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New Medicines, Novel Insights: Advancing Rare Disease Development

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In this report

Bringing rare disease treatments to market, faster

Novel therapies for rare diseases offer hope for thousands of patients and their families. Bringing rare disease treatments to market, faster: This is the goal of every biopharmaceutical company – and for Parexel. However, speed and efficiency in the drug development process have value only when driven by a thorough understanding of the illness from the perspective of patients and caregivers. In this report, we share best practices to illustrate how companies can infuse a thorough embrace of patient centricity throughout the many interconnected processes along the journey.

Of course, that is easier said than done. While it has been more than a decade since the concept of patient-centricity emerged in our field, the industry lags far behind other sectors in focusing product development on the people it serves.

Why do many companies fail to engage effectively with patients before designing their trials and selecting endpoints? For one thing, multiple stakeholders have divergent and even conflicting priorities. And it takes time and money to understand a rare disease and how it progresses. Meanwhile, many companies find it daunting to communicate with patients and fear that direct collaboration could raise legal or ethical issues.

Individually, any one of these stakeholders can recognize the signs of improved quality of life for a given patient, even for a young child. But collectively, they don't know how to do that. And while companies cannot make a drug commercially viable if it is not compliant with technical standards, that doesn't much matter if a product does not address what patients care about. **That's why focusing on patients from the earliest stages of development makes pragmatic sense.**

Endpoint Selection

Selecting the right endpoints to establish clinical benefit is one of the most challenging aspects of drug development for rare and ultra-rare diseases. The starting point for determining relevant and sensitive efficacy endpoints is understanding the etiology of the disease and the drug's precise mechanism of action (MOA). But with rare and ultra-rare diseases, often little is known about the condition's natural course, and the experimental agent's MOA may not be fully elucidated. Patients are often difficult to locate, making it hard to power a study to measure treatment effects adequately. However, Parexel has identified five best practices to guide decision-making.

Seek optimal endpoints, not just those that are relevant or convenient. Sponsors are often uncertain when faced with many possible endpoints, about which are the most meaningful clinically and statistically and which are most meaningful to patients. We advise a multidisciplinary approach, conducting thorough due diligence on the condition – for example, interviewing key opinion leaders, reviewing published literature, and analyzing briefing documents of approved drugs in similar indications. Endpoint selection should be science- and data-driven and reflect patients' priorities whenever possible.

Parse the rare disease patient population thoroughly. Endpoint selection needs to proceed from a thorough understanding of the heterogeneity of patients and disease expression across different age groups that will be studied in a trial. For example, research shows that more than 80 percent of rare diseases are genetic, and about 50 percent affect infants and children. In this setting, endpoints often need to be customized by age group and genotype or phenotype. Further, patients in different age groups suffering from a rare disease will be at different stages of disease progression and likely harbor different subtypes of genetic profiles.

Work with regulators to co-develop and validate endpoints. Regulators understand that developers often struggle to identify and validate endpoints in rare and ultra-rare diseases. In October 2022, the FDA launched its Rare Disease Endpoint Advancement (RDEA) Pilot Program to support novel endpoint development and help sponsors qualify endpoints that have "never been used to support drug approval." The RDEA pilot program represents an excellent opportunity for developers with an active pre-investigational new drug (IND) or IND program for a rare disease that want to use novel endpoints. This initiative offers a new pathway that envisions sponsors collaborating with regulators, patient groups, thought leaders and other stakeholders to drive novel endpoint development.

Conduct correlation analyses to validate a novel biomarker or endpoint. In rare diseases, many endpoints, such as patient-reported outcomes (PROs), are subjective. In contrast, a biomarker endpoint is an objective measure. At Parexel, we conduct biomarker and endpoint evaluation and qualification. For example, correlation analyses between the biomarker and subjective measures can assess whether either or both are valid for rare diseases and rare types of common diseases. Correlation analyses require computational biologists and statistical geneticists who understand the biomarker data, genetics, and clinical conditions. These analyses are crucial to validating biomarkers or endpoints; developing a treatment using a non-validated biomarker will likely end in regulatory failure.

Ensure accurate interpretation of complex genetic testing data in trials. The misinterpretation of highly heterogeneous genetic profiles or biomarker testing results, especially in global studies involving multiple laboratories and personnel, can lead to missed or mistaken patient enrollment. Once a sponsor has defined the mutational profile of the target patient population, the clinical operations team must administer genetic tests and interpret complex results to ensure that only eligible patients enroll in a study. A common problem at this stage of development is choosing non-qualified laboratories or assays to analyze the samples.

At Parexel, we have dealt with the diverse reporting standards for genetic testing in numerous trials. We've learned that reading these reports requires specialized expertise. The documents can be over ten pages long, and there is no straightforward line related to the trial's entry criteria. Site staff must scrutinize the entire report and frequently need to consult a genomic expert for conclusive recommendations on patients with ambiguous and complex genetic readouts. For global trials, additional complications are caused by translation issues and the lack of harmonization in testing results.

When we take on a trial that targets a small genetic slice of a patient population, it's our best practice to conduct robust site training because sites are critical to this process. They need access to our biomarker and genomic medicine experts.

Site Management

Of course, drug developers also need to keep the patient top of mind in site management. Gene therapy trials, in particular, are complex, and when they involve pediatric patient populations with rare diseases, feasibility and scrupulous data protection are imperative. In fact, project and data management often pose greater challenges than clinical or patient-related issues. Cell and gene therapy trial protocols often have as many as 10 or 15 amendments, requiring great attention to detail from project managers. And preparing for monitoring visits can add significantly to the site workload.

While there are no simple solutions, different approaches might work for different sites. For example, more frequent monitoring visits could reduce the number of queries per visit, spacing work out and allowing time for other projects.

Key to success is a multidisciplinary team that includes research nurses, physicians, lab and manufacturing staff, project managers, and data managers, constantly learning, adapting, and improving.

Ideally, sites will have a dedicated data manager overseeing protocol amendments, monitoring visits, and data audits, and resolving issues in real time.

Remote patient monitoring has offered a positive revolutionary change for patients. However, important clinical data can be lost without a physical connection with patients. Caring for patients involves more than blood samples or data trends. **Face-to-face interactions are still valuable, particularly early in a study.**

Good care requires good communication, an area where many drug developers fall short. After the excitement of a trial startup, patients often find themselves in an information vacuum. **A plan for patient communications should be high on the agenda.**

Innovative Trial Designs

What about trial design in this area? Often, a complex innovative trial design (CID) is more practical for ultra-rare disease than randomized controlled trials. CIDs can answer multiple questions about one or more compounds in one or more conditions or patient subgroups. Prespecified, "adaptive" modifications of the trial protocol can allow changes during the study based on interim data analyses. These adaptations can include sample size adjustments, dropping arms because of futility or safety findings, or enriching the target population.

CIDs are efficient (enroll patients quickly), informative (yield more data about a treatment's effects), and ethical (patients may be less likely to receive a placebo). They are also more complicated, costly, logistically challenging, and at greater risk of operational and analytical bias.

Parexel has learned from experience what works and what doesn't. The following are best practices that have helped sponsors in conducting CIDs:

Review essential criteria for emergent risks weekly. A master protocol can evaluate more than one drug in more than one patient population, and a basket trial can include several studies in one. But the risk management plan must be tailored to each indication or cohort. For example, if one arm enrolls pediatric or elderly patients, it will have risks specific to that cohort. A complex design involves running several trials simultaneously rather than sequentially, and it complicates risk-review logistics exponentially.

At Parexel, a dedicated project risk lead oversees initial and ongoing risk management activities using a system-based risk assessment and categorization tool (RACT). We develop an integrated risk management and mitigation plan that looks at each cohort separately and then at the overall picture. Risk management proceeds on a set schedule throughout the trial, and the RACT includes prespecified remediations if a risk emerges.

Condense the time between data collection and cleaning. Trials with adaptive elements require precise planning for the data needed at each stage. That data must be monitored, analyzed, and cleaned continuously. Throughout these trials, sponsors must communicate with independent data monitoring committees (IDMCs) to review the data and make timely decisions about stopping, modifying, or expanding the study to a new indication or patient population.

Continuous data cleaning requires tight coordination between data teams and clinical teams. At Parexel, we have adopted a data-cleaning approach that can deliver interim analyses to IDMCs with a minimal lag time after the last patient's assessment. Our process shows that only about three percent of data needs correcting or changing. We continually interrogate the data to spot emerging risks, mitigate them, and make decisions to protect the integrity of the dataset.

Give sites comprehensive and dedicated support. Trials involving multiple cohorts can be logistically and emotionally challenging for study staff when they enroll many cohorts for one trial at a single site. For example, one site might enroll pediatric and adult patients in separate arms in a rare disease multi-cohort study. The risks, doses, data collection schedules, informed consent materials and other study documents will differ between the arms. Before a CID trial begins, we determine what each site will need and set up a logistical infrastructure to provide site-specific training and support for a successful trial.

Closely track and manage patient onboarding. Patients with rare diseases often have rapidly progressive, terminal conditions. For many, the trial represents the only treatment and follow-up care they will receive. And due to the small patient populations in rare disease trials, every patient's data are much more valuable. Knowing when you can onboard each patient into the study is critical, and there should be no delays. At Parexel, we track the

allocation of patient "slots" in each trial to achieve a streamlined progression from qualification to informed consent to the first treatment. We always have backup patients ready to fill in if a patient or site must change the schedule. In this way, we avoid disappointing patients and principal investigators (PIs), who have likely made promises to their patients about when they can join the trial.

Plan enough drug support for every protocol modification. Adapting a protocol to include a new arm or expand an existing arm can cause drug supply shortages, especially for expensive products with complex manufacturing procedures or limited supply. Frequent protocol changes require flawless supply chain logistics to avoid delays and disruptions in patient recruitment due to inadequate drug supplies. At Parexel, we scrutinize the drug supply plan of every protocol to ensure that, before the first patient enrolls in a trial, the drug supply will be adequate to cover every potential forecast increase.

Regulatory Strategies

Bringing a successful treatment to patients and families desperate for a cure requires a thorough understanding of regulatory processes. For many, this should encompass familiarity with the FDA's Center for Biologics Evaluation and Research (CBER) and the recently renamed Office of Therapeutic Products (OTP) and their view of orphan drug–designated cell and gene therapies (CGTs). Following are five important clarifications that are often misunderstood among drug developers.

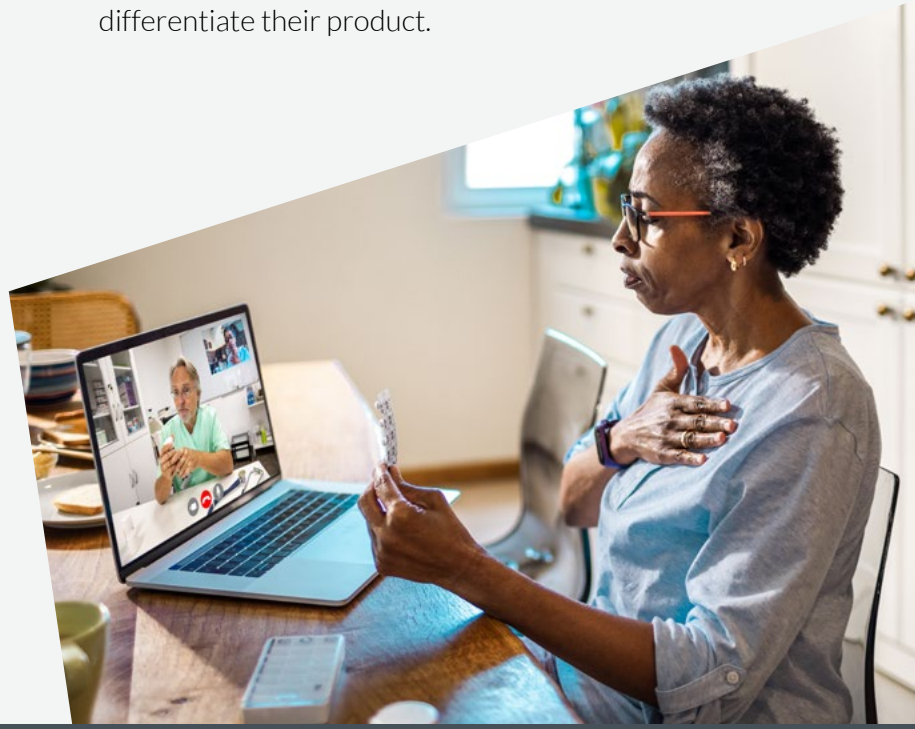
Expedited programs do not lower the evidence bar and accelerate development. The FDA often approves a novel drug or biologic in an orphan drug–designated indication on smaller, single-arm pivotal trials. But additional studies may be required if the product is not associated with a transformative clinical benefit. A well-designed natural history study or other rigorous external control data may also be required. These requirements may slow development down, not speed it up.

An orphan CGT will not automatically get special attention from the FDA. In September 2022, the FDA announced that it "elevated" the Office of Tissues and Advanced Therapies (OTAT) within CBER and renamed it the Office of Therapeutic Products (OTP), citing the increased workload. Breakthrough Therapy (BTD) or Regenerative Medicine Advanced Therapy (RMAT) designation is now a prerequisite for prioritized meetings with OTP. A benefit of RMAT designation is the RMAT Initial Comprehensive Meeting, a multidisciplinary discussion of the sponsor's clinical trial and manufacturing development strategy. We've received feedback from several clients that the initial meeting is a boon, and every meeting for an RMAT-designated program will be scheduled at a Type B priority. We've helped clients prepare for these interactions to maximize the opportunity.

An orphan CGT does not automatically get Accelerated Approval on a clinically meaningful endpoint. The European Medicines Agency (EMA) has a licensure option known as conditional marketing authorization (CMA), which allows patients access to drugs despite incomplete benefit-risk data.

The closest comparable pathway to CMA in the United States is the FDA's Accelerated Approval (AA) pathway. But there is a critical difference between the two. CMA relates to the amount of evidence available for a drug, while the FDA interprets AA to relate to efficacy data collected for a specific type of endpoint. Companies often confuse these two pathways. Regardless of precedent, making assumptions about an expedited regulatory pathway is risky. We advise that you discuss and agree on endpoints and other aspects of the AA pathway with OTP before finalizing your development plans.

Well-designed long-term follow-up (LTFU) studies can yield great value for the sponsor. LTFU trials can cost almost as much as the pivotal trial – as much as $30 million – because any type of healthcare follow-up is costly. However, sponsors can design and execute LTFU studies to collect data that promote patient safety, support a product's value proposition, and optimize product lifecycle management. At Parexel, when we design LTFU studies, we always ask our clients whether they want to meet the bare minimum FDA requirement for safety monitoring or whether they also want to generate data that could differentiate their product.



Regulators are not responsible for making critical development decisions for you. Early meetings with the FDA offer you a chance to de-risk your development strategy and optimize trial designs, endpoints, and the evidence generation plan before submitting an investigational new drug (IND) application. Many developers hope to receive definitive answers to complex development questions during these exchanges. But regulators have neither the expertise nor the remit to make pivotal development decisions for companies. In the end, developers have to make the critical decisions. The best way to arrive at good ones is to listen carefully to regulators and then, with all the data at your disposal, use your best judgment to make thoughtful tradeoffs and take defensible calculated risks.

Timing and data are critical to winning BTD. Because this designation targets drugs for serious conditions with unmet medical needs, it is frequently central to rare disease drug development. However, success depends on timing and the data supporting the application. Because of the nature of the clinical evidence needed to fulfill BTD criteria, BTD can only be obtained after Phase 2 of development. To maximize the program's advantages, you should ideally submit a BTD request before Phase 3 trials begin. Companies with drugs that receive BTD earlier in development have more interactions with the FDA over time and more opportunities to align on streamlined programs, which can shorten the development timeline. But BTD is not a guarantee of development speed or success.

For more comprehensive insights on these topics, please explore our interactive digital report on rare diseases. You'll find additional observations and recommendations from Parexel experts who are doing everything humanly possible to deliver on the promise of patient-focused drug development.

Market Access

Getting novel therapies to patients waiting for them is the ultimate goal, and that requires authorization from payers. As you start thinking about launching a rare disease product, **consider how you will engage with payers as partners**.

Payers are increasing their scrutiny of rare disease therapies. It is wise to model options ahead of time to predict how payers may react to a trial design. Parexel employs tools in pricing analysis, market research, and health economic modeling methodologies to demonstrate value and align payers and manufacturers on pricing constructs. We also model managed-entry agreements between firms and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance.

Value-based contracts are powerful tools. These contracts reduce the risk for the payer while allowing the manufacturer to obtain market access quickly. It's very effective because payers appreciate having their concerns listened to, and having prepared the ground, we can ask them for quicker reviews. Start that process around two years before the anticipated launch to have the agreements in place.

We're always available for a conversation.

With Heart™

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