveraging and integrating existing knowledge to bridge from adults to pediatric patients or to explore mechanisms that are unique to neonates and infants.[19] Pharmacometric approaches comprise not only pharmacokinetic (PK) -based models for exposure matching such as population pharmacokinetic (popPK) modeling and more empiric exposure-response (E-R) models, but also methodologies like model-based meta-analysis (MBMA) and more mechanistic approaches such as physiology-based pharmacokinetic (PBPK) models and QSP models that aim to describe the underlying physiology and pharmacology. The ICH E11A guideline[20] mentions the potential of using Bayesian approaches and external controls for overcoming the problem of small study populations, which is even more relevant for pediatric rare diseases than for general pediatric drug development. Along these lines, the FDA draft guideline[21] *Rare Diseases: Natural History Studies for Drug Development* tries to provide a framework for when and how natural disease history data could be appropriately incorporated into a clinical study as an external control group.While we have focused our efforts on the area of extrapolation, we should acknowledge that, in general, modeling of developmental physiology in pediatric medicine is a complex task that often requires a multidisciplinary approach. By incorporating developmental biology, age-specific physiological data, computational modeling, and clinical expertise, a broader pharmacometrics-based model can be developed to better understand and predict the growth, development, and health outcomes of children.

In the following sections, we will present two case examples from the pharmaceutical industry to illustrate best practices in using modeling and simulation approaches for the development of drugs for pediatric patients with rare diseases.

Case example 1: *Partial extrapolation of nintedanib based on exposure-matching and limited efficacy data*

In this case study, a partial extrapolation concept was applied, in which exposure matching was further supported by extrapolation of efficacy from adults to the pediatric patient population based on limited pediatric efficacy data.

Nintedanib is a triple angiokinase inhibitor that reduces the rate of decline in forced vital capacity (FVC) in adult patients with idiopathic pulmonary fibrosis (IPF), systemic sclerosis-associated interstitial lung disease (SSc-ILD) and chronic fibrosing ILDs with a progressive phenotype. The standard dose of nintedanib for all adult indications is 150 mg BID, with the option for dose reduction to 100 mg BID or treatment interruption to manage adverse events.

The nintedanib pediatric program was based on the clinical efficacy of nintedanib in adults and presumed similarities in the pathophysiology of fibrotic lung remodeling in adults and children.[22] It supports the extrapolation of adult efficacy data in the proposed indication, thereby not requiring a fully powered confirmatory Phase 3 trial in the pediatric population, which in a rare disease such as fibrosing ILD in pediatric patients would not be feasible. A small Phase 3 trial in children and adolescents (6–17 years of age) with clinically significant fibrosing ILD was conducted to confirm exposure-matching and assess the safety of nintedanib administration in a pediatric population, while collecting limited efficacy data.[19] Partial extrapolation was performed to support dose-selection and benefit–risk assessment in pediatric patients with clinically significant fibrosing ILDs. An overview of the components of the extrapolation concept are provided in **Figure 2**.

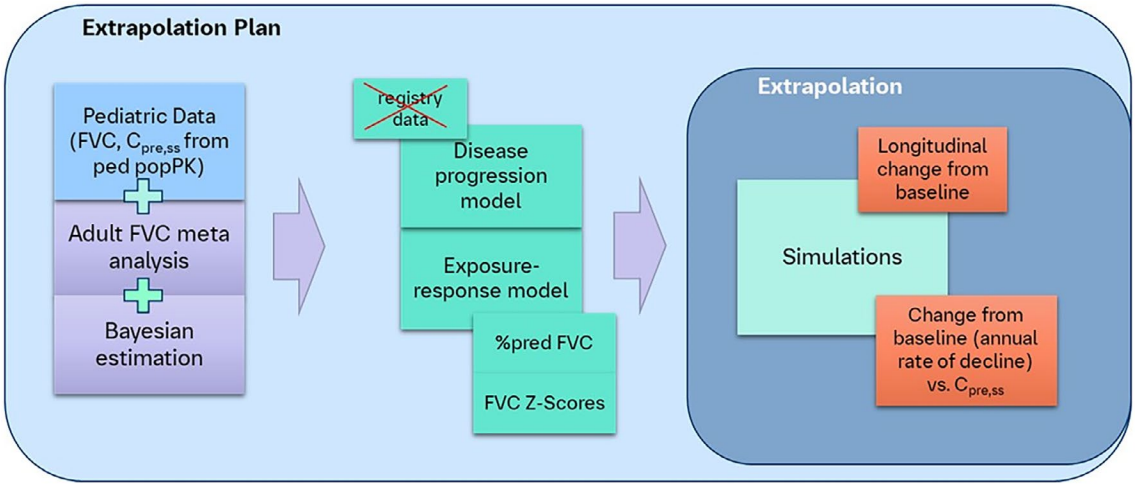

Figure 2 Scheme of the (partial) extrapolation approach applied for the nintedanib pediatric program.

Previously developed popPK and efficacy E-R meta-models across all pulmonary indications of nintedanib in adults were used as the basis for partial extrapolation to pediatric patients. The aim was to (i) define the dosing regimen in children and adolescent patients (from 6 to 18 years of age) (ii) characterize the disease course, and (iii) make inferences regarding the efficacy of nintedanib in the pediatric population.

Dose selection for the pediatric patients was based on body weight, with the aim to achieve comparable exposures as seen in adults at the approved dose of 150 mg nintedanib BID. PopPK modeling with allometric scaling was utilized to define the doses to be used in the pediatric Phase 3 trial. Appropriateness of the predetermined doses/dosing regimens applied in the pediatric Phase 3 trial was assessed using a Bayesian model-based extrapolation approach: the observed nintedanib concentrations in the pediatric patients were incorporated into the previously developed popPK model based on adult data. Parameter estimation was supported by the adult priors, with an attempt to release model parameters to achieve independent estimation based on the pediatric data only. Simulations with the pre-defined pediatric doses as applied in the pediatric Phase 3 trial showed that the exposures in pediatric patients were overall well in agreement with those observed in adult patients at the 150 mg BID dose, confirming the suitability of the proposed weight-based dosing regimen.

The aim of the efficacy ER models was to characterize the relationship between nintedanib exposure and the annual rate of change in FVC %predicted and FVC *Z*-score in children and adolescents with clinically significant fibrosing ILD and compare the disease progression and treatment effect of nintedanib in pediatric patients to adult patients. For extrapolation of efficacy, a similar approach as for PK was applied, with previously developed E-R models based on adult data serving as prior for the pediatric E-R models. Inclusion of data from a pediatric registry study was originally planned to provide additional support of disease course in pediatric patients. However, that data was not considered sufficiently robust to be included in the extrapolation approach. While the adult priors did have a considerable impact on the parameter estimation in the pediatric model and the majority of parameters could not be estimated independently of the prior due to sparseness of the data, relevant parameters such as baseline FVC and disease progression in children as well as the variability terms could be estimated independently. The result of the simulations with the final FVC %predicted and FVC Z-score models showed that the nintedanib exposure achieved after weight-based dosing leads to a comparable improvement (over placebo) in adult and pediatric patients, which was the starting assumption the (partial) extrapolation was built on (**Table 2**). The plasma exposures that were achieved in the pediatric population were above the EC_{50} values for both endpoints in most pediatric patients, suggesting an efficacious dosing regimen.

Case example 2: *Informing the Opdualag dose recommendation in adolescent melanoma using MIDD*

Opdualag, a fixed-dose combination (FDC) of nivolumab (anti-PD-1 antibody) and relatlimab (anti-LAG-3 antibody), has been approved in the United States and other countries for the treatment of unresectable or metastatic melanoma in adult and pediatric patients 12 years of age or older.[23]

Adolescent melanoma is an unmet medical need with limited treatment options. Such patients are rare and difficult to accrue in clinical trials. The pivotal phase 2/3 RELATIVITY-047 trial allowed the enrolment of pediatric patients 12 years of age or older; however, no adolescent subjects were enrolled. The extrapolation of adult efficacy and safety to adolescent melanoma patients was supported by the following considerations, namely (i) primary characteristics of melanoma tumors, including histology, clinical presentation, and risk factors, are similar between adolescents and adults[24,25]; and (ii) based on the similarity of disease and expected similarity of the outcome to the treatment, the E-R relationships for safety and efficacy are assumed to be similar between adolescents and adults.

The PK-based extrapolation approach was used to determine a recommended dosing regimen of nivolumab plus relatlimab FDC for the treatment of adolescents (ages, ≥ 12–17 years) with

Table 2 Parameter estimates of the final pediatric FVC %predicted exposure-response model for nintedanib compared to the adult model

		Pediatric model			Adult reference model		
Parameter	Unit	Value	RSE (%)	Shrinkage (%)	Value	RSE (%)	Shrinkage (%)
Baseline	%	54.9	5.54		71.0		
Slope[a]	%/year	−4.74	4.24		−4.78		
Rate of change in FVC %predicted at maximum drug effect (E_{max})[a]	%/year	4.17	12.6		4.34		
EC50[a]	nM	8.05	28.8		8.24		
Pediatric change in slope[b]	%/year	2.28	41.2		—		
IIV RUV	CV	0.468	12.7	5.48	0.395		0
IIV Baseline	CV	0.401	9.85	0	0.221		0
IIV Slope[a]	SD, %/year	5.55	2.15	26.1	5.58		25.0
Add. RUV	%	3.26	7.77	2.16	2.13		0

CV, coefficient of variation; IIV, inter-individual variability; RSE, residual standard error; RUV, residual unexplained variability; SD, standard deviation. [a]Supported by adult priors. [b]Translating into a slope of −2.45 FVC%predicted/year for a pediatric patient.

unresectable or metastatic melanoma. The PK and safety of nivolumab (ie, one of the components of the FDC product) in pediatric solid tumor patients have been well established.[26] In the absence of clinical data for relatlimab in adolescent patients, its PK were characterized by extrapolating from adult data, and it was assumed that the linear clearance (CL) and central volume of distribution (VC) for relatlimab would be similar to those observed for nivolumab in pediatric patients. This assumption was considered reasonable because of the expected similarity in the PK of IgG4 mAbs, and similar effects of covariates on nivolumab and relatlimab PK parameters (particularly CL and VC) were observed.

The recommended dose of nivolumab and relatlimab FDC was determined by comparison of simulated exposures in adolescent patients with melanoma that are similar to that of the corresponding exposures of nivolumab 480 mg and relatlimab 160 mg Q4W in adults.[27] The predicted median exposure (eg. average concentration after first dose, Cavg1) in adolescent patients was comparable (< 30% difference) to corresponding exposures in adults with the same body weight group and generally within the range of the 5th and 95th percentile of adult exposures. At recommended doses of nivolumab 480 mg and relatlimab 160 mg Q4W FDC, nivolumab and relatlimab exposure in adolescent subjects who weighed at least 40 kg is expected to result in similar safety and efficacy to that of adults. Notably, Opdualag represents the first example of providing a medication to adolescents by applying MIDD without generation of clinical data in adolescent patients.

DATA SHARING CONSIDERATIONS

One emerging area is the use of real-world data. RWE can support regulatory decision-making by providing additional data that demonstrate treatment efficacy and safety in the real world. Regulators are increasingly using real-world data to assess treatments for rare conditions, and it can help fill the gap when clinical trial data is sparse. RWE from pediatric cancer registries or compassionate use programs might provide data on the off-label use of targeted therapies (e.g., tyrosine kinase inhibitors or immunotherapies) in rare cancers such as pediatric sarcomas or retinoblastoma. Such data can help inform the design of future clinical trials or even lead to the development of new treatment strategies. Many pediatric cancer treatments, such as chemotherapy or radiation, can have long-term side effects, including impacts on growth, development, and organ function. These effects may not always be captured in clinical trials, especially when such trials are relatively short-term. In this example, RWE can track long-term outcomes and late effects of treatment in pediatric cancer survivors, such as secondary cancers, cognitive dysfunction, or cardiovascular issues.

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[28,29] 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.[14] 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 FDA approved the first medication, called omaveloxolone, to treat Friedreich Ataxia in individuals 16 years of age or older. This was done based on data shared via the C-Path RDCA-DAP platform. This product was also approved in Europe in Feb. 2024 [Biogen Press Release 2024; https://investors.biogen.com/news-releases/news-release-details/biogen-received-european-commission-approval-skyclarysr].

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 (**Figure 3**). 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.

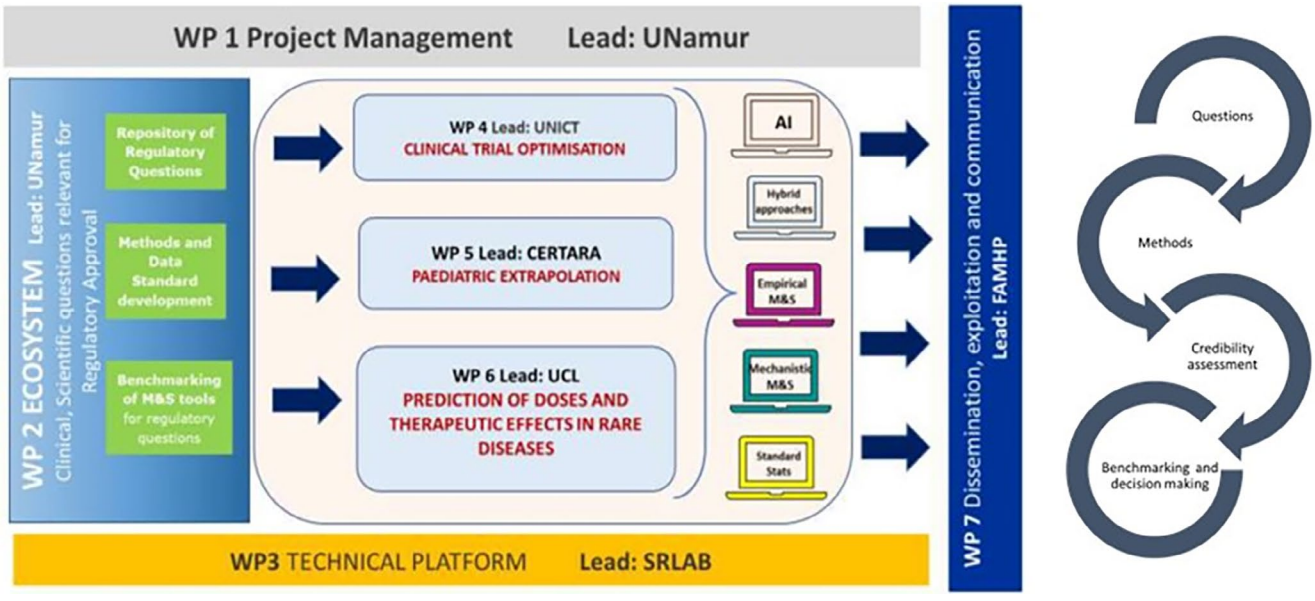

Figure 3 ERAMET stakeholders, work package relationships, and reliance on the DRE as the technical platform (WP3).

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 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 EMA for broader use supporting rare disease drug development.

The ERAMET project relies on 3 pillars of the ecosystem: (i) a repository connecting questions, data, and methods, (ii) development and validation of high-quality standards for data and methods, and (iii) an AI-based approach for automation of data collection and credibility assessment. All aspects of the grant activities, including data ingestion, project management, metadata cataloguing, and tool development, will be managed through the creation of the ERAMET DRE.[30] The DRE will enable stakeholder communities in three different scientific domains (ataxia, transfusion-dependent haemoglobinopathies and drug induced cardiovascular toxicity) broad access to data and tools relevant for their domain. Analytical tools, including AI-driven platforms and computational tools for assessing the methods and data credibility, will be developed, refined, and applied to the three use cases to foster improved ability in terms of both basal research on disease characterization and the development of health interventions and supportive methods such as diagnostic methods, risk detection, and monitoring tools.

THE FUTURE OF PEDIATRIC RARE DISEASES THERAPEUTIC DEVELOPMENT: CATALYSTS FOR POSITIVE CHANGE

Pediatric rare diseases represent a unique and complex challenge in the field of therapeutic development because of the small patient population size, the heterogeneity of disease manifestations that may be different from adults, and the lack of sufficient clinical data. Regulatory health authorities universally accept the growing value of MIDD tools in the drug development of rare adult and pediatric diseases.

The first mention of the adoption of modeling and simulation approaches in pediatric development was in the ICH E11 Addendum E11(R1)[20] which supplements the E11 guideline with approaches to extrapolation, modeling and simulation, and trial methodologies (https://www.ema.europa.eu/en/ich-guideline-e11a-pediatric-extrapolation-scientific-guideline). The term, pediatric extrapolation, is notable in regard to the implicit importance of modeling in generating evidence with regard to the course of the disease and the expected response to a medicinal product, and supports disease and response similarity between the adult and pediatric populations. The two case studies discussed herein showcase the benefits of the extrapolation framework.

It is also instructive to note that in their guidance on pediatric studies of molecularly targeted oncology drugs,[1] the FDA makes particular mention of the importance of MIDD integration to "predict clinical outcomes, inform clincial trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse events." The FDA goes on to indicate their encouragement for the use of innovations in study design, such as the platform trials and PROs, topics we discuss in this whitepaper.

There is always a healthy tension within drug development on staging pediatric clinical trials in the context of adult development. This is true whether or not it is for a rare or a common disease. With the FDARA implementation, there is an opportunity to integrate pediatric subjects into adult development, including but not limited to including pediatric cohorts in adult trials, nested design for pediatric cohorts in the adult trials, or just by lowering the age limit of an adult trial by including adolescents. These approaches allow the potential to use MIDD to assess within trial similarities between adult and pediatric subjects, leading to better coordination of dose selection and treatment response.

One way to mitigate against the scarcity of the patient population, whether for rare or ultrarare pediatric indications, is to mention the usefulness of platform trials Incorporating novel biomarkers into platform trials is an untapped opportunity, allowing sponsors to develop adaptive, multi-arm, and multi-disease trials that evaluate several therapies simultaneously. Platform trials allow researchers to test multiple interventions against different diseases or subgroups of diseases within a single trial, thereby reducing the time and resources required for staged phased drug development. By including novel biomarkers such as digital biomarkers and digital twins in these trials, we can assess the impact of investigative treatmentson disease progression.

In a hypothetical pediatric rare disease platform trial, novel biomarkers could be used to identify responders a priori, identifying patients that are most likely to benefit from a particular therapy based on their genetic profile or disease subtype. This enables the trial to more effectively target patients who are likely to respond to the treatment, thus improving the chances of demonstrating efficacy and reducing the overall trial duration. Biomarkers can also serve as endpoints in these trials, providing additional data points beyond traditional clinical outcomes like survival rates, and enabling the early detection of treatment effects. This is particularly valuable in pediatric rare diseases, where clinical symptoms may take years to manifest, and early intervention can dramatically improve long-term outcomes. The Children's Tumor Foundation and the Global Coalition for Adaptive Research are leveraging the EU-PEARL's model for a platform trial for patients with neurofibromatosis-1 and schwannomatosis, which is a good example (https://www.ctf.org/news/ctf-gcar-announce-strategic-alliance-nf-platform-clinical-trial/).

One area that we have not focused a whole lot on is the area of systems medicine. Briefly, systems biology integrates molecular, cellular, and organ-level data to create detailed models of disease. For rare pediatric diseases, where understanding of the disease may be limited due to a small patient population, systems medicine can provide a better understanding of underlying disease mechanisms by incorporating multiple layers of biological data (e.g., genomic, transcriptomic, proteomic, and metabolomic data). A more detailed understanding of disease mechanisms allows for the identification of biomarkers that can be used to track disease progression

and predict treatment outcomes, even in small populations. This is particularly useful in rare pediatric diseases where specific biomarkers may be scarce or not well characterized. Moreover, systems medicine, through multi-scale modeling, can help build more accurate models by incorporating data from a variety of disparate sources including animal models, cell cultures, and other related diseases with similar pathophysiological features. These considerations may be particularly helpful for rare pediatric diseases that are more genetic in nature.

Lastly, cross-industry data sharing allows all stakeholders to pool knowledge, expertise, and datasets. One of the most significant advantages of data sharing is the ability to consolidate large, diverse datasets that can improve the robustness and predictive power of novel biomarkers of disease. Understanding the genetic basis of diseases or uncovering novel mechanisms of action can be accelerated when different stakeholders contribute their data. In the context of rare diseases, where patient populations are small and fragmented, data sharing becomes particularly crucial. Seminal efforts such as the rare disease cures accelerator, a data analytics platform 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, are good examples of data sharing opportunities, paving the way for a more integrated one-industry solution to rare pediatric diseases.

SUMMARY

Both conventional MIDD and newer integrative quantitative methods can provide a more efficient and data-driven approach to rare pediatric disease drug development, aiding in a better understanding of the PK/PD similarities between adults and pediatric subjects as well as accounting for disease heterogeneity when translating from adults. As more integration is achieved with the use of newer methodologies such as digital biomarkers, digital twins, and patient-centric measures, we expect that there will be a further streamlined approach to pediatric rare disease drug development.

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CONFLICTS OF INTEREST

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