

Improving the Rigor, Reproducibility and Translatability of Preclinical Research for Alzheimer's Disease:

The Alzheimer's Disease Preclinical Efficacy Database – **AlzPED**

The AlzPED Team
National Institute on Aging

What is preclinical research ?

In therapy development **preclinical research** is the stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data is collected.

Preclinical Research

- Target identification/validation
- Lead identification/optimization
 - PKPD/ADME
- Toxicity in Rodents, Canines, NHP
- *Drug Efficacy in a Disease Model*



Clinical Trials

Safety and
Efficacy in Humans

What are the Needs to be Addressed ?

The Failure Of AD Therapies in the Clinic

- The extremely high rate of attrition of drugs in Phase II (92%) and Phase III (98%) with more than half failing due to issues of efficacy.
- During the decade 2002-2012 -244 compounds were tested in 413 clinical trials (Ph I-Ph III) and one (memantine) was advanced to the FDA and approved for marketing, giving an approval rate of 0.4% (>99% attrition).

Status of AD Drugs in the Clinic

Table 1

Current status of selected anti-Alzheimer's drugs in clinical trials.

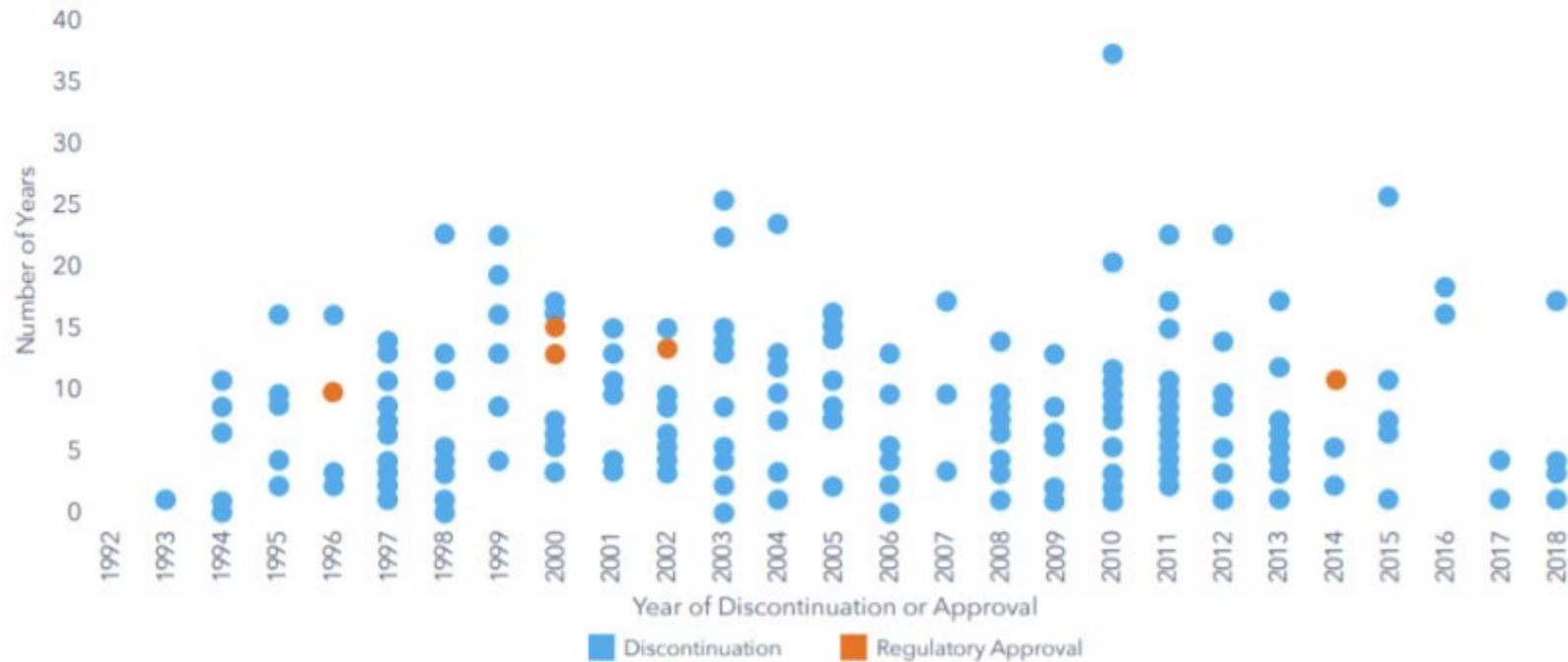
Drug	Mechanism of action	Clinical stage	Status
AN-1792	Anti-A β vaccine	Phase II	Discontinued
CAD106	Anti-A β vaccine	Phase II	Terminated
ACC-001	Anti-A β vaccine	Phase II	Terminated
Bapineuzumab	Humanized monoclonal anti-A β antibody	Phase III	Discontinued
Solanezumab	Humanized monoclonal anti-A β antibody	Phase III and II/III	Ongoing
Gantenerumab	Humanized monoclonal anti-A β antibody	Phase II/III	Ongoing
Crenezumab	Humanized monoclonal anti-A β antibody	Phase II	Ongoing
IVIG	Human polyclonal anti-A β antibody	Phase III	Ongoing
GSK933776	Humanized monoclonal anti-A β antibody	Phase I	Terminated
BAN-21	Humanized monoclonal anti-A β antibody	Phase I/II	Ongoing
AADvac1	Anti-tau vaccine	Phase I	Ongoing
ACI-35	Anti-tau vaccine	Phase I	Ongoing
Semagacestat	γ -Secretase inhibitor	Phase III	Discontinued
Avagacestat	γ -Secretase modulator	Phase II	Discontinued
Begacestat	γ -Secretase modulator	Phase I	Terminated
NIC5-15	γ -Secretase modulator	Phase II	Ongoing
CHF-5074	γ -Secretase modulator	Phase II	Terminated
MK-8931	β -Secretase inhibitor	Phase II/III	Ongoing
LY2886721	β -Secretase inhibitor	Phase II	Discontinued
AZD 3293	β -Secretase inhibitor	Phase II/III	Ongoing
LY3314814	β -Secretase inhibitor	Phase II/III	Ongoing
E2609	β -Secretase inhibitor	Phase II/III	Ongoing
Tideglusib	GSK-3 β inhibitor	Phase II	Terminated
Intranasal Humulin R	GSK-3 β inhibitor	Phase II	Ongoing
Intranasal glulizine	GSK-3 β inhibitor	Phase II	Terminated
Idalopirdine with donepezil	5-HT $_6$ receptor antagonist	Phase III	Ongoing
SB742457 with donepezil	5-HT $_6$ receptor antagonist	Phase II	Terminated
ABT-288	H $_3$ receptor antagonist	Phase II	Terminated
GSK239512	H $_3$ receptor antagonist	Phase II	Terminated
Azeliragon	RAGE inhibitor	Phase III	Ongoing
Encenicline	α 7-nAChR inhibitor	Phase III	Ongoing
Nivaldipine	Calcium antagonist	Phase III	Ongoing

Failure due to lack of efficacy or toxicity

AD Clinical Trial Failures by Year

Total of 85
just since
2008

Exhibit 23: Number of Years Since Product's First Patent Filing to Discontinuation or Regulatory Approval of Alzheimer's Therapies



Source: IQVIA Pipeline Intelligence, Feb 2019; ARK Patent Intelligence, Feb 2019



New Alzheimer's treatment fully restores memory function

TIME

There is no lack of successful drug treatment trials in AD mouse models

This Alzheimer's Breakthrough Could Be a Game Changer



Mouse study hints at possible Alzheimer's cure

The Telegraph

Has Stanford University found a cure for Alzheimer's disease



Problem: Preclinical Drug Efficacy has Not Translated to the Clinic

- **More than 300 therapeutic agents have been reported to be efficacious in ameliorating pathology and/or cognitive deficits in transgenic AD animal models.**
- **This success has not translated to success in the clinic. In fact, none of these agents have been advanced to the FDA for approval to market as an effective disease modifying therapy for AD.**
- **Evidence of the Poor Translational Validity of Drug Trials in AD Animal Models**

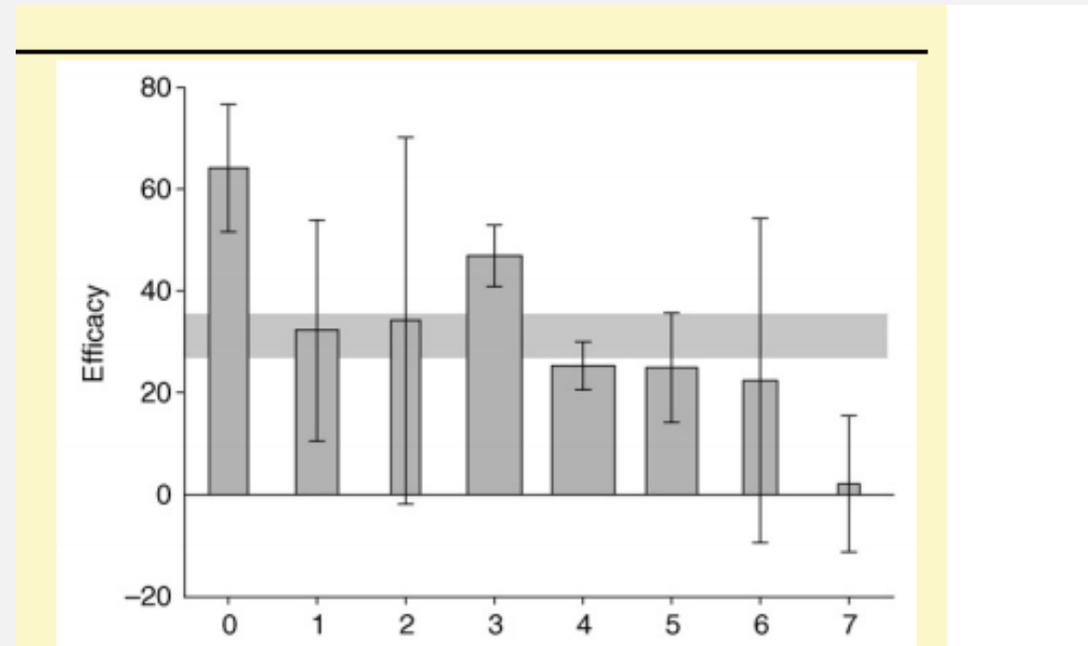
Key Factors Contributing to the Poor Translation of Efficacy Studies in AD Animal Models

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

Common Critical Elements of Clinical Trial Study Design

1. Power Analysis and Sample Size Calculation
2. Randomization
3. Blinding (treatment allocation and outcome measures)
4. Balancing for Sex/Gender
5. Age Matching
6. Eligibility Criteria (inclusion and exclusion criteria)
7. Use of Biomarkers as Key Outcome Measures

Relationship Between Use of Critical Design Elements and Estimates of Preclinical Efficacy



It's a inverse relationship

Review of the Neuroscience Literature Reveals that the Majority of Animal Studies Lack Rigor in Study Design

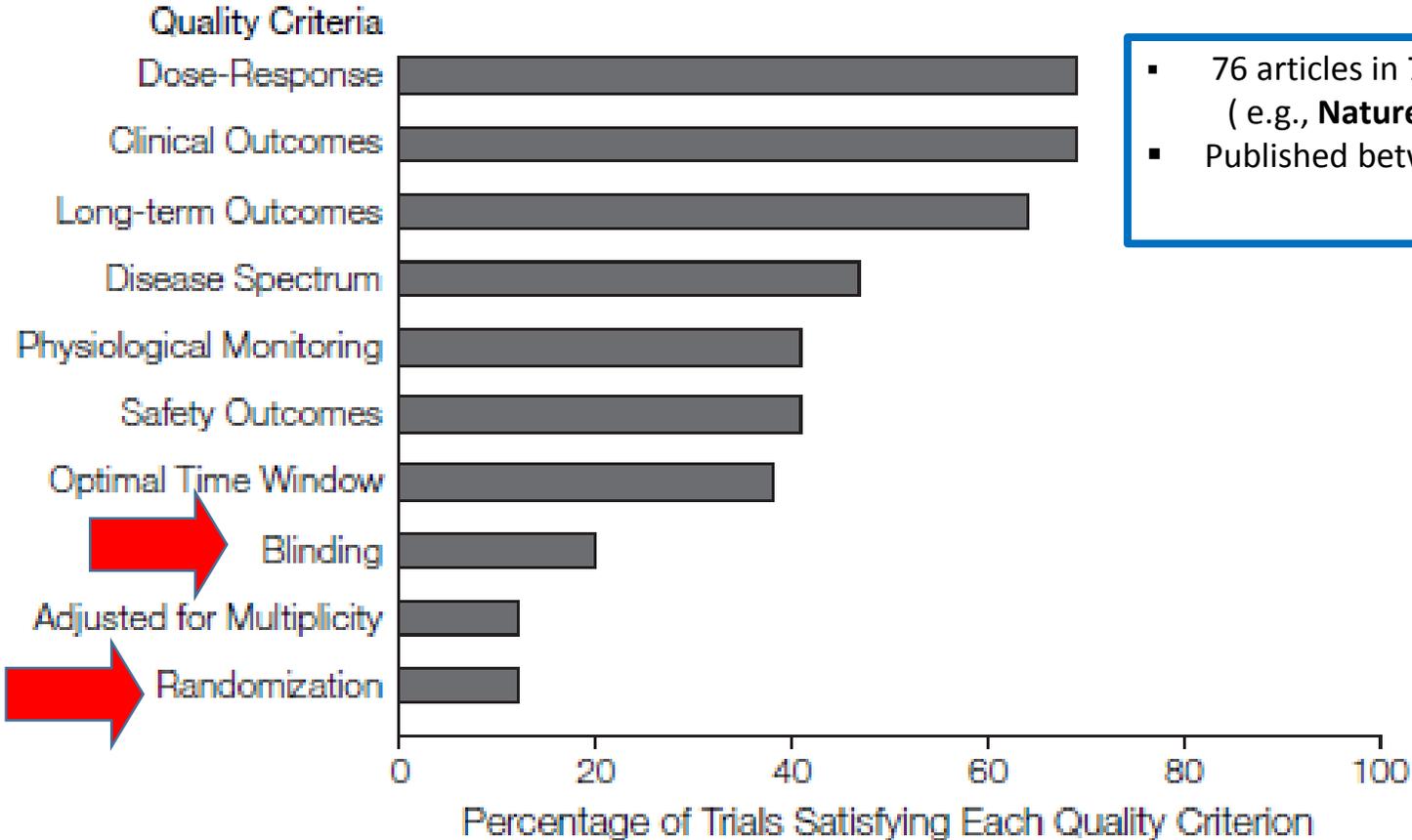
Table 1. Number and percentages of studies across the modeling of different neurologic diseases reporting measures to reduce the risk of bias

	<i>Number of publications</i>	<i>Masked assessment of outcome (%)</i>	<i>Random allocation to group (%)</i>	<i>Allocation concealment (%)</i>	<i>Sample size calculation (%)</i>
Alzheimer's disease ³⁰	428	95 (22)	67 (16)	NA	0 (0)
Multiple sclerosis ¹¹	1,117	178 (16)	106 (9)	NA	2 (<1)
Parkinson's disease ³¹	252	38 (15)	40 (16)	NA	1 (<1)
Intracerebral hemorrhage ³²	88	43 (49)	27 (31)	7 (8)	0 (0)
<i>Focal ischemia</i>					
NXY 059 ¹³	9	4 (44)	3 (33)	5 (56)	2 (22)
Hypothermia ¹²	101	38 (38)	36 (36)	4 (4)	0 (0)
Erythropoietin ³³	19	8 (42)	7 (37)	4 (21)	0 (0)
Tirilazad ³⁴	18	13 (72)	12 (67)	1 (6)	0 (0)
tPA ¹⁴	113	24 (21)	42 (37)	23 (20)	8 (7)

NA, not applicable; tPA, tissue plasminogen activator.

Preclinical Studies Published in Leading Scientific Journals Lack Scientific Rigor in Study Design

Figure 1. Methodological Quality of Animal Trials (n=76)



- 76 articles in 7 leading scientific journals (e.g., **Nature, Science, Cell, Neuron** etc)
- Published between 1980-2000

EDITORIAL

Should clinicians care about preclinical
animal research?

Poorly conducted preclinical efficacy studies can lead to failure in the clinic

Neurobiology of Disease 10, 268–278 (2002)
doi:10.1006/nbdi.2002.0487

Minocycline Slows Disease Progression in a Mouse Model of Amyotrophic Lateral Sclerosis

Jasna Kriz, Minh Dang Nguyen, and Jean-Pierre Julien

Centre for Research in Neurosciences, McGill University, Research Institute of the McGill University Health Centre, Montréal, Québec, H3G 1A4, Canada

NEUROPHARMACOLOGY AND NEUROTOXICOLOGY

NEUROREPORT

Minocycline delays disease onset and mortality in a transgenic model of ALS

Ludo Van Den Bosch,^{CA} Petra Tilkin, Griet Lemmens and Wim Robberecht

letters to nature

Minocycline inhibits cytochrome *c* release and delays progression of amyotrophic lateral sclerosis in mice

Shan Zhu^{*}, Irina G. Stavrovskaya[†], Martin Drozda^{*}, Betty Y. S. Kim^{*}, Victor Ona^{*}, Mingwei Li^{*}, Satinder Sarang[‡], Allen S. Liu^{*}, Dean M. Hartley[§], Du Chu Wu^{||}, Steven Gullans[‡], Robert J. Ferrante[¶]#, Serge Przedborski^{||}☆, Bruce S. Kristal^{††*} & Robert M. Friedlander^{*}

Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial

Paul H Gordon, Dan H Moore, Robert G Miller, Julaine M Florence, Joseph L Verheijde, Carolyn Doorish, Joan F Hilton, G Mark Spitalny, Robert B MacArthur, Hiroshi Mitsumoto, Hans E Neville, Kevin Boylan, Tahseen Mozaffar, Jerry M Belsh, John Ravits, Richard S Bedack, Michael C Graves, Leo F McCluskey, Richard J Barohn, Rup Tandan, for the Western ALS Study Group*

Summary

Background Minocycline has anti-apoptotic and anti-inflammatory effects in vitro, and extends survival in mouse models of some neurological conditions. Several trials are planned or are in progress to assess whether minocycline slows human neurodegeneration. We aimed to test the efficacy of minocycline as a treatment for amyotrophic lateral sclerosis (ALS).

Methods We did a multicentre, randomised placebo-controlled phase III trial. After a 4-month lead-in phase, 412 patients were randomly assigned to receive placebo or minocycline in escalating doses of up to 400 mg/day for 9 months. The primary outcome measure was the difference in rate of change in the revised ALS functional rating scale (ALSF_{RS}-R). Secondary outcome measures were forced vital capacity (FVC), manual muscle testing (MMT), quality of life, survival, and safety. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00047723.

Findings ALSF_{RS}-R score deterioration was faster in the minocycline group than in the placebo group (-1.30 vs -1.04 units/month, 95% CI for difference -0.44 to -0.08; $p=0.005$). Patients on minocycline also had non-significant tendencies towards faster decline in FVC (-3.48 vs -3.01, -1.03 to 0.11; $p=0.11$) and MMT score (-0.30 vs -0.26, -0.08 to 0.01; $p=0.11$), and greater mortality during the 9-month treatment phase (hazard ratio=1.32, 95% CI 0.83 to 2.10; $p=0.23$) than did patients on placebo. Quality-of-life scores did not differ between the treatment groups. Non-serious gastrointestinal and neurological adverse events were more common in the minocycline group than in the placebo group, but these events were not significantly related to the decline in ALSF_{RS}-R score.

Interpretation Our finding that minocycline has a harmful effect on patients with ALS has implications for trials of minocycline in patients with other neurological disorders, and for how potential neuroprotective agents are screened for use in patients with ALS.

What Program Development Work has Already Been Completed ?

Advisory Meetings and Workshops examining the causes of the poor predictive power/translatibility of animal models preclinical efficacy studies:

- **National Institute on Aging**
 - Advisory Meeting: “Advancing AD Therapy Development”2010
 - NIH AD Summits 2012 & 2015
- **Alzheimer’s Drug Discovery Foundation**
 - Advisory Panel 2010
- **National Institute of Neurological Disorders and Stroke**
 - Workshop 2012
- **Institute of Medicine**
 - Workshop 2012

Recommendations Aimed at Increasing Predictive Power of Drug Efficacy in AD Animal Models:

1

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

2

The database should be a knowledge platform for data sharing, mining and analysis relating to the preclinical testing of candidate therapeutic agents in AD animal models.

3

The database should help identify critical experimental design elements and methodology missing from studies, reducing their rigor, reproducibility and translational value.

Recommendations: Best Practices and Study Design Guidelines for Preclinical Animal Studies

- Power Analysis/Sample Size**
- Statistical Analysis Plan**
- Inclusion, Exclusion Criteria**
- Randomization**
- Blinding (treatment allocation and outcome measures)**
- Balance for Sex as a Biological Variable**
- Report Age of Animals**
- Report Genetic Background**
- Dose, Frequency of Administration, Route of Delivery**
- Employ Translatable Biomarkers**
- Use PK/PD, ADME to Characterize Candidate Therapeutic Agents**
- Report Toxicology Measures**
- Report Potential Conflicts of Interest**

Responding to the Recommendations: Alzheimer's Disease Preclinical Efficacy Database

Launched Jan 2016

AlzPED Transparent. Reproducible. Translatable.
ALZHEIMER'S DISEASE
PRECLINICAL EFFICACY DATABASE

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AlzPED is a publically available, searchable, data resource that aims to increase the transparency, reproducibility and translatability of preclinical efficacy studies of candidate therapeutics for Alzheimer's disease.

Search by Model, Therapeutic Agent, Therapeutic Target or PI Name **SEARCH**

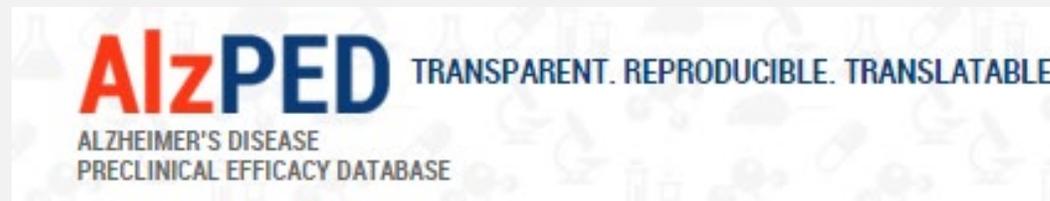
MORE SEARCH OPTIONS

GETTING STARTED

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- How AlzPED Citations are Selected

AlzPED MEMBER ORGANIZATIONS

- National Institute on Aging [↗](#)
- National Institutes of Health Library [↗](#)
- Alzheimer's Drug Discovery Foundation [↗](#)
- Alzheimer's Association [↗](#)



Overview of Scope:

- **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**
- **Provide search capability across relevant translational criteria data sets:**
 - **Therapy Type**
 - **Therapeutic Agent**
 - **Therapeutic Target**
 - **Animal Model**
 - **PI Name**
 - **Funding source**
- **Influence the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics.**
- **Provide funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design**



Data Sources:

- Published data is extracted from the scientific literature and curated.
- In collaboration with Sage Bionetworks Unpublished (positive and negative data) data is obtained directly from researchers.

AlzPED Data Submission Portal

SUBMIT YOUR DATA (Select "published" or "unpublished" below prior to entering your study information.)

Published Unpublished

1 BIBLIOGRAPHIC 2 THERAPEUTIC 3 ANIMAL MODEL 4 EXPERIMENTAL DESIGN 5 OUTCOMES

Year of Publication
The year when the Study was published (if applicable).

2019

Title of Study *
Title of Study
Show special characters.

Contact PI Last Name * ? Contact PI First Name * Contact PI Middle Initial

Contact PI Last Name Contact PI First Name Contact PI Middle Initial

Contact PI Affiliation ?
Contact PI Affiliation

Co-Authors
Co-Authors

Primary Reference (PubMed ID)

SUBMIT YOUR DATA (Select "published" or "unpublished" below prior to entering your study information.)

Published Unpublished

1 BIBLIOGRAPHIC 2 THERAPEUTIC 3 ANIMAL MODEL 4 EXPERIMENTAL DESIGN 5 OUTCOMES

Title of Study *
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Contact PI Last Name * ? Contact PI First Name * Contact PI Middle Initial

Contact PI Affiliation ?

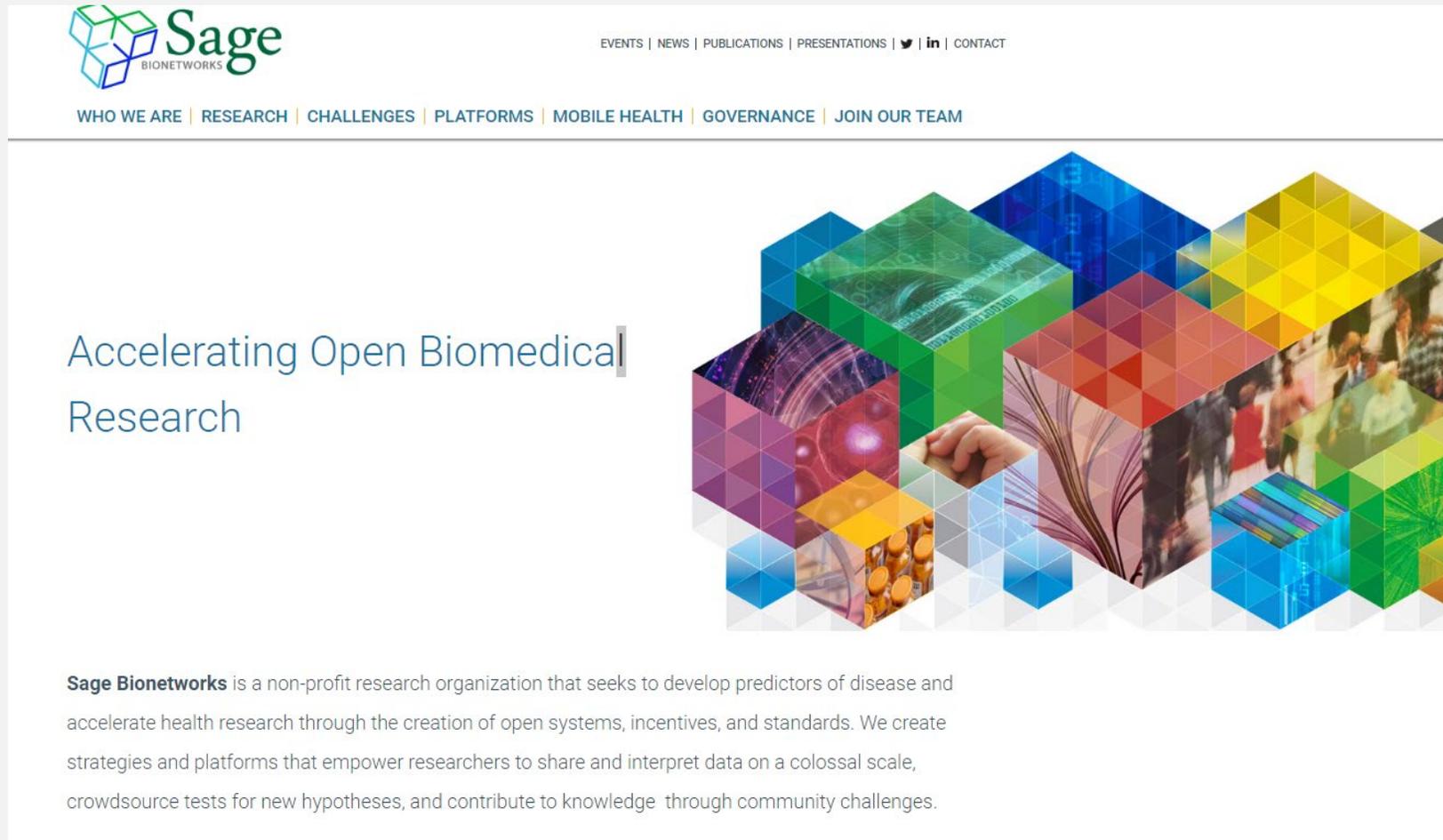
Co-Authors

Primary Reference (DOI) ?

Funding Source
Enter or Select Option(s)

Conflict of Interest ?

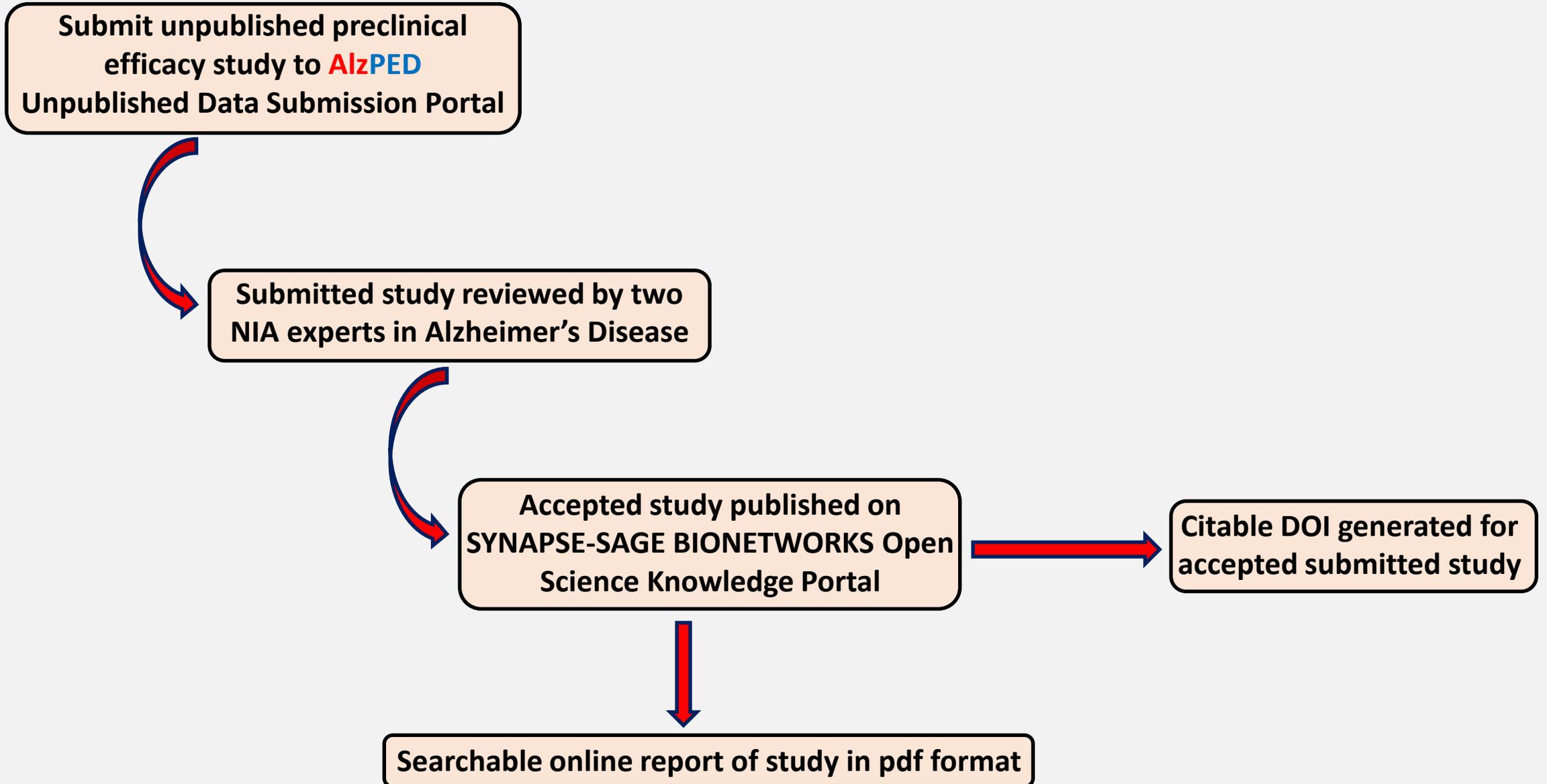
Open Science Partners: **AlzPED** and Sage Bionetworks



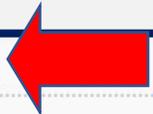
The image shows a screenshot of the Sage Bionetworks website. At the top left is the Sage Bionetworks logo, which consists of a stylized green and blue cube icon followed by the text "Sage BIONETWORKS". To the right of the logo is a navigation menu with the following items: "EVENTS | NEWS | PUBLICATIONS | PRESENTATIONS |  |  | CONTACT". Below this is a secondary navigation menu: "WHO WE ARE | RESEARCH | CHALLENGES | PLATFORMS | MOBILE HEALTH | GOVERNANCE | JOIN OUR TEAM". The main content area features the headline "Accelerating Open Biomedical Research" in a blue serif font. To the right of the text is a large, colorful graphic composed of many overlapping, semi-transparent geometric shapes (cubes and triangles) in various colors (blue, green, yellow, red, purple). These shapes contain various images related to biomedicine, such as a hand holding a test tube, a brain scan, and a group of people. Below the graphic is a paragraph of text: "Sage Bionetworks is a non-profit research organization that seeks to develop predictors of disease and accelerate health research through the creation of open systems, incentives, and standards. We create strategies and platforms that empower researchers to share and interpret data on a colossal scale, crowdsource tests for new hypotheses, and contribute to knowledge through community challenges."

The **AlzPED** and Sage Bionetworks partnership aims at enabling the curating unpublished preclinical efficacy studies and creating searchable online reports that are available in a pdf format. Submitting PIs will receive a citable DOI.

AlzPED Unpublished Data Submission Process



AlzPED Search Functions

Bibliographic Info 

Study type

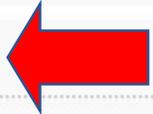
Funding Source

Full Text Search

PI Name 

Title

Primary Reference ID

Therapeutic Agent 

Therapeutic Agent 

Therapy Type 

Therapeutic Target 

Animal Model 

Model Name 

Model Type 

SEARCH

AlzPED Search Functions

Bibliographic Info

Study type
All

Funding Source
Select Option(s)

Full Text Search
Full Text Search

PI Name ?
PI Name

Title
Title

Primary Reference ID
Primary Reference ID

Therapeutic Agent

Therapeutic Agent ?
Select Option(s)

Therapy Type ?
Select Option(s)

Therapeutic Target ?
Gamma secretase x

Animal Model

Model Name ?
Select Option(s)

Model Type ?
Select Option(s)

SEARCH

Study type

All

Full Text Search

Full Text Search

Title

Title

PI Full Name

PI Name

Primary Reference

Primary Reference ID

SEARCH

RESET

Filter by therapeutic agent:

CHF5074 (9)

Ibuprofen (7)

DAPT (6)

R-flurbiprofen (6)

LY-411575 (5)

...

Filter by therapeutic target:

Gamma secretase

Multi Target (222)

beta amyloid peptide (125)

BACE1 (26)

Acetylcholinesterase (20)

Search Results

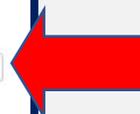
Displaying 1 - 15 of 44

- Choose an operation -

EXECUTE

Selected: 0 items.

APID	Title	Year	PI Name	Therapeutic Agent(s)	<input type="checkbox"/>
9311115	Peptides of presenilin-1 bind the amyloid precursor protein ectodomain and offer a novel and specific therapeutic approach to reduce β -amyloid in Alzheimer's disease	2015	Dewji N Nazneen	• PS-1 NH2- terminal peptides	<input type="checkbox"/>
10761110	Oral treatment with a gamma-secretase inhibitor improves long-term potentiation in a mouse model of Alzheimer's disease	2010	Townsend Matthew	• MRK-560	<input type="checkbox"/>
10811107	The novel gamma secretase inhibitor N-[cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl]-1,1,1-trifluoromethanesulfonamide (MRK-560) reduces amyloid plaque deposition without evidence of notch-related pathology in the Tg2576 mouse	2007	Best D Jonathan	• MRK-560	<input type="checkbox"/>
11261209	Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease.	2009	Jacobsen Steven J	• GSI-953 (Begacestat)	<input type="checkbox"/>
11560310	Chronic treatment with a novel gamma-secretase modulator, JNJ-40418677, inhibits amyloid plaque formation in a mouse model of Alzheimer's disease	2010	Mercken Marc	• JNJ-40418677	<input type="checkbox"/>



Sample of a Curated Record on AlzPED

Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease.

VIEW EDIT

BIBLIOGRAPHIC THERAPEUTIC AGENT ANIMAL MODEL EXPERIMENTAL DESIGN OUTCOMES

Bibliographic

Year of Publication: 2009

Contact PI Name: J Steven Jacobsen

Contact PI Affiliation:

Wyeth Research, Departments of Discovery Neuroscience

Co-Authors:

Robert L. Martone, Hua Zhou, Kevin Atchison, Thomas Comery, Jane Z. Xu, Xinyi Huang, Xiaohai Gong, Mei Jin, Anthony Kref, Boyd Harrison, et al

Primary Reference (PubMed ID): 19671883

Funding Source:

Wyeth Research

Study Goal and Principal Findings:

Gamma secretase is widely regarded as a viable target to achieve therapeutically relevant reductions of A β in AD, and multiple classes of GSIs have been reported including peptidomimetics and sulfonamides. The goal of this study was to report on the pharmacological properties of the novel thiophene sulfonamide gamma secretase inhibitor (GSI), GSI-953, also known as begacestat. In summary, the preclinical data for GSI-953 demonstrate a potent Abeta lowering activity, with nano molar potency, and in vitro selectivity against Notch processing. Cellular assays of Notch cleavage reveal that this compound is approximately 16-fold selective for the inhibition of APP cleavage. In addition, the drug exhibited robust in vivo efficacy for the lowering of brain, CSF, and plasma Abeta levels and the reversal of Abeta-dependent cognitive deficits in Tg2576 mice. Finally the drug was found lower of plasma Abeta (a potential biomarker) levels in humans. These data provide evidence supporting GSI-953 treatment as a potential disease modification in the development of AD.

Therapeutic Agent

Therapeutic Information:

Therapy Type: Small Molecule

Therapeutic Agent: GSI-953 (Begacestat)

PubMed PubChem ClinicalTrials Patents

Therapeutic Target: Gamma secretase

Open Targets Pharos

Animal Model

Model Information:

Species: Mouse

Model Type: APP

Model Name: Tg2576 ALZFORUM

Strain/Genetic Background: Not Reported

Species: Rat

Model Type: Non-transgenic

Strain/Genetic Background: Sprague-Dawley

Species: Dog

Model Type: Non-transgenic

Strain/Genetic Background: Not Reported

Experimental Design

Is the following information reported in the study?:

- | | |
|---|---|
| <input checked="" type="checkbox"/> Power/Sample Size Calculation | <input checked="" type="checkbox"/> Randomized into Groups |
| <input checked="" type="checkbox"/> Blinded for Treatment | <input checked="" type="checkbox"/> Blinded for Outcome Measures |
| <input checked="" type="checkbox"/> Pharmacokinetic Measures | <input checked="" type="checkbox"/> Pharmacodynamic Measures |
| <input checked="" type="checkbox"/> Toxicology Measures | <input checked="" type="checkbox"/> ADME Measures |
| <input checked="" type="checkbox"/> Biomarkers | <input checked="" type="checkbox"/> Dose |
| <input checked="" type="checkbox"/> Formulation | <input checked="" type="checkbox"/> Route of Delivery |
| <input checked="" type="checkbox"/> Duration of Treatment | <input checked="" type="checkbox"/> Frequency of Administration |
| <input checked="" type="checkbox"/> Age of Animal at the Beginning of Treatment | <input checked="" type="checkbox"/> Age of Animal at the End of Treatment |
| <input checked="" type="checkbox"/> Sex as a Biological Variable | <input checked="" type="checkbox"/> Study Balanced for Sex as a Biological Variable |
| <input checked="" type="checkbox"/> Number of Premature Deaths | <input checked="" type="checkbox"/> Number of Excluded Animals |
| <input checked="" type="checkbox"/> Statistical Plan | <input checked="" type="checkbox"/> Genetic Background |
| <input checked="" type="checkbox"/> Inclusion/Exclusion Criteria Included | <input checked="" type="checkbox"/> Conflict of Interest |

Outcomes

Outcome Measured	Outcome Parameters
Behavioral	<ul style="list-style-type: none"> Contextual Fear Conditioning
Biochemical	<ul style="list-style-type: none"> Notch Selectivity Gamma Secretase Inhibition Brain-beta amyloid peptide 40 Brain-beta amyloid peptide 42 Plasma-beta amyloid peptide 40 Plasma-beta amyloid peptide 42 CSF-beta amyloid peptide 40 CSF-beta amyloid peptide 42
Biomarker	<ul style="list-style-type: none"> Plasma-beta amyloid peptide 40 Plasma-beta amyloid peptide 42 CSF-beta amyloid peptide 40 CSF-beta amyloid peptide 42
Pharmacokinetics	<ul style="list-style-type: none"> Cmax Area Under the Curve (AUC) Brain/Plasma Ratio PK/PD relationship
Pharmacodynamics	<ul style="list-style-type: none"> Target Engagement (reduction beta amyloid peptides-brain)
Toxicology	<ul style="list-style-type: none"> Tissue Histopathological Profile Body Weight Mortality Behavior (general)

AlzPED Curated Record on PubMed

NCBI Resources ▾ How To ▾

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed ▾

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Format: Abstract ▾ Send to ▾

J Pharmacol Exp Ther. 2009 Nov;331(2):598-608. doi: 10.1124/jpet.109.152975. Epub 2009 Aug 11.

Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease.

[Martone RL](#)¹, [Zhou H](#), [Atchison K](#), [Comery T](#), [Xu JZ](#), [Huang X](#), [Gong X](#), [Jin M](#), [Kreft A](#), [Harrison B](#), [Mayer SC](#), [Aschmies S](#), [Gonzales C](#), [Zaleska MM](#), [Riddell DR](#), [Wagner E](#), [Lu P](#), [Sun SC](#), [Sonnenberg-Reines J](#), [Oganesian A](#), [Adkins K](#), [Leach MW](#), [Clarke DW](#), [Huryn D](#), [Abou-Gharbia M](#), [Magolda R](#), [Bard J](#), [Frick G](#), [Raje S](#), [Forlow SB](#), [Balliet C](#), [Burczynski ME](#), [Reinhart PH](#), [Wan HJ](#), [Pangalos MN](#), [Jacobsen JS](#).

⊕ **Author information**

Abstract

The presenilin containing gamma-secretase complex is responsible for the regulated intramembraneous proteolysis of the amyloid precursor protein (APP), the Notch receptor, and a multitude of other substrates. gamma-Secretase catalyzes the final step in the generation of Abeta(40) and Abeta(42) peptides from APP. Amyloid beta-peptides (Abeta peptides) aggregate to form neurotoxic oligomers, senile plaques, and congophilic angiopathy, some of the cardinal pathologies associated with Alzheimer's disease. Although inhibition of this protease acting on APP may result in potentially therapeutic reductions of neurotoxic Abeta peptides, nonselective inhibition of the enzyme may cause severe adverse events as a result of impaired Notch receptor processing. Here, we report the preclinical pharmacological profile of GSI-953 (begacestat), a novel thiophene sulfonamide gamma-secretase inhibitor (GSI) that selectively inhibits cleavage of APP over Notch. This GSI inhibits Abeta production with low nanomolar potency in cellular and cell-free assays of gamma-secretase function, and displaces a tritiated analog of GSI-953 from enriched gamma-secretase enzyme complexes with similar potency. Cellular assays of Notch cleavage reveal that this compound is approximately 16-fold selective for the inhibition of APP cleavage. In the human APP-overexpressing Tg2576 transgenic mouse, treatment with this orally active compound results in a robust reduction in brain, plasma, and cerebral spinal fluid Abeta levels, and a reversal of contextual fear-conditioning deficits that are correlated with Abeta load. In healthy human volunteers, oral administration of a single dose of GSI-953 produces dose-dependent changes in plasma Abeta levels, confirming pharmacodynamic activity of GSI-953 in humans.

PMID: 19671883 DOI: [10.1124/jpet.109.152975](https://doi.org/10.1124/jpet.109.152975)

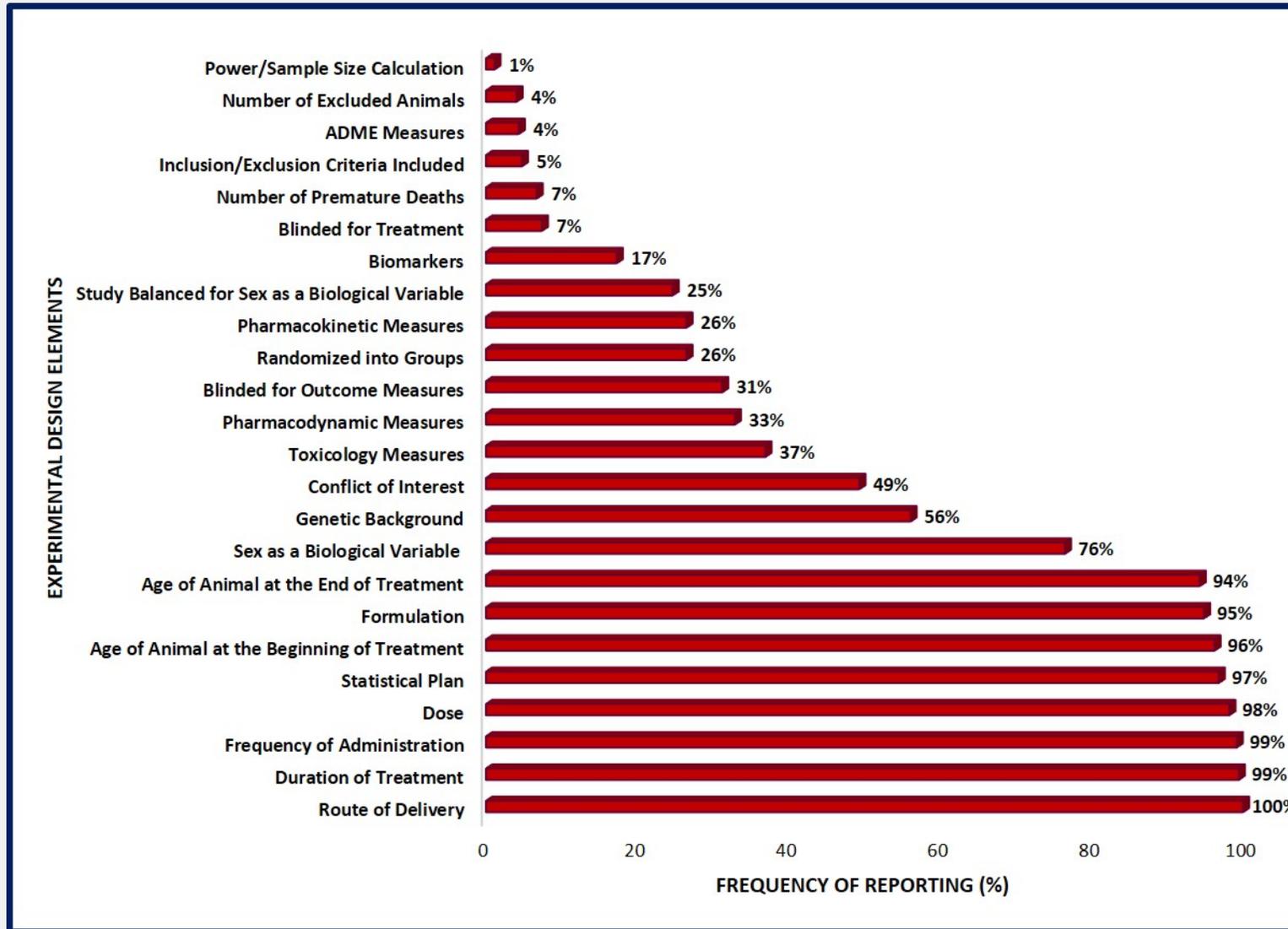
AlzPED Tracks Critical Elements of Design for Each Curated Study

1	2	3	4	5																								
BIBLIOGRAPHIC	THERAPEUTIC	ANIMAL MODEL	EXPERIMENTAL DESIGN	OUTCOMES																								
<h3>Bibliographic Information</h3> <p>Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease.</p> <p>APID: 11261209</p> <p>PI Name: Jacobsen, J, Steven</p> <p>Year of Publication: 2009</p>																												
<p>Is the following information reported in the study?</p> <table><tbody><tr><td><input type="checkbox"/> Power/Sample Size Calculation ?</td><td><input type="checkbox"/> Randomized into Groups ?</td></tr><tr><td><input type="checkbox"/> Blinded for Treatment ?</td><td><input type="checkbox"/> Blinded for Outcome Measures ?</td></tr><tr><td><input checked="" type="checkbox"/> Pharmacokinetic Measures ?</td><td><input checked="" type="checkbox"/> Pharmacodynamic Measures ?</td></tr><tr><td><input checked="" type="checkbox"/> Toxicology Measures ?</td><td><input type="checkbox"/> ADME Measures ?</td></tr><tr><td><input checked="" type="checkbox"/> Biomarkers ?</td><td><input checked="" type="checkbox"/> Dose ?</td></tr><tr><td><input checked="" type="checkbox"/> Formulation ?</td><td><input checked="" type="checkbox"/> Route of Delivery ?</td></tr><tr><td><input checked="" type="checkbox"/> Duration of Treatment ?</td><td><input checked="" type="checkbox"/> Frequency of Administration ?</td></tr><tr><td><input checked="" type="checkbox"/> Age of Animal at the Beginning of Treatment ?</td><td><input checked="" type="checkbox"/> Age of Animal at the End of Treatment ?</td></tr><tr><td><input type="checkbox"/> Sex as a Biological Variable</td><td><input type="checkbox"/> Study Balanced for Sex as a Biological Variable</td></tr><tr><td><input type="checkbox"/> Number of Premature Deaths ?</td><td><input type="checkbox"/> Number of Excluded Animals ?</td></tr><tr><td><input checked="" type="checkbox"/> Statistical Plan ?</td><td><input type="checkbox"/> Genetic Background ?</td></tr><tr><td><input type="checkbox"/> Inclusion/Exclusion Criteria Included ?</td><td><input type="checkbox"/> Conflict of Interest ?</td></tr></tbody></table>					<input type="checkbox"/> Power/Sample Size Calculation ?	<input type="checkbox"/> Randomized into Groups ?	<input type="checkbox"/> Blinded for Treatment ?	<input type="checkbox"/> Blinded for Outcome Measures ?	<input checked="" type="checkbox"/> Pharmacokinetic Measures ?	<input checked="" type="checkbox"/> Pharmacodynamic Measures ?	<input checked="" type="checkbox"/> Toxicology Measures ?	<input type="checkbox"/> ADME Measures ?	<input checked="" type="checkbox"/> Biomarkers ?	<input checked="" type="checkbox"/> Dose ?	<input checked="" type="checkbox"/> Formulation ?	<input checked="" type="checkbox"/> Route of Delivery ?	<input checked="" type="checkbox"/> Duration of Treatment ?	<input checked="" type="checkbox"/> Frequency of Administration ?	<input checked="" type="checkbox"/> Age of Animal at the Beginning of Treatment ?	<input checked="" type="checkbox"/> Age of Animal at the End of Treatment ?	<input type="checkbox"/> Sex as a Biological Variable	<input type="checkbox"/> Study Balanced for Sex as a Biological Variable	<input type="checkbox"/> Number of Premature Deaths ?	<input type="checkbox"/> Number of Excluded Animals ?	<input checked="" type="checkbox"/> Statistical Plan ?	<input type="checkbox"/> Genetic Background ?	<input type="checkbox"/> Inclusion/Exclusion Criteria Included ?	<input type="checkbox"/> Conflict of Interest ?
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Summary of Capabilities

- Hosts curated summaries from **720** published preclinical efficacy studies
- Searchable by:
 - Therapeutic Target (**146 Therapeutic Targets**)
 - Therapeutic Agent (**641 Therapeutic Agents**)
 - Animal Model (**149 Models**)
 - Principal Investigator
 - Funding Agency
- Includes links to databases for:
 - Related Publications (**PubMed**)
 - Therapeutic Targets (**Open Targets & Pharos**)
 - Therapeutic Agents (**PubChem**)
 - Related Clinical Trials (**ClinicalTrials.gov**)
 - Patents (**Google Patents**)
- Provides a platform for creating **citable reports/preprints** of unpublished studies, including studies with **negative data**. Full reports and data hosted on Synapse/AMP-AD Knowledge Portal
- Summarizes Elements of Experimental Design (**reports on RIGOR of each study**)

AlzPED Identifies 24 Experimental Design Elements that Improve Rigor and Translational Value of Preclinical Studies



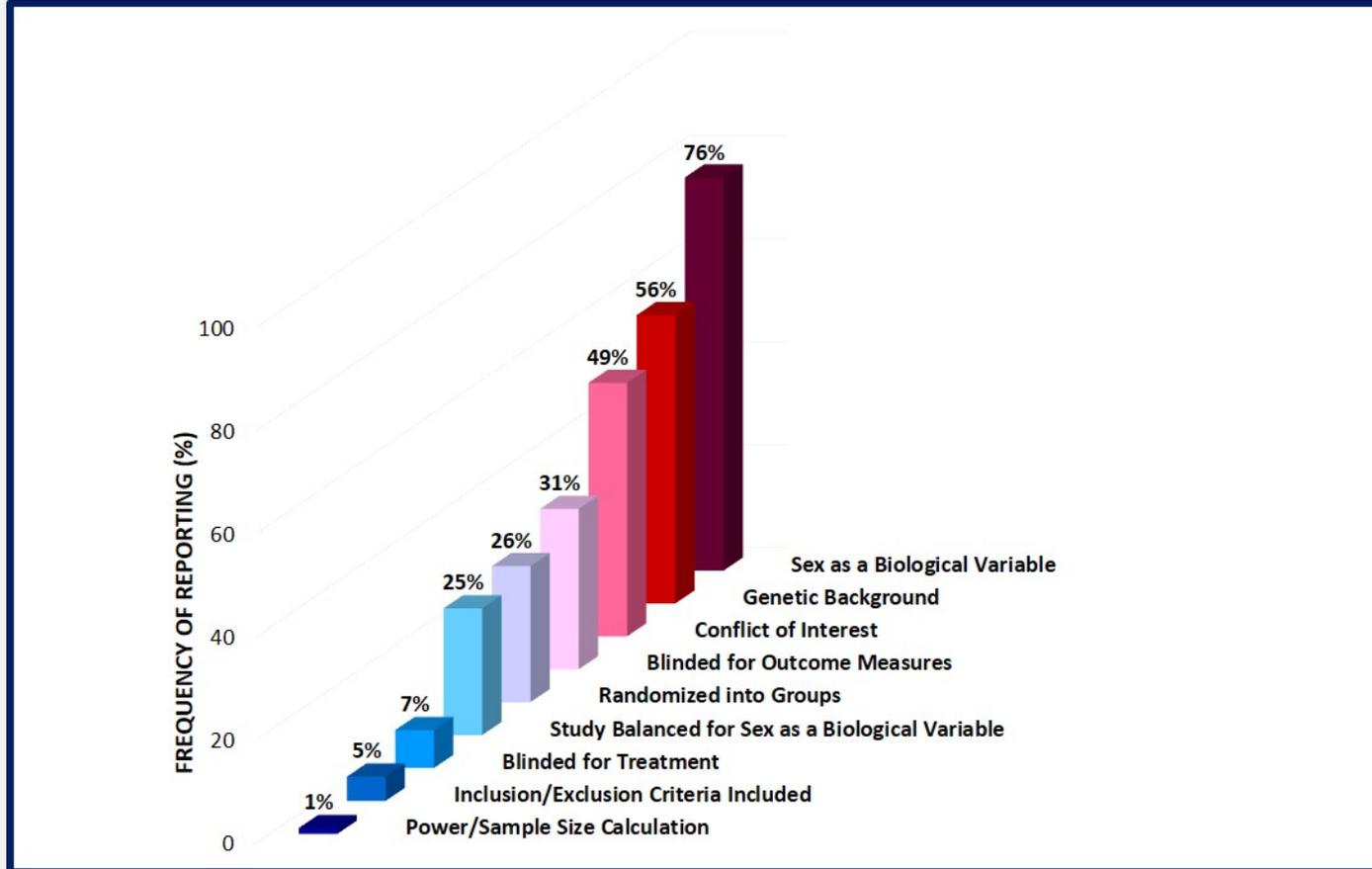
EXPERIMENTAL DESIGN ELEMENTS	%
Power/Sample Size Calculation	1
Number of Excluded Animals	4
ADME Measures	4
Inclusion/Exclusion Criteria Included	5
Number of Premature Deaths	7
Blinded for Treatment	7
Biomarkers	17
Study Balanced for Sex as a Biological Variable	25
Randomized into Groups	26
Pharmacokinetic Measures	26
Blinded for Outcome Measures	31
Pharmacodynamic Measures	33
Toxicology Measures	37
Conflict of Interest	49
Genetic Background	56
Sex as a Biological Variable	76
Age of Animal at the End of Treatment	94
Formulation	95
Age of Animal at the Beginning of Treatment	96
Statistical Plan	97
Dose	98
Frequency of Administration	99
Duration of Treatment	99
Route of Delivery	100

Most Reported Elements

Least Reported Elements

Data presented as percentage reported, calculated from 720 curated studies

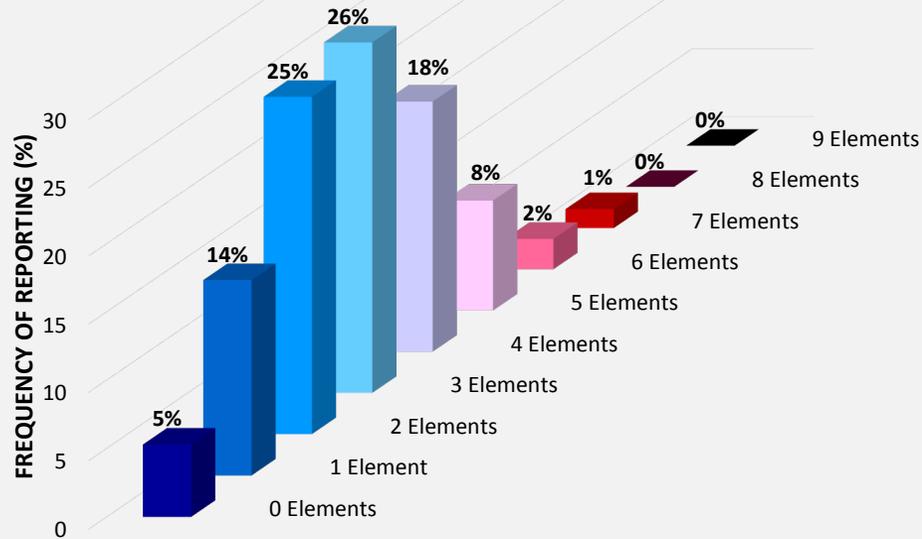
AlzPED Identifies 9 Core Experimental Design Elements that are Essential for Improving Rigor and Translational Value of Preclinical Studies



CORE EXPERIMENTAL DESIGN ELEMENTS	%
Power/Sample Size Calculation	1
Inclusion/Exclusion Criteria Included	5
Blinded for Treatment	7
Study Balanced for Sex as a Biological Variable	25
Randomized into Groups	26
Blinded for Outcome Measures	31
Conflict of Interest	49
Genetic Background	56
Sex as a Biological Variable	76

Data presented as percentage reported, calculated from 720 curated studies

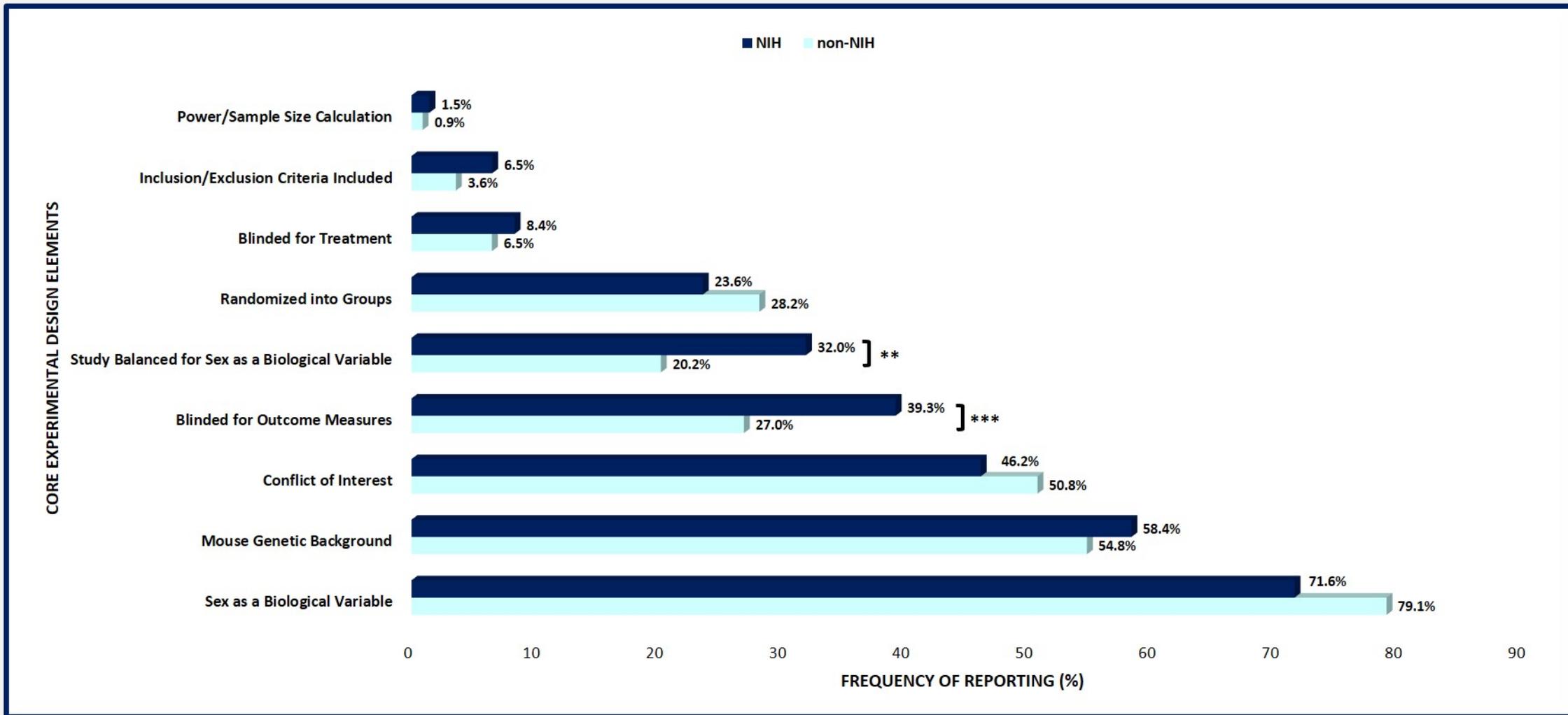
AizPED Summary: Percentage of Curated Studies Reporting 0-8 Core Experimental Design Elements Essential for Rigor and Reproducibility



NUMBER OF ELEMENTS	%
0 Elements	5
1 Element	14
2 Elements	25
3 Elements	26
4 Elements	18
5 Elements	8
6 Elements	2
7 Elements	1
8 Elements	0
9 Elements	0

DATA PRESENTED AS PERCENTAGE REPORTED, CALCULATED FROM 720 CURATED STUDIES

AlzPED Compares the Reporting Trends in 9 Core Experimental Design Elements Between NIH-Funded and Non-NIH Funded Studies



Data presented as percentage reported, calculated from 275 NIH-funded studies and 445 non-NIH funded studies, and analyzed using two-tailed t test; **p=0.0126, ***p=0.0019

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Alzheimer's Disease Preclinical Efficacy Database (AlzPED)

ALZHEIMER'S DISEASE PRECLINICAL EFFICACY DATABASE

National Institute on Aging

See contact info

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Washington D.C. Metro Area

Add profile section More...

- Publicly available and searchable data resource designed to improve the reproducibility and translatability of animal model efficacy testing studies for Alzheimer's Disease and related dementias.
- Hosts curated summaries of published studies and provides easy access to information on study design methods and outcomes, animal models, therapeutic agents, therapeutic targets, patents and related clinical trials.
- Provides a platform for creating citable reports/preprints of unpublished studies, including studies with negative findings.

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AlzPED LinkedIn Page

Join at:

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efficacy-database-alzped-13631a177](https://linkedin.com/in/alzheimer's-disease-preclinical-efficacy-database-alzped-13631a177)



Member Organizations



Alzheimer's
Drug Discovery
Foundation



National Institute on Aging
Turning Discovery Into Health

alz.org[®] | alzheimer's  association[®]



AlzPED Contact Information

Website Homepage:

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