



Clinical Trial Design in Alzheimer's Disease

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Our understanding of Alzheimer's disease (AD) has drastically improved during the past decade as multiple large-scale studies have been implemented. For instance, the FINGER and the World-Wide FINGERS trials are large-scale lifestyle-based randomized clinical trials aiming to find effective preventive measures for AD and reduce the risk of cognitive decline (1).

Two other large studies are the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS) and Alzheimer's Disease Neuroimaging Initiative (ADNI) (2, 3).

These studies try to provide a large data set of markers and characteristics of patients with AD. By analyzing these data and implementing machine-learning methods, various markers and factors involved in the disease progression or pathophysiology are coming to light each day. These markers could improve AD's clinical trials in various ways, such as staging the disease and being used as an outcome measurement. Furthermore, some factors such as education, physical activity, sleep, trauma, and having other diseases and the medications the patient takes are established to affect the disease progression and are needed to be accounted for in clinical trials (4). Other factors such as the level of blood-brain barrier disruption also vary significantly in patients with AD (5).

The complexity of these factors and the disease itself have hindered the introduction of novel therapeutic strategies for patients with AD. The success rate of clinical trials in AD is significantly low. This issue has been addressed in multiple publications, and they also tried to provide some recommendations on features of a good clinical trial in AD. Some of these recommendations are improving the

interpretation of animal models, using novel and more reliable biomarkers, combination therapy, clinical trial simulators, and using a large enough sample size to compensate for the variability in the patients' characteristics. Additionally, doing sub-group analysis in a trial where the positive effects are seen in a small population of the recruited patients would be misleading as they may not be properly randomized, and the power of the study may be too low for such a small sample size. Hence, implementing a phase III clinical trial based on the post hoc analysis of a previous negative study could result in another negative study (6, 7).

The sum of these data leads us to the importance of individualized therapy in AD. We propose the idea of implementing future clinical trials in AD in a more specified population of AD patients based on the mechanism of action of the drug candidate, stage of the disease, and markers involved in the pathogenesis and severity of the disease. The derived results of such trials will not have the problems of doing a post hoc analysis, and although it may harm the generalizability of the results, we may find novel and effective treatment approaches for AD patients with similar characteristics.

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