# AlzPED: Optimizing the Predictive Power of Drug Efficacy Studies in Alzheimer's Disease Animal Models

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ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE

Session 4-VO-09:
Nonhuman: A Potpourri Of Preclinical Diagnostic And Therapeutic Studies
July 29, 2021

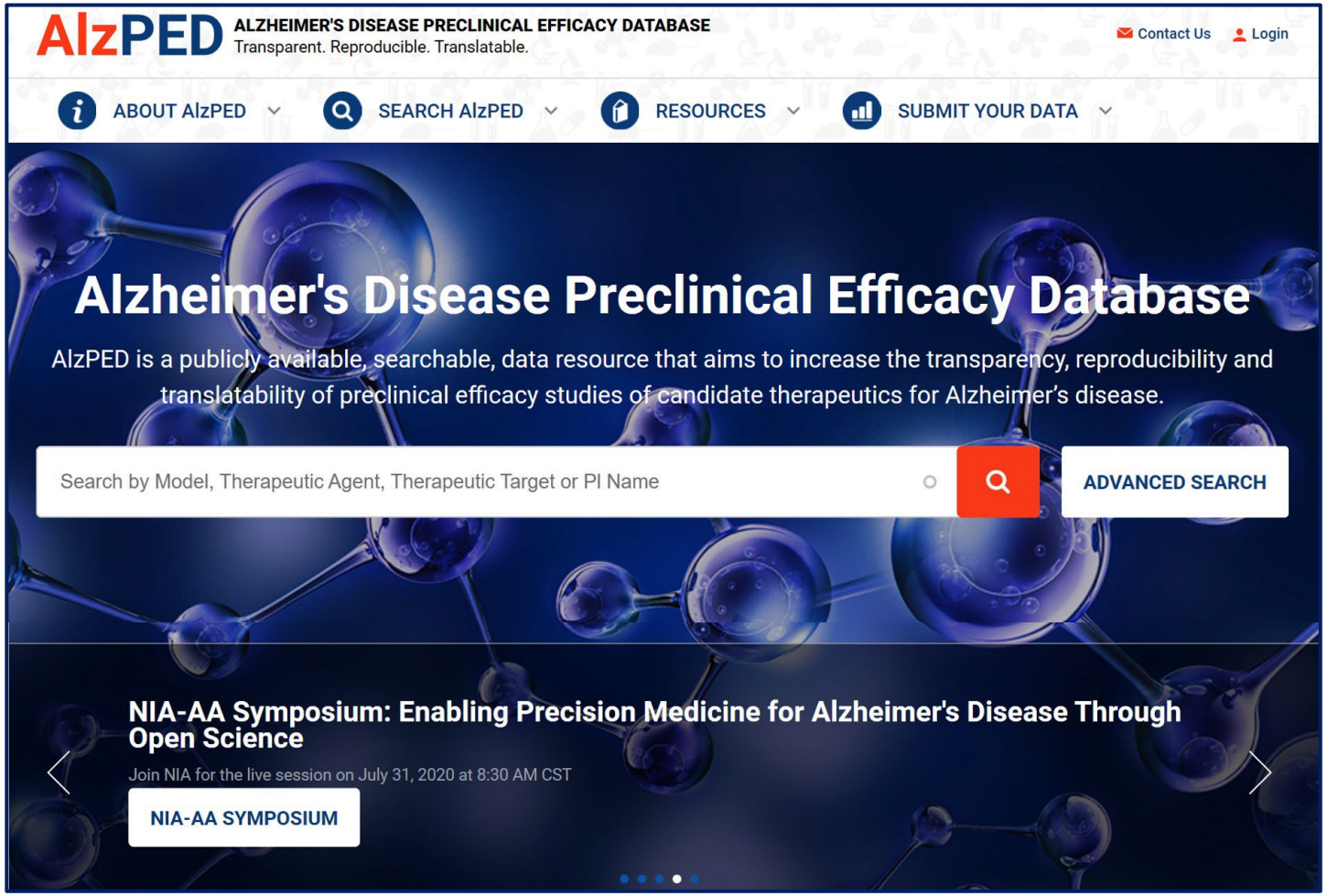
# Disclosures

Nothing To Disclose

# Background: Recommendations from 2015 NIA AD Summit

## Increasing the Predictive Value and Enabling Transparent and Reproducible Preclinical Efficacy Testing in AD Animal Models

- ❑ Develop a publicly available database of preclinical therapeutic studies that incorporates experimental details of positive and negative data for the AD scientific community




https://alzped.nia.nih.gov/

- Hosts curated summaries of ~1200 published studies (1996-2020) and provides easy access to information on study design methods, animal models, therapeutic agents, therapeutic targets, outcomes, patents and related clinical trials.
- Provides a platform for creating citable reports of unpublished studies, including studies with negative findings.
- Reports on the rigor of each curated study by summarizing the elements of experimental design and identifying critical elements of experimental design missing from the study.

# Article Selection and Curation Workflow

## Article Selection:

- **Published studies** are collected from databases like PubMed and Embase using key word search strings specific to preclinical therapeutic testing in AD animal models.
- **Unpublished studies** (including negative data) are obtained directly from researchers.

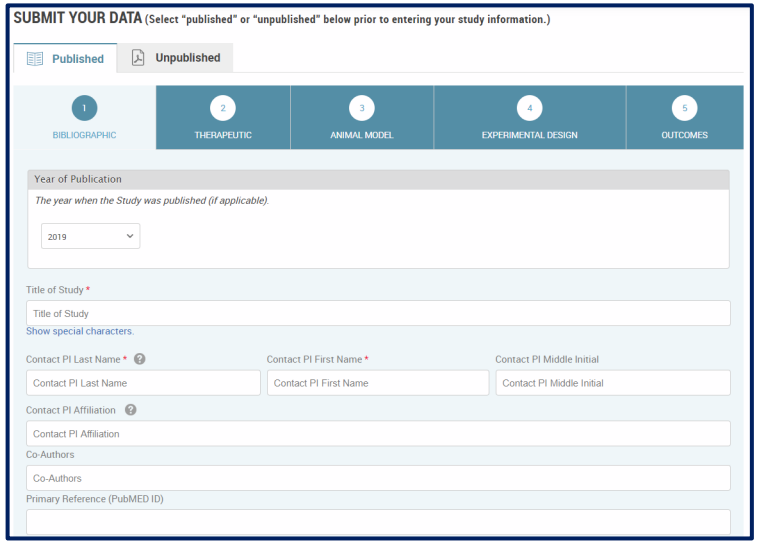
## Curation Workflow:

- Each study is curated by 2 experts in AD research for bibliographic details, funding source, study goals, data on relevant translational criteria like therapy type, therapeutic target, animal models, and AD-related outcome measures.
- Each curated study provides additional information about therapeutic targets, therapeutic agents, and animal models through external databases.
- Each curated study is assessed for scientific rigor using a "Rigor Report Card" which identifies the experimental design elements reported and those missing from the study.

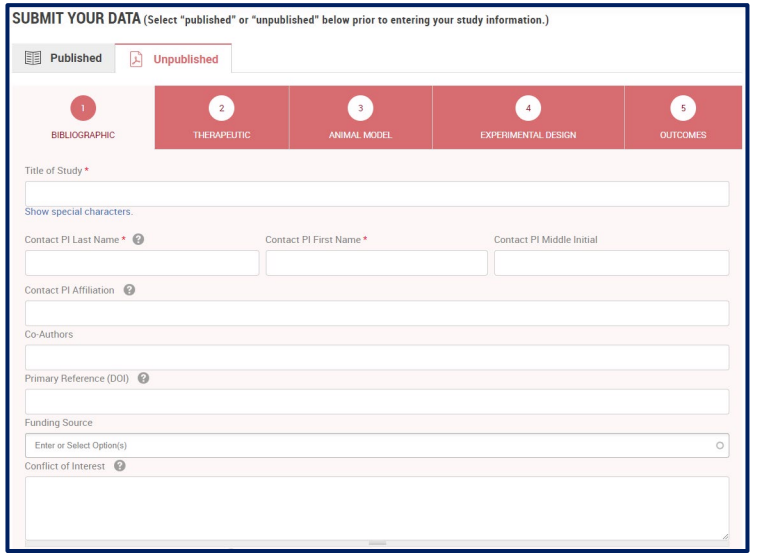
## Unpublished and Negative Data:

- Accepted study will be given a citable D.O.I.
- A downloadable pdf of the study will be available on the AD Knowledge Portal

## Published Data Submission Platform




## Unpublished Data Submission Platform



# Sample of a Curated Record on AlzPED

## Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease.

VIEW | EDIT

BIBLIOGRAPHIC | THERAPEUTIC AGENT | ANIMAL MODEL | EXPERIMENTAL DESIGN | OUTCOMES

### Bibliographic

**Year of Publication:** 2009

**Contact PI Name:** J Steven Jacobsen

**Contact PI Affiliation:**
Wyeth Research, Departments of Discovery Neuroscience

**Co-Authors:**
Robert L. Martone, Hua Zhou, Kevin Atchison, Thomas Comery, Jane Z. Xu, Xinyi Huang, Xioahai Gong, Mei Jin, Anthony Kreft, Boyd Harrison, et al

**Primary Reference (PubMED ID):** 19671883

**Funding Source:**
Wyeth Research

**Study Goal and Principal Findings:**
Gamma secretase is widely regarded as a viable target to achieve therapeutically relevant reductions of Aβ in AD, and multiple classes of GSIs have been reported including peptidomimetics and sulfonamides. The goal of this study was to report on the pharmacological properties of the novel thiophene sulfonamide gamma secretase inhibitor (GSI), GSI-953,also known as begacestat.In summary, the preclinical data for GSI-953 demonstrate a potent Abeta lowering activity, with nano molar potency, and in vitro selectivity against Notch processing. Cellular assays of Notch cleavage reveal that this compound is approximately 16-fold selective for the inhibition of APP cleavage. In addition, the drug exhibited robust in vivo efficacy for the lowering of brain, CSF, and plasma Abeta levels and the reversal of Abeta-dependent cognitive deficits in Tg2576 mice. Finally the drug was found lower of plasma Abeta ( a potential biomarker) levels in humans. These data provide evidence supporting GSI-953 treatment as a potential disease modification in the development of AD.

### Therapeutic Agent

**Therapeutic Information:**

**Therapy Type:** Small Molecule
**Therapeutic Agent:** GSI-953 (Begacestat)
PubMed PubChem ClinicalTrials Patents
**Therapeutic Target:** Gamma secretase
Open Targets Pharos

### Animal Model

**Model Information:**

**Species:** Mouse
**Model Type:** APP
**Model Name:** Tg2576 ALZFORUM
**Strain/Genetic Background:** Not Reported

**Species:** Rat
**Model Type:** Non-transgenic
**Strain/Genetic Background:** Sprague-Dawley

**Species:** Dog
**Model Type:** Non-transgenic
**Strain/Genetic Background:** Not Reported

### Experimental Design

**Is the following information reported in the study?:**

| | |
|---|---|
| ✗ Power/Sample Size Calculation | ✗ Randomized into Groups |
| ✗ Blinded for Treatment | ✗ Blinded for Outcome Measures |
| ✓ Pharmacokinetic Measures | ✓ Pharmacodynamic Measures |
| ✓ Toxicology Measures | ✗ ADME Measures |
| ✓ Biomarkers | ✓ Dose |
| ✓ Formulation | ✓ Route of Delivery |
| ✓ Duration of Treatment | ✓ Frequency of Administration |
| ✓ Age of Animal at the Beginning of Treatment | ✓ Age of Animal at the End of Treatment |
| ✗ Sex as a Biological Variable | ✗ Study Balanced for Sex as a Biological Variable |
| ✗ Number of Premature Deaths | ✗ Number of Excluded Animals |
| ✓ Statistical Plan | ✗ Genetic Background |
| ✗ Inclusion/Exclusion Criteria Included | ✗ Conflict of Interest |

### Outcomes

| Outcome Measured | Outcome Parameters |
|---|---|
| Behavioral | • Contextual Fear Conditioning |
| Biochemical | • Notch Selectivity<br>• Gamma Secretase Inhibition<br>• Brain-beta amyloid peptide 40<br>• Brain-beta amyloid peptide 42<br>• Plasma-beta amyloid peptide 40<br>• Plasma-beta amyloid peptide 42<br>• CSF-beta amyloid peptide 40<br>• CSF-beta amyloid peptide 42 |
| Biomarker | • Plasma-beta amyloid peptide 40<br>• Plasma-beta amyloid peptide 42<br>• CSF-beta amyloid peptide 40<br>• CSF-beta amyloid peptide 42 |
| Pharmacokinetics | • Cmax<br>• Area Under the Curve (AUC)<br>• Brain/Plasma Ratio<br>• PK/PD relationship |
| Pharmacodynamics | • Target Engagement (reduction beta amyloid peptides-brain) |
| Toxicology | • Tissue Histopathological Profile<br>• Body Weight<br>• Mortality<br>• Behavior (general) |

# AlzPED Monitors Rigor in Study Design for Each Curated Study

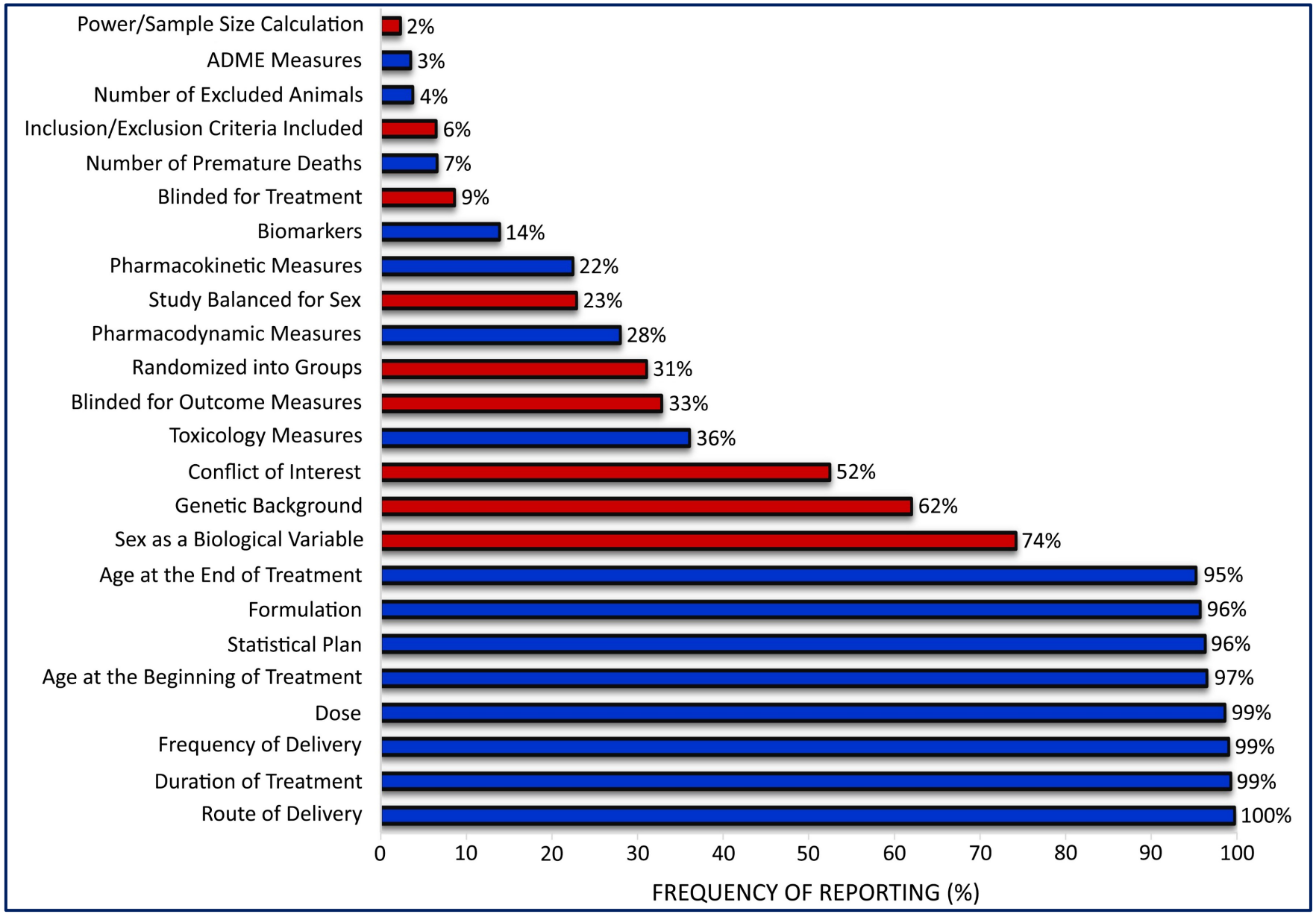
**Experimental Design** *Rigor Report Card*

**Is the following information reported in the study?:**

| | |
|---|---|
| ✓ Power/Sample Size Calculation | ✓ Randomized into Groups |
| ✓ Blinded for Treatment | ✓ Blinded for Outcome Measures |
| ✗ Pharmacokinetic Measures | ✗ Pharmacodynamic Measures |
| ✗ Toxicology Measures | ✗ ADME Measures |
| ✗ Biomarkers | ✓ Dose |
| ✓ Formulation | ✓ Route of Delivery |
| ✓ Duration of Treatment | ✓ Frequency of Administration |
| ✓ Age of Animal at the Beginning of Treatment | ✓ Age of Animal at the End of Treatment |
| ✓ Sex as a Biological Variable | ✓ Study Balanced for Sex as a Biological Variable |
| ✗ Number of Premature Deaths | ✓ Number of Excluded Animals |
| ✓ Statistical Plan | ✓ Genetic Background |
| ✓ Inclusion/Exclusion Criteria Included | ✓ Conflict of Interest |

AlzPED is designed to monitor the scientific rigor of curated studies with a “Rigor Report Card” consisting of a standardized set of 24 experimental design elements recommended by expert advisory groups.

# Critical Elements of Experimental Design are Under-Reported

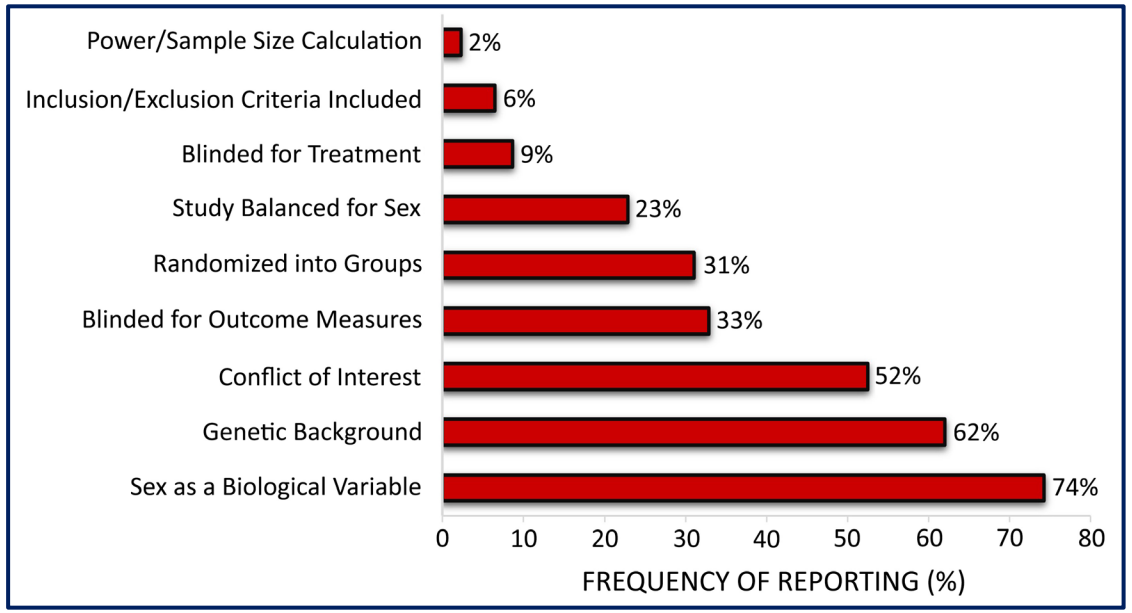



Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements, calculated from 1172 published preclinical studies curated to AlzPED. The red bars represent the 9 core design elements critical for scientific rigor and reproducibility.

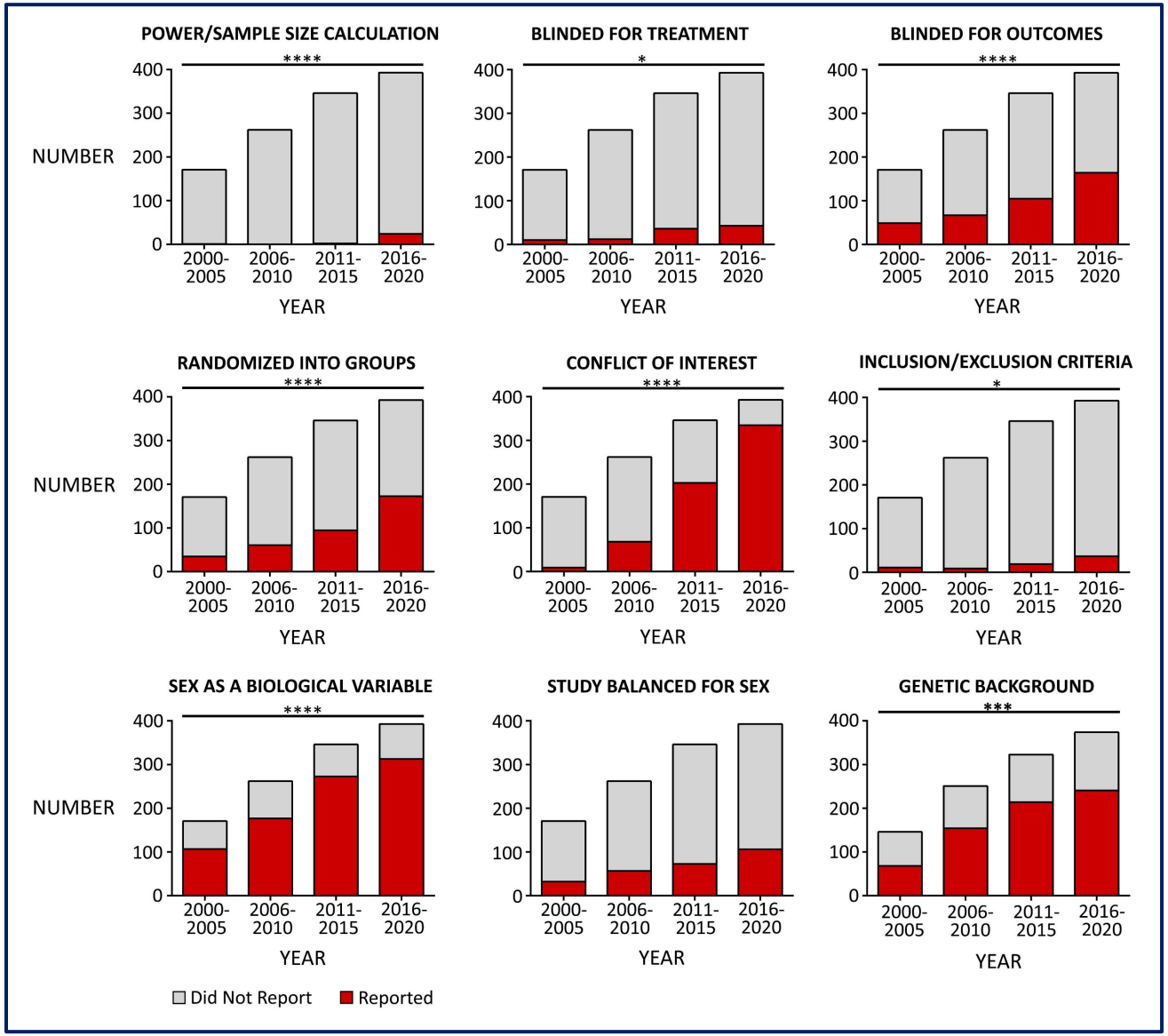
Detailed Analytics Summary is available on the AlzPED Analytics page.

# Reporting Trends In The 9 Core Design Elements

9 core design elements are derived from Shineman et al., 2011, Landis et al., 2012, Snyder et al., 2016 and ARRIVE guidelines.




Graphs show reporting trends for the 9 critical core experimental design elements evaluated over 5-year spans from 2000 to 2020. Data analyzed using Chi square test; *p<0.05, ***p<0.001, ****p<0.0001. Data presented as number that reported Vs number that did not report core experimental design elements, calculated from 171, 262, 346 and 393 curated studies published between 2000-2005, 2006-2010, 2011-2015 and 2016-2020 respectively.



# Conclusions

- Analysis of ~1200 curated studies demonstrates serious deficiencies in reporting critical elements of study design and methodology which diminish the scientific rigor, reproducibility and predictive value of preclinical therapeutic studies done in AD animal models.

- Adoption of a standardized set of best practices is very likely to improve the predictive validity of preclinical studies done in AD animal models. This measure is likely to promote the effective translation of preclinical drug testing data to the clinic.

- Federal funding agencies, private foundations and scientific journal publishers must continue to collaborate on this issue and enforce a standardized set of best practices, so that funded and published research are sufficiently rigorous, transparent and reproducible.

# Acknowledgements


## NIA

Shreaya Chakroborty
Katerina Mancevska
Zane Martin
Suzana Petanceska
Lorenzo Refolo
Ali Sharma
Erika Tarver
Jean Yuan

## NIH Library

Bridget Burns
James King
Cindy Sheffield

## Sage Bionetworks

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