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Where better medicines begin

With Heart™

Insights

Foreword: A new era of complexity for early-stage development

Scientific, regulatory, and societal upheavals in the last three years are making early-stage product development more complex. The COVID-19 pandemic highlighted ethnic and racial disparities in clinical research access and health outcomes, prompting regulatory agencies to scrutinize the diversity of patients in clinical trials; precision medicines have expanded beyond oncology and often demand the simultaneous development of companion diagnostics and massively parallel sequencing to identify genetic mutations and stratify patients; the hunt for validated biomarkers that correlate with drug response requires the collection, processing, and storage of blood and tissue samples from the earliest stages of development; adaptive trial designs that enroll multiple cohorts pose operational and statistical challenges; and assembling a globally relevant and compliant clinical evidence dossier requires localized regulatory expertise because international harmonization has not yet materialized.

In our recent work with clients, we've found that a multidisciplinary approach to early-stage development is the most cost-effective way to mitigate risks while navigating this complexity. Integrating regulatory, clinical pharmacology, modeling and simulation, and biomarker strategies enables more informed advancement decisions. Companies can learn fast and lay a solid early foundation for future success or "fail smart"[1] with every asset in their portfolio. In this eBook, we share our best thinking on where better medicines begin, focusing on four early-stage imperatives:

1. Getting the most out of **early interactions with regulators**
2. Using clinical pharmacology and modeling and simulation to optimize **first-in-human (FIH) trial design**
3. Multiplying the feedback loops of learning and efficiency with **biomarkers**
4. Planning early for **patient diversity** in clinical trials

We hope you find these articles helpful on your journey to commercial success.

Oliver Fuhrmann
Executive Vice President and Global Head of Enterprise Account Group

1 "Don't Fail Fast — Fail Smart," *Forbes*, February 2020.

Expert spotlight

Paul Bridges
Executive Vice President and Global Head of Consulting
Parexel International

As a pharmacist by training, Dr. Bridges earned a PhD in respiratory medicine and spent his early career as reviewer for the UK regulatory agency and as a nominated EU expert for EMEA. With additional experience from also working in the biotech sector, Dr. Bridges now focuses on consulting for the pharmaceutical industry. Along with his team, he specializes in promoting opportunities to de-risk drug development and promote patient access.

Amy McKee, MD
Chief Medical Officer and Head of Oncology Center of Excellence
Parexel International

Amy has 11 years of experience at the U.S. FDA, most recently as Deputy Director of the Oncology Center of Excellence (OCE) and Supervisory Associate Director of the Office of Hematology and Oncology Products (OHOP). At OHOP, Amy was responsible for four divisions performing scientific reviews of drugs and biologics. She is experienced in early-phase drug development, including new methodologies for early dose-finding trials, dose optimization, and endpoint selection.

Q&A: How early interactions with regulators bring better medicines, faster

Initial meetings offer a chance to de-risk a filing and define an efficient evidentiary path to approval

Companies get just one or two chances to elicit specific early feedback from regulators before initiating a clinical drug development program. These consultations are as critical to success as a pre-new drug application (NDA) or pre-marketing authorization application (MAA) meeting. We asked Parexel's Executive Vice President and Global Head of Consulting, Paul Bridges, and Parexel's Chief Medical Officer and Head of Oncology Center of Excellence, Amy McKee, how early regulatory interactions can streamline development.

If early regulatory meetings add value, why doesn't every company seek them?

Paul Bridges: Understandably, many companies feel they know their asset better than anyone else and view external advice as a drag on their timelines. True, it takes time to prepare for these meetings. What's more, if regulators suggest additional toxicology studies and more modeling and simulation, it could delay the start of a first-in-human study, possibly disappointing investors. But what I've learned in two decades of working with clients is that blowing through a pre-investigational new drug (IND) or pre-clinical trial application (CTA) meeting is a mistake. Any false assumption in non-clinical work that is later challenged by regulators can massively disrupt your application. Flawed development decisions made early in a hurry and in a vacuum have a magnifier effect as a product advances. We've spent as long as five months preparing a client for a single, high-impact early advice meeting. The payoff is often no regulatory delays or surprises.

What mistakes do companies commonly make in early meetings?

Amy McKee: When I work with sponsors to prepare an IND submission, I often find insufficient crosstalk between the clinical pharmacology, non-clinical, and clinical teams. Toxicology work in animals supports the starting dose in humans, safety assessments, and the dose escalation strategy. Unless the clinical team understands what the non-clinical team is saying, they can't design an appropriate FIH trial. Another common problem is inadequate chemistry, manufacturing, and controls (CMC) data—which can sink the application.

New FDA standards for cancer drugs mean sponsors who do not vet their dose-exposure findings from preclinical work and present meticulous dosing justification data for early human studies may incur clinical holds. Companies that have conducted modeling and simulation analyses to predict human doses based on their preclinical data will have an advantage.

Do sponsors need to have a global regulatory strategy in Phase 1?

Paul Bridges: With China and Japan joining the International Conference on Harmonization (ICH), product development is now truly global, and with that, companies can no longer lean too heavily on local or regional regulatory perspectives. We recently helped a client who had relied on EU experts to design their early-phase studies but could not convince the FDA that they had the right approach. It was an expensive mistake because they had to redo much of their preclinical work.

So, companies need a global strategy. The US market is a priority for most sponsors, but by making a few small tweaks—such as adding a contingent of Japanese patients to the Phase 1 trial—companies can put together an early-stage program that will work in all the major markets.

In Europe, the early-stage process is less well-defined and more convoluted than in the United States. In January of 2022, the EMA began its three-year phase-in of the European Union Clinical Trial Regulation 536/2014 (EU-CTR), creating a streamlined CTA process via a single electronic entry point: the EU Portal. While the process is more standardized, it is also more complex. By January 31, 2023, sponsors must use the portal to apply for new clinical trials, and by 2025, they must record ongoing legacy trials in the system.

How can a sponsor get the most value from a pre-IND meeting?

Amy McKee: The focus of early meetings is the FIH study, and the requirements for an IND filing are relatively rigid. That said if you plan to push the regulatory envelope with an innovative trial design or novel biomarker, use the pre-IND meeting to determine if the agency will be flexible.

My advice to clients who want to speed up the time to initiating an FIH study is 1) have all good laboratory practice (GLP)/toxicology work completed; 2) generate as much CMC data as possible to de-risk the IND submission; 3) prepare a complete protocol synopsis or, even better, a full protocol to pressure test the design (you can even begin submitting an FIH design to institutional review boards for review while preparing for the pre-IND meeting); 4) respond constructively and nimbly to feedback from the pre-IND meeting and—most important—incorporate the advice into your final FIH protocol design; and 5) if you are developing a cancer drug, ask for scrutiny of your starting dose and dose escalation strategy.

A successful pre-IND process eliminates the need to scramble during the 30-day IND review period because the major issues have already been addressed.

We've spent up to five months preparing a client for a single, high-impact early advice meeting. The payoff is often no regulatory delays or surprises.

Slow down to speed up: Three early-phase strategies for streamlining clinical development

Parexel clinical pharmacology experts outline three best practices to inform better advancement decisions and streamline the overall development program. These early-stage approaches can help companies optimize the development of promising candidates and weed out weaker products earlier in the process.

1 Provide a sound scientific justification for the first-in-human trial dose

Inadequate scientific justification for the starting and maximum dose in first-in-human (FIH) trials increases risks for study participants and can lead to regulatory delays and remedial work. FIH study design depends heavily on the extent and quality of preclinical research. Therefore, an exhaustive preclinical program can help companies avoid a last-minute scramble to fill gaps in their initial regulatory submissions.

We advise clients to use all the available preclinical pharmacokinetic and pharmacodynamic (PK/PD) data to predict human PK/PD. Sponsors can use animal PK data to predict human PK based on allometric principles (certain physiologic volumes and rates scale by body size). Quantitative approaches, such as modeling and simulation (M&S), are central to this process (Figure 1).

Expert spotlight

Laura Iavarone
Senior Director, Clinical Pharmacology, Modeling and Simulation
Parexel International

With 30 years of experience in drug development focused on pre-clinical, clinical, and translational aspects of pharmacokinetics, Laura and her team perform PK/PD data analysis to define optimal dose regimens and streamline clinical development. Laura contributes to interpreting PK/PD analysis across several therapeutic areas and supports companies in applying model-based drug development and clinical pharmacology guidance.

Elise Dunzo, Ph.D.
Scientific Director, Clinical Pharmacology, Modeling and Simulation
Parexel International

Elise serves as a subject matter expert for partnerships in the early-phase of drug development, providing expertise in both clinical pharmacology and pharmacokinetics. With over 20 years of experience spanning both the sponsor side of drug development as well as consulting, she serves her clients with a comprehensive view of their clinical development programs.

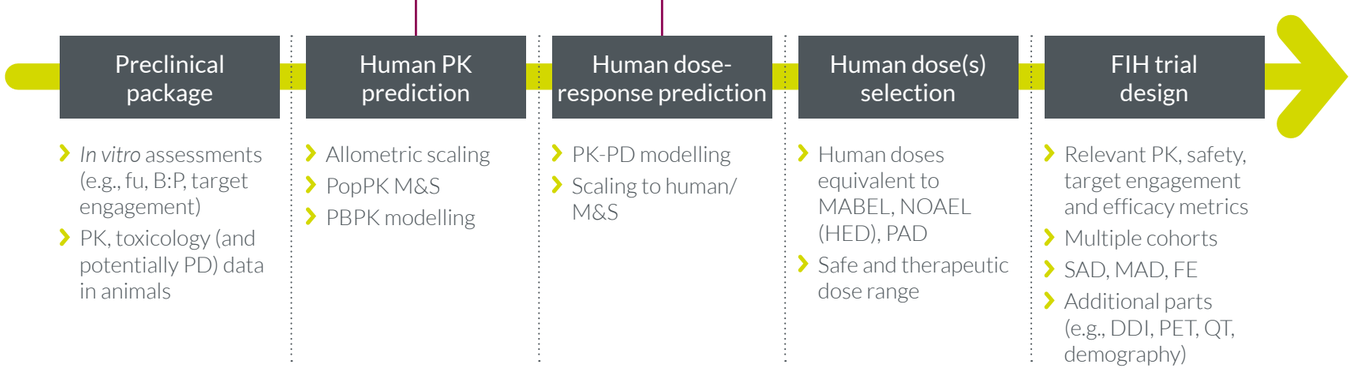
Silvia Maria Lavezzi
Associate Scientific Director, Clinical Pharmacology, Modeling and Simulation
Parexel International

Silvia provides PK/PD input to clinical trial designs and dose selection, plans and performs data analysis (via non-compartmental analysis and modeling), and provides result interpretation across different study phases and therapeutic areas. By leveraging and integrating information from preclinical and clinical studies, she and her team optimize drug development to help doctors match the right patient to the right treatment and at the right dose.

Based on preclinical PK/PD data, we can assess how drug exposure relates to the desired response—in terms of efficacy or target engagement— and identify the minimal anticipated biological effect level (MABEL). Toxicology studies in animals define exposure at the no-observed adverse effect level (NOAEL). With these data, our experts can predict the pharmacologically active dose (PAD) and the dose corresponding to the NOAEL exposures in humans—that is, the human equivalent dose (HED). Depending on factors such as drug class, therapeutic area, degree of translational uncertainty, and knowledge of the drug's intended target, sponsors can justify an FIH starting dose based on a fraction of the NOAEL, on the MABEL, or on the PAD. The FDA offers advice on non-clinical data and FIH study design through its Model-Informed Drug Development (MIDD) pilot program[2] for sponsors who qualify to participate.

Recently, we assisted a client in revising the starting dose for their FIH study using M&S based on their preclinical data. Our calculated starting dose was much lower than the sponsor had proposed. For the same study, we also revised the maximum dose in light of preclinical data that did not demonstrate an exposure threshold for toxicity. The company changed the protocol based on our calculations, and a regulatory agency approved it.

Figure 1. The path from preclinical package to FIH study design.



Acronym Key: B:P: blood-to-plasma ratio; fu: fraction unbound; DDI: drug-drug interactions; FE: food effect; HED: human equivalent dose; MABEL: minimal anticipated biological effect level; MAD: multiple ascending doses; M&S: modeling and simulation; NOAEL: no adverse effect level; PAD: pharmacologically active dose; PBPK: physiologically-based pharmacokinetic; PD: pharmacodynamic; PET: positron emission tomography; PK: pharmacokinetic; PopPK: population pharmacokinetic; QT: time from the start of the Q wave to the end of the T wave; SAD: single ascending dose.

2 Model-Informed Drug Development Paired Meeting Program, FDA, October 2022.

2 Choose a flexible Phase 1 trial design to generate more informative data

A flexible protocol may use an adaptive design or combine multiple objectives in a single study. Adaptive designs analyze the cumulative trial data at pre-specified time points under strict statistical rules and then modify the study's arms, doses, or regimens to generate more informative results. A flexible protocol that combines multiple objectives—sometimes in sequential parts with transparent decision processes—can maximize information gathering, save resources and time, and allow earlier and smarter go-no-go decisions. In some cancer and rare disease indications, the line between Phase 1 and 2 has blurred, and early studies routinely evaluate both safety and efficacy.

Flexible designs can be more complex operationally and statistically. However, the added time and cost of collecting comprehensive data pays off in products with a well-characterized risk-benefit profile, a smoother regulatory path, fewer post-marketing requirements and commitments, and better patient compliance.

Recently, a client approached us after the FDA asked for additional safety and efficacy data to justify the Phase 2 dose they had chosen for a specific indication. We reviewed their Phase 1 studies of the same agent in other indications and found they had collected a wealth of relevant data. Because they had focused on safety, PK/PD, and efficacy as interrelated objectives with a flexible trial design, our experts could mine the available data and extrapolate the dose- and exposure-response relationships. We successfully addressed the agency's questions, avoiding the time and cost of additional clinical studies.

3 Enhance or replace clinical studies with modeling and simulation

Many of our clients seek advice on whether they can use modeling and simulation (M&S) to support or serve as a surrogate for clinical studies, such as those required to address drug-drug interactions (DDIs) or special populations. For example, DDI trials examine how interactions with concomitant medications may alter a drug's exposure, impacting safety or efficacy. M&S can support DDI trial design by predicting the relevance of potential interactions and optimizing clinical study design, including dose selection. In some cases, M&S can fully replace a clinical study. In this instance, we validate the model and outline all assumptions to ensure sponsors have a complete description of the analytical approach for regulatory experts to review.

We recently helped a client predict the relevance of a DDI interaction using physiologically based pharmacokinetic (PBPK) modeling. Our M&S experts reviewed the preclinical in vivo and in vitro data and the FIH clinical data to investigate the allowed concomitant medications for their Phase 2 trial. The results suggested that inhibitors of the relevant metabolic pathway did not impact the exposure of the drug because other metabolic pathways could compensate. However, medications that are enzyme inducers could reduce the drug's exposure, affecting efficacy. With this knowledge, the sponsor broadened the criteria for concomitant medications for the Phase 2 trial. Our PBPK analysis took three months, requiring far less time and money than a DDI trial.

We advise clients to use all the available preclinical pharmacokinetic and pharmacodynamic (PK/PD) data to predict human PK/PD.

Expert spotlight

Angela Qu, MD, PhD
Senior Vice President,
Biomarker Genomic Medicine
Parexel International

Angela is a global team leader in biomarker, genomics, precision medicine innovative trial strategy development and execution with 25+ years drug development experience across Oncology, Immunology, CNS, Metabolic, and Rare Diseases. With extensive experience in leading innovative genomics and biomarker projects across preclinical and clinical phases, she is a core member of Parexel's Oncology Centre of Excellence, and is published in 50+ peer-reviewed scientific publications in translational medicine and drug development.

Graeme Clark, PhD
Senior Director,
Translational & Genomic Medicine
Parexel International

Graeme's work in pharmaceutical drug discovery and development is a product of his extensive career within biotech, large pharma and contract research positions. As Senior Director, Translational and Genomic Medicine at Parexel, he leads the Bioanalytical & Biomarker Consulting services function from First-in-Human studies through to post-marketing activities and acts as scientific and regulatory subject matter expert in support of traditional small molecules, biotherapeutics, and cell & gene therapies.

Shaun Martin, PhD
Vice President, Integrated Solutions
Parexel International

With 33 years of experience including 25 with a CRO and 5 with Sponsors, Shaun leads a global team of clinical trial strategists responsible for operationalizing all Parexel trials from Phase I through approval. He is skilled in therapeutic areas include Autoimmunity and Infectious disease including Virology. His particular strengths include preclinical, CMC, BioA and early clinical development.

How biomarkers enrich and accelerate the feedback loop of drug development

The probability that a compound will make it from Phase 1 to market doubles[3] when trials use patient preselection biomarkers. We asked a team of Parexel experts to advise on incorporating biomarkers in the early stages of drug development.

Early-stage drug development has traditionally been viewed as a linear progression from preclinical work to safety to proof-of-concept to pharmacokinetics and pharmacodynamics (PK/PD), ending with the optimal efficacy dose for confirmatory trials. But by leveraging biomarker data, developers can enrich the journey with multiple feedback loops along the way (Figure 2). This path may appear circuitous but can go faster because biomarkers can inform smarter and earlier product advancement and termination decisions.

Start early

Once preclinical data suggest a mechanism of action (MOA), it's time to evaluate whether a biomarker strategy can inform a feasible development program. Often, biomarker strategies that work well preclinically may not work as well in humans. To mitigate that risk, developers can identify and include potential biomarkers for the selection and stratification of patients and for mediating disease. And this is not just a cancer phenomenon: biomarkers play a critical role across multiple therapeutic areas. For example, they stratify patients for Alzheimer's and Parkinson's disease trials. It's best to use biomarkers for more than just safety surveillance because markers of activity and efficacy can speed development later.

3 Clinical Development Success Rates and Contributing Factors 2011-2020. Biotechnology Innovation Organization, Informa Pharma Intelligence, and QLS Advisors, February 2021.

Late-stage trial designs can maximize benefits and minimize risks if early trials identify a biomarker-defined subpopulation of patients that benefits most from therapy or has more adverse events. There are three main biomarker approaches to enriching and stratifying patients in later-phase study designs:

1. **Enrichment:** Enroll only biomarker-positive patients to boost study efficiency by increasing the effect size, thus reducing the sample size needed to show efficacy.
2. **Treatment interaction:** Enroll both biomarker-positive and –negative patients to maximize the chance of effect.
3. **Adaptive:** Adapt enrollment criteria during the trial, narrowing the population down to those who benefit.

Extensive genetic testing in clinical trials can slow patient recruitment but choosing the right platform technology, such as next-generation sequencing, enables faster, more cost-effective screening.

Figure 2. How biomarkers multiply the feedback loops of drug development.

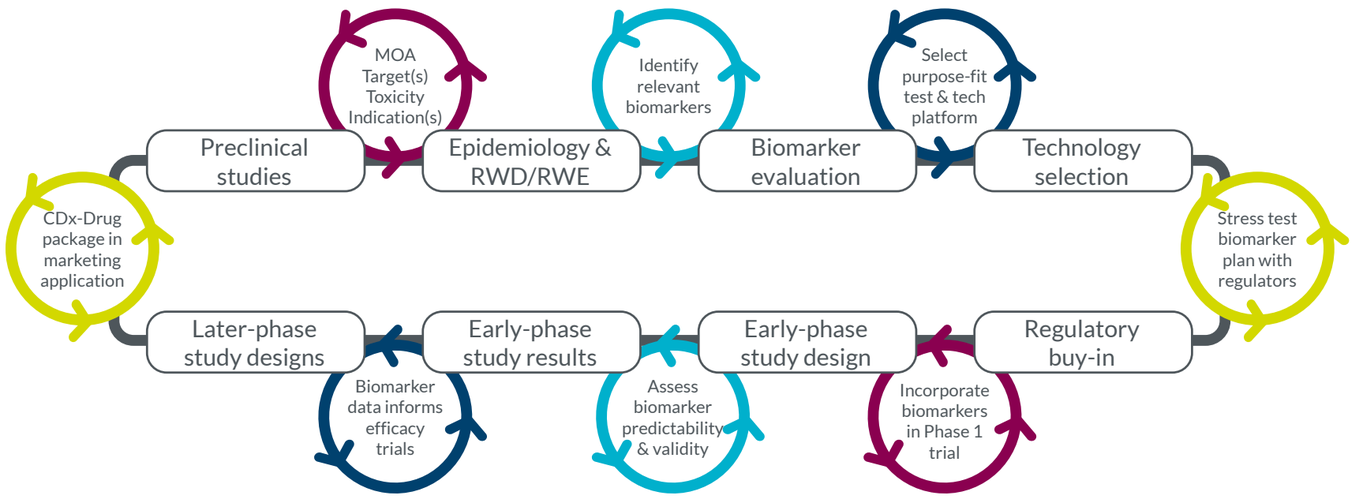


Figure 2. Preclinical work establishes the MOA, target(s), and toxicity of a drug. Epidemiology studies and real-world evidence (RWE) derived from real-world data (RWD) map the disease course. Both inform biomarker evaluation and technology selection. Regulators review the biomarker approach and early-phase trial designs for validity. New biomarkers may emerge during development that can improve later-stage trial designs.

Regulators are increasingly open to novel biomarkers, but sponsors need to be mindful of the purpose and limitations of biomarkers in early development.

Leverage epidemiology and RWD/RWE

To complement non-clinical data, companies can conduct retrospective or prospective epidemiology studies that gather real-world biomarker data from electronic health records (EHRs). One challenge of using registries for retrospective natural history studies is that they often do not contain the relevant biomarker data or store patient samples properly for later access. To meet this challenge, at Parexel, we are working on ways to digitalize biomarker data and apply advanced analytical methods to derive insights whenever feasible.

For example, traditional pathology biomarker testing is a labor-intensive, error-prone process in which individual reviewers manually look at slides of tissue samples and record findings. Instead, AI and machine learning tools could evaluate digital pathology reports or other types of imaging biomarker data faster and with greater objectivity. At Parexel, our computational scientists are working on automating the complex process of extracting and analyzing biomarker data. The goal is to integrate historically inaccessible biomarker data into meta-analyses, providing more precise disease categorization and patient selection criteria in clinical trials.

Evaluate tests and technology platforms thoroughly

Knowledge of the underlying MOA and disease pathophysiology informs how to segment the target patient population with biomarkers. To develop a biomarker strategy that can speed development, companies thus need a clear understanding of the MOA and a precise target product profile. After identifying which biomarkers to evaluate, developers can:

- Assess technologies or methods to capture the relevant biomarkers accurately. This may require developing and validating an assay.
- Select the appropriate laboratories to conduct these specialized tests and develop a management plan to oversee their work.
- Ensure that results will align with regulatory requirements.

Qualifying or validating a novel biomarker—versus a well-established one—can be challenging. Assays must be highly sensitive and specific, often a stumbling block. For the process to be efficient, it is essential to make go-no-go decisions on novel biomarkers early. Companies must determine whether a suitable assay exists or can be developed. Extensive genetic testing in clinical trials can slow patient recruitment but choosing the right platform technology, such as next-generation sequencing, enables faster, more cost-effective screening. As well, non-invasive liquid biopsy testing can diagnose, screen, and monitor patients.

Listen to regulators

Regulators are increasingly open to novel biomarkers, but sponsors need to be mindful of the purpose and limitations of biomarkers in early development. When selecting, testing, and establishing biomarkers for use in traditional or innovative early-stage trials—such as integrated Phase I/II or adaptive trials—sponsors can engage with regulators early to test their rationales and data. Blanket validation and agreement are not achievable for most novel biomarkers, but early regulatory feedback can improve a biomarker plan. A company must have a valid scientific rationale for ignoring regulators' advice.

Don't underestimate operational challenges

It is increasingly rare for companies to conduct an early-phase study without collecting biomarker samples and data. That's because sponsors recognize the value of information about a drug's impact on the body in addition to how the body metabolizes a drug. Designing and conducting trials that gather and utilize biomarker data takes expertise in operations, biosample handling, and specialized analytic techniques, among other disciplines. For example, "seamless" Phase 1/2 trials or adaptive trial designs are more complex logistically and statistically, requiring the right people, tools, and training.

Many companies underestimate the mundane yet myriad challenges of storing blood samples. When studies collect whole blood, lab technicians must separate the cells from the plasma or serum within hours. After adding stabilizing agents, technicians store the samples. The number of early-phase studies collecting complex biomarker data via flow cytometry is increasing. At Parexel, we have a flow cytometry lab at the investigative site for Phase 1 studies because blood degrades quickly, and shipping blood samples can cause molecule shedding. We've learned that flow cytometry readouts and the scientists evaluating them can vary markedly: therefore, it is best practice to use the same machine and scientists for all samples.

Good planning, done early, will pay off

A well-considered biomarker strategy can streamline development and improve portfolio prioritization decisions. It's nearly impossible to devise and execute a biomarker strategy ad hoc or, even worse, in crisis mode partway through development. Genomically-targeted drugs, properly developed, have an inherent advantage over drugs that are not, but their success will depend critically on good planning done early.

A practical approach to diversity in early-stage clinical trials

It has always been challenging for companies to reflect the diversity of patient populations in their clinical trials. And as our understanding of diversity expands, new considerations are continually emerging. In this article, Parexel experts explain how companies can best achieve diversity in their early-phase research.

Historically, diversity in clinical research was primarily defined in terms of race and biological sex. While a National Academies report[4] found that women represent more than half of clinical trial participants in the U.S., it revealed that racial and ethnic diversity in clinical research is "largely stagnant." To address persistent issues of unequal access, the FDA recently published a Draft Guidance[5] recommending that sponsors submit a "Race and Ethnicity Diversity Plan" with their investigational new drug (IND) applications when possible, but no later than the End of Phase 2 (EOP2) meeting.

The topic of diversity, equity, and inclusion now encompasses many special populations and groups routinely excluded from early-stage research. People over 65, children, women who are pregnant, lactating, or of reproductive age, LGTBQIA+ communities, patients with a BMI of more than 30, and those with disabilities are among the populations who often face barriers to participating in clinical trials. For example, recent Parexel research[6] found a lack of guidance on safe and inclusive practices for transgender and nonbinary individuals in clinical research. Incomplete data on dosing best practices may present a potential safety risk for people taking hormone therapy. Yet researchers must balance risks with offering fair and equitable access to clinical trials and potential new medications. More research and country-specific regulatory guidance are needed to ensure inclusive trial practices for the LGTBQIA+ community.

At Parexel, we've created a disability steering committee called "ParAbility" to enhance access for patients with a disability. According to the World Health Organization[7], more than one billion people live with some form of disability. And a majority of these conditions, such as chronic pain, hearing and vision loss, or mental and neurological limitations, are not outwardly visible.[8] Enabling access to clinical trials for volunteers, patients, and caregivers with disabilities is critical to achieving health equity.

4 Improving Representation in Clinical Trials and Research, National Academies, May 2022.
5 Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry, FDA, April 2022.
6 A targeted literature review exploring solutions for inclusivity of transgender and non-binary patients in clinical research, Parexel Poster #P109, Drug Information Association Annual Meeting, June 2022.
7 Disability and Health Fact Sheet, World Health Organization, November 2021.
8 What is an invisible disability? Invisible Disabilities Association, Accessed October 2022

Expert spotlight

Mwango Kashoki, MD, MPH
Vice President, Regulatory Affairs
Parexel International

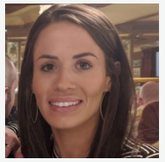
With 16+ years' experience in drug review, development and regulatory at the FDA, Mwango is an expert in development of analgesic and addiction therapies and post-approval activities (pharmacovigilance, risk management, Phase IV studies) with deep knowledge of review and development of small molecules and biologics, OTC products and generics. Mwango earned her MD from the Johns Hopkins University School of Medicine, an MPH from the Columbia Mailman School of Public Health, and is board certified in Preventive Medicine and General Public Health.

Rosamund Round
Vice President, Patient Engagement
Parexel International

Rosamund Round leads Parexel's Patient Innovation Center and decentralized clinical trials (DCT) service, dedicated to improving patient access to and experiences in clinical trials. In this role, she focuses on the reduction of geographical, financial, and practical barriers. As executive sponsor of Parexel's diversity in clinical research team and member of the PRIDE Committee (dedicated to improving both the workplace and trial experiences for the LGBTQ+ community), Rosamund views optimizing research access for all patients as a critical need.

Stanford Jhee, PharmD
Corporate Vice President
Scientific Affairs
Parexel International

Stan is a clinical pharmacologist with over 30 years of pharmaceutical development experience specializing in early-phase development from First-in-human to Proof-of-concept studies with an emphasis in CNS therapeutic area. He pioneered the ethnobridging study providing ethnic sensitivity studies, allowing global development, especially in Asia, and has published over 90 manuscripts and 4 books on drug development topics.



Amy Roach
Senior Director, Unit Head
Parexel International

Amy has a broad background in the management of phase I/II/III clinical trials and oversees recruitment and enrollment activities for all healthy and patient projects at the Baltimore EPCU. She assesses study protocols, prospective budgets, and clinical plans to determine feasibility and best approach with 10 years of clinical research experience.

Prioritizing equity and inclusion results in optimized patient recruitment and scientific rigor, making this a business imperative rather than a nice-to-have.

Build diversity into product planning

Regulatory agencies expect sponsors to evaluate new products in populations that reflect the patients who will be using them. For example, to fully understand the pharmacokinetics of an investigational Alzheimer's drug, Phase 1 studies need to enroll elderly patients as well as young, healthy subjects.

The two critical objectives of diversity in clinical research are to optimize access to research studies and to determine whether the treatment effect of an agent varies by biological or physiological factors. Establishing physiologic differences or genetic variation requires evidence. For example, numerous studies demonstrate that people of Asian descent have different pharmacologic activities and metabolize drugs differently. Phase 1 trials must account for this genetic variability. Physiological differences between genders, such as body weight, affect how they metabolize and clear drugs from their bodies.

An optimal drug development program should comprise representative percentages of the relevant population subgroups. Epidemiological desk research, including extensive literature reviews, can identify the prevalence rates of a disease or condition across different subsets of the population. Sponsors can use this epidemiological information to monitor patient recruitment continuously to ensure the trials meet the targets.

Test the diversity plan for a clinical trial. Is it feasible to recruit and retain the relevant patients? Do the investigative sites and principal investigators chosen for the study have a track record of enrolling the target population? Is the plan aligned with both product development objectives and regulatory requirements?

Pursue diversity as early as possible

Historically, phase 1 trials have sought to enroll a homogenous population to get a clean read on the pharmacokinetic (PK) data versus placebo. As a result, incorporating diverse patients in first-in-human (FIH) trials has not been prioritized. However, in a recent letter to the editor[9] of *Nature Medicine*, industry researchers called the belief that Phase 1 trials cannot enroll diverse patients a "myth."

There is a solid scientific and medical rationale for population selection in early-phase trials and for sponsors to identify opportunities for diversification. To prepare for later-stage studies, the FDA encourages the early collection of PK, pharmacodynamic (PD), and pharmacogenomic (PGx) data from a diverse population to inform drug exposure and response analyses.

At Parexel, we deploy multiple tools and services to engage with underrepresented communities, inform them of opportunities to participate in trials, and make enrolling easier. For example, we partner with trusted community advocates, conduct decentralized clinical trials, and work with trusted pharmacies via our Community Alliance Network[10] to expand access to clinical research for historically underserved groups.

9 Myths about diversity in clinical trials reduce return on investment for industry, *Nature Medicine*, June 2022.
10 Parexel Expands Patient Access to Clinical Trials Through New Community Alliance Network, Parexel Corporate Press Release, June 2022.

View health equity and optimized enrollment as a business imperative

Recent Parexel research[11] suggests that barriers to diversity include mistrust and skepticism of clinical research, stigmas around illness in some communities, time and travel burdens of trial participation, and the concentration of academic research sites in major cities. Companies that address these obstacles can ensure that their trial data are more generalizable to the relevant patient population. And during the clinical trial design phase, they can gather a broader range of patient opinions about which clinical and quality-of-life outcomes are most important to evaluate. In addition, reducing or eliminating practical barriers and partnering with communities to build trust can accelerate trial enrollment. Prioritizing equity and inclusion results in optimized patient recruitment and scientific rigor, making this a business imperative rather than a nice-to-have.

Why do some Phase 1 studies enroll a limited patient population?

At Parexel, we rely on early-phase clinical units (EPCUs) to recruit healthy volunteers for clinical trials testing the safety and tolerability of new investigational products. We run EPCUs in four key cities: Baltimore, Los Angeles, Berlin, and London. They are strategically located and have built strong relationships with diverse populations to expand access. We rely on community partners who can help overcome barriers to clinical research participation.

Often when we recruit healthy volunteers for a study enrolling patients of a certain race or ethnicity, we understandably receive questions about the restrictions. Potential participants, or the general public, may be skeptical of studies that require a specific group for enrollment, but such parameters are only in place out of scientific necessity. For example, one recent EPCU study recruited participants of West African (African American or Afro Caribbean) ancestry. This was necessary because the trial involved an investigational drug designed to reduce the formation of a specific protein. Variants of this protein are found only in people of West African descent, and they play a central role in the development of a severe chronic disease. If the experimental drug proves effective, it could treat the disease caused by these variants and save lives.

The FDA encourages the early collection of pharmacokinetic, pharmacodynamic, and pharmacogenomic data from a diverse population to inform drug exposure and response analyses.

11 Parexel Research Report: Discussion on Diversity, Parexel, May 2021.

With Heart™

We’re always available for a conversation

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