Principal Investigator

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General Information

Key Personnel (in addition to PI):
First Name: Sheng
Last name: Luo
Degree: PhD
Primary Affiliation: Duke University
SCOPUS ID:

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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_luo.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. NCT00034762 - RIS-USA-232/CR002764 - Efficacy And Safety Of A Flexible Dose Of Risperidone Versus Placebo In The Treatment Of Psychosis Of Alzheimer's Disease
2. NCT00253188 - GAL-INT-1 - Efficacy, Tolerability and Safety of Galantamine in the Treatment of Alzheimer's Disease
3. NCT00236574 - CR003145 // GAL-INT-11 - A Randomized Double Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Galantamine in Patients With Mild Cognitive Impairment (MCI) Clinically at Risk for Development of Clinically Probable Alzheimer's Disease
4. NCT00236431 - GAL-INT-18 - A Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Galantamine in Patients With Mild Cognitive Impairment (MCI) Clinically at Risk for Development of Clinically Probable Alzheimer's Disease
5. 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

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6. NCT00216593 - GAL-ALZ-302 (PMID # 19042161-CR003940) - Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing Home, or Geriatric Residential Setting: Evaluation of Efficacy and Safety of Galantamine Hydrobromide in a Randomised, Doubleblind, Placebo-Controlled Study
7. 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
8. 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

Reanalysis of Alzheimer’s Disease Clinical Trials Using Longitudinal Latent Trait Models

Narrative Summary:

In this project, we plan to reanalyze the datasets of Alzheimer’s disease clinical trials. The objectives are to investigate which cognitive domains carry the most information on the earliest signs of cognitive decline, and which subject characteristics are associated with a faster decline.

Scientific Abstract:

Background: Alzheimer’s disease (AD) studies collect data from multiple longitudinal neuropsychological, functional, and behavioral assessments which consist of multiple components and items whose responses and scores are often summed up. The sum scores are analyzed using GEE and mixed model, which ignore differences between response patterns leading to the same sum-score and the sum scores are discrete. To address these issues, we have developed a suite of longitudinal latent trait models that have been successfully applied to Parkinson’s disease. We seek to develop similar applications to increase the efficiency of drug development clinical trials for AD.
Objective: To investigate which cognitive domains carry the most information on the earliest signs of cognitive decline, and which subject characteristics are associated with a faster decline.
Study design: To apply our novel longitudinal latent trait model to reanalyze the efficacy of experimental drugs in multiple AD clinical trial datasets. Compare results with those from traditional analysis methods.
Participants: We will analyze participant-level original data elements and variables.
Main outcome measures: item-level AD Assessment Scale-cognitive Subscale and activities of daily living (ADAS-Cog, and ADAS-ADL), mini-mental state examination (MMSE), Disability Assessment for Dementia (DAD), Clinical Dementia Rating Scale (CDR), Digit Symbol Substitution Test (DSST), severe impairment battery (SIB), and minimum dataset-activities of daily living (MDS-ADL).
Statistical Analysis: Latent trait models

Brief Project Background and Statement of Project Significance:

We will identify the cognitive domains and items that are most sensitive to changes for subjects in different AD disease stages (e.g., prodromal, mild, and moderate). This will increase the probability of success in future AD clinical trials.

Specific Aims of the Project:

AIM 1: Develop & validate the longitudinal latent trait models for Alzheimer's Disease Assessment Scale-cognitive Subscale (ADAS-Cog) and mini-mental state examination (MMSE).
Aim 2: Analyze multiple datasets of Alzheimer’s disease clinical trials to investigate the efficacy of experimental

drugs and to identify the cognitive domains and items that are most sensitive to changes for subjects in different AD disease stages.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Confirm or validate previously conducted research on treatment effectiveness
Develop or refine statistical methods

Research Methods

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

Selected participants must have baseline and longitudinal Alzheimer's Disease Assessment Scale-cognitive Subscale (ADAS-Cog) and mini-mental state examination (MMSE) measurements, patient characteristics, and date of diagnosis.

Main Outcome Measure and how it will be categorized/defined for your study:

Main outcomes to be analyzed are item-level AD Assessment Scale-cognitive Subscale and activities of daily living (ADAS-Cog, and ADAS-ADL), mini-mental state examination (MMSE), Disability Assessment for Dementia (DAD), Clinical Dementia Rating Scale (CDR), Digit Symbol Substitution Test (DSST), severe impairment battery (SIB), and minimum dataset-activities of daily living (MDS-ADL).

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

patient characteristics, disease stages, treatments, ApoE 4, baseline MMSE, use of acetylcholinesterase inhibitor or memantine, diseases at baseline, baseline CDR memory score.

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

Demographics, labs, ApoE staus, vitals, time since symptom onset, time since diagnosis.

Statistical Analysis Plan:

We will first conduct descriptive analyses. Then we will develop and validate longitudinal latent trait models for ADAS-Cog and MMSE to analyze multiple datasets from Alzheimer's disease clinical trials. Specifically, the latent trait model has two levels. The first level multidimensional latent trait (MLT) model
quantifies the relationship between a patient’s multiple latent disease severity scores and the observed multivariate outcomes, while the second level linear mixed model (LMM) connects the latent disease scores to observed covariates (e.g., treatment and disease duration), time, and subject-specific random effects. Because the number of latent disease scores is much smaller than the number of observed outcomes, the latent trait model can be used with a large number
of outcomes and is more computational scalable than multivariate marginal and random-effects models. We will consider a Bayesian-based framework and inferential tools that naturally address the complex and heterogeneous nature of the data. We will use noninformative prior distributions on all parameters and we will conduct extensive sensitivity analysis to prior distributions. The convergence of MCMC chains will be monitored using various tools including trace plots, autocorrelation plots, and Gelman-Rubin scale reduction statistics.
Software Used:
RStudio
Project Timeline:

Project start date: Sep 16, 2020.
Analysis completion date: May 31, 2021.
Manuscript drafted and submission date: July 31, 2021.
Results reported back to the YODA project: August 31, 2021

Dissemination Plan:

We expect that the applications we develop will be useful for drug development. We plan to publish the results in journals related to Alzheimer's disease (e.g., Journal of Alzhiemer's Disease, Alzheimer's & Dementia).

Bibliography:

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