
Improving Animal Trials for Alzheimer's Disease:

Recommendations for Best Practices

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Improving the Predictive Value of Animal Trials for Alzheimer's Disease: Recommendations for Best Practices

- Animal models have contributed to our understanding of the *mechanisms* of Alzheimer's disease
- >300 interventions reported to ameliorate Alzheimer's type pathology and/or behavior in mice. None have resulted in disease-modifying therapies for humans.

Improving the Predictive Value of Animal Trials for Alzheimer's Disease: Recommendations for Best Practices

- The methodological quality and predictive value of animal model research on novel therapeutics can be improved by bringing the rigor and principles of human clinical trials to animal studies.
- *Methods:* An expert advisory panel of academic, industry and government scientists was convened to make *recommendations for best practices* for animal studies testing AD investigational therapies.
- *Funding:* Cosponsored by The Alzheimer's Drug Discovery Foundation (ADDF) and Charles River Discovery & Imaging Services/Cerebricon Ltd.

Perspectives on Animal Models of AD: Modeling *Targets*, Not *Disease*

- *There is no “one-model” for Alzheimer’s disease.*
 - Rodent models can test *pharmacodynamic* properties of candidate molecules on drug targets that may be involved in AD
 - *Use a model that exhibits pathology relevant to the target of interest based on the hypothesized mechanism of action of investigational treatment*
 - Eg. amyloid plaques, tau pathology, neuronal pathology, oxidative stress, inflammatory changes, etc
- Non-transgenic models should also be considered, including pharmacologically-induced models and aging rodent models.

Key Considerations for Preclinical Animal Studies

Clearly delineate an *a priori* hypothesis for the study that includes primary and secondary outcomes

- Pre-specify specific measure to assess the primary and secondary outcomes
- Attempt to employ translatable biomarkers
- Consider issues of sex, timing of treatment, age of animals
- Determine inclusion and exclusion criteria

Carefully design a statistical analysis plan prior to initiation of the study

- Perform power analysis and sample size estimates prior to initiation of the study taking into account previously measured variability in the outcome measures
- Include randomization methods for treatment groups and blinding procedures for those doing assessments
- Include procedures for dealing with dropouts and deaths of animals in statistical analyses

Reduce publication bias

- Report both positive AND negative results in peer-reviewed journals or other open-access format
- Report details of strain, housing, diet, drop-out events/in-trial exclusions, etc. so variables can be assessed
- Analogous to clinical trials, report the flow of animals through the treatment plan of the study
- Report potential conflicts of interest and whether investigators are third party or primary investigators invested in the hypothesis





Defining Exploratory Vs. Therapeutic Animal Studies

Goal:	<i>Exploratory Studies:</i> Mechanism/Target Focused	<i>Therapeutic Studies:</i> Compound Focused
Study Design:	Randomized, placebo controlled, blinded, with dose response	
	Characteristics of <i>in vivo</i> model – Inclusion and Exclusion Criteria Eg. pathogenic stage, age, length of treatment required, etc	
	Efficacy data assessed through multiple outcome measures	Efficacy results in more than one model



Defining Exploratory Vs. Therapeutic Animal Studies

Goal:	<i>Exploratory Studies:</i> Mechanism/Target Focused	<i>Therapeutic Studies:</i> Compound Focused
ADME:	Initial physicochemical property considerations (stability, etc.) and terminal blood and brain tissue sampling for possible PK verification	ADME profiling and full PK/PD analysis – Distribution/exposure of parent compound and metabolites
Toxicity:	Toxicity assessment not needed Basic drug tolerability assay included	Assess toxicology, with treatment conducted at levels reliably below adverse event doses
Statistics Plan:	Statistical considerations not as stringent Power analysis should take into account variability in the model and in outcome measures	Prospective study design including power analyses, complete statistical evaluation plan for primary and secondary outcome measures
	Estimated cost approximately \$100-300,000 USD*	Estimated cost approximately \$500-1,000,000 USD*



Implementing Recommendations for Best Practices

- Disseminate and educate
 - Guidelines disseminated at major meetings
 - Consensus recommendations published in peer-reviewed journal
- Promote adoption of best practices
 - Standardize review of animal studies in grant applications and scientific publications
 - Work with journals to adopt best practices for reporting quality studies and reduce publication bias
- Build resources
 - Working with NIA, industry and other non-profits to implement “best practices” and build resources in “pre-competitive space”

Accelerating Drug Discovery
for Alzheimer's Disease:
Best Practices for Preclinical
Animal Studies

Shineman et al. *Alzheimer's Research & Therapy* 2011, 3:28
<http://alzres.com/content/3/5/28>



REVIEW

Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies

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Through Drug Discovery**