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

Alzheimer's Disease Preclinical Efficacy Testing Database (AlzPED)

Shreaya Chakroborty, PhD
Translational Research Branch, Division of Neuroscience
Email: shreaya.chakroborty@nih.gov

NIH National Institute on Aging

WORKSHOP ON PRINCIPLES & TECHNIQUES FOR IMPROVING PRECLINICAL TO CLINICAL TRANSLATION IN ALZHEIMER'S DISEASE RESEARCH
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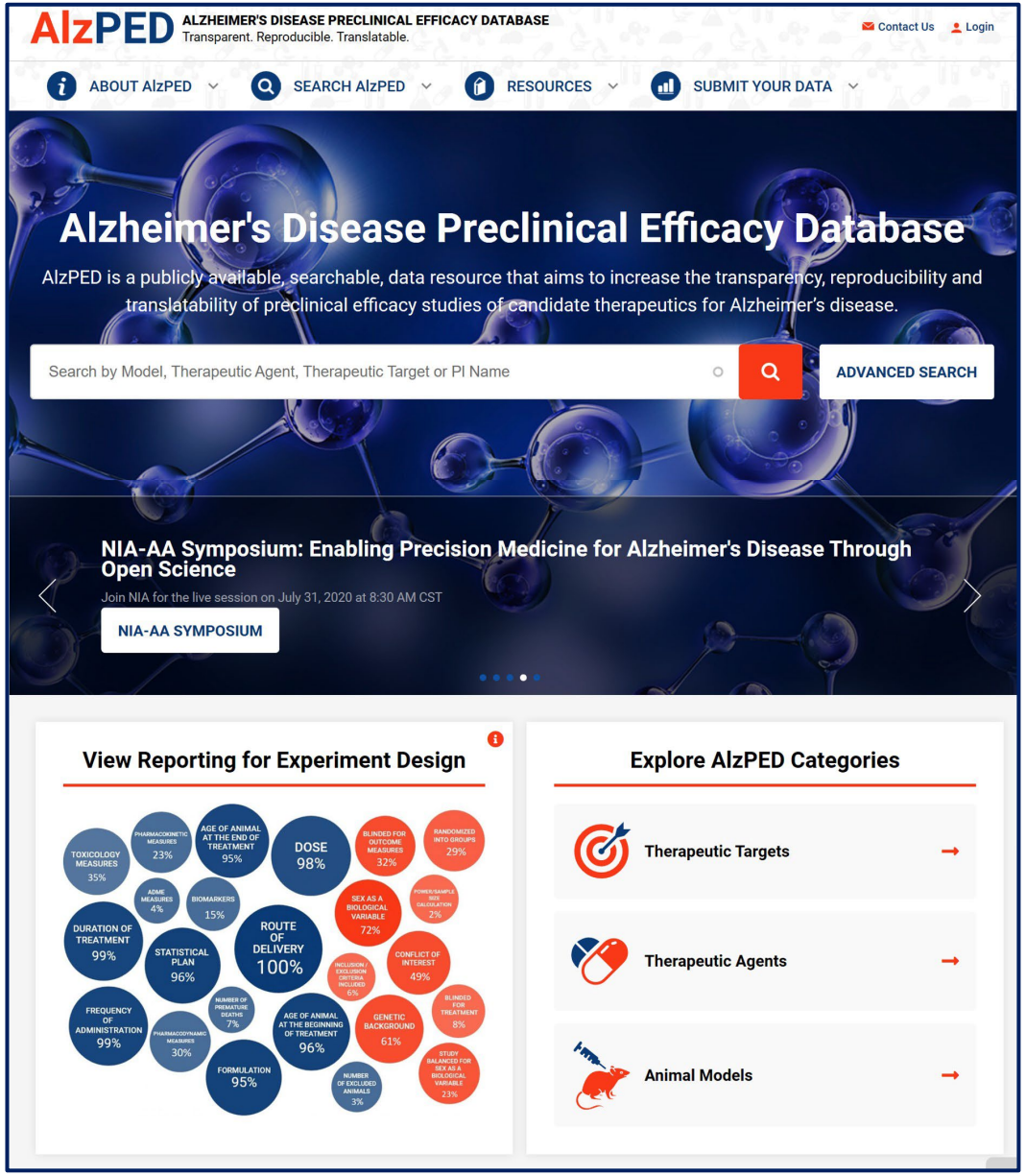
Background: Recommendations from 2015 NIA AD Summit

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 1298 preclinical therapeutic studies in AD animal models published between 2000 and 2021.
  - 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- Provides a platform for creating citable reports of unpublished studies, including studies with negative findings.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 (1119 Therapeutic Agents)
  - Therapeutic Target (250 Therapeutic Targets)
  - Animal Model (210 Animal Models)
  - Principal Investigator
  - Funding Source

  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and Drug Bank)
  - 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

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.

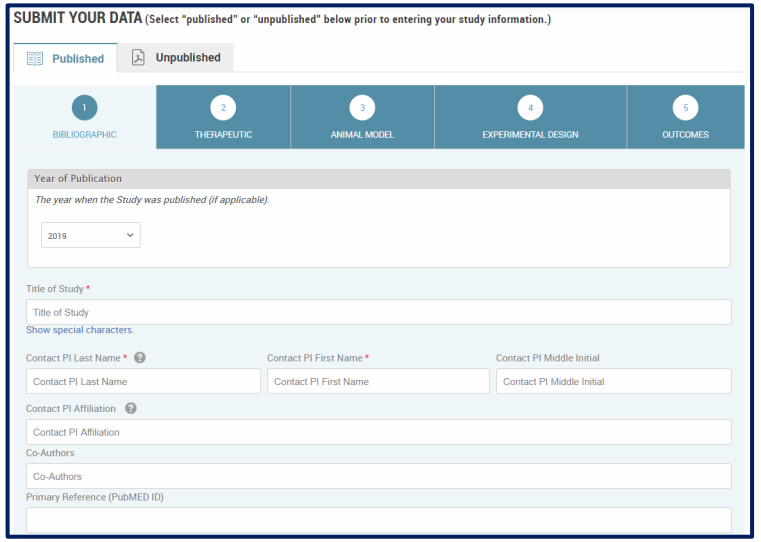
Curation Workflow:

- 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.

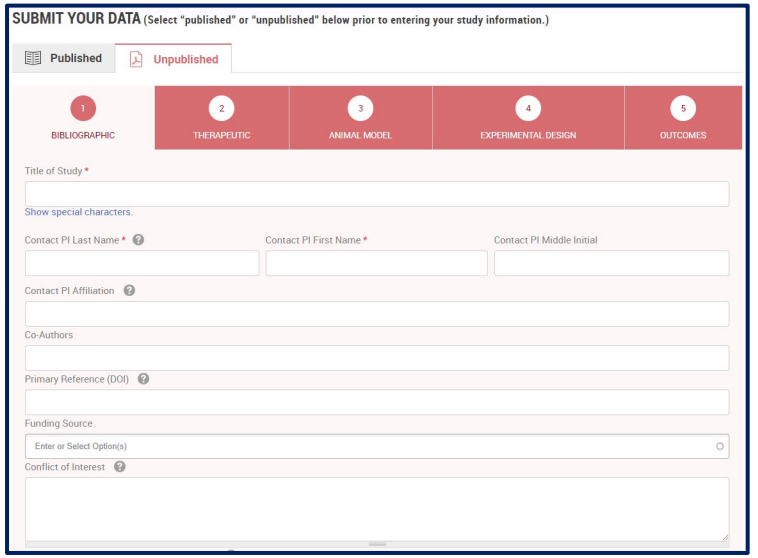
Unpublished and Negative Data:

- 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

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

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
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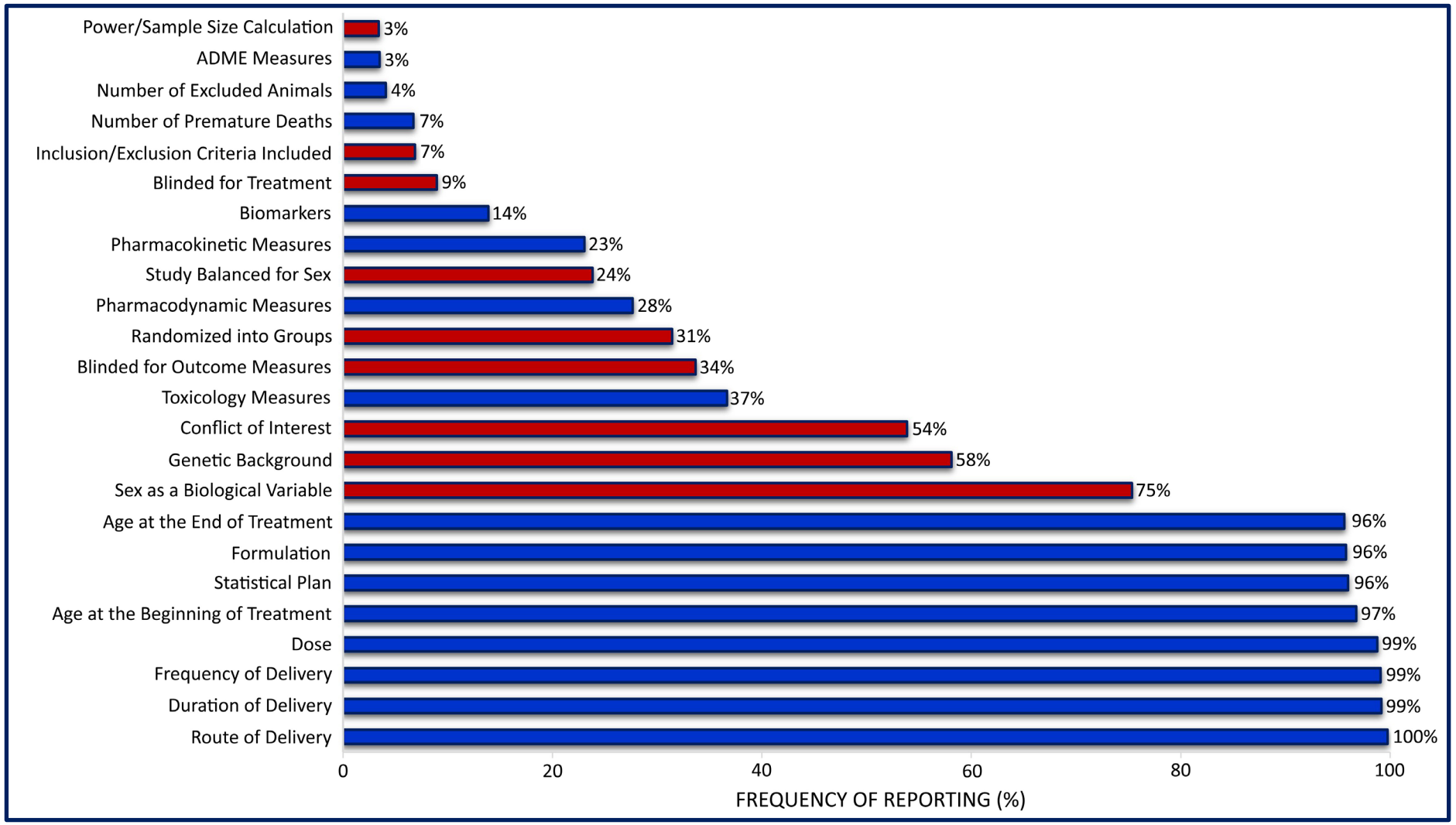
✓ Biomarkers	✓ Dose
✓ Formulation	✓ Route of Delivery
✓ Duration of Treatment	✓ Frequency of Administration
✓ Age of Animal at the Beginning of Treatment	✓ Age of Animal at the End of Treatment
✓ Sex as a Biological Variable	✓ Study Balanced for Sex as a Biological Variable
✓ Number of Premature Deaths	✓ 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 for preclinical efficacy studies

Critical Elements of Experimental Design are Under-Reported

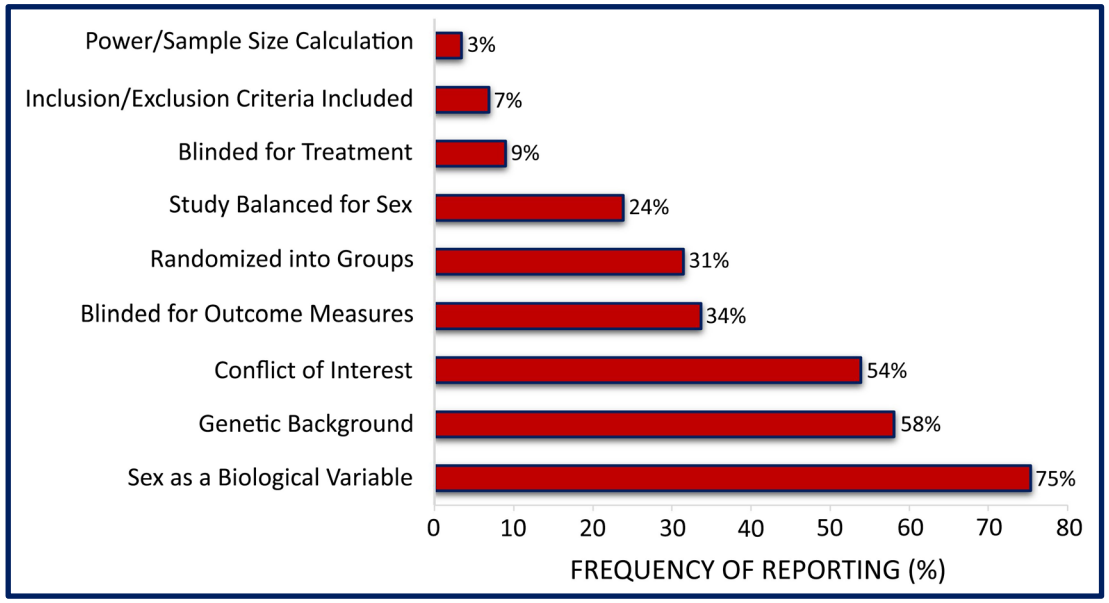


Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements, calculated from 1298 published preclinical studies curated to AlzPED. The red bars represent the 9 core design elements critical for scientific rigor and reproducibility.

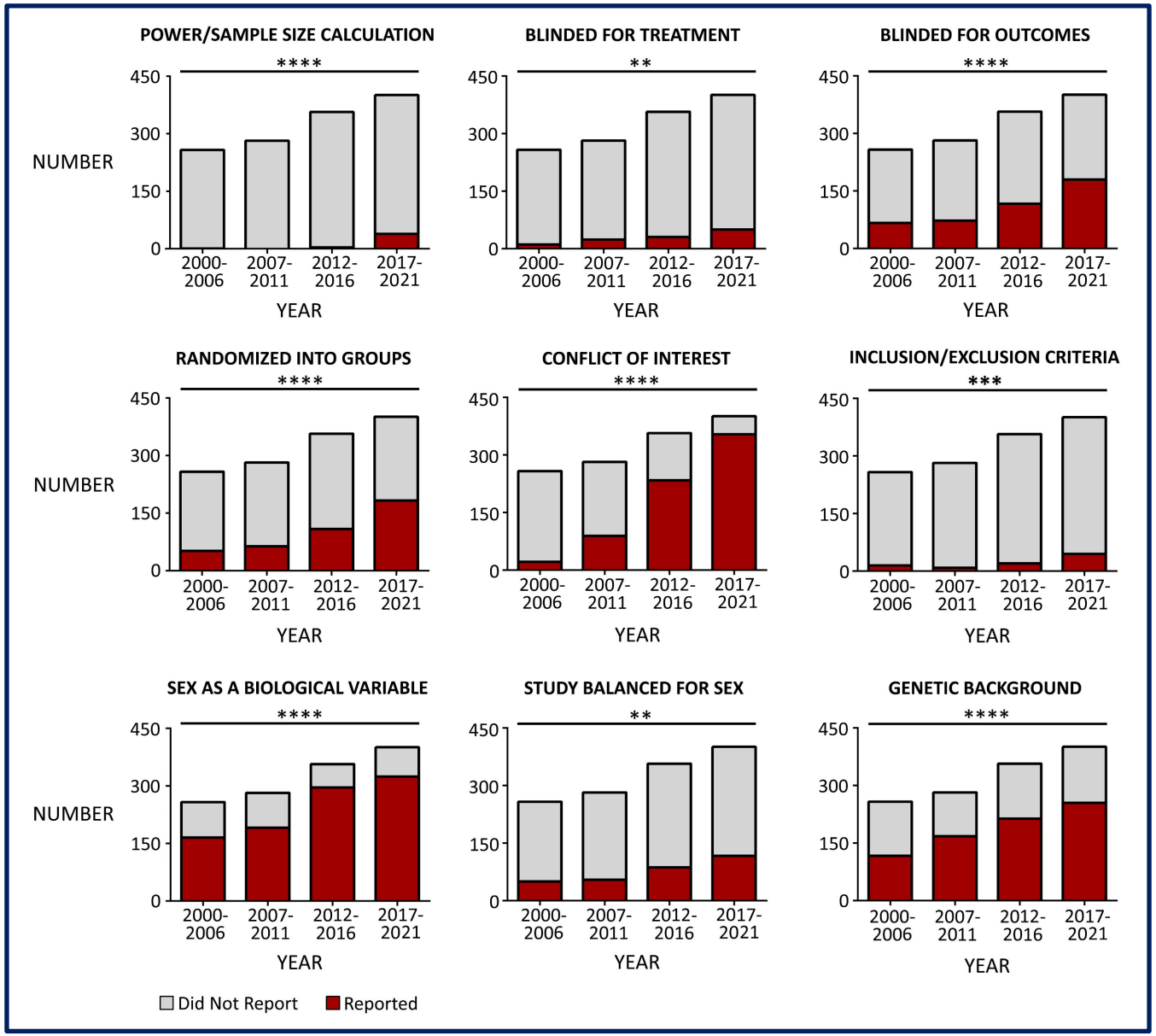
Detailed Analytics Summary is available on the AlzPED Analytics page.

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 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.



Conclusions

- Analysis of ~1300 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

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Partner Organizations

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

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

alzped@nih.gov

Rigor-related Resources

- **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/
- **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/
- **Global Preclinical Data Forum:** https://www.preclinicaldataforum.org/

Trainee Resources

- **NIH Research Training and Career Development: https://researchtraining.nih.gov/**
- **Institutional Training Grants: https://researchtraining.nih.gov/programs/training-grants**
- **Fellowships: https://researchtraining.nih.gov/programs/fellowships**
- **Research Career Development Awards: https://researchtraining.nih.gov/programs/career-development**
- **Other Training-related Awards: https://researchtraining.nih.gov/programs/other-training-related**

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