Building a program for patient-guided clinical research for Alzheimer's disease

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This article is part of a series about challenges and opportunities in developing treatments for dementia.

The topic of patient-guided clinical trials is prominent in all of the discussions with our sponsor clients. Nowhere is the patient-first ethos more critical than in developing treatments for Alzheimer's disease. As the disease progresses, patients typically have a diminishing ability to communicate how they feel and function, yet data must identify endpoints related to outcomes. To be successful, trials must be designed with sensitivity to these realities. Further, by the very nature of the disease, the studies are long-term, spanning a year or more. Participants represent an adult population, perhaps just beginning to experience mild cognitive impairment (MCI) but fully functioning and possibly in employment. Being mindful of demands on their time is critical. We need to remember that the patients' goal is not to provide evidence; their goal is to be screened, to be monitored, and to receive an effective treatment. In a disease like Alzheimer's, we must consider the burden on families and caregivers – and their importance – along with the perspective of the patient.

Certainly, regulatory requirements for evidentiary data are always paramount in trial design. But we should ask ourselves what data the regulators actually need, and in what volume. This allows us to plan development programs that meets objectives with data points that are not just "nice to have." Do we really need 25 secondary endpoints, with instruments for

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cognitive testing and assessments of quality of life and daily living activities taking place over six hours every two weeks? What is the right sample size? What is the right number of assessments, and how often are the assessments necessary? These are some of the fundamental design questions.

Less-frequent efficacy assessments

At Parexel, we are continually exploring different data collection methods to demonstrate safety and efficacy while mitigating the patient burden. It is important to consider if we can collect data for efficacy assessments less frequently to reduce the challenge for patients. For example, we can look at pharmacokinetics (PK) assessments as an analogy. One approach is rich sampling, where we measure every 15 minutes in the first two hours, and then every half hour, then every hour over a 24- or 48-hour period. But often, we use a sparse sampling design that follows essentially the same sampling intervals but uses multiple patients to establish a pattern and, based on statistical modeling, still derives the required information. We can potentially think about this approach, not necessarily for a comprehensive assessment, but as a model that could offer a more convenient way for patients to participate in a clinical trial for Alzheimer's disease.

Genomic and biomarker classification

As we continue to learn more about genetics, there are opportunities for drug developers to design early-phase trials to identify subtype patients through genomic or biomarker classification. We are using this approach widely in other therapeutic areas, including oncology and lung cancer, to characterize patients who respond to a certain treatment. For example, about 4% of non-small-cell lung cancer patients have a type with a mutation in the anaplastic lymphoma kinase (ALK) gene. Developments in this area aim to produce compounds to target this biomarker. For patients with Duchenne Muscular Dystrophy, Exon skipping and identifying the specific missing gene seems to be a promising approach to developing patient-specific treatments. The same approach can feasibly be used to help us better understand Alzheimer's disease. Identifying subgroups would enable us to develop compounds targeting this subtype , identify the track where the treatment is effective and exclude other subtypes that don't respond.

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Digital technologies

Digital technologies offer the same potential for developing therapies for Alzheimer's disease that we saw 15 years ago with measuring vital signs. With diabetes, for example, the patient had to be present at a clinic for a blood draw for continuous glucose monitoring. Now, we give them a monitor for a remote assessment. This concept can be extended to Alzheimer's patients: Master protocols and tracking platforms are being designed to monitor mild cognitive endpoints to gauge changes and differentiate stages of severity. In some cases, they include sensors and wearables for monitoring and tracking. For example, a mobility app measures whether the patient is moving around or sitting still. This can be done while the patient is at home even more effectively than at a clinic, without intervention by a nurse or an investigator. When we define the data that will be required by regulators and payers and begin to design our studies, digital technology assessment will be critical.

Alternate trial designs

Finally, recent studies for treating Alzheimer's disease have demonstrated that adaptive trial designs and alternate approaches can be effective in demonstrating efficacy and safety without causing undue stress on participants. A few examples:

- A new compound that recently received accelerated approval from the FDA was based on Phase II data proved to reduce disease progression by 27%. This explorative 18-month study used PET scan analysis with 1,800 patients randomized in two arms. A response-adaptive randomization was implemented to assign more patients to the better-working treatment arm. This reduced the overall sample size as fewer patients were assigned to less-effective arms.
- In another case, two sponsors ran a basket trial with one control arm for two drugs. The sponsors opted to use a single independent contract research organization (CRO) to support the trials, resulting in a more efficient governance structure without exposing confidential data to one another. This flexible approach eliminated the need for two trials and two separate control arms.
- Other approaches include an umbrella design, where different compounds are tested for one disease, and a basket design that tests one compound in different diseases. A master protocol can specify subprotocols, where each compound is tested for a specific indication. All of these adaptive trial designs can be more efficient.

1 https://www.alzheimer-europe.org/research/projects/european-prevention-alzheimers-dementia-consortium

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- Another good example is research being conducted by the European Prevention of Alzheimer's Dementia Consortium (EPAD). This study involves multiple compounds with a single control arm. EPAD aims to create a disease register of people who consented to enter secondary prevention trials and delivers a degree of readiness that ensures better knowledge of a participant's suitability and a more rapid throughput of screening for the trials.[1]

As the risk of dementia continues to grow with the aging of the world's population, the urgency is increasing to advance the science of drug development for Alzheimer's disease. With promising treatments entering the pipeline, recruiting, and retaining patients for clinical trials is crucial.

Parexel is leading the way in this regard. We have decades of experience with Alzheimer's treatments, working closely with drug developers on innovative approaches to trial design. This has led to creative, comprehensive strategies for putting the patient first – which is central to everything we do at Parexel. By keeping the patient's needs and experience at the forefront, drug developers can increase enrollment levels, run trials more smoothly, control costs, and get effective treatments more quickly to people who await them.

Partnership with Parexel

With a team of 1000+ regulatory professionals, including 80+ former regulators, Parexel has the knowledge, insights and technology-enabled processes to accelerate and streamline your drug development journey. With experience in more than 110 countries, we provide strategic regulatory advice, proactively identify and mitigate risks and navigate the ever-evolving regulatory landscape. Our deep therapeutic insight and proven track record make us a reliable partner for achieving regulatory success.

The earlier we start working together, the better we can shape the plan and craft the best strategy for global engagement with regulators. In partnership, we develop proof-of-concept protocols with an approach that will allow collecting the information supporting decision-making when moving to pivotal studies.

Further, we can help design the program to be as streamlined and patient-centric as possible. For instance, we work with other SMEs to devise a flexible and efficient strategy and ensure that assessments implemented in the protocol are manageable for the patients. If the properties of the drug allow, we consider combining healthy volunteers and patients in one study to streamline the process.

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