

Principal Investigator

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General Information

Key Personnel (other than PI):

First Name: Frederik

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SCOPUS ID: 7102989379

Requires Data Access? Yes

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?: Colleague

Conflict of Interest

<https://yoda.yale.edu/wp-content/uploads/2023/11/Confirmation-YODA-Project-Data-Use-Agreement-Training-Completed.pdf>

<https://yoda.yale.edu/wp-content/uploads/2023/11/COI-Oxtoby.pdf>

<https://yoda.yale.edu/wp-content/uploads/2023/11/COI-Barkhof.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. [NCT00574132 - 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](#)
2. [NCT00575055 - 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](#)

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

Research Proposal

Project Title

ARIA detection, predictability, and relationship to treatment response

Narrative Summary:

Our overarching goal is to contribute to medical education for physicians now that monoclonal antibody therapies are entering healthcare settings. Specifically, we want to help the field to understand the appearance of amyloid-related imaging abnormalities (ARIA), which are the primary side effect of such therapies that influences treatment decisions. We will perform our own analyses for understanding ARIA on this data and others — including analysing imaging, clinical, medical, and demographic data using both traditional visual reads and computational methods (including machine learning models and data-driven disease progression models (Young & Oxtoby, et al., Nat. Rev. Neurosci. 2024)). The outputs of our work will contribute invaluable insight and knowledge to the global community through publications and subsequent open resource of educational and outreach materials.

Scientific Abstract:

Background: As Alzheimer's disease modifying treatments are coming to market, it is vital for healthcare practitioners, including non-expert physicians and researchers alike, to understand the primary side effect: amyloid related imaging abnormalities (ARIA). There is an urgent unmet need for ARIA education, training, and standardisation in detection and management.

Objective: Understand ARIA including its relationship to treatment response using traditional visual reads and computational methods, compiling published knowledge into online educational resources.

Study Design: We will analyse imaging data using visual read and computational lesion-detection/quantification methods (such as used for white-matter hyperintensity detection) to characterise presence/absence/severity of ARIA, followed by an association study with risk factors, demographics, trial endpoints, and other adverse events. We will compare performance of visual methods and computational methods for ARIA detection using classification metrics such as AUC. **Participants:** all participants in all arms.

Primary and Secondary Outcome Measure(s): associations between ARIA and trial endpoints (ARIA relationship with drug efficacy), along with risk factors, demographics (ARIA risk prediction) and adverse events (ARIA risk management).

Statistical Analysis: Associations between ARIA and relevant outcomes (see above) using traditional statistical analyses (e.g., ANOVA) and predictive models, e.g., data-driven disease progression models (Young & Oxtoby, et al., Nat. Rev. Neurosci. 2024).

Brief Project Background and Statement of Project Significance:

Excitement surrounding emerging amyloid (and other) antibody therapies in Alzheimer's disease is tempered by side-effects, most notably those caused by amyloid-related imaging abnormalities (ARIA). While ARIA rates vary by drug, their appearance is similar across this class. As drugs come to market, non-expert doctors will increasingly see such cases and so there is an urgent unmet need for ARIA education, training, and standardisation in detection, quantification, and management. Improved ARIA understanding is needed now because these drugs are already entering the market. Our project will contribute to understanding ARIA risk/prediction/management including the complementary role of traditional visual reads alongside computational decision support systems. This will benefit the global Alzheimer's research and healthcare community.

Specific Aims of the Project:

Aim 1: compare traditional visual reads versus computational methods for ARIA detection and

quantification. We hypothesise that computational approaches will outperform visual reads for subtle ARIA lesions. For this aim, we will hold out a subset of test data for evaluation after model training.

Aim 2: predict treatment response in subgroups, including those defined post hoc by the presence/absence of ARIA, ARIA risk factors, and computational biological subtyping models (e.g., Young et al., Nature Communications 2018). We hypothesise that there will be differential treatment response across subgroups, which could reveal biological insights into ARIA risk.

Aim 3: incorporate knowledge gained through this study within an online portal on ARIA education we are building.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

New research question to examine treatment safety

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:

We will analyse all individuals in these trials, across all treatment and placebo arms. We are also requesting neuroimaging data (we understand from Lisa Ford that you are piloting this and that the imaging data has already been anonymised).

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

All primary and secondary endpoints from the original trials. All AEs from the original trials. We will analyse relationships, e.g., statistical associations, between all these outcomes/events and ARIA.

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

We're interested in ARIA detection, quantification, and prediction (risk characterisation). The key predictors are demographics including include age, sex, genetics (e.g., APOE4), and known and unknown risk factors such as family history of Alzheimer's, baseline microhaemorrhages, concomitant medications, and others.

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

Secondary predictors include those from predefined sub-studies of the trials: brain imaging features and fluid biomarkers. Brain imaging features include regional volumes from structural MRI, and SUVr values from amyloid PET. Biomarkers include CSF phospho-tau levels.

Statistical Analysis Plan:

Aim 1 (ARIA detection): the primary outcome measure will be ARIA presence/absence (secondary:

ARIA lesion type and location), which will be defined by visual reads — both from the original trial (if this flag is available in the data) and defined by our own visual reads of the raw MRI. Statistical analysis includes association studies (e.g., ANOVA/regression), risk/survival analyses (e.g., hazard models), and classification analyses (e.g., AUC).

Aim 2 (treatment response): we will repeat primary and secondary analyses of the original trials, with the additional covariate of ARIA presence/absence/severity. Primary statistical analyses will use the mixed model for repeated measures (MMRM) — as in the original trials. We will also investigate alternative models such as recent spline models (Donohue et al., *Pharmaceutical Statistics* 2023). Example outcomes include relevant trial endpoints: Alzheimer’s Disease Assessment Scale–Cognitive subscale (ADAS-Cog); Disability Assessment for Dementia (DAD); and the Clinical Dementia Rating Sum of Boxes (CDR-SB).

Software Used:

Python

Project Timeline:

Month 0: Receipt of data.

Month 1: Data wrangling complete.

Month 3: Quantitative image analyses Phase 1 completed: feature generation (e.g., brain volumes).

Month 6: Experiments completed: computational detection of ARIA.

Month 8: Statistical analysis of Visual reads vs Computational detection of ARIA.

Month 10: Manuscript circulated.

Month 12: Additional experiments completed following manuscript comments. Manuscript submitted.

Dissemination Plan:

1. ariaeducation.eu content: embedding our scientific findings within broader educational content aimed at non-expert doctors who will increasingly see patients treated by anti-amyloid therapies.
2. Peer-reviewed submissions to conferences (CTAD, AAIC, AD/PD) and journals (*Alzheimers Dement*, *Radiology*, etc.). Aimed at clinical and computational researchers in the field.
3. ARIA education events, e.g., symposia, et al.

Bibliography:

Young & Oxtoby, et al., *Nat. Rev. Neurosci.* (2024). DOI: [10.1038/s41583-023-00779-6](https://doi.org/10.1038/s41583-023-00779-6)

Donohue et al., *Pharmaceutical Statistics* 22, pp 508–519 (2023). DOI: [10.1002/pst.2285](https://doi.org/10.1002/pst.2285)

Young et al., *Nature Communications* 9, 4273 (2018). DOI: [10.1038/s41467-018-05892-0](https://doi.org/10.1038/s41467-018-05892-0)