AlzPED: Improving the Scientific Rigor, Reproducibility and Predictive Value of Preclinical Research in Alzheimer's Disease

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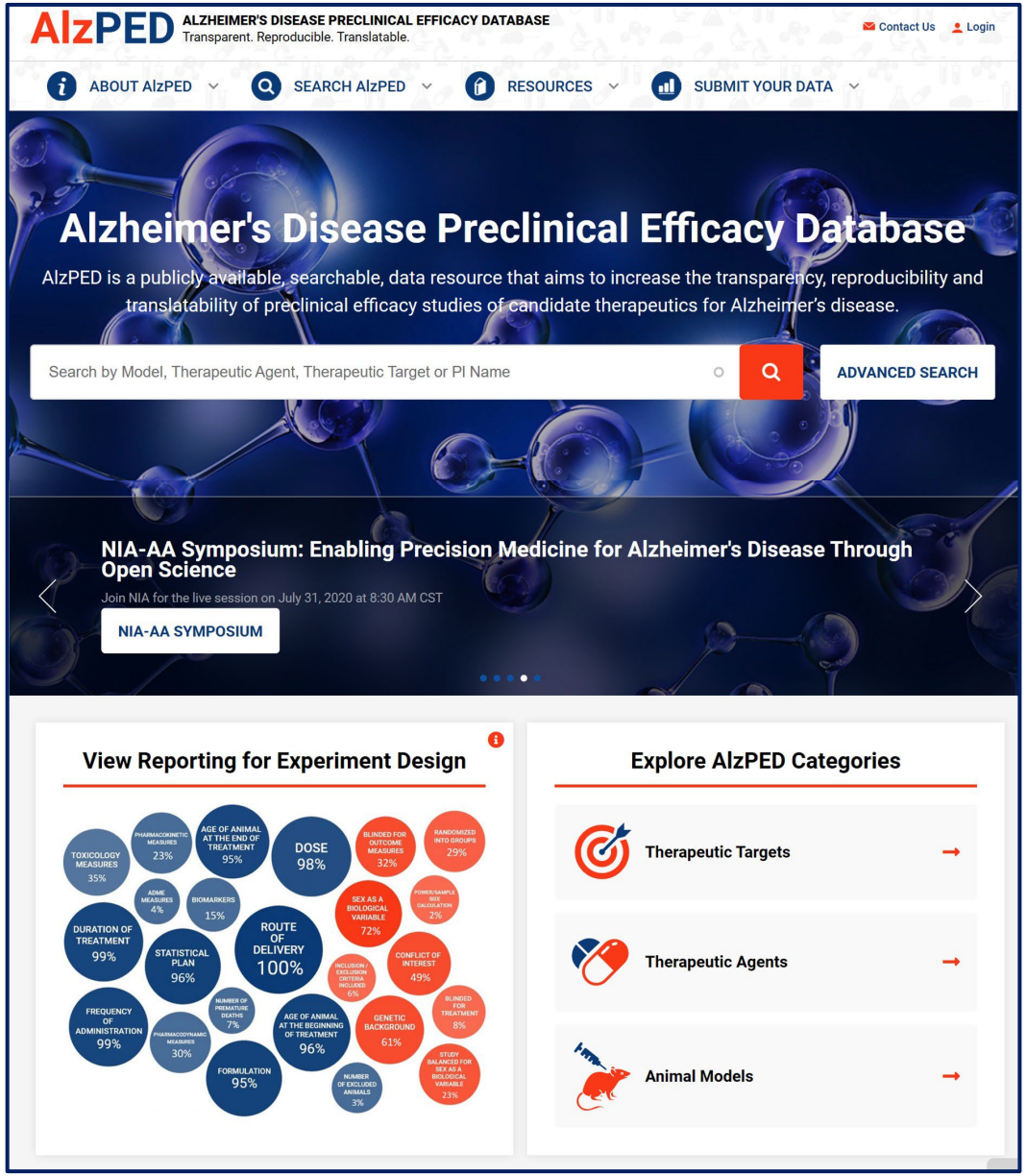
Background: Recommendations from 2015 NIH AD Summit

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 1171 preclinical therapeutic studies in AD animal models published between 1996 and 2020.
  - 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 for preclinical therapeutic efficacy studies.
  - 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- Provides a platform for creating citable reports of unpublished studies, including studies with negative findings.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 (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)

AlzPED Monitors Rigor in Study Design for Each Curated Study

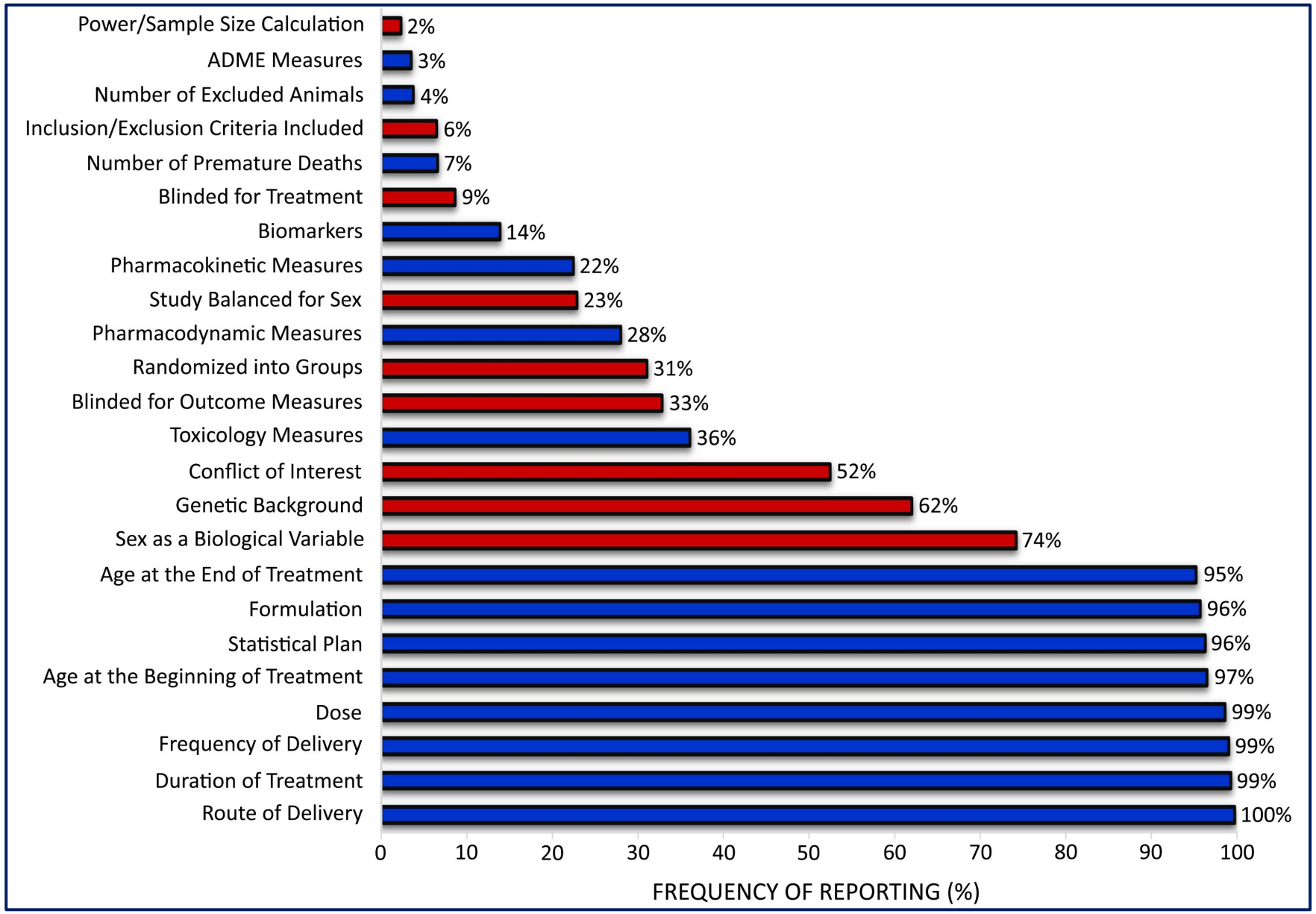
Experimental Design *Rigor Report Card*

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 for efficacy studies.

Critical Elements of Experimental Design are Under-Reported

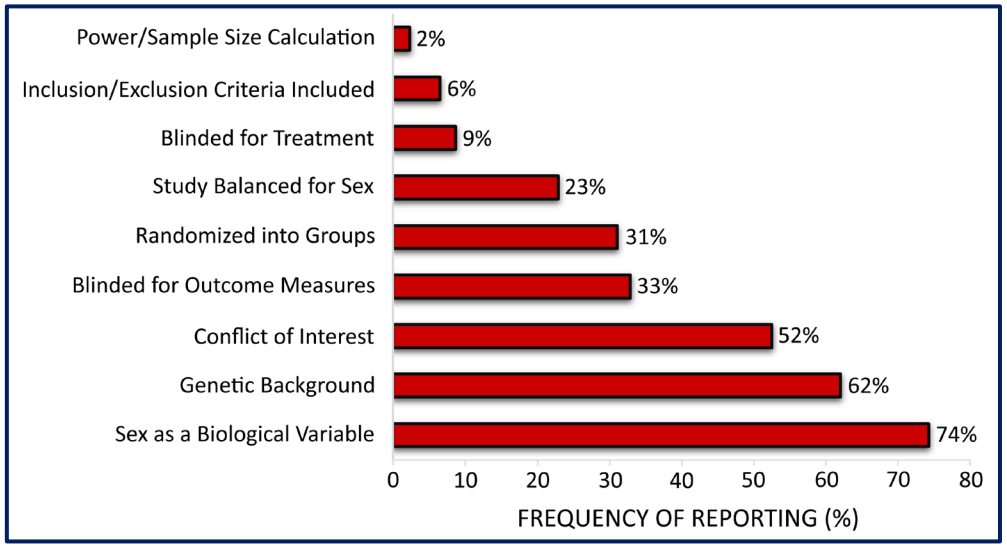


Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements, calculated from 1172 published preclinical studies curated to AlzPED. The red bars represent the 9 core design elements critical for scientific rigor and reproducibility.

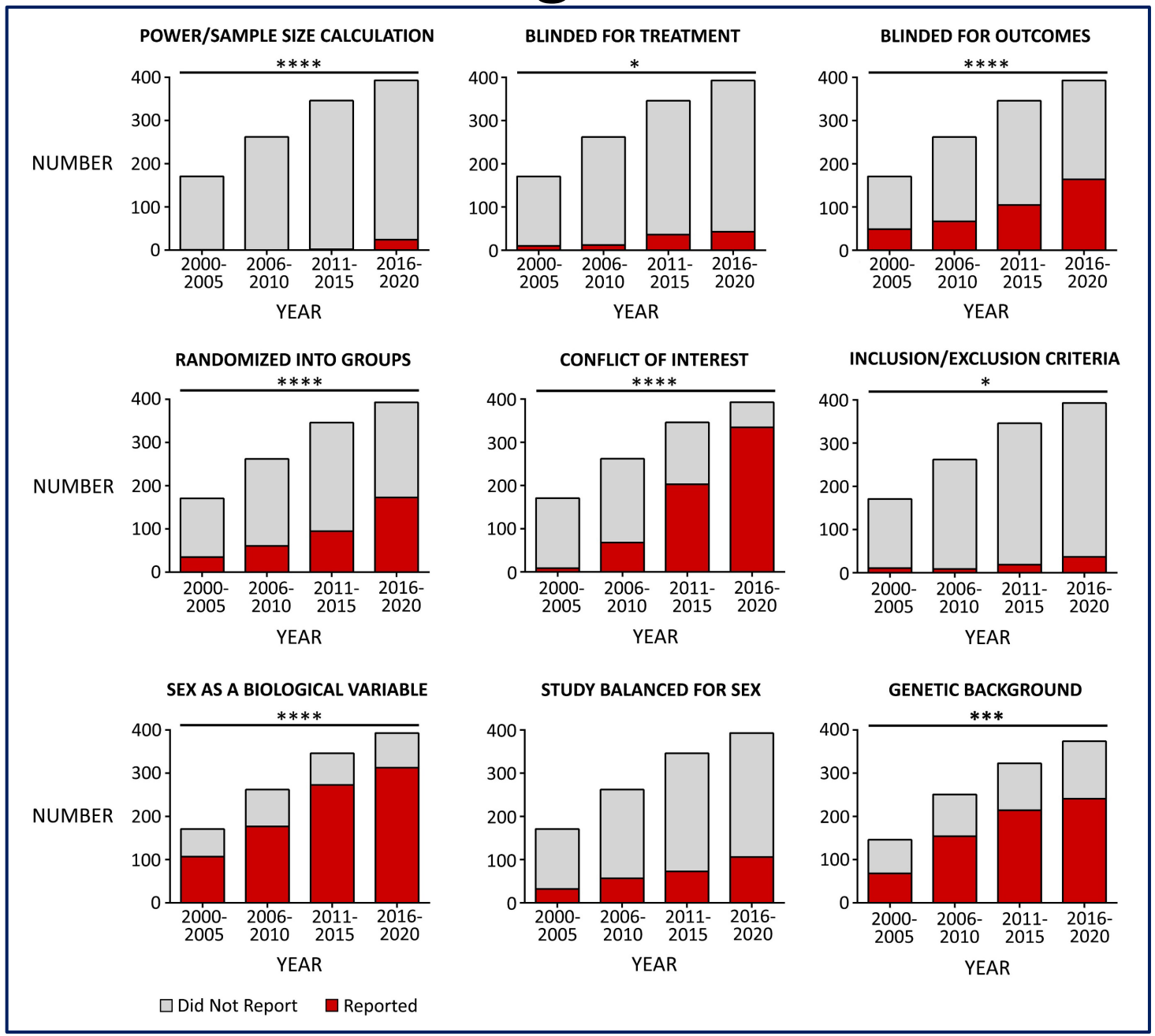
Detailed Analytics Summary is available on the AlzPED Analytics page.

Reporting Trends for 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 were analyzed using Chi square test; *p<0.05, ***p<0.001, ****p<0.0001.



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.

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