Regulatory considerations in designing clinical trials for Alzheimer's disease

Simona Stankeviciute, MD, Principal Consultant, Regulatory Affairs

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

When planning clinical trials for Alzheimer's disease, sponsors know that they need to think creatively about how to evaluate the effect of their product. Drug developers must make sure that both early- and later-stage studies will satisfy global regulatory requirements. They also need to consider the mechanism of action (MoA), especially in the earlier stages of development. The disease progresses slowly, and clinical outcomes might be revealed only over an extended period. Thus, all early evidence of effect, including pharmacodynamics, is very important.

Best practices and creative approaches

We have identified several best practices and creative approaches for sponsors to consider in planning their strategies for trial design and thinking ahead for regulatory submissions. These apply across the board, regardless of company size, geographic region, and the complexity of the trials.

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Consider how to ensure that the dose selection strategy is robust. It is always critical that the correct dose and dosing strategy are chosen to be used in pivotal studies. Implementing additional pharmacodynamic endpoints – if they can be informative based on the MoA of the drug – can facilitate and strengthen the dose selection process. For example, for some molecules in the pipeline, Quantitative Electroencephalogram (qEEG) or simple EEG was successfully used to substantiate dose selection for the studies to follow. However, these additional endpoints potentially increase the patient burden, requiring more visits and more time in the clinic. Be sure to ascertain that any additional assessments are truly necessary. When they are, and the rationale is clearly communicated, we find that patients will typically consent.

Be mindful of alternative protocol designs. Adaptive study designs, with pre-specified interim analysis, can be useful to facilitate development programs. However, diligent planning and early collaborative discussions with regulators are needed to ensure that studies with adaptive designs will yield results that will be accepted for benefit-risk assessment. We have yet to see how real-world evidence (RWE) might serve as part of benefit-risk assessment in the context of regulatory decisions on treating Alzheimer's disease. In our experience, regulators have a high bar for RWE to consider when assessing benefit-risk.

Understand the course of the disease. Sponsors eager to bring treatments to those in need might be tempted to move ahead with what might seem to be the fastest pathway – for example, by relying heavily on biomarkers. In the case of Alzheimer's disease, natural history is very important to understand the course of the disease and how the suggested biomarkers plot on that course. Natural history studies can inform the choice of the most informative endpoints and timing of assessments and can help us to contextualize results. Further, natural history studies can provide insights into potentially different disease characteristics or symptoms in diverse populations. These data allow us to build innovative prognostic models that can be used in clinical studies. For example, the availability of good-quality historical data on Alzheimer's disease led to the European Committee for Medicinal Products for Human Use (CHMP) qualifying PROCOVA procedure and prognostic score adjustment in 2022.[1]

Recruit diverse populations. The more diverse the clinical trial participants, the more we can learn about the safety and efficacy of a potential treatment. For some medicines, there are variations in ethnicity that might lead to different PK and, in turn, have implications for efficacy. For these reasons and more, the U.S. Federal Drug Administration (FDA) has for some time encouraged sponsors to develop diversity plans, with draft guidance issued in April 2022.

1 Qualification opinion for Prognostic Covariate Adjustment (PROCOVA), September 2022.

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In December 2022, Congress granted the FDA a provision requiring sponsors to submit diversity action plans in connection with Phase III or other pivotal studies.

Another significant finding is that when study populations include historically marginalized groups, people who identify with those populations are more likely to feel comfortable using the drug in real life. Ensuring diverse enrollment will not only satisfy statutory requirements but also increase trust in the drug once it is approved. We also advise examining the protocol for inclusion/exclusion criteria. Are HIV-positive patients excluded, or those with viral hepatitis or another chronic condition? Sometimes, exclusions like these are carried over from previous protocols and have no real justification.

Recognize potential divergence in agency expectations. Regulatory agencies can make different decisions based on the same data. While some regulators will apply a degree of flexibility in areas of high unmet needs, as with Alzheimer's disease, that will vary across regions. The case of aducanumab is a good example. The FDA approved it with initial data; however, the European Medicines Agency (EMA) did not grant the marketing authorization, and the sponsor eventually withdrew the application in the EU.

Engage with regulators and think globally. It is important not only to understand the reasons behind these divergent decisions but also to engage with regulatory agencies in the markets of interest in a strategic and timely manner. We advise that sponsors plan for success and think ahead about commercializing widely, even if the initial plan is separate from global marketing.

Agencies across the globe have developed certain programs to speed up the development of drugs for diseases with unmet needs – for example, PRIME in the EU, Breakthrough Therapy Designation in the U.S., and Breakthrough Designation/Priority Review in Japan. They, too, should be leveraged for quicker access to different markets. In certain cases, joint meetings are possible with, for example, the FDA and the EMA.

Sponsors can also leverage Access Consortium, which encompasses Australia, Canada, Singapore, Switzerland, and the United Kingdom, for faster approval in these countries.

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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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