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New Medicines, Novel Insights: Accelerating the New Frontiers in Neuroscience

An Executive Summary

In this report

Nearing the tipping point in neuroscience

Judging from the enormous progress being made in treatment modalities and better understanding of how the brain works, neuroscience research has reached a major tipping point. At Parexel, we understand how the research in this challenging field is poised to accelerate scientifically, clinically, and commercially, much as cardiology and oncology did decades ago.

At a tipping point, as progress accelerates, we still have to navigate increasingly complex challenges in clinical development to deliver safe and effective treatments to the patients who need them. What will carry us forward?

Urgency. The neuroscience community must communicate an urgency commensurate with the burdens and crises these diseases impose on individuals and societies. **Neurological and psychiatric diseases often evolve slowly, but time matters; disease-modifying treatments must start early to impact progression.** The World Health Organization estimates that half of adult mental health disorders start by age 14, and depression and anxiety are a leading cause of illness and disability among adolescents globally.[1]

Better endpoints. Endpoint selection and interpretation remain significant challenges. We can apply lessons from advances in treating multiple sclerosis (MS), where limitations of the mainstream Expanded Disability Status Score (EDSS) and Annualized Relapse Rate (ARR) led researchers and patients to advocate for more sensitive, disease mechanism-related, and patient-relevant endpoints.

More reliable biomarkers. There is a lack of reliable and easy-to-access biomarkers for early diagnosis and disease treatment monitoring. The development and validation of wide spectrum of biomarkers — genetic, molecular, clinical, digital — will accelerate development of precision medicine in neuroscience.

Boldness and courage. Understanding comes with trial and error, including high-profile, expensive failures. It comes with a committed investment in research. At Parexel, we advise sponsors on how to minimize risk and accelerate development using innovative trial designs and novel endpoints. Working closely with regulators and conducting rigorous feasibility testing can mitigate the risks in these approaches.

In this report, Parexel experts share insights and best practices that can help drug developers navigate complexity and move closer to achieving their goals — all while staying focused on the patient journey.

Innovative trial design

Neuroscience trials typically remain traditional because of the heterogeneity of neurologic, neurodegenerative, and psychiatric diseases and the relative absence of actionable biomarkers. **Yet adaptive approaches and biomarkers could optimize trial designs and make development more efficient.**[2]

Recent advances in the field, including the emergence of new blood and imaging biomarkers in MS, Alzheimer's disease (AD), and major depressive disorders (MDD), suggest the time has come for invention and cross-fertilization. At Parexel, we advise sponsors on using innovative trial designs, novel biomarkers, and external data to accelerate neuroscience drug development.

Navigating market access in neuroscience

While focus on the patient during clinical phases is paramount, a new treatment will benefit a broad population only if payers provide access. Therapeutics in neuroscience pose a special challenge in this regard. Despite great strides in understanding neurological and psychiatric conditions, most conditions progress slowly, and the symptoms are not easily captured through endpoints that clearly demonstrate immediate benefits. This creates a new paradigm both for regulatory approval and payer acceptance since we are not addressing survival or a set of clinical symptoms.

For this reason, we advise our clients to start planning market access strategies as early as possible, ideally when entering the clinic. At the very latest, the strategy should be in place as Phase I studies conclude and the transition to Phase II begins. The initial priority is to identify the target product profile. What is the unmet medical need? What patient segments are being addressed and for what symptoms? And beyond the regulatory framework, what is the caregiver burden and how does this impact utilization of other healthcare services?

Determining the target patient profile and ultimately, the value story, requires a deep understanding of the patient journey and the outcomes that the patient considers meaningful and beneficial.

This knowledge drives the strategy for data generation and the choice of primary and secondary endpoints throughout each phase of the clinical trial. And when patients are involved in the conversation about study designs, they can help drug developers understand whether or not a certain endpoint characterizes their disease.

That said, non-clinical endpoints can also be important in building the value proposition. Biomarkers, for example, can give us a clearer understanding about the mode of action of a therapy. That can help payers understand a specific clinical benefit and how a therapy today can influence the progress of the disease tomorrow. In this realm, we expect to see more focus on imaging and fluid biomarkers and how these non-clinical parameters can help treat disease.

Risk mitigation through feasibility assessment

How can we improve the success rate of clinical trials in neuroscience? Assessing the feasibility of a study's design before it starts can mitigate or avoid many of the risks unique to neuroscience studies. High-quality feasibility testing helps sponsors optimize protocols and empowers them to make contingency plans that would have been overlooked or unidentified. Sponsors can focus on the following factors.

Patient needs. Feasibility in neuroscience trials is uniquely challenging due to the complexity of the central nervous system, limited biomarkers, and difficulties in patient recruitment and outcomes measurement. These challenges are compounded by the subjective nature of many symptoms and the long study durations often required to demonstrate efficacy. Many neuroscience trials target newly diagnosed patients or those with early-stage disease. However, understanding the patient's disease progression journey and the impacts of the disease on every functioning — cognition, movement, depression, and so on — is critical to adapting protocols. **Drug developers need to listen, learn, and incorporate the patient's voice in this multifaceted process.**

Disease studied. Sponsors can recruit participants faster, help them stay in studies, and collect high-quality data by accommodating specific needs in neurodegenerative and psychiatric conditions. However, they must consider the patient's condition and caregiver circles in feasibility assessments to plan proactively for a successful trial.

FDA-mandated diversity. Feasibility analyses must include a sound strategy for meeting or exceeding FDA-mandated diversity requirements. In 2022, we helped a sponsor prepare one of the first diversity plans for a bipolar study, and we have worked on countless others since.

Strategies for expanding trial diversity

True diversity in neuroscience clinical trials goes beyond race, ethnicity, and gender. It encompasses age, apparent and non-apparent disabilities, cultural differences, and socioeconomic status. Enrolling a diverse and representative population of patients in these trials requires that we include those with varying degrees of ability. Standard eligibility criteria often exclude patients with low mobility, cognition, communication skills, or technological proficiency. But in real life, many neurological patients are challenged in one or more of these areas.

Some exclusions ensure patient safety, and these won't change, but others may be unnecessary. Patients with co-morbidities, such as high blood pressure, high cholesterol, or overweight, might minimally affect the adverse event profile of an experimental agent but will generate data that are more generalizable to real-life patients. For diseases of aging, overly strict eligibility criteria can result in studies that routinely enroll younger- and healthier-than-average participants who are not representative of the target patient population.[3]

Site selection and partnership can increase diversity in two ways: selecting sites that serve a diverse population and supporting them in accommodating those patients. At Parexel, we use real-world data (RWD) to identify a mix of urban, suburban, and rural sites where a trial can be run.

It's essential to balance the budget against the needs. This is critical because many strategies for boosting recruitment, engagement, and retention cost money. We build the care into the budget and the recruitment projections. If patients' costs are not sufficiently covered, we often encounter problems in retention and compliance.

For many people, the biggest hurdle is getting themselves or a loved one diagnosed. Often, critical symptoms are not evident to patients or their families. Late presentation and diagnosis of neurodegenerative diseases impede early participation.

Precision psychiatry: critical for early intervention and disease management

Yet diagnosing, prognosing, and predicting neurological and psychiatric illnesses more precisely is critical for early intervention and better disease management. Traditional diagnostic and treatment pathways primarily rely on clinical interviews, somatic symptoms, and clinicians' subjective opinions. Precision psychiatry aims to combine diverse markers, such as clinical presentation, biological, neuroimaging, genetic, metabolomic, and digital biomarkers, to create a more objective and holistic phenotype for patients.[4] **Rather than starting with an illness definition, precision psychiatry seeks to link symptoms to specific neurobiological pathways that novel treatments can target.** Developing a symptom-targeted drug across a variety of mental illnesses is new territory in neuroscience.

At Parexel, we increasingly collaborate with sponsors to explore how to incorporate precision medicine techniques in developing treatments for these conditions. It's a nascent effort with a long road ahead, but we do see progress in critical areas.

Precision medicine in neuroscience is challenging because we don't have clear molecular targets or etiologies. However, as more researchers and sponsors collect and validate novel, multivariate forms of biomarker data and correlate them with outcomes, we draw closer to a diagnosis and treatment framework that can offer patients more personalized and effective therapies.

Early identification of Alzheimer's Disease (AD)

Early-stage AD trials often present a high burden for patients and their families, including extended inpatient stays and invasive procedures, such as lumbar punctures. In early 2023, Parexel investigators launched a clinical trial that uses blood testing to identify healthy older adults in the early stages of beta-amyloid (Aβ) and tau protein accumulation who have previously participated in a Phase I clinical trial. We wrote a protocol to identify and follow healthy research participants who may be at risk of developing AD based on Aβ and tau blood biomarker data or cognitive testing results. The only burdens for those participants are a blood draw and cognitive testing by a trained rater.

Building on our longstanding relationships with hundreds of active, healthy EPCU volunteers, we contacted those aged 60 and over who had participated in a study within the last five years. Participation rates have been high, and the database is growing.

When we demonstrate our commitment to the well-being of patients and families, we build relationships. Bringing scientific advances and technical expertise to the patients who need them requires building relationships with people in the community and understanding their individual stories.

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Regulatory pathways for psychedelic drugs

There is an ongoing unmet medical need for new and effective therapies to treat mood and other neurological and psychiatric disorders and legitimate excitement about the possibility of psychedelics being approved and regulated as medical treatments. The FDA and other regulatory agencies are still establishing how to best evaluate psychedelics as medical treatments and setting standards for their development.[5,6] **Companies and regulators will need to build experience together over the next few years to establish the best approaches.** At Parexel, we have identified five strategies to maximize the likelihood of clinical development and regulatory success:

- **Characterize the investigational psychedelic product comprehensively.** We strongly agree with the FDA's and EMA's advice that sponsors meet early and often with the regulators to discuss development plans.
- **Provide sound scientific justification for the dosing strategy and early clinical development.** For psychedelics with hallucinogenic and other adverse effects, it is vital to find the lowest possible dose (or range of doses) that produces the intended treatment effect and

minimally induces undesirable effects. At Parexel, we advise sponsors to establish an effective dose through a systematic dose exploration strategy.

- **Design clinical trials to minimize bias and unblinding.** Clinical trial designs require meticulous planning and rigor to ensure that the results are interpretable. When testing a new psychedelic agent with supportive psychotherapy, standardizing the delivery of psychotherapy is essential to minimize bias.
- **Prepare for intense scrutiny of proposals for at-home use of psychedelic medicines.** Sponsors considering outpatient self-administration should be prepared to collect substantial data from well-designed studies to support the safety of at-home, unmonitored use.
- **Explore opportunities for expedited program designation.** Psychedelic drugs offer a potentially effective new class of treatment for challenging conditions. A developer of new psychedelic medicines who conducts a well-designed nonclinical and clinical development program can seek expedited program designation, particularly fast track designation (FTD) and breakthrough therapy designation (BTD).

At Parexel, we play an essential role in this exciting journey of advancing therapeutics for neurological and psychiatric disorders. With dedication, expertise, and passion, our team stands ready to further the promising progress being made in this challenging field.

For more comprehensive insights on these topics, please explore our interactive digital report, "*Accelerating the New Frontiers in Neuroscience*." You'll find additional observations and recommendations from Parexel experts who are doing everything humanly possible to advance treatments in neuroscience to improve outcomes for patients and their families.

1 Fact Sheet: Adolescent and young adult health, World Health Organization (April 28, 2023, *accessed September 9, 2024*).

2 Phase III Trial Failures: Costly, But Preventable, *Applied Clinical Trials* (August 1, 2016).

3 Clinical trials in older people, *Age and Aging* (May 2022).

4 Precision Medicine Approaches to Mental Health Care, *Physiology* (September 13, 2022).

5 Psychedelic Drugs: Considerations for Clinical Investigations, FDA Draft Guidance for Industry (June 26, 2023).

6 https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-investigation-medicinal-products-treatment-depression-revision-3_en.pdf.

››› We're always available for a conversation.

With Heart™

Parexel International Corporation
2520 Meridian Pkwy, Durham, NC 27713, USA
+1 919 544-3170

Offices across Europe, Asia, and the Americas
www.parexel.com

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