AlzPED: Improving the Predictive Power and Translational Validity of Preclinical Testing of Candidate Therapeutics in Alzheimer's Disease Animal Models

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BACKGROUND

A major challenge to the successful development of therapies for Alzheimer's disease (AD) is the poor translation of preclinical efficacy from animal models to the clinic. Key contributing factors to the unsuccessful translation of therapeutic efficacy include:

- the failure of animal models to fully recapitulate human AD,
- poor rigor in study design, methodology and data analysis,
- failure to match outcome measures used in preclinical animal studies and clinical studies,
- poor reproducibility of published data, and
- publication bias in favor of reporting positive findings and under reporting negative findings.

To address key factors contributing to poor translation of preclinical efficacy from animal models to the clinic in AD therapy development, several advisory meetings and workshops including the National Institutes of Health (NIH) AD Summits in 2012 and 2015 were held. In response to expert recommendations from these meetings, the National Institute on Aging (NIA) and the NIH Library have created an open science knowledge portal – the **Alzheimer's Disease Preclinical Efficacy Database** or **AlzPED**. Through the following capabilities, AlzPED is intended to guide the development and implementation of strategies and recommendations for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics:

1. Publicly available database of preclinical efficacy studies that houses experimental designs and analyses of **positive and negative data** to overcome publication bias.

2. Knowledge platform for data sharing, mining and analysis of experimental details, designs, data and methods relating to the preclinical testing of candidate therapeutic agents in AD animal models.

3. Database identifying critical experimental design elements and methodology missing from studies, making them susceptible to misinterpretation and reducing their reproducibility and translational value.

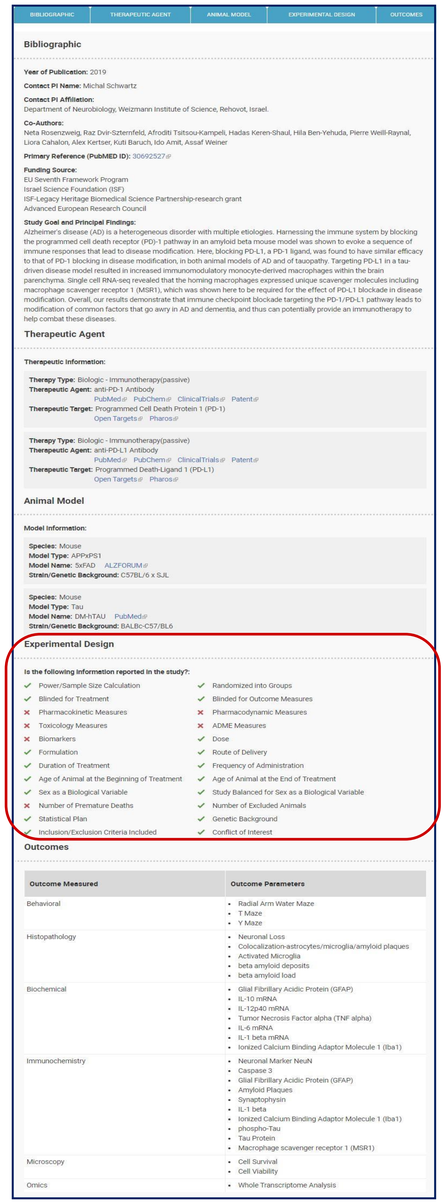
CAPABILITIES AND SCOPE

AlzPED has the following capabilities:

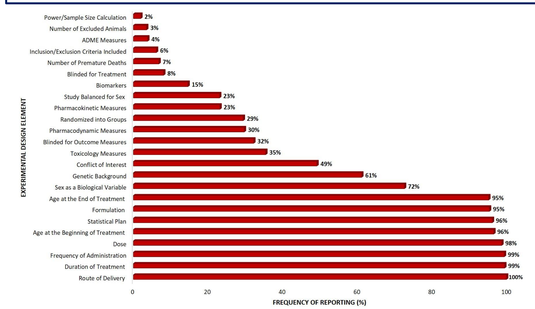
- Provides researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the **elements of rigorous study design** and **requirements for transparent reporting**.
- Currently hosts curated summaries from **1030** preclinical efficacy studies published between 1996 and 2019.
- Influences the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics.
- Provides search capability across relevant translational criteria data sets and external databases:
  - Therapy Type (14 therapy types)
  - Therapeutic Agent (890 agents)
  - Therapeutic Target (173 targets)
  - Animal Model (188 models)
  - Principal Investigator
  - Funding Source
  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and DrugBank)
  - Therapeutic Targets (Open Targets and Pharos)
  - Animal Model (Alzforum)
  - Related Clinical Trials (ClinicalTrials.gov)
  - Related Patents (Google Patents and USTPO)
- Provides funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.
- Provides a platform for creating **citable reports/preprints** of **unpublished studies**, including studies with **negative data**.
- **Reports on the rigor of each study by summarizing the elements of experimental design.**

ANALYTICS

A CURATED RECORD IN AlzPED: EXAMPLE OF RIGOROUS STUDY DESIGN

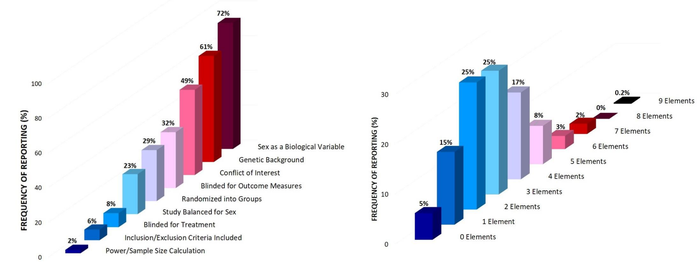


KEY ELEMENTS OF RIGOROUS EXPERIMENTAL DESIGN



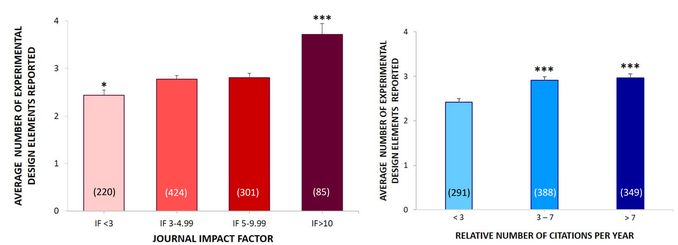
Frequency of reporting the 24 recommended elements of experimental design that improve the reproducibility and translational value of preclinical efficacy research is variable, with elements like dose and formulation of the therapeutic agent being examined and treatment paradigms being reported with consistency, while critical elements like power calculation, blinding, and randomization are less frequently reported. Data are presented as percentages calculated from 1030 published preclinical efficacy studies curated in AlzPED. The studies were published between 1996 and 2019.

9 CORE ELEMENTS OF RIGOROUS EXPERIMENTAL DESIGN ARE POORLY REPORTED



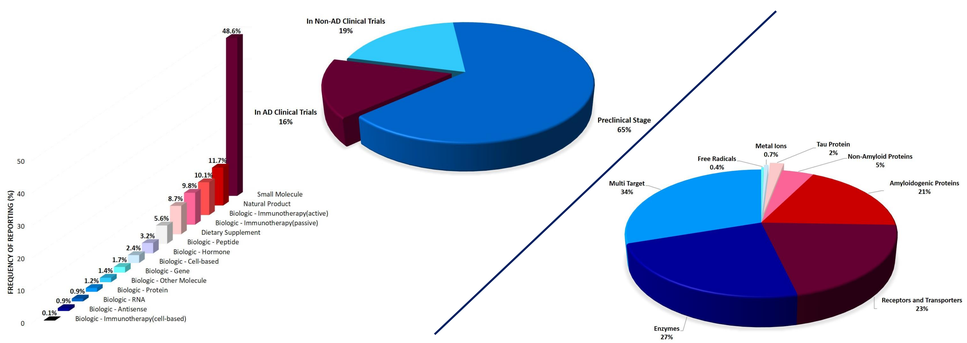
RIGHT: Frequency of reporting the 9 core elements of experimental design that are critical for ensuring scientific rigor of preclinical efficacy research. **LEFT:** Few studies report more than 5 core design elements, most reporting only 2-4 core design elements. Data are presented as percentages calculated from 1030 published preclinical efficacy studies curated in AlzPED. The studies were published between 1996 and 2019.

THE 9 CORE ELEMENTS ARE POORLY REPORTED IN HIGH IMPACT FACTOR JOURNALS AND HIGHLY CITED PUBLISHED PRECLINICAL EFFICACY RESEARCH IN ALZHEIMER'S DISEASE



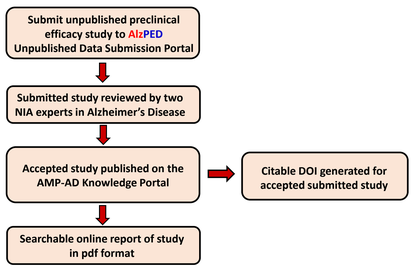
Reporting trends for the 9 core design elements based on 2019 journal impact factors (**LEFT**) and number of citations per year from studies published between 1996 and 2019 (**RIGHT**). Note that, while there are statistically significant differences in reporting these 9 core elements in publications from high impact journals and highly cited studies, overall the data show poor reporting practices irrespective of journal impact factor and number of citations per year. Data are presented as Mean ± SEM and analyzed using t tests, *p<0.05, ***p<0.001, samples sizes for each group are listed on the graphs.

THERAPEUTICS: AGENTS AND TARGETS



LEFT: 890 therapeutic agents are catalogued in 14 categories. Within the 890 therapeutic agents catalogued in AlzPED, 140 agents (or 16% of the total number of agents) are currently in AD clinical trials, and 172 agents (or 19%) are in clinical trials for non-AD indications, and 580 (65%) therapeutic agents are in the preclinical testing phase. **RIGHT:** 173 therapeutic targets are catalogued in 8 categories. Data are presented as percentages calculated from 1030 published preclinical efficacy studies published between 1996 and 2019 and curated in AlzPED.

UNPUBLISHED STUDY SUBMISSION PORTAL



Overview of the submission process for unpublished studies including negative data. Accepted studies are published in the AMP-AD Knowledge Portal. The Digital Object Identifier (DOI) provided is citable in grant applications and peer-reviewed publications.

SUMMARY

In summary:

- Analysis of curated studies in AlzPED, demonstrates **serious deficiencies in reporting critical elements of methodology** such as power calculation, blinding for treatment/outcomes, randomization, sex of animal used and balancing for sex, animal genetic background and others. This is demonstrated in high impact factor journals as well as highly cited published preclinical research.
- These deficiencies in study design and methodology diminish the scientific rigor, reproducibility and translational value of the preclinical studies.
- **It is evident that a standardized set of best practices is required for successful translation of therapeutic efficacy in AD research.**
- AlzPED serves as a platform for reporting unpublished negative findings to mitigate publication bias that favors reporting of positive findings.