PIPELINE PRESENTATION

ASENT 2021 ANNUAL MEETING

February 23, 2021

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

|| Alzheimer's Preclinical Efficacy Testing Database (AlzPED) ||

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Partner Organizations

National Institute on Aging

Alzheimer's Drug Discovery Foundation

SageBionetworks

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NIH Library
nihlibrary.nih.gov

Background

Key Factors Contributing to Preclinical to Clinical Translation Gap:

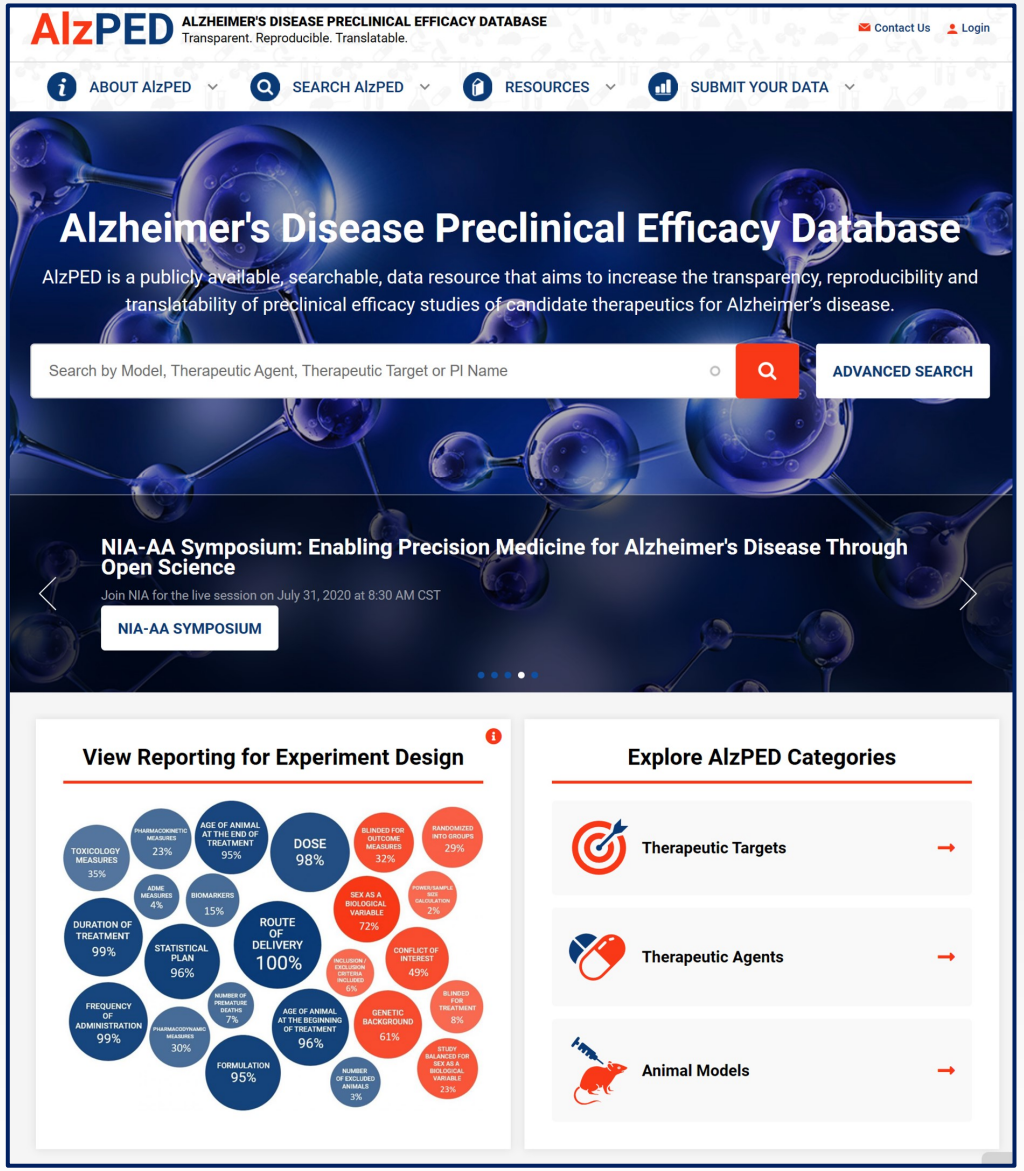
- Poor rigor in study design and methodology
- Poor reproducibility of published data
- Publication bias in favor of reporting positive findings and under reporting negative findings

NIH AD Research Summits 2012, 2015, 2018

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.

NIA response to recommendations:



Scope and Capabilities

- Provide researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the elements of rigorous study design and requirements for transparent reporting – hosts curated summaries from 1172 preclinical efficacy studies published between 1996 and 2020.

- Influence the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics.

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

  - Therapy Type (16 Therapy Types)
  - Therapeutic Agent (1019 Therapeutic Agents)
  - Therapeutic Target (225 Therapeutic Targets)
  - Animal Model (195 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)

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

- Provide a platform for creating citable reports/preprints of unpublished studies, including studies with negative data.

- Report on the rigor of each study by summarizing the elements of experimental design.

AlzPED Monitors Rigor in Study Design for Each Curated Study

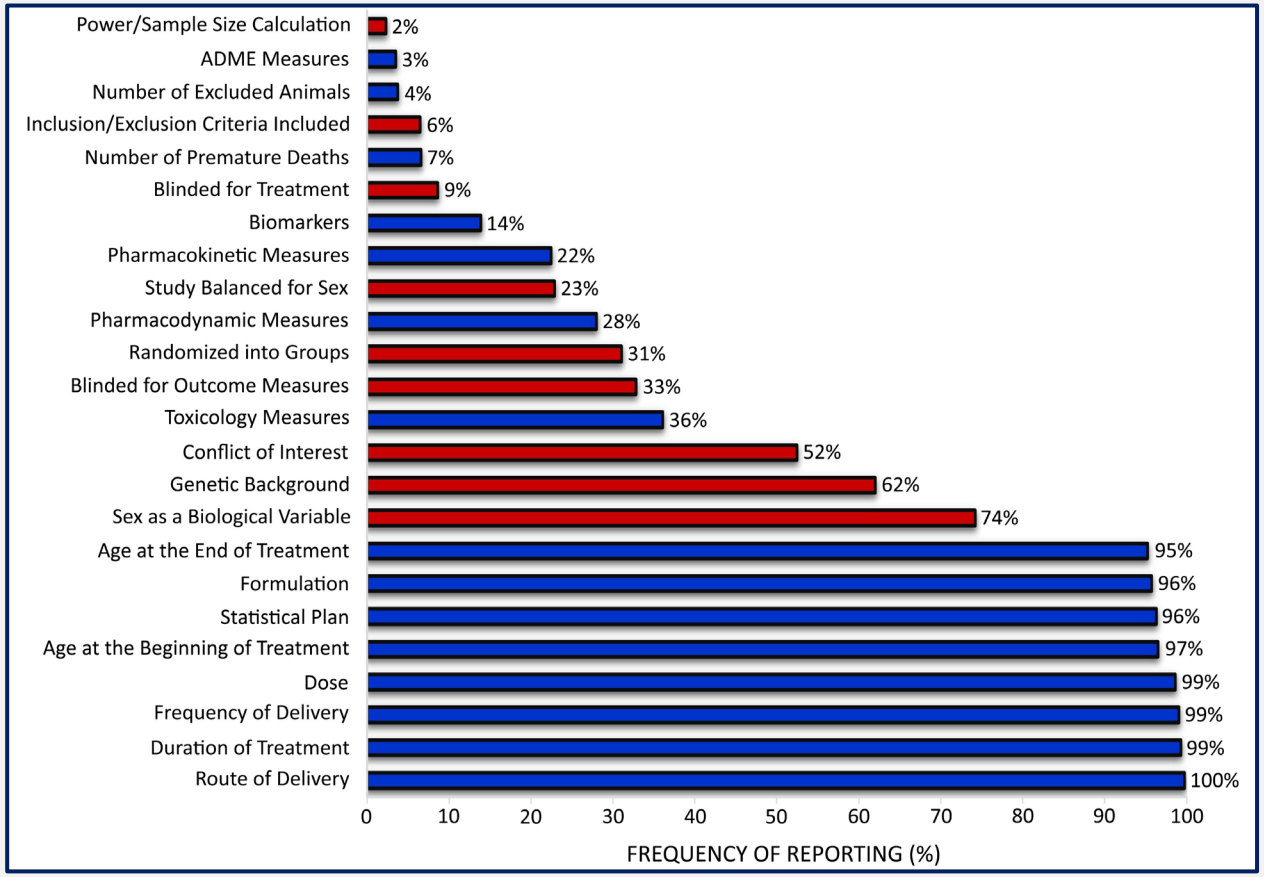
Experimental Design *Rigor Report Card*

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

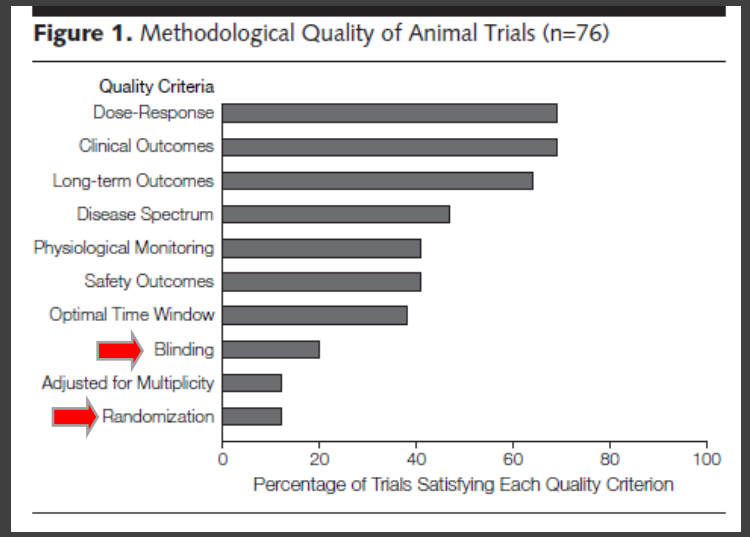
AlzPED is designed to monitor the scientific rigor of curated studies with a "Rigor Report Card" consisting of a standardized set of 24 experimental design elements recommended by expert advisory groups.

Critical Elements of Experimental Design are Under-Reported



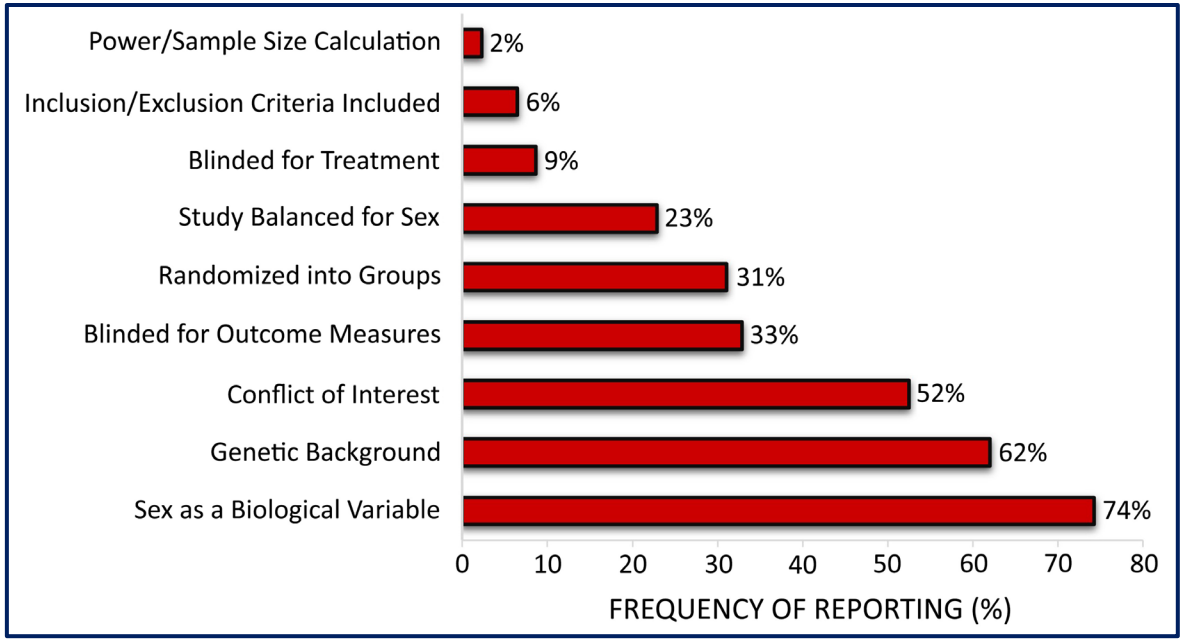
Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements. The red bars represent the 9 core design elements critical for scientific rigor and reproducibility. Data presented as percentage reported, calculated from 1172 published preclinical studies curated to AlzPED. Detailed Analytics Summary is available on the AlzPED Analytics page.

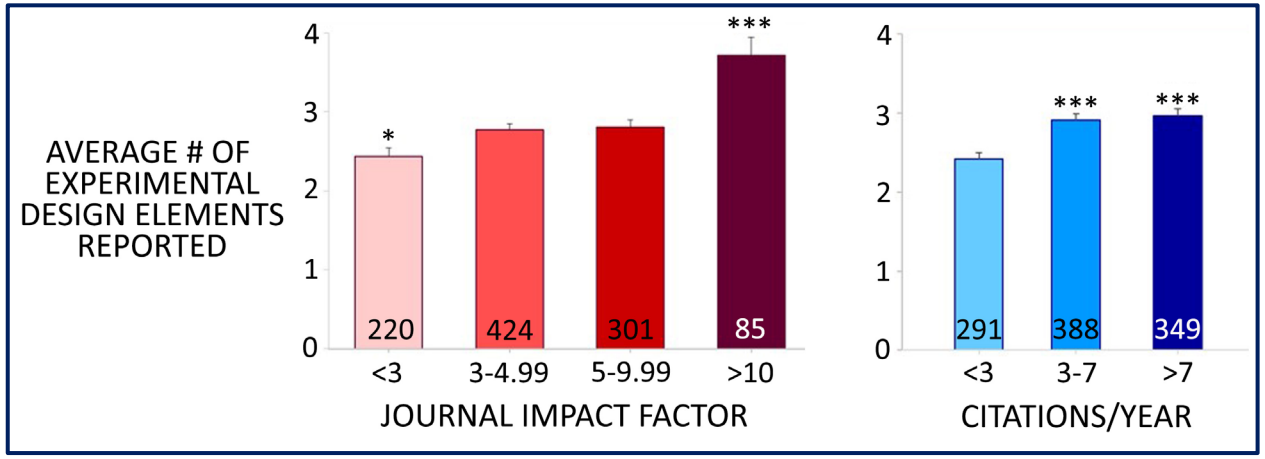
Critical Elements of Experimental Design are Under-Reported in High Impact Factor Journals and in Highly Cited Studies



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

- 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).





TOP: 9 core design elements are derived from Shineman et al., 2011, Landis et al., 2012, Snyder et al., 2016 and ARRIVE guidelines. BOTTOM: Reporting trends for the 9 core design elements based on journal impact factor and relative citations/year. Data are presented as Mean ± SEM and analyzed using two-tailed t-tests, *p<0.05, **p<0.01 and ***p<0.001.

View more AlzPED data analyses at the poster session (2.23.21, 1:30-2:30PM ET) – POSTER 15

Conclusions

- **Analysis of more than 1100 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 candidate drug testing to the clinic.**

- **Journals should require investigators to follow these best practices and study design guidelines to ensure that the studies they publish are sufficiently rigorous, transparent and reproducible.**

- **Funding agencies should require grantees to use accepted best practices and study design guidelines to ensure that the research they fund is rigorous, transparent and reproducible.**