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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Other

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/04/AkihiroHirakawa-YODA-COI-FORM.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/RyoichiHanazawa-YODA-COI-FORM.pdf
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https://yoda.yale.edu/wp-content/uploads/2024/04/MasayaWatanabe-YODA-COI-FORM.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00679627 - GALALZ3005 - A Randomized, Double-Blind, Placebo-controlled Trial of Long-term (2-year) Treatment of Galantamine in Mild to Moderately-Severe Alzheimer's Disease
2. NCT00575055 - ELN115727-302 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Carriers
3. NCT00574132 - ELN115727-301 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Non-Carriers

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Development of statistical methodology considering placebo response in randomized controlled trials targeting Alzheimer's disease

Narrative Summary:

Alzheimer's disease (AD) causes long-term cognitive decline and is a major cause of dementia. With over 55 million people worldwide living with dementia, AD is involved in 60-70% of cases. As the population ages, finding effective treatments is crucial. Clinical trials often compare potential treatments with placebos. However, a high placebo response, where placebo groups show significant improvement in cognitive function, can mask true drug effects and lead to seemingly unsuccessful trials. This study examines the impact of placebo response in AD clinical trials and develop novel statistical methods to account for placebo response in trial design.

Scientific Abstract:

Background: Clinical trials for AD treatments often fail due to high placebo responses, where placebo groups show significant cognitive improvement, obscuring the true effects of drugs. This study aims to use data from past AD clinical trials to identify placebo high responders and their characteristics. Understanding and adjusting for placebo responses can improve future AD drug trials and lead to effective treatments.

Objective: Examine the impact of placebo response in AD clinical trials and develop novel statistical methods to account for placebo response in trial design, assessing their utility using the randomized controlled trials (RCTs) datasets.

Study Design: Perform integrated analysis using data on patient demographic factors and cognitive function test scores from placebo groups of the requested RCTs.

Participants: Data from placebo groups of clinical trials requested through the YODA project and the Vivli platform.

Primary and Secondary Outcome Measures: Categorical variable indicating placebo high responder status for identifying and evaluating placebo high responders, and cognitive function test scores for evaluating operating characteristics through simulations considering placebo response and enrichment designs.

Statistical Analysis: Based on existing research, define and classify placebo high responders. Explore associated factors and develop enrichment designs to account for their influence. Simulations using placebo group data will evaluate operating characteristics of clinical trial with developed enrichment designs.

Brief Project Background and Statement of Project Significance:

Alzheimer's disease (AD) is one of the causes of dementia, which is characterized by long-term decline in cognitive function. Currently, more than 55 million people worldwide are living with dementia, and AD is thought to be involved in 60-70% of cases. As more people live longer, more individuals are developing AD. We urgently need to find effective treatments. Clinical trials are commonly conducted to find effective treatments. These trials compare potential medicine with placebos, which are fake medicines with no real treatment. However, in trials testing potential treatments for AD, most medicine didn't work better than placebos (Schneider et al., 2014).
One potential reason why these clinical trials have failed is the high placebo response, where groups that took a placebo (placebo groups) showed high improvement in cognitive function, making it hard to detect the true effects of the drugs being tested.
Other disease areas like depression have extensively studied the placebo response (Khin et al., 2011). Research in this field suggests that the high placebo response caused many clinical trials for depression drugs to seem unsuccessful, even if the drugs were truly effective. Scientists are developing new statistical methods to account for the placebo response when analyzing the results of these trials (Chi et al., 2016). However, research examining the placebo response in clinical trials for AD has been limited (Ito et al., 2013; Zhang et al., 2020). For AD trials as well, understanding the placebo response could greatly contribute to finding better treatments.
In this study, we will use data from the placebo groups of past AD clinical trials. Based on previous research, placebo high responders will be defined. Each patient's data will be examined to determine if they are placebo high responders. Using this information, the study will investigate the extent to which placebo response impacts results in clinical trials, and identify characteristics of patients prone to be placebo high responders. It will identify which types of AD patients are prone to be placebo high responders and develop new statistical methods to evaluate treatment efficacy while considering placebo response.
If we can better identify placebo high responders and adjust for their influence, the risk of promising treatments failing in clinical trials due to the participation of placebo responders would decrease. This could make future AD drug trials more successful. Ultimately, this research could help provide effective treatments for Alzheimer's patients worldwide.

Specific Aims of the Project:

Specific hypothesis I: What are the magnitudes of the impact of the placebo response on clinical trials for AD? What kind of individuals are more likely to be high placebo responders?
Specific aim I: To examine the impact of the placebo response in AD clinical trials on evaluation of therapeutic effects.

Specific hypothesis II: How do we account for the placebo response in the trial design of AD clinical trials?
Specific aim II: To develop novel statistical methodologies to evaluate treatment effects considering placebo response, and assess the utility of the developed methodology using the RCTs datasets for AD.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

Develop or refine statistical methods

Research on clinical trial methods

Research on comparison group

Research on clinical prediction or risk prediction

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

In this study, we will use placebo group data from several clinical trials requested through the YODA project and the Vivli platform.
Depending on the situation, patient demographic factors, measured cognitive function tests and the number of measurements after baseline may be considered as inclusion or exclusion criteria.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

For the identification of placebo high responders and evaluation of their characteristics, we will define placebo high responders based on the longitudinal cognitive function test scores, and utilize whether or not an individual is a placebo high responder as a categorical variable for the outcome.
For the evaluation of operating characteristics through simulation considering the placebo response and enrichment designs, we will use the cognitive function test scores as the outcome.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The patient demographic factors (such as age and gender) from the requested clinical trial data will be utilized as predictor variables to analyze which factors are characteristic of placebo high responders. These factors will be converted into categorical variables as needed.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other demographic factors that have not been used above will also be utilized as needed.

Statistical Analysis Plan:

Identification and Evaluation of Placebo Response:
Based on existing researches, we will define placebo high responders (for example, as those whose change in cognitive function evaluation scores from baseline to endpoint is less than X points).
We will refer to patient-level data from the placebo groups of each clinical trial and classify each patient as a placebo high responder or not, based on the defined criteria for placebo high responders. Then, we will conduct multivariate logistic regression analysis with the outcome variable being the presence of placebo high response and the predictor variables being the patient demographic factors, aiming to explore factors associated with placebo high response.

Development of Trial Design Considering Placebo Response:

Within the placebo group data, we will consider a certain short period (such as 6 months) following randomization as a placebo run-in period. Using data from the patient demographic factors and the changes in cognitive function test scores measured during this placebo run-in period, along with data on the presence of placebo high response at the endpoint, we will explore factors predictive of placebo high responders at the endpoint through multivariate logistic regression analysis.
Using the identified factors, we will develop several enrichment designs to account for the influence of placebo high responders and evaluate the operating characteristics using simulations. In simulations, we will create simulation data through resampling from the placebo group data. We will generate simulation data by overlaying treatment effects onto resampled data from the placebo group as a pseudo-treatment group. Operating characteristics will be evaluated based on parameters such as type I error rate, power, point estimates of treatment effects, bias, mean squared error, and coverage probability of 95% confidence intervals.

In the abovementioned analyses, if only a small amount of data is missing, it will be excluded from the analysis. However, if a substantial amount of missing data is present, we will consider performing multiple imputation methods.

We have also requested the study data of five clinical trials (NCT01900665, NCT00904683, NCT00905372, NCT00594568, NCT00762411) through the Vivli platform.

The clinical trial data obtained through the YODA project and the Vivli platform will be integrated and analyzed on the Vivli platform.

Software Used:

I am not analyzing participant-level data / plan to use another secure data sharing platform

Please clarify software used:

We will integrate patient-level data from multiple clinical trials requested through the YODA Project and the Vivli platform and conduct analyses on the Vivli platform.

Project Timeline:

Project start date: June 17, 2024
Analysis completion date: June 17, 2029
Date manuscript drafted: September 1, 2029
Date first submitted for publication: March 1, 2030
Date results reported back to the YODA Project: June 1, 2030

Dissemination Plan:

We plan to submit our research findings to peer-reviewed journals targeted at medical, AD, and biostatistical scientific community such as Alzheimer’s Research & Therapy, Statistics in Medicine, and Statistical Methods in Medical Research.

Bibliography:

Chi, G. Y. H., Li, Y., Liu, Y., Lewin, D., & Lim, P. (2016). On clinical trials with a high placebo response rate. Contemporary Clinical Trials Communications, 2, 34–53.

Ito, K., Corrigan, B., Romero, K., Anziano, R., Neville, J., Stephenson, D., & others. (2013). Understanding placebo responses in Alzheimer’s disease clinical trials from the literature meta-data and CAMD database. Journal of Alzheimer’s Disease, 37(1), 173–183.

Khin, N. A., Chen, Y.-F., Yang, Y., Yang, P., & Laughren, T. P. (2011). Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. Journal of Clinical Psychiatry, 72(4), 464–472.

Schneider, L. S., Mangialasche, F., Andreasen, N., Feldman, H., Giacobini, E., Jones, R., et al. (2014). Clinical trials and late-stage drug development for Alzheimer's disease: An appraisal from 1984 to 2014. Journal of Internal Medicine, 275(3), 251–283.

Zhang, N., Zheng, X., Liu, H., Zheng, Q., & Li, L. (2020). Testing whether the progression of Alzheimer's disease changes with the year of publication, additional design, and geographical area: A modeling analysis of literature aggregate data. Alzheimer's Research & Therapy, 12(1), 64.