# Improving the Rigor, Reproducibility and Predictive Validity of Preclinical Research for Alzheimer's Disease

# Alzheimer's Disease Preclinical Efficacy Testing Database (AlzPED)

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NIH National Institute on Aging

BRIGHTFOCUS ALZHEIMER'S FAST TRACK
**November 9-11**, 2022

# What is Preclinical Research?

**In therapy development preclinical research is the stage of research that begins before clinical trials can begin, and during which important iterative testing, feasibility, efficacy in disease models, and drug safety data is collected.**

**Preclinical Research**

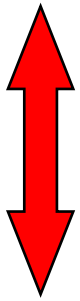
Target identification/validation

Lead identification/optimization

PK-PD/ADME

***Therapeutic Agent Efficacy in a Disease Model***

Toxicity in Rodents, Canines, NHP



**Translation to the clinic is often dependent on the predictive validity of preclinical studies**

**Clinical Trials**

**Safety and**

**Efficacy in Humans**

# What is Predictive Validity?

- **How well an animal model successfully discriminates between successful and unsuccessful treatments for the human disease condition.**

- **How well does the candidate drug testing performed in animal models translate into the clinic.**

- **Predictive Validity is also known as Translational Validity.**

# Preclinical to Clinical Translation Gap

- More than 200 therapeutic agents have been reported to be efficacious in ameliorating pathology and/or cognitive deficits in transgenic AD animal models.
- This success has not translated to success in the clinic. In fact, none of these agents have been advanced to the FDA for approval to market as an effective disease modifying therapy for AD.

*Zahs & Ashe, Trends in Neurosciences, 2010*

- High rate of attrition of AD drug candidates in Phase II (92%) and Phase III (98%) with more than half failing due to lack of efficacy.
- From 2002 to 2012, 244 drug candidates were tested in 413 clinical trials (Ph I - Ph III) only one (memantine) received FDA approval (approval rate of 0.4%; >99% attrition)

*Cummings et al., Alzheimer's Research & Therapy 2014,*
*Cummings et al., Alzheimer's & Dementia 2018*

Science alert

TIME

**This Alzheimer's Breakthrough Could Be a Game Changer**

PRI

**Mouse study hints at possible Alzheimer's cure**

The Telegraph

**Has Stanford University found a cure for Alzheimer's disease**

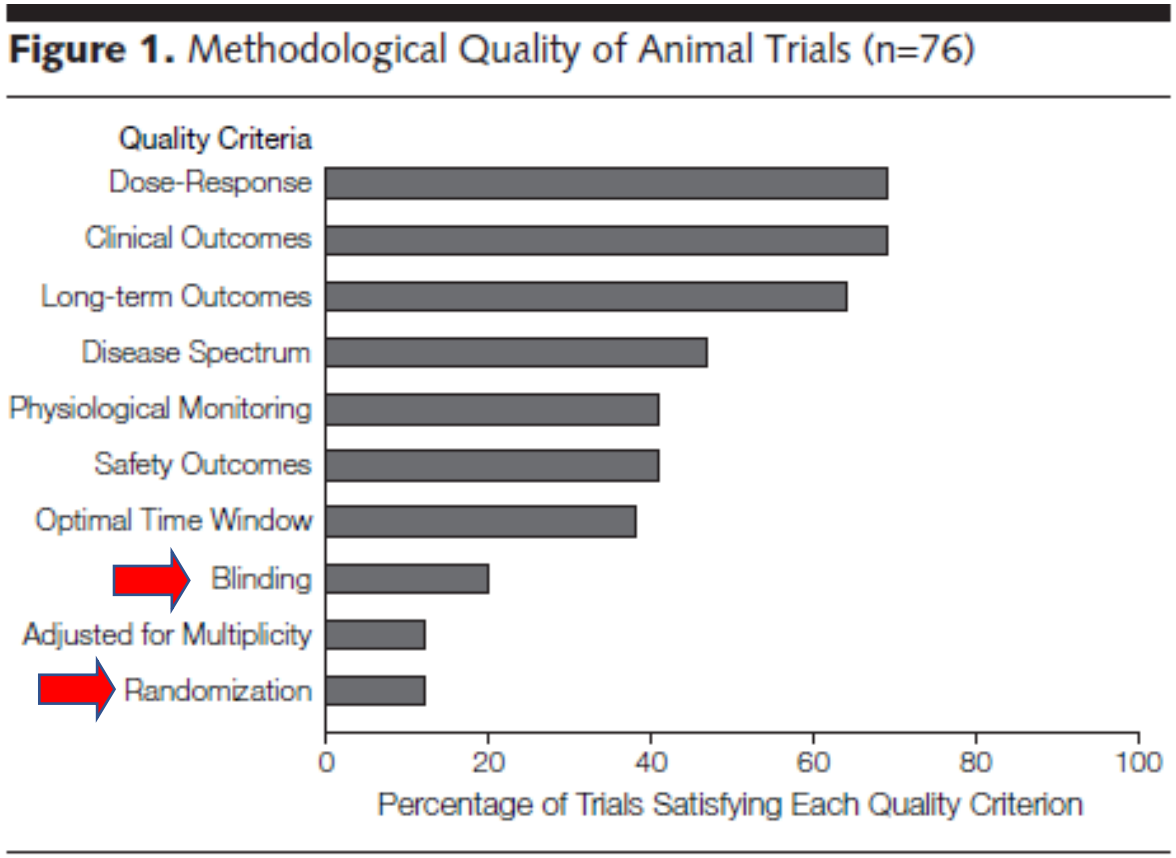
# Factors Contributing to Poor Translation of Preclinical Efficacy Testing

- The AD animal models do not accurately recapitulate human AD.
- Lack of reliable preclinical biomarkers that translate to the clinic.
- Failure to match outcome measures used in clinical studies.
- Lack of standardization and rigor in study design and analysis of data.
- Publication bias due to under reporting of negative results in the literature.
- Poor reproducibility of published data.

*Shineman et. al., Alzheimer's Research &Therapy, 2011; Landis et al., Nature, 2012; Snyder et al., Alzheimer's & Dementia, 2016.*

# Scientific Rigor in Study Design is Lacking in Preclinical Efficacy Studies

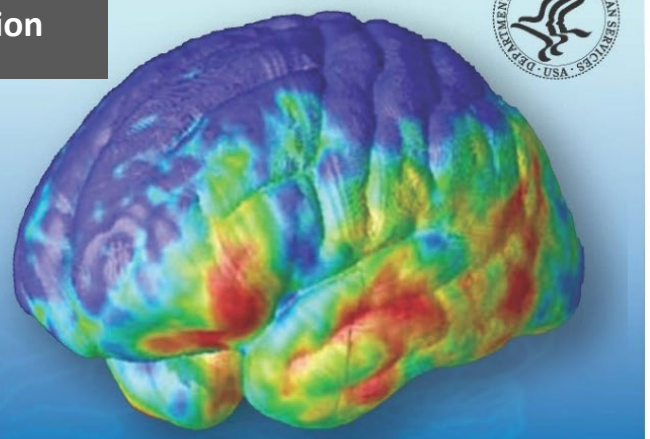
## (Including those published in high impact journals)




- **Data from 76 animal studies published between 1980-2000 in 7 leading scientific journals (Science, Nature, Cell, Nature Medicine, Nature Genetics, Nature Immunology and Nature Biotechnology).**
- **Median citation count of 889 (range of 639-2233 citations).**

***DG Hackam, JAMA , 296:1731-2, 2006***

NIH AD Research Summits:
Path to Treatment and Prevention



May 14-15, 2012
Feb 9-10, 2015
March 1-2, 2018
April 19-22, 2021

**Overarching Goal: Formulate a blueprint for an integrated, translational research agenda that will enable the development of effective therapies (disease modifying and palliative) across the disease continuum for the cognitive as well as neuropsychiatric symptoms of Alzheimer's disease.**

# NIH AD Summits :

## Recommendations Aimed at Increasing the Predictive Validity of Preclinical Studies in AD Animal Models

- **Identify consensus experimental design elements and best practices and incorporate them into study design guidelines for preclinical studies in AD animal models.**
- **Develop a publicly available database that serves as a knowledge platform for data sharing, mining and analysis relating to the preclinical testing of candidate therapeutic agents in AD animal models.**
- **The database should help identify critical experimental design elements and methodology missing from studies, making them susceptible to misinterpretation and reducing their rigor, reproducibility and translational value.**
- **The database of preclinical efficacy studies that houses experimental designs and analyses of positive and negative data to overcome publication bias**

# Recommendations: Best Practices and Study Guidelines for Preclinical Animal Studies

- Power Analysis/Sample Size
- Statistical Analysis Plan
- Inclusion/Exclusion Criteria
- Randomization
- Blinding (treatment allocation and outcome measures)
- Balance for Gender
- Report Age of Animals
- Report details of Strain, Housing, Diet
- Employ *translatable biomarkers* as key measures
- Use PK/PD, ADME to Characterize Candidate Therapeutic Agents
- Report Toxicology Measures
- Report Potential Conflicts of Interest
- **Develop a Publicly Available Database of Preclinical Efficacy Studies (Similar to Clinical Trials.gov.)**

**Common Critical Elements of Clinical Trial Study Design**

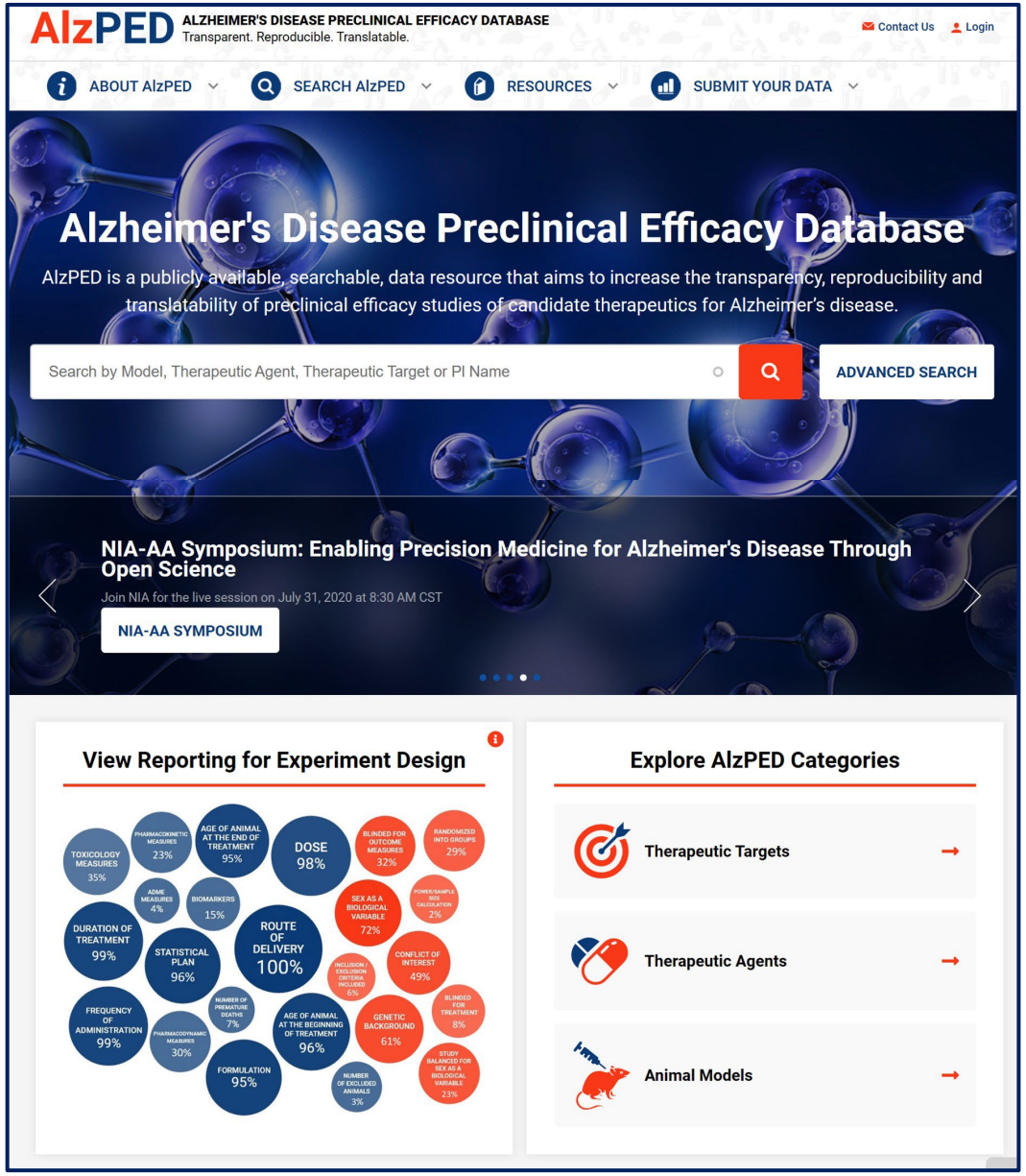
*Shineman et. al., Alzheimer's Research &Therapy, 2011; Landis et al., Nature, 2012; Snyder et al., Alzheimer's & Dementia, 2016.*

# Background: Recommendations from 2015 NIA AD Summit

## NIA Response to Recommendations

**Recommendations Aimed at Increasing Predictive Power of Preclinical Testing in AD Animal Models:**

1. House experimental details relating to the preclinical testing of candidate therapeutic agents in AD animal models.
2. Identify critical elements of design and methodology missing from studies.
3. House experimental details of positive and negative data to overcome publication bias.




https://alzped.nia.nih.gov

Launched in 2016

# AlzPED: Scope and Capabilities

- Growing database, currently hosts curated summaries of 1298 preclinical therapeutic studies in AD animal models published between 2000 and 2021
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- Provide
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  - Th
  - Th
  - Therapeutic Target (250 Therapeutic Targets)
  - Animal Model (210 Animal Models)
  - Principal Investigator
  - Funding Source

es,

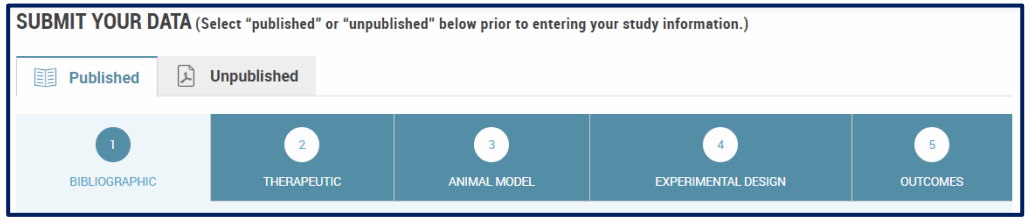
**Is the following information reported in the study?**

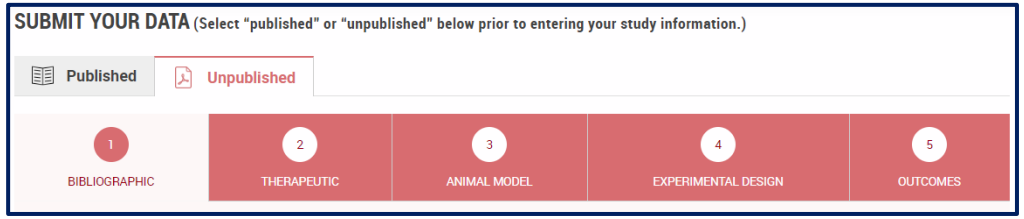
- [ ] Power/Sample Size Calculation ?
- [ ] Blinded for Treatment ?
- [ ] Pharmacokinetic Measures ?
- [ ] Toxicology Measures ?
- [ ] Biomarkers ?
- [ ] Formulation ?
- [ ] Duration of Treatment ?
- [ ] Age of Animal at the Beginning of Treatment ?
- [ ] Sex as a Biological Variable
- [ ] Number of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

  - Therapeutic Targets (Open Targets and Pharos)
  - Animal Model (Alzforum)
  - Related Clinical Trials (ClinicalTrials.gov)
  - Related Patents (Google Patents and USPTO)

# Article Selection and Curation Workflow

## AlzPED Data Submission Portal:




## 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:

Submitted study reviewed and curated by 2 NIA experts in AD research for

- Bibliographic details, funding source, study goals
- Therapeutics – therapy type, therapeutic agent and target
- Animal model
- Scientific rigor and experimental design (using Rigor Report Card)
- AD-related outcome measures

↓

Curated summary is hosted on AlzPED

# Sample of a Curated Record on AlzPED

## Prophylactic evaluation of verubecestat on disease and symptom modifying effects in 5XFAD mice

Unpublished

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

### Bibliographic

**Year of Publication:** 2021

**Contact PI Name:** Stacey J. Sukoff Rizzo

**Contact PI Affiliation:**
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

**Co-Authors:**
AL Oblak, ZA Cope, SK Quinney, R Pandey, C Biesdorf, AR Masters, KD Onos, L Haynes, KJ Keezer, JA Meyer, J Peters, SC Persohn, AA Bedwell, K Eldridge, R Speedy, G Little, S-P Williams, M Sasner, G Howell, G Carter, H Williams, BT Lamb, PR Territo

**Primary Reference (DOI):** 10.7303/syn26560918

**Conflict of Interest:**
Dr. Lamb has served as a consultant for AvroBio and Eli-Lilly

**Study Goal and Principal Findings (Abstract):**
Alzheimer's disease (AD) is the most common form of dementia. Beta-secretase (BACE) inhibitors have been proposed as potential therapeutic interventions however initiating treatment once disease has significantly progressed has failed to effectively stop or treat disease. Whether BACE inhibition may have efficacy when administered prophylactically in the early stages of AD has been under-investigated. The present studies aimed to evaluate prophylactic treatment of the BACE inhibitor verubecestat in an AD mouse model using the NIA resources of the MODEL-AD Preclinical Testing Core (PTC) Drug Screening Pipeline. 5XFAD mice were administered verubecestat ad libitum in chow from 3-6 months of age, prior to the onset of significant disease pathology. Following treatment, in vivo imaging was conducted with 18F-AV45 and 18-FDG-PET/MRI, brain and plasma beta-amyloid (Aβ) were measured, and the clinical and behavioral characteristics of the mice were assessed and correlated with pharmacokinetic data. Prophylactic verubecestat treatment resulted in dose- and region-dependent attenuations of 18F-AV45 uptake in male and female 5XFAD mice. Plasma Aβ40 and Aβ42 were also dose-dependently attenuated with treatment. Across the dose range evaluated, side effects including coat color changes and motor alterations were reported, in the absence of cognitive improvement or changes in 18F-FDG uptake. Prophylactic treatment with verubecestat resulted in attenuated amyloid plaque deposition when treatment was initiated prior to significant pathology in 5XFAD mice. At the same dose range effective at attenuating Aβ levels, verubecestat produced side-effects in the absence of improvements in cognitive function. Taken together these data demonstrate the rigorous translational approaches of the MODEL-AD PTC for interrogating potential therapeutics and provide insight into the limitations of verubecestat as a prophylactic intervention for early-stage AD.

**Funding Source:**
National Institutes of Health (NIH)
National Institute on Aging (NIA)

## 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 |

## Therapeutic Agent

**Therapeutic Information:**

**Therapy Type:** Small Molecule

**Therapeutic Agent:** Verubecestat

PubMed | PubChem | DrugBank | ClinicalTrials | Patents

**Therapeutic Target:** BACE1

Open Targets | Pharos | Agora

## Animal Model

**Model Information:**

**Species:** Mouse

**Model Type:** APPxPS1

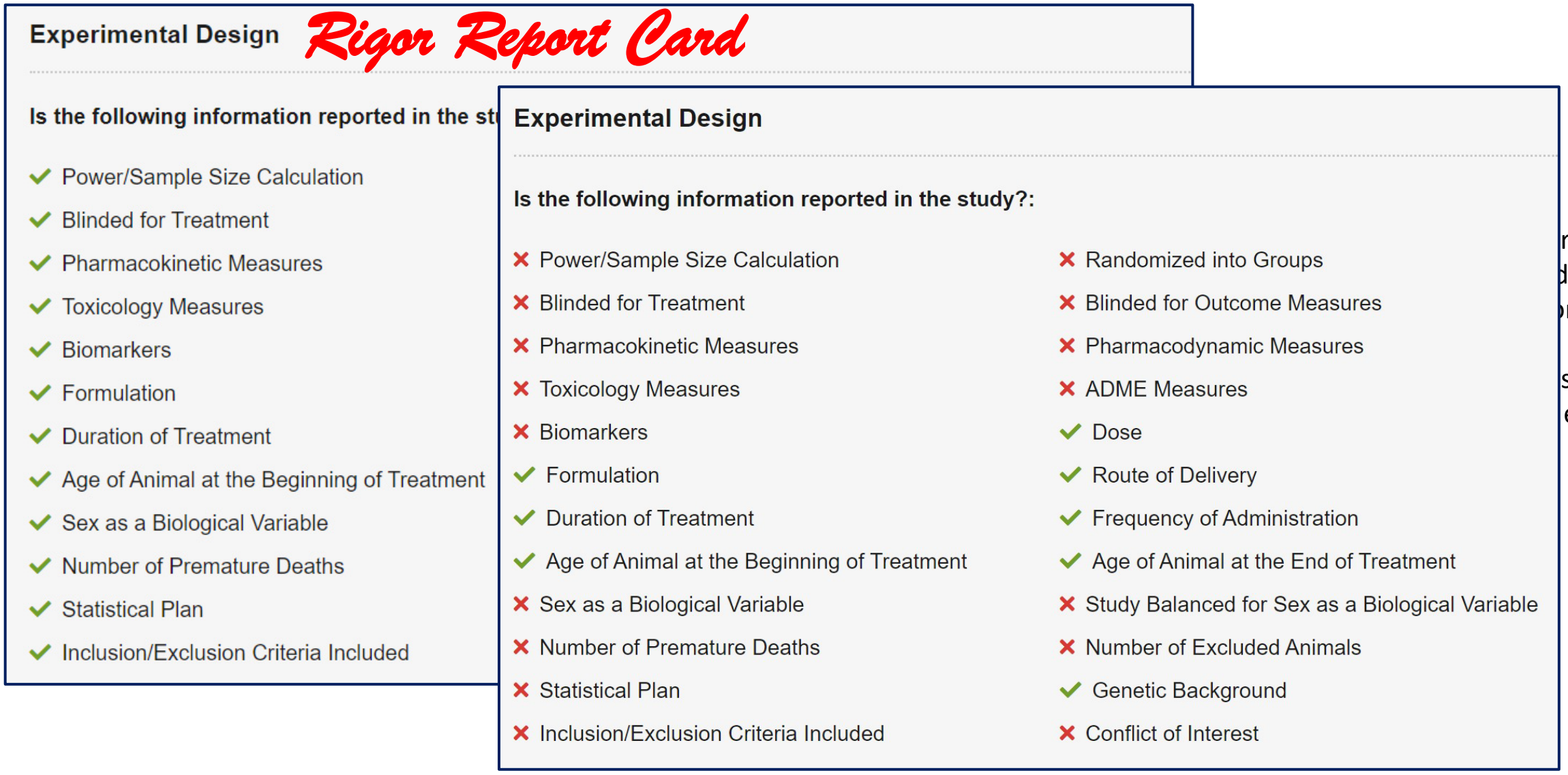
**Model Name:** 5xFAD ALZFORUM

**Strain/Genetic Background:** C57BL/6J

## Outcomes

| Outcome Measured | Outcome Parameters |
|---|---|
| Behavioral | • Exploratory Activity<br>• Frailty Index<br>• Open Field Test<br>• Spontaneous Alternation |
| Motor Function | • Locomotor Activity<br>• Path Length<br>• Rotarod Test<br>• Thigmotaxis |
| Histopathology | • Activated Microglia<br>• beta Amyloid Deposits |
| Biochemical | • Brain-Buffer Soluble beta Amyloid Peptide 40<br>• Brain-Buffer Soluble beta Amyloid Peptide 42<br>• Brain-Formic Acid Soluble beta Amyloid Peptide 40<br>• Brain-Formic Acid Soluble beta Amyloid Peptide 42 |
| Immunochemistry | • Ionized Calcium Binding Adaptor Molecule 1 (Iba1) |
| Spectroscopy | • Mass Spectrometry |
| Imaging | • [18F]AV45-PET<br>• [18F]FDG-PET<br>• Magnetic Resonance Imaging (MRI)<br>• Standardized Uptake Value Ratio (SUVR) |
| Biomarker | • Plasma-beta Amyloid Peptide 42<br>• Plasma-beta Amyloid Peptide 40 |
| Pharmacokinetics | • Brain/Plasma Ratio<br>• Clearance (L/h/kg)<br>• Cmax<br>• Drug Concentration-Plasma<br>• Drug Concentration-Brain<br>• PK/PD Modeling<br>• t1/2 (Elimination Half-Life)<br>• Tmax<br>• Volume of Distribution (V) |
| Pharmacodynamics | • Target Engagement (Reduction beta Amyloid Peptide 40-Brain)<br>• Target Engagement (Reduction beta Amyloid Peptide 42-Brain)<br>• Target Engagement (Reduction beta Amyloid Peptide 40-Plasma)<br>• Target Engagement (Reduction beta Amyloid Peptide 42-Plasma) |
| Toxicology | • Body Weight<br>• Coat Color Change<br>• General Behavior<br>• Physical Appearance |
| Omics | • Gene Expression Profile-Alzheimer's-Related Genes |

# AlzPED Monitors Rigor in Study Design for Each Curated Study

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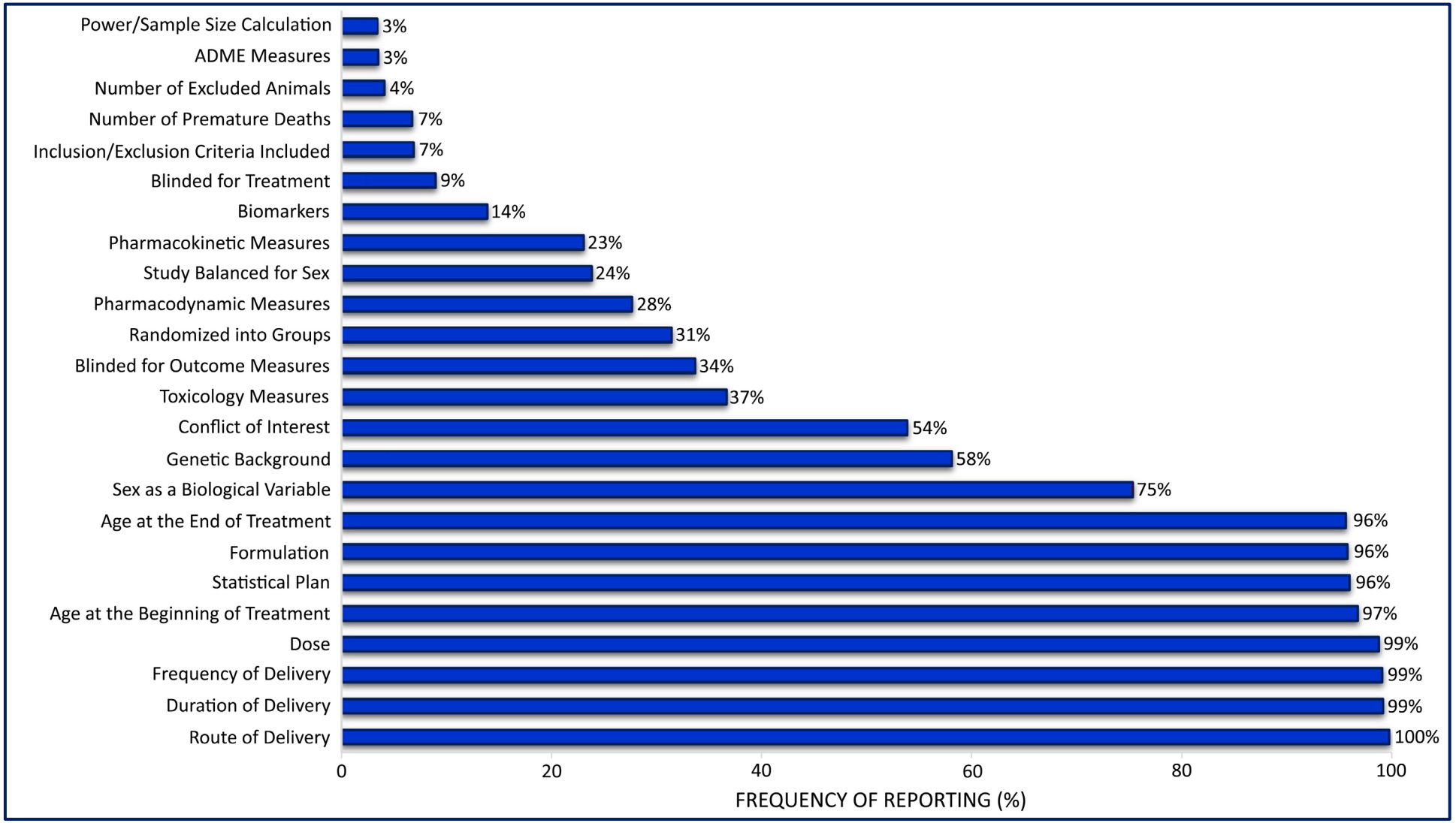
# Critical Elements of Experimental Design are Under-Reported

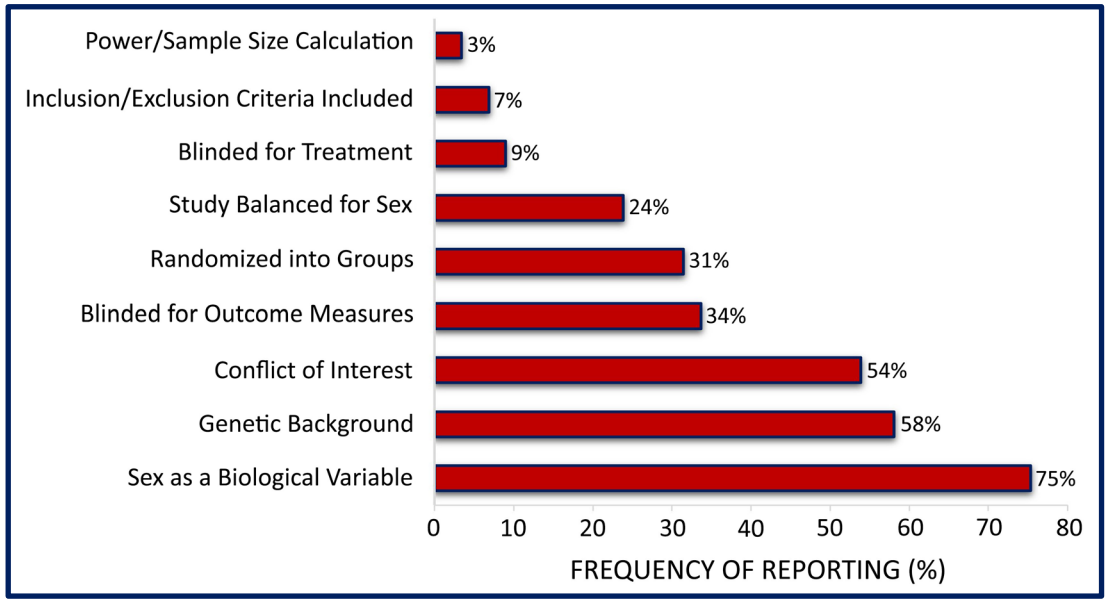



Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements, calculated from 1298 published preclinical studies curated to AlzPED.

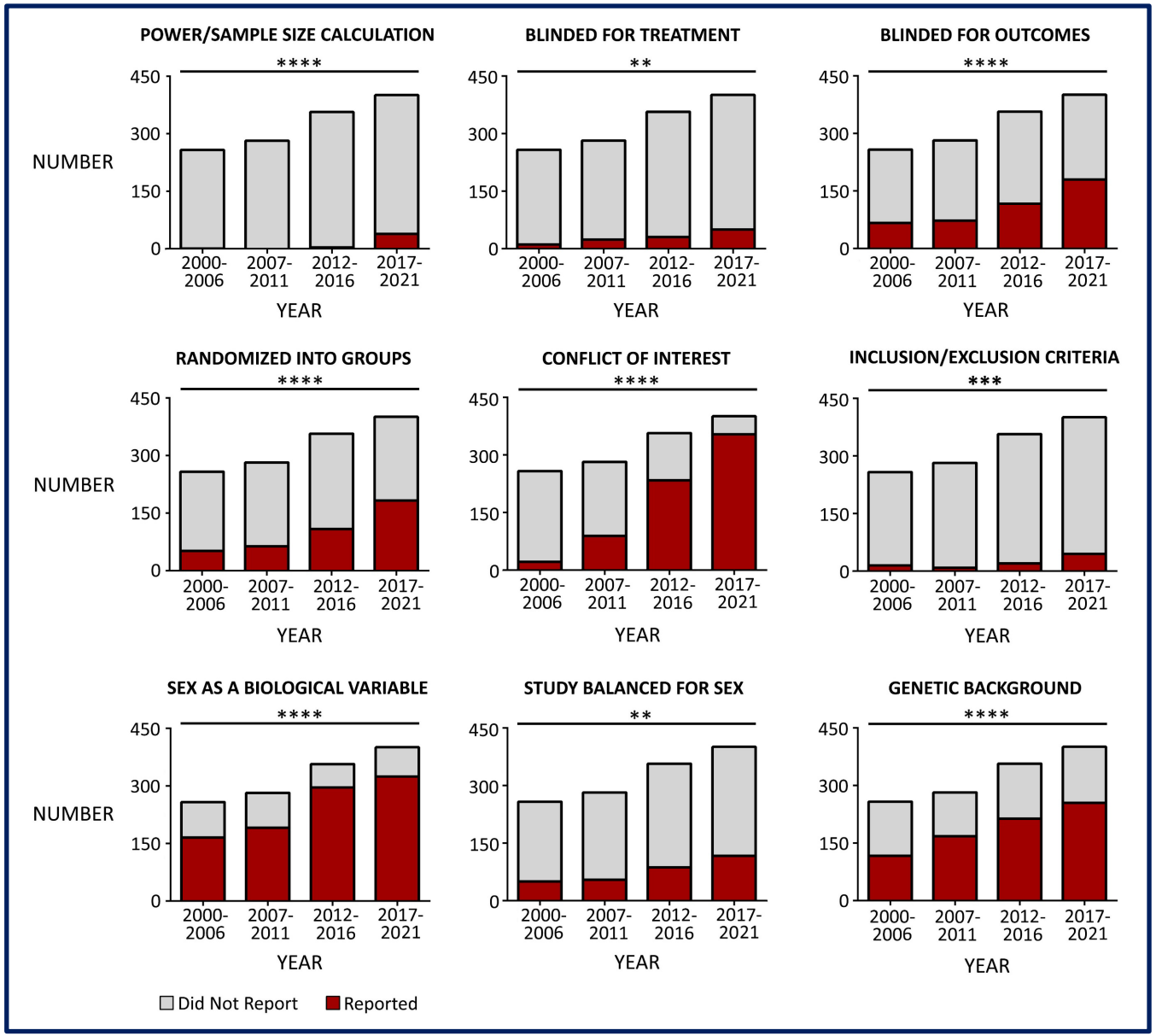
Detailed Analytics Summary is available on the AlzPED Analytics page.

# 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 2021. Data analyzed using Chi square test; **p<0.01, ***p<0.001, ****p<0.0001. Data presented as number that reported Vs number that did not report core experimental design elements, calculated from 258, 282, 357 and 401 curated studies published between 2000-2006, 2007-2011, 2012-2016 and 2017-2021 respectively.



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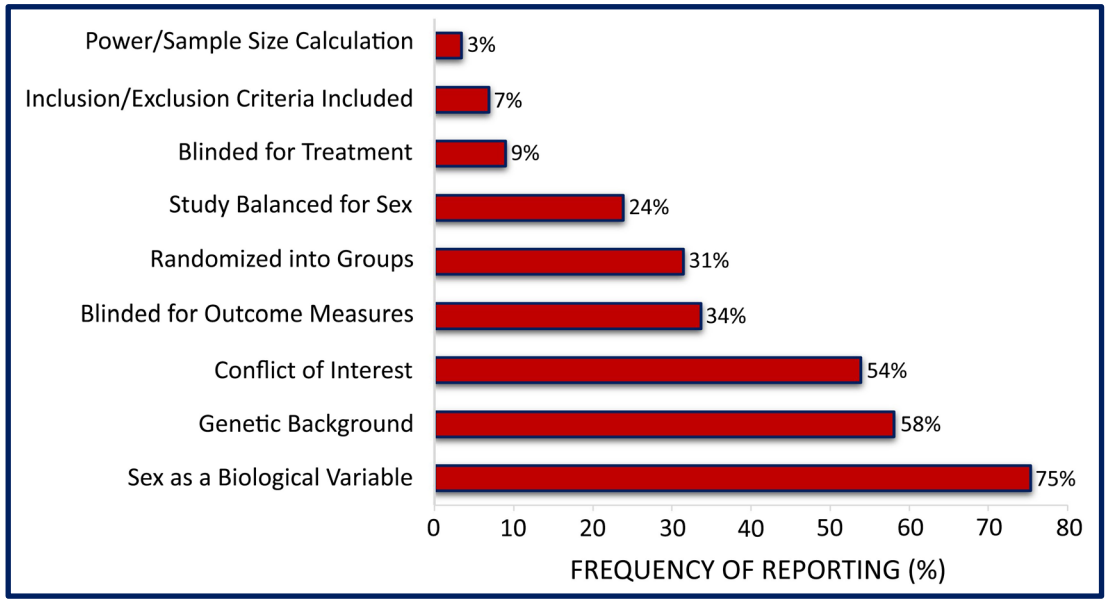


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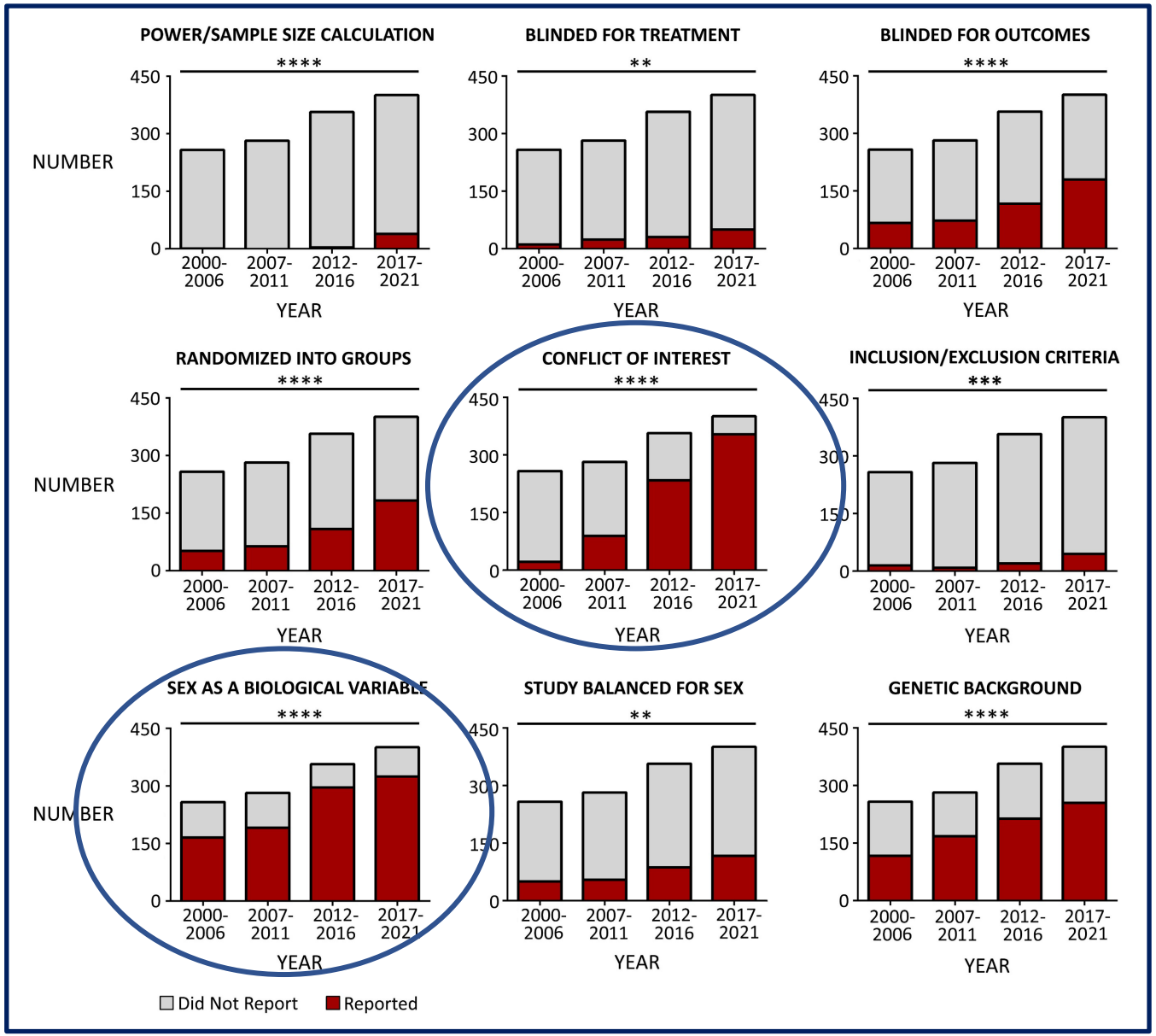


## Role of NIH Policies in Improving Rigor – evidence from reporting trends over 20 years from the AlzPED Database

NOT-OD-11-109 requires transparency in reporting financial conflicts of interest, and

NOT-OD-15-102 requires consideration of sex as a biological variable.

Enforcement of these policies clearly improved the reporting of these core experimental design elements.

## NIA Funding Opportunity: *Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (U01)* PAR-22-228

All findings from preclinical efficacy studies, including both negative and positive findings, are expected to be incorporated in AlzPED no later than 9 months after study completion or at the time of first manuscript publication, whichever comes first.

Published studies will be incorporated in AlzPED as a curated record; unpublished studies will be incorporated in AlzPED as a citable pre-print.

# Who Can Benefit from AlzPED

**Academic and Industry Researchers**

**Leverage the AlzPED data to inform the design of your efficacy testing studies. Create citable reports of your (old and new) unpublished work including studies with negative findings.**

**Data Scientists**

**Use the multifaceted data to conduct a variety of meta-analyses and generate new insights on disease targets and candidate therapeutics.**

**Funding Agencies**

**Use AlzPED to assess the quality of the research you support and as a tool to enforce requirements for transparent reporting and rigorous study design.**

**Register for a free account:**

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

**Submit your unpublished studies and get a citable preprint with a d.o.i**

alzped@nih.gov

# Rigor-related Resources

- **AlzPED Resources:** https://alzped.nia.nih.gov/resources
- **AlzPED and NIA Translational Research Blogs:** https://alzped.nia.nih.gov/blogs-and-presentations
- **AlzPED LinkedIn** – we post every few weeks with AlzPED, conference/workshop, and other NIA rigor and policy-related updates: https://www.linkedin.com/in/alzheimer%E2%80%99s-disease-preclinical-efficacy-database-alzped-13631a177/

- **NIH Advisory Committee to the Director Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research:** https://acd.od.nih.gov/working-groups/eprar.html
- **NIH Principles and Guidelines for Reporting Preclinical Research:** https://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research
- **NIH Resources for Preparing Your Application:** https://grants.nih.gov/policy/reproducibility/resources.htm
- **NIH Rigor and Reproducibility Training Modules:** https://grants.nih.gov/reproducibility/module_1/presentation_html5.html

- **ARRIVE Guidelines:** https://arriveguidelines.org/
- **ARRIVE Guidelines 2.0:** https://arriveguidelines.org/arrive-guidelines

- **National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs):** https://www.nc3rs.org.uk/
- **Global Preclinical Data Forum:** https://www.preclinicaldataforum.org/

# Training on conducting preclinical efficacy studies using mouse models of AD – Jax workshop

**Principles and Techniques for Improving Preclinical to Clinical Translation in Alzheimer's Disease Research**

MAY 8–12, 2023

*An immersion workshop focusing on the improvement of preclinical translation in Alzheimer's Disease research. This workshop will leverage the expertise and facilities of the Indiana University (IU)/JAX Model Organism Development for Evaluation of Late Onset Alzheimer's Disease (MODEL-AD) Precision Medicine consortium.*

https://www.jax.org/education-and-learning/course-and-conferences/principles-and-techniques-of-alzheimers-disease

## NIA AlzPED Team


Shreaya Chakroborty
Maria Fe Lanfranco Gallofre
Suzana Petanceska
Lorenzo Refolo
Erika Tarver
Jaya Viswanathan


**AlzPED Poster Presentation at SfN 2022**

**Monday Nov. 14, 2022**
**1:00 PM - 5:00 PM**

**Presentation Number: 371.13**

## AlzPED Partner Organizations

NIH National Institute on Aging

NIH Library nihlibrary.nih.gov

SageBionetworks

alz.org® | alzheimer's association®

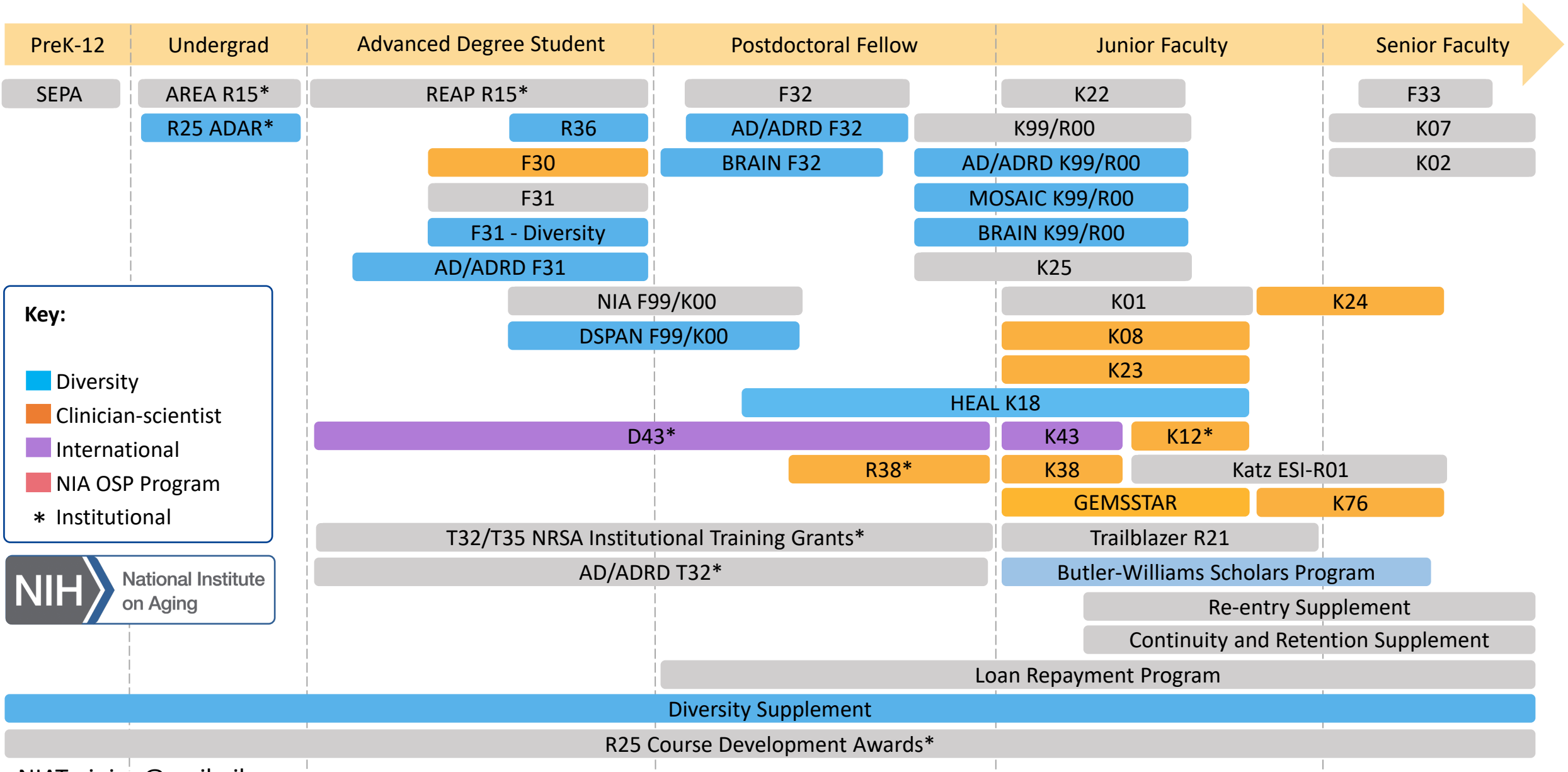
Alzheimer's Drug Discovery Foundation

Cohen Veterans Bioscience

# NIA Translational Research Resources

- **International Alzheimer's and Related Dementias Research Portfolio (IADRP)** – database brings together funded research supported by public and private organizations both in the US and abroad all categorized using the Common Alzheimer's and Related Dementias Research Ontology (CADRO): https://iadrp.nia.nih.gov/
- **AD+ADRD Research Implementation Milestones:** https://www.nia.nih.gov/research/milestones
- **2021 NIH Alzheimer's Research Summit: Path to Precision Medicine for Treatment and Prevention:** https://www.nia.nih.gov/2021-alzheimers-summit
- **Alzheimer's Disease and Related Dementias Funding Opportunities:** https://www.nia.nih.gov/research/grants-funding/announcements
- **Accelerating Medicines Partnership® Program for Alzheimer's Disease (AMP® AD):** https://www.nia.nih.gov/research/amp-ad
- **AD Knowledge Portal:** https://adknowledgeportal.synapse.org/#/
- **Agora:** https://agora.adknowledgeportal.org/genes
- **Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD):** https://www.model-ad.org/
- **Target Enablement to Accelerate Therapy Development for AD (TREAT-AD):** https://treatad.org/
- **Screening the Optimal Pharmaceutical for Alzheimer's Disease (STOP-AD):** https://stopadportal.synapse.org/#/
- **NIH Reporter:** https://reporter.nih.gov/
- Inside NIA – A Blog for Researchers: https://www.nia.nih.gov/research/blog
- **NIA and the National Plan to Address Alzheimer's Disease:** https://www.nia.nih.gov/about/nia-and-national-plan-address-alzheimers-disease

# NIA Training and Career Development Landscape




NIATraining@mail.nih.gov

# Aducanumab to treat Alzheimer’s

*NIA statement on FDA approval of aducanumab for Alzheimer’s disease*

*NIA statement on proposed CMS Medicare coverage decision for aducanumab to treat Alzheimer’s*