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New Medicines, Novel Insights: Achieving Patient-Guided Drug Development

An Executive Summary

In this report

Best practices for patient-focused drug development

In drug development, the natural tendency has long been to prioritize the science of treatment over patient access and engagement. Yet, while research and development are foundational to our profession, it is the patient who is our ultimate consumer. At Parexel, we have clearly determined the need to reverse this equation: that addressing the concerns patients care most about is essential to commercial success in a complex and competitive market. Moreover, the U.S. Federal Drug Administration (FDA) has prioritized patient-guided drug development, issuing four guidance documents over the last four years.[1]

However, a patient-guided approach might sound more like an aspiration than an achievable goal. How can drug developers listen, learn, and incorporate the patient's voice in a multifaceted process involving so many different stakeholders? What does it really mean to be patient-guided?

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. We have seen that sponsors can make a dramatic difference in their development programs by involving patients in a sustained, systematic way throughout the development continuum. **In every therapeutic area, patients are increasingly being recognized as critical stakeholders for product evaluation and should be engaged early and often.**

This approach begins with early asset planning: an integrated set of activities that aim to maximize an asset's value over its lifecycle, from early clinical development through commercialization. It starts at the early clinical or even preclinical stage, setting the foundation and determining much of the future trajectory of the asset.

By understanding and integrating patients' needs at this juncture, sponsors can help ensure that the drugs they develop are effective and resonate with the target population. Early asset planning applies to individual assets; but it can and should be applied to a company's entire portfolio in a particular therapeutic area.

Integrated Development

The patient journey encompasses everything from the initial symptoms that lead a patient to present at a clinician's office all the way through to long-term outcomes. It comprises the diagnostic journey, whether patients go to an academic medical center or a community practice, and who manages them over the long term. It includes treatment choices at different points in time, the individual patient's causes of disease burden, and outcomes across a wide range of clinical and nonclinical measures.

All those factors are important for understanding the right patient profile for clinical trials, the primary and secondary endpoints, and where a treatment is most likely to demonstrate improvement. There are several ways to collect information about the patient journey during asset planning:

Interviews with patients provide the most in-depth understanding of their experiences and perspectives. Interviews allow a deep exploration of patient perspectives and can uncover valuable insights that surveys alone may not capture. Prescription data or a survey can indicate that patients are not using a newly approved product, for instance. But qualitative feedback from individual patients is vital for understanding why, and therefore how, any uptake issues can best be addressed.

Conversations in early development will become increasingly valuable for informing a therapy's target population and competitive positioning and differentiating the new product. For instance, one sponsor assumed that a novel oral formulation of an orphan drug would command the vast majority of market share when approved. However, through conversations with patients, we learned that improvements in efficacy and safety would be needed to attain the forecast sales. As a result, the development program was refined to build a data package that could demonstrate meaningful clinical improvement for patients. **As markets become more competitive, value arguments need to become more specific.**

Surveys can be conducted with many patients or clinicians to obtain quantitative information on patient demographics, treatment patterns, and outcomes, with different goals for each group. Patients have a greater sense of the day-to-day disease burden and factors impacting their quality of life, while clinicians are generally more oriented toward data-driven endpoints.

Once developers have a strong qualitative understanding of patients' needs and expectations, surveys can strengthen patient population categorization, assumptions about patient preferences, and commercial forecasts. We often conduct patient surveys to refine revenue forecasts for different geographies and sites of care, particularly when patients of academic centers and community practices have different treatment goals.

Interviews with key opinion leader clinicians are valuable for understanding how the patient population may evolve with pipeline therapies and novel diagnostics. These clinicians are keenly interested in the possible evolution of treatments with future drug approvals. Conversations with them are useful at every stage of product development for understanding where a future product may fit in a rapidly evolving landscape, how to recruit patients for trials, and the commercial implications of recent developments.

Patient advocacy groups play a crucial role in representing the interests and needs of patients to a range of stakeholders, including manufacturers and regulators. Engaging with these groups can provide valuable insights into the patient experience and help shape research and development efforts. **Patient advocacy groups (PAGs) have a wealth of knowledge about specific conditions and can provide a collective voice for patients.**

For example, Sarepta's success in Duchenne muscular dystrophy (DMD) is largely due to engagement with patient advocacy groups, and understanding clinical measures that matter to patients and their caregivers. Likewise, the vocal support of patients helped encourage the FDA to approve Exondys 51, despite opposition from reviewers and experts to a data package that was not overly convincing. The patient voice said that the risk-benefit was favorable because of the hope for meaningful functional improvement in the face of limited effective options, and that view resonated with regulators.

Of course, some PAGs, particularly in rare diseases, have limited bandwidth and many interested biopharma partners. In those situations, it is important to enter into conversations with a compelling value argument that can be iteratively refined with the PAG. Because competition for trial patients can be fierce, building early excitement in the patient community will help uptake and expedite early and later-stage clinical trials with more effective patient recruitment. Many rare-disease PAGs are best positioned to improve access to trial-eligible patient populations and build support for regulatory access and commercial use.

PAGs also play a strong role in enabling market access where state government funding is critical to ensuring patient access. For a developer of HIV therapies, we interviewed heads of national PAGs to understand the needs and perspectives of patients. This feedback was crucial in shaping our understanding of the minimal product attributes patients wanted in their treatment and prophylaxis regimens. As HIV therapies became more effective and patient management became chronic, the longer-term toxicity and side-effect profile were more important than we had realized. This information had significant implications for the optimal combinations of products in our recommended regimens. The interviews were also critically helpful in ensuring that novel combination products were aligned with local funding, helping ensure access throughout the patient community.

Patient-Relevant Clinical Outcome Assessments

A patient-focused approach can also help drug developers build an evidence case for unmet needs – important because products addressing unmet needs often enjoy accelerated regulatory review and reimbursement. To identify an unmet medical need, sponsors must first understand a disease or condition and assess the current and future competitive landscape through literature searches, natural history studies, and consulting experts. But that won't yield a complete picture. Patients are critical to identifying and quantifying unmet needs; they are experts in their disease journey and know which outcomes matter to them. There is no single answer or definition of what is patient-relevant because what patients care about most is impacted by the stage of disease, line of treatment, available options, and personal preferences.

In any case, the insights gained must translate into sound, measurable endpoints in a clinical trial design that collects enough data to prove safety and efficacy. Clinical outcome assessments (COAs) – utilized and validated early in development and employed in pivotal studies – can demonstrate that a product meets an unmet need. **COAs allow sponsors to measure patient experiences and perceptions that have not been measured by traditional research endpoints.**

For example, many people assume that a cure or tumor shrinkage is the top priority for all cancer patients. Yet some patients with advanced cancer may prefer a less-effective drug with fewer side effects to the most up-to-date but very toxic treatment. A patient with an incurable disease and short life expectancy may value quality time free of symptoms and side effects more than a patient who could be cured by treatment.

There are four types of COAs:

- Patient-reported outcomes (PROs) – Self-reported by trial participants via paper or electronic format: often questionnaires that ask patients to rank symptom severity on a scale or to log the number of specific events over time.
- Observer-reported outcomes (ObsROs) – Reported by someone other than the patient or a health professional, such as a caregiver or family member, who observes the patient daily. Also, typically, questionnaires.
- Clinician-reported outcomes (ClinROs) – Reported by a trained healthcare professional after observing the patient. May involve clinical judgment or interpretation.
- Performance outcomes (PerfOs) – Reported by a patient or a trained individual. Based on a standardized task performed following a set of instructions.

COA instruments that are relevant to patients typically center around three factors that impact their quality of life while on a medication:

- Symptoms: Does the drug lessen the disease burden by eliminating or mitigating complications such as pain, fever, a lump or bump, or difficulty sleeping?
- Functions: Does the drug allow them to participate in activities of daily life when they otherwise could not?
- Intrusiveness of medication: Does the drug involve intrusive administration paraphernalia (bulky inhalers, injector pens, or hospital visits), monitoring procedures (lumbar punctures or serial blood tests), or side effects?

Sponsors often overlook intrusiveness when selecting COAs, but it is central to patients' decision-making.

Some sponsors are so focused on proving whether a drug works at the cellular level or is compliant with good manufacturing practices (GMP) that they forget how intrusive it may be in a patient's everyday life.

Sponsors must balance time and cost when incorporating patient perspectives, but if they fail to submit adequate evidence of a drug's impact on patient-relevant outcomes, their products could fail when challenged by regulators, HTA reviewers, and payers. To convince HTA agencies and payers, sponsors increasingly need to submit quality-of-life evidence to support pricing. Before they make an expensive new product available, they demand compelling data on patient benefits. It is important to carefully select COAs that – when measured adequately – can be modified by the investigational treatment and demonstrate clinically meaningful differences between study arms within the time frame of the planned clinical trial. And the COAs should reflect an aspect of health that is important to patients.

At Parexel, we apply key performance indicators to new or existing COAs to determine if they are fit for purpose.
Sometimes we find an existing COA that works or can be modified. At other times, it is necessary to develop a wholly new COA or combine elements of existing ones into a new measure. When we determine that a COA is critically flawed, often because they are difficult for patients to understand, we move on and find better ones. Here are our best practices for COA development:

- Start planning for COAs while designing Phase 2 trials. Phase 3 development is too late to agree on a COA strategy with regulatory agencies.
- Follow guidance documents from regulatory agencies and seek COA advice as early as possible. We advise sponsors to propose a strategy for COAs and real-world evidence (RWE) at the End of Phase 1 (EOP1) meeting.
- Meet with HTA agencies to outline your COA strategy and receive feedback.
- Talk to the COA experts and consultants available to you in your company, clinical research organization (CRO), or at a standalone COA consultancy.

Advancing PRO Data

Specifically, PROs provide direct input about how a patient feels and functions without amendment or interpretation by a clinician or anyone else. However, many companies spend time and effort collecting PROs in pivotal efficacy trials and submit the data to the FDA, but the information often does not appear on product labels. As a result, it's not readily available to U.S. providers and patients.

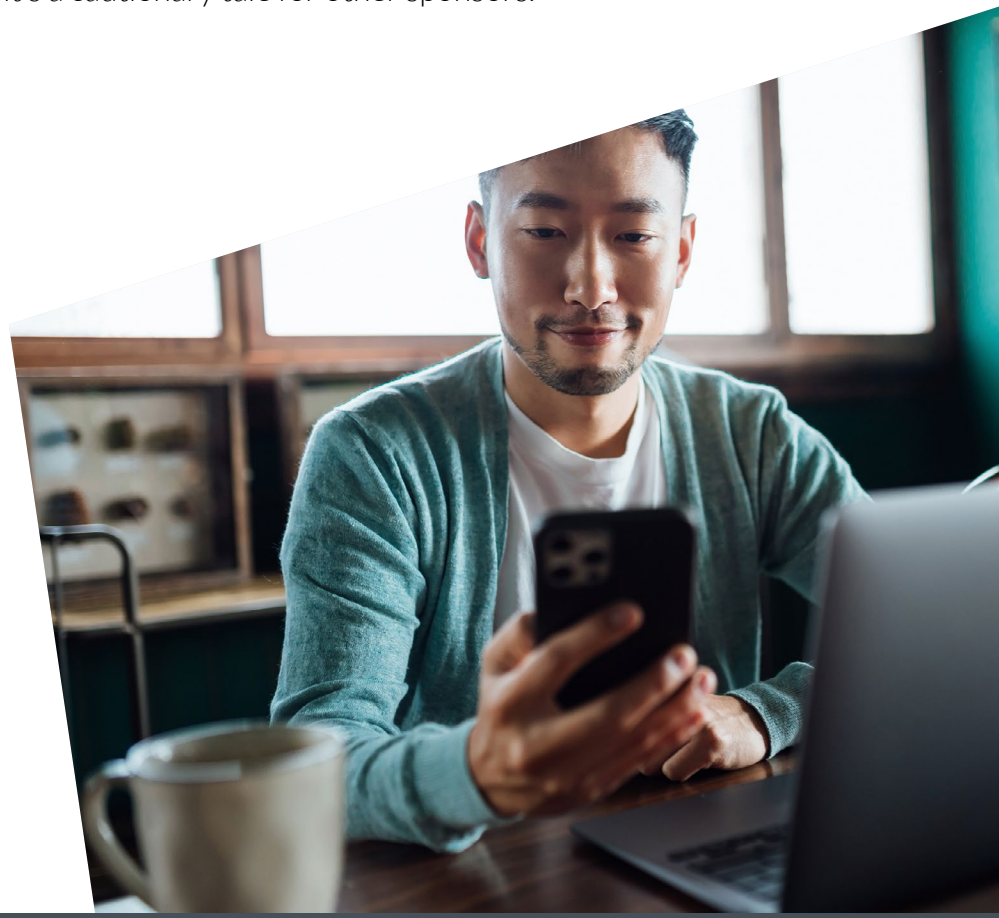
To understand why, Parexel analyzed the FDA clinical review documents for 164 novel orphan drugs and biologics approved from 2017-2022.[2] We found that just 13% (21) of the products included PRO data on the label, even though 63% (103) of the sponsors collected it during pivotal efficacy trials.

Of course, sponsors collect PRO data for various reasons besides seeking a formal U.S. label claim from the FDA. Sponsors may be aiming at the European Medicines Agency (EMA) or to support European reimbursement decisions. Nevertheless, our analysis of FDA review documents for orphan drugs suggests that PRO data is not utilized efficiently or widely disseminated to patients, at least in the U.S. Furthermore, PRO data suffers from persistent methodological problems. **If patients are to reap the benefits of patient-focused drug development, the art and science of developing, collecting, and analyzing PRO data must advance.**

For sponsors, the ideal strategy is to identify high-quality measures of patient health that can be used to construct a meaningful, evidence-based PRO endpoint. Parexel recommends three best practices to ensure the scientific rigor of PROs.

Validate the PRO and define a "clinically meaningful" threshold for change. PRO instruments must have "content validity," meaning they must be relevant and specific to the disease being studied. That requires a clear understanding of the natural history of the disease, the key symptoms that may improve from treatment, and an appropriate length of time to see a clinical benefit. Specify and define concepts such as signs, symptoms, and impacts that are important to the target patient population and likely to demonstrate meaningful and interpretable changes in clinical trials. Seek input from patients and expert clinicians. And ensure that the patient population can validly and reliably self-report (some patients may be too young or sick) and select a PRO that accommodates a spectrum of cognition and mobility levels.

For statistical validity and comparability, the mechanism used to report PRO data should be consistent throughout a trial. A drug recently approved by the FDA for an orphan metabolic disorder used a daily questionnaire to measure patients' hunger levels. However, partway through the pivotal study, patients switched from answering the questions on paper to using an e-diary. The sponsor did not subject the new e-diary device to usability testing or conduct patient cognitive interviews to assess its functionality, questionnaire comprehension, and ease of use. The FDA concluded there was insufficient data to demonstrate that patients understood one of the questions. Although the PRO data, in this case, made it onto the label (the PRO was the primary endpoint of the study), it's a cautionary tale for other sponsors.



Adopt a sound, prespecified statistical analysis plan from day 1. In our analysis, we determined that FDA reviewers frequently noted the lack of a prespecified statistical analysis plan (SAP) or correction for Type 1 errors (results due to chance). One way to avoid this problem is to agree with the agency on the SAP before initiating a pivotal trial. When a PRO is designated as a secondary endpoint, a hierarchical testing framework with an alpha level (the level of significance required to show that the result is not due to chance) adjusted for multiple comparisons can help ensure valid results.

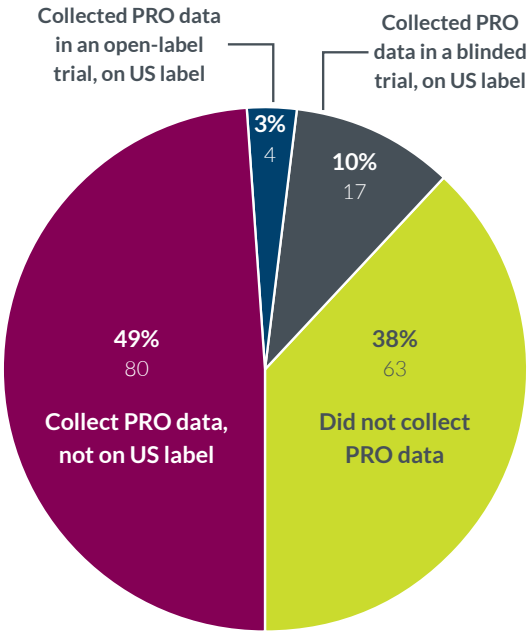
Another considerable problem cited by the FDA was missing data due to death, disease progression, or a high dropout rate for the trial. Sicker patients and those who do not respond to treatment are less likely to complete patient-reported quality-of-life instruments as a trial proceeds, skewing results. Although missing data is inevitable in trials, sponsors can take steps to prevent it. Sponsors thus need to ensure that study designs make sense, are practical, and will achieve the goals outlined in the protocol.

Design blinded, controlled trials whenever possible. Of the 21 orphan drug labels from 2017-2022 that contained PRO data, just four (19%) reported data from open-label studies. Most PRO data the FDA approved for inclusion on product labels were generated in blinded, controlled studies. PRO data from open-label or single-arm studies has limited interpretability. That's because treatment effects can be systematically over- or under-estimated by patients who know the treatment assignment.

Randomized, controlled trials (RCTs) are the most efficient way to neutralize confounding factors and, therefore, the best way to study risks and benefits. Double-blinded assignment to treatment and control can provide unbiased comparisons for known and unknown factors. Sometimes, a comparator arm is neither feasible nor ethical for some modalities, such as cell and gene therapies with remarkable activity and indications, such as advanced cancers or ultra-rare diseases with no existing treatments. Use of active controls, external control arms, natural history studies, and historical controls as comparators can help.

However, even a single-arm open-label trial can collect useful PRO data. In our analysis of orphan drugs, we found a CAR-T cell therapy for cancer that the FDA approved based on a single-arm, open-label Phase 2 study. This pivotal study captured three different PROs as secondary endpoints. Although the PRO data did not meet the FDA's standard for inclusion on the product label, the data did appear on the EMA label and was later published in a peer-reviewed journal.[3] An editorial accompanying the journal report stated: "… the authors should be commended for their efforts to provide the scientific community with unprecedented PROs information on the burden of this CAR T-cell therapy. Despite several open questions, which should be elucidated in further studies, the results reported in their article are highly encouraging and hopefully will stimulate other high-quality research initiatives in this area."[4]

The most important lesson from our review is that sponsors should select or develop a PRO in collaboration with patients and disease specialists to agree with regulators ahead of pivotal trials. **Wider capturing and publishing of the effects of drugs as experienced by patients will help drive more holistic, patient-focused therapies.**



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

1 Patient-Focused Drug Development: Collecting Comprehensive and Representative Input (2020); Patient-Focused Drug Development: Methods to Identify What Is Important to Patients (2022); Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments (2022); Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making (2023).

2 Numbers include original new drug applications (NDAs) and biological license applications (BLAs) only, not supplemental applications (label extensions or new formulations). The dataset includes only orphan-designated products that achieved U.S. licensure for the first time between 2017 and 2022 and contained a new molecular entity or new active moiety. For CBER approvals, we excluded assays, fractionated plasma products, patch tests, reagents, vaccines, and tissue transplant products.

3 https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30493-0/fulltext

4 https://pubmed.ncbi.nlm.nih.gov/31606418/

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