AlzPED: Raising the Standards for Preclinical Efficacy Testing of Candidate Therapeutics in Alzheimer's Disease

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National Institute on Aging

ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE

Session 5-20-FRS-C:
Preclinical Therapeutic Targets and Early Phase Studies
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Disclosures

Nothing To Disclose

Preclinical to Clinical Translation Gap

Symptomatic Full Approval	Disease Modifying Monoclonal Ab Accelerated Approval
Donepezil Aricept; 1996	**Aducanumab** Aduhelm Anti-amyloid; 2021;
Rivistagimine Exelon; 2000	**Lecanemab** Lecembi Anti-amyloid; 2023
Galantamine Razadyne; 2001	
Memantine Namenda; 2003	
Donepezil and Memantine Namzaric; 2014	

- **More than 200 therapeutic agents have been reported to be efficacious in ameliorating pathology and/or cognitive deficits in transgenic AD animal models.**
- **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.**
- **Till date, only 7 drugs have received FDA approval as disease-modifying therapeutics.**

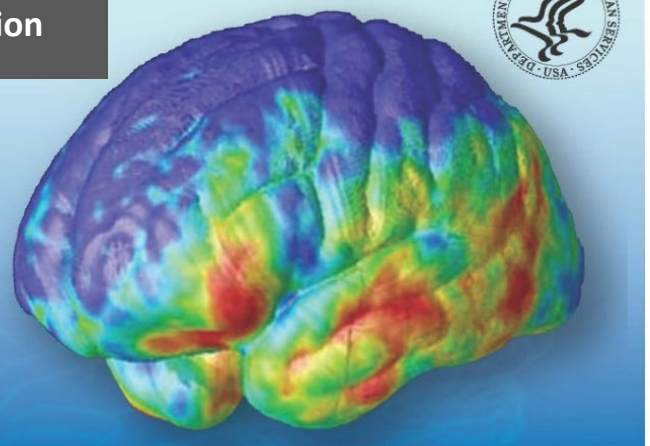
Zahs & Ashe, Trends in Neurosciences, 2010
Cummings et al., Alzheimer's Research & Therapy 2014
Cummings, Drugs 2023

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.
- Poor reproducibility of published data.
- Publication bias due to under reporting of negative results in the literature.

Shineman et. al., Alzheimer's Research &Therapy, 2011

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.)**

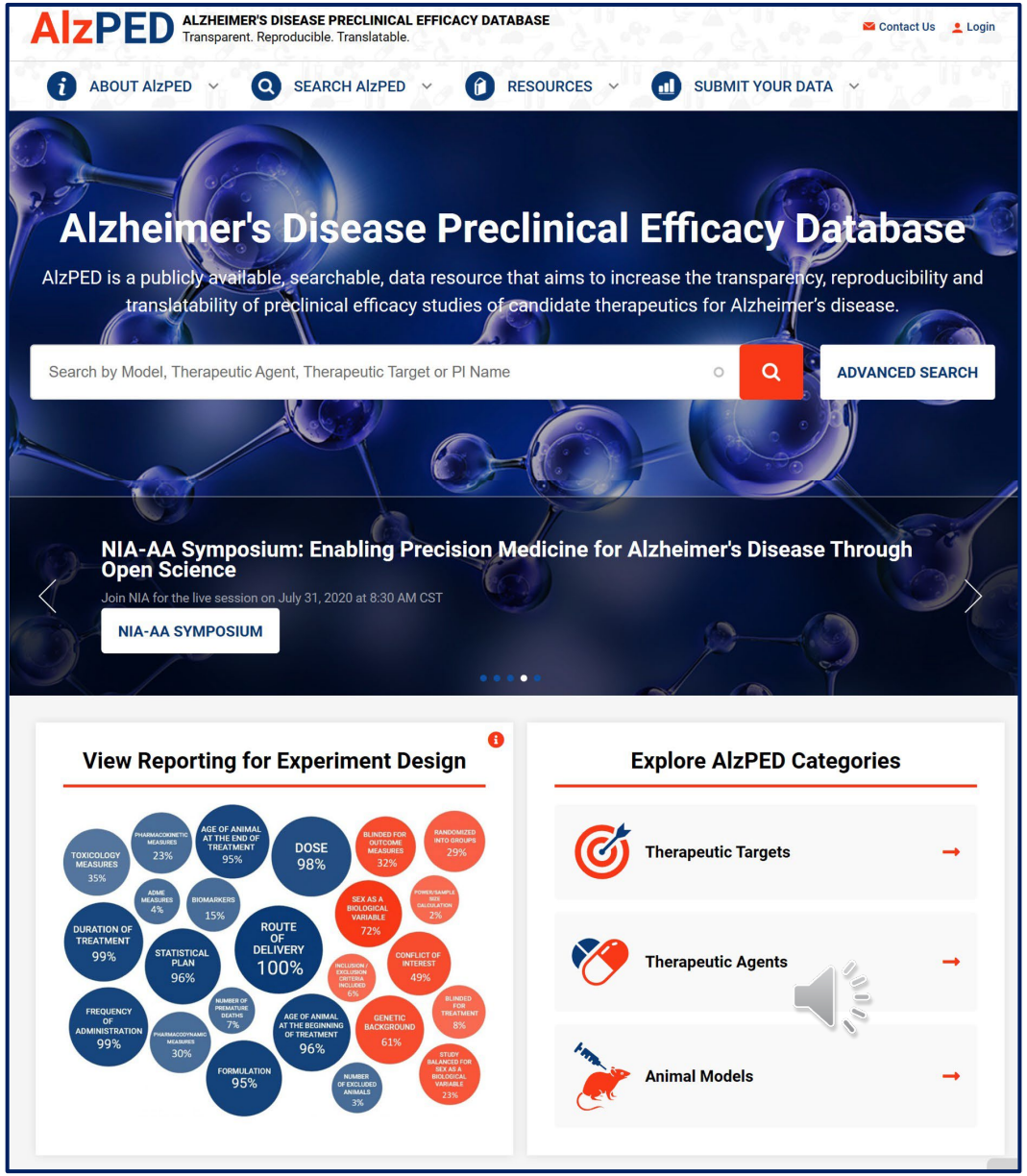
Common Critical Elements of Clinical Trial Study Design

van der Worp et al PLoS, 2010

Recommendations from 2015 NIA AD Summit

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

AlzPED: Scope and Capabilities

- Growing database, currently hosts curated summaries of 1400 preclinical therapeutic studies in AD animal models published between 2000 and 2022.
  - Provides the research community with an easy way to survey existing AD preclinical therapy development literature with access to information on study design and methodology, animal models, therapeutic agents, therapeutic targets, outcomes, patents and related clinical trials.

- 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 during the 2015 NIH AD Summit.
  - 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.

- Provides a platform for creating citable reports of unpublished studies, including studies with negative findings.
  - Mitigates publication bias due to under-reporting of negative results in the literature.

- Provides funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.

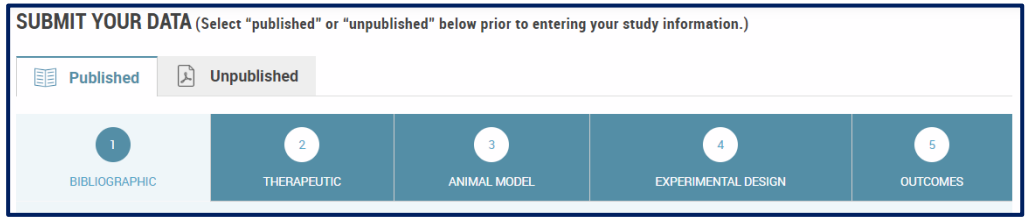
- Provides search capability across relevant translational criteria data sets and external databases:

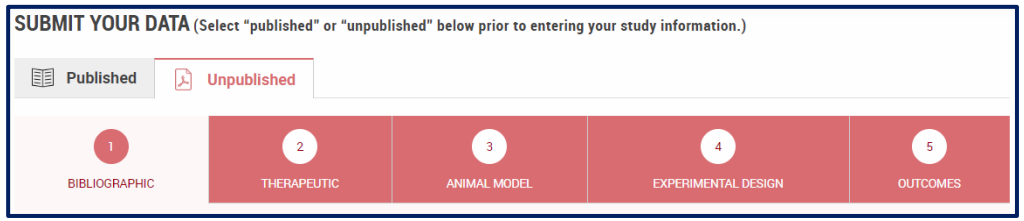
  - Therapy Type (16 Therapy Types)
  - Therapeutic Agent (1201 Therapeutic Agents)
  - Therapeutic Target (274 Therapeutic Targets)
  - Animal Model (226 Animal Models)
  - Principal Investigator
  - Funding Source

  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and Drug Bank)
  - Therapeutic Targets (Open Targets, Pharos and Agora)
  - 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

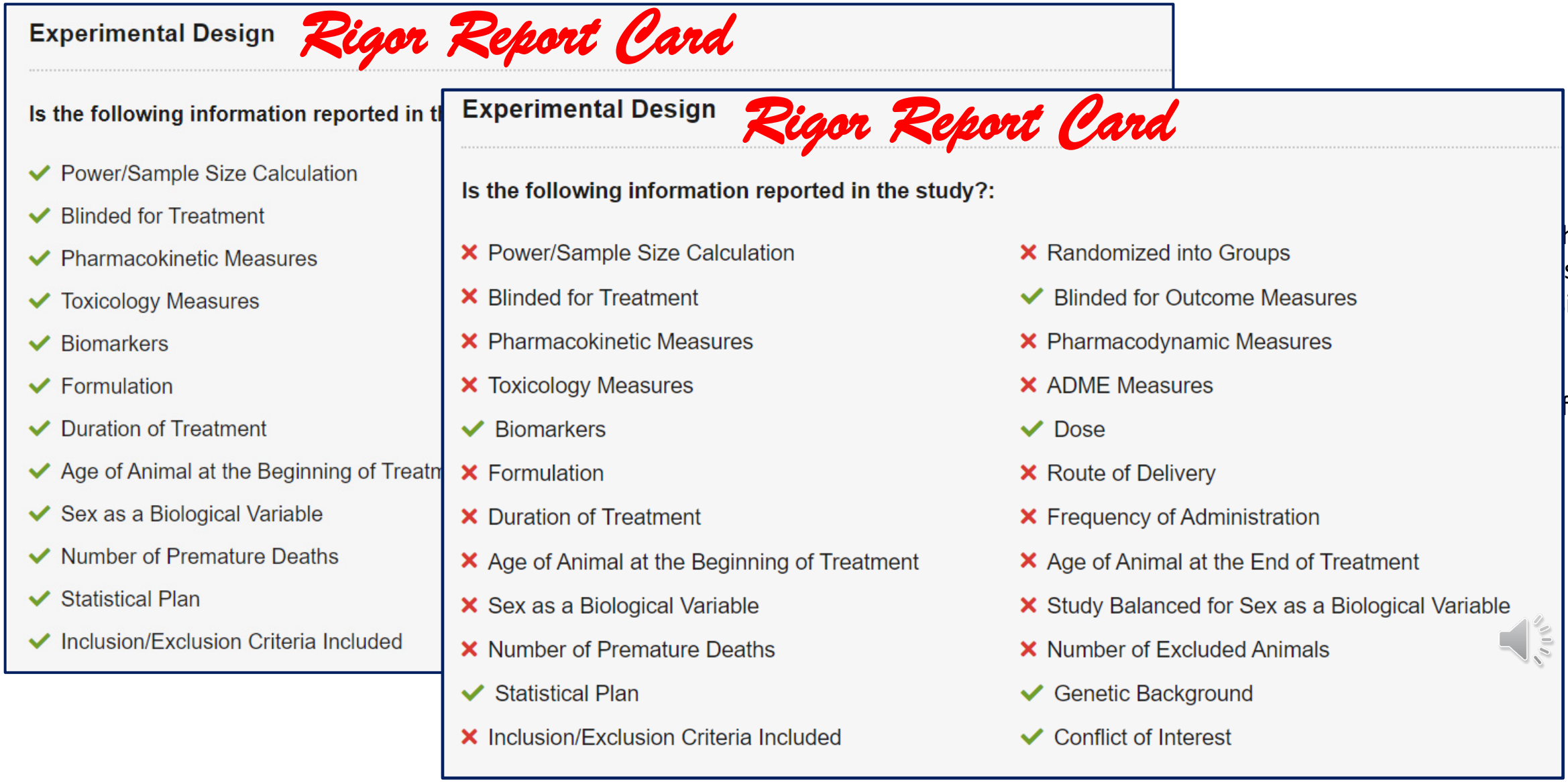
Model Name: 5xFAD ALZFORUM

Strain/Genetic Background: C57BL/6J

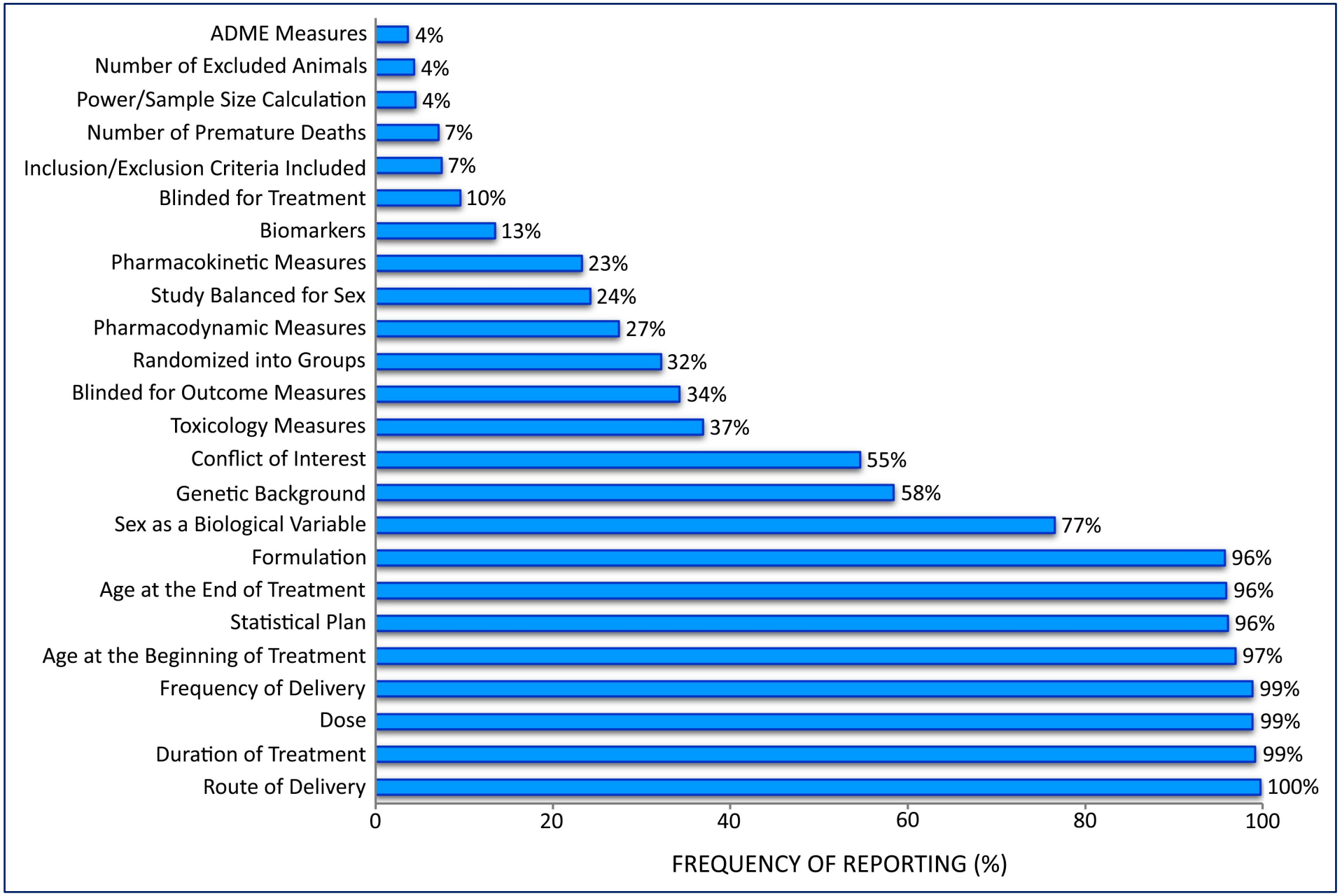
Outcomes

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

AlzPED Monitors Rigor in Study Design for Each Curated Study



Critical Elements of Experimental Design are Under-Reported

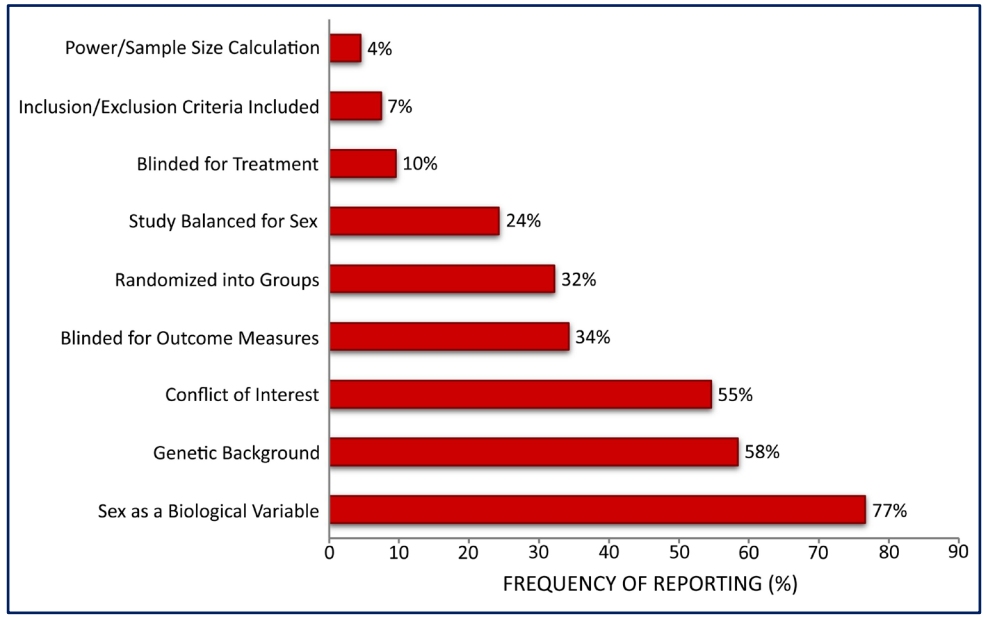


Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements, calculated from 1400 published preclinical studies curated to AlzPED.

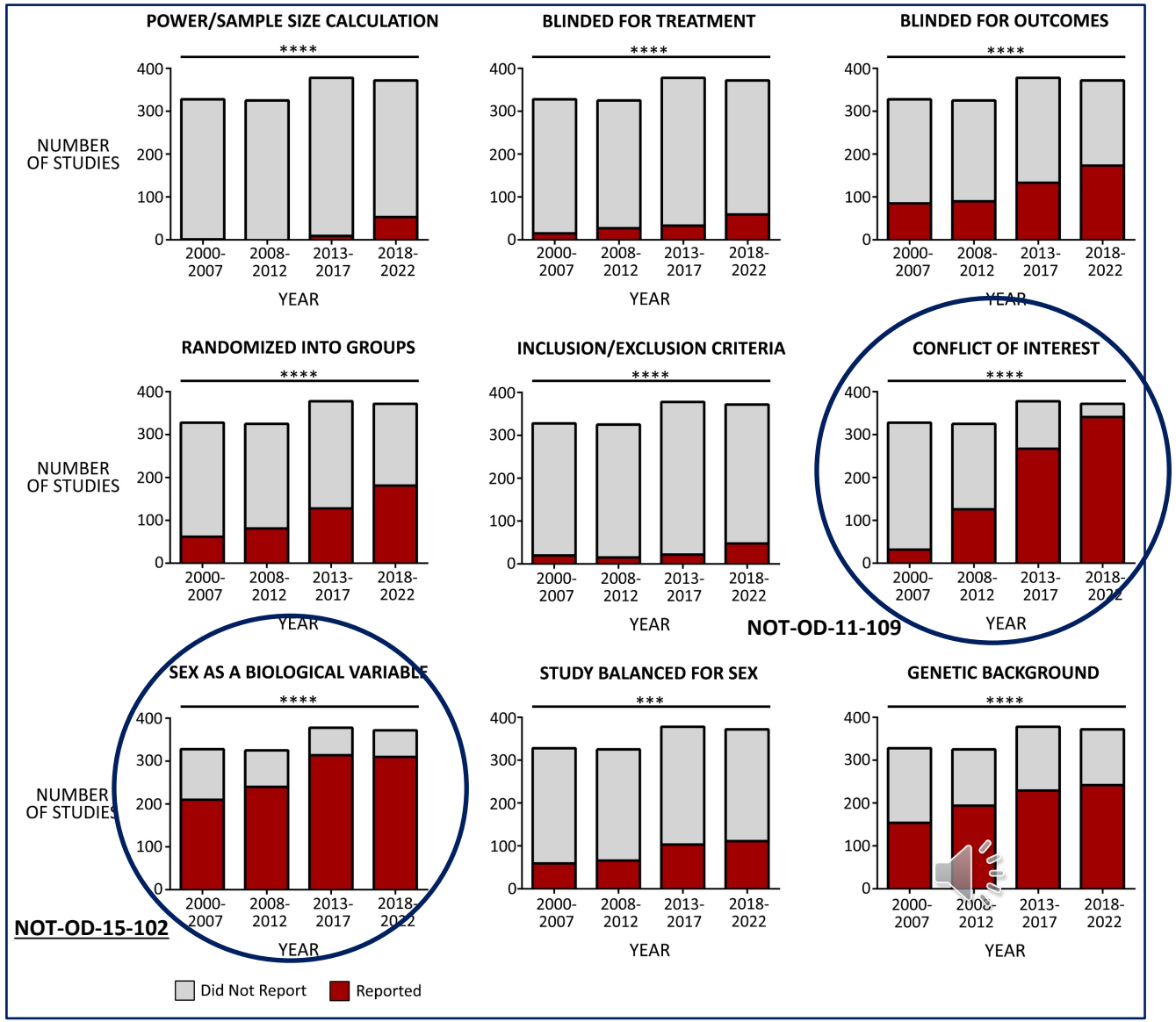
Detailed Analytics Summary is available on the AlzPED Analytics page.

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 2022. Data analyzed using Chi square test; ***p<0.001, ****p<0.0001. Data presented as number that reported Vs number that did not report core experimental design elements, calculated from 328, 325, 378 and 372 curated studies published between 2000-2007, 2008-2012, 2013-2017 and 2018-2022 respectively.



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-23-082

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 DOI

alzped@nih.gov

Acknowledgements

NIA

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Partner Organizations

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