Trial Design in the Era of Disease-Modifying Therapies for Alzheimer's disease

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Agenda/Main points

- Trials are essential to instruct clinical practice and we are entering into an exciting period with new options for treatment testing
- Biomarkers play key roles in AD/ADRD trials, but not yet as surrogate outcome measures for efficacy
- Several trial designs remain ethical in the era of approved disease modifying therapies
- ADRCs will continue to play key roles in treatment development

Opportunities for ADRCs

- Greater synergy with trials and trial networks
- Educating participants, specific communities, and the public at large about importance of trials and need for participation
- Phenotyping/staging and referring participants to appropriate trials
- Long-term follow-up of trial participants, including to autopsy

Critical Definitions

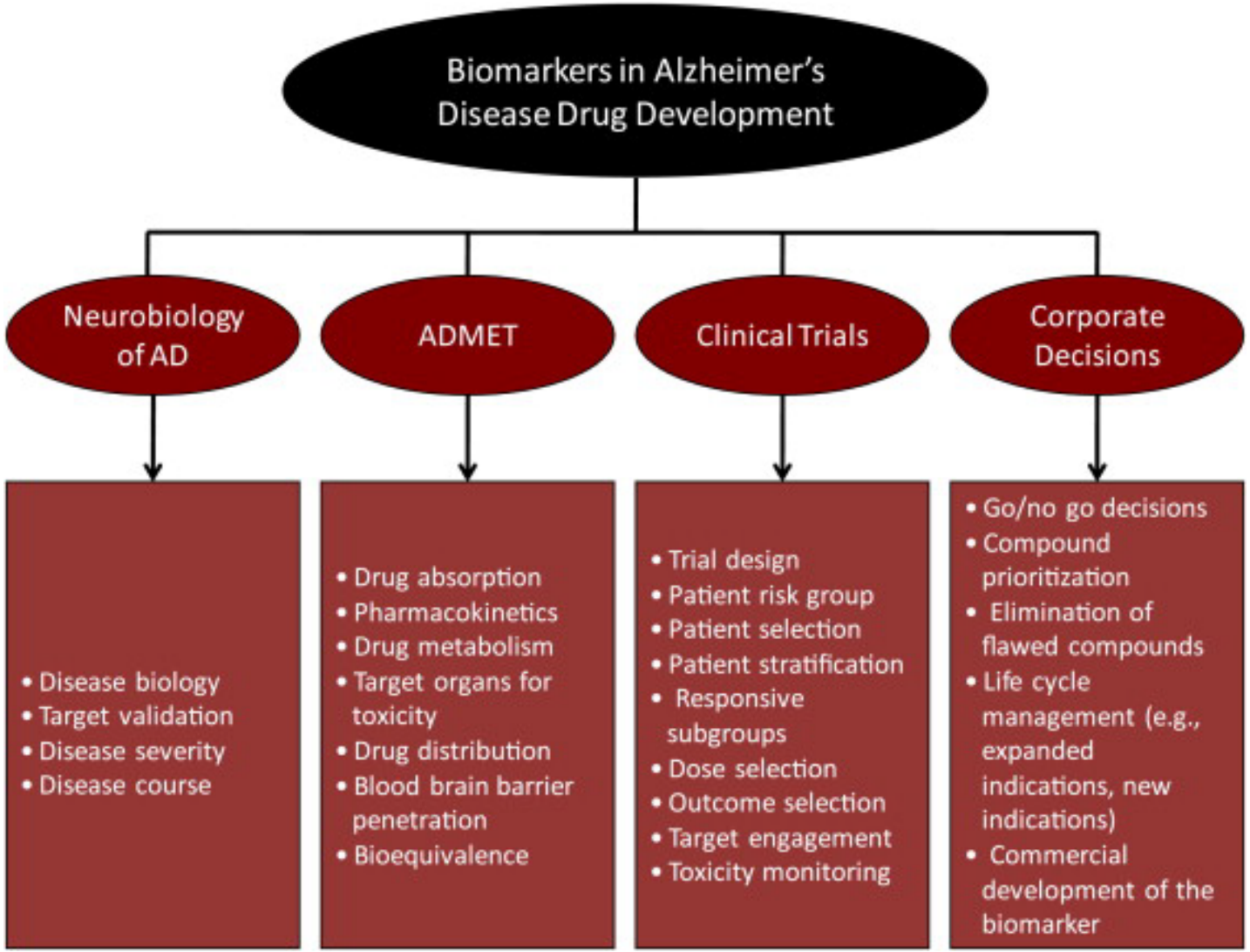
- Failed drug: an investigational product for which evidence does not support further development or clinical use
- Failed trial: a study of an intervention that does not answer the proposed scientific question

State of the Field

- 1993-2004 Cholinesterase inhibitors and memantine
- 1995-2021 >1000 trials; >240 agents; no approved agents
- 2021 Accelerated approval of aducanumab
  Positive topline Phase 2 results for donanemab
- 2022 Positive topline Phase 3 results for lecanemab
- 2023 Accelerated approval of lecanemab
  Full approval of lecanemab?
  CMS Coverage?

Cummings J, et al. Alz & Dem 2022; 18: 469-477

Biomarkers in AD/ADRD Drug Development



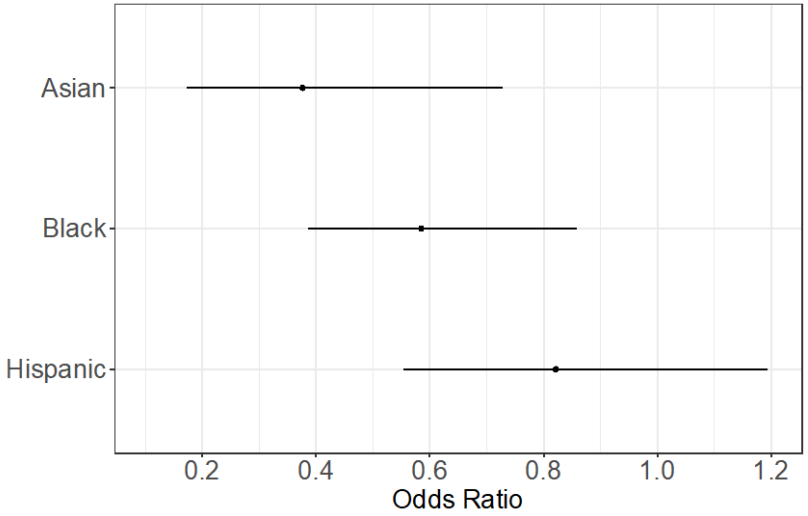
Cummings. Alz & Dement 7 (2011) e13–e44

Biomarker Eligibility: Competing Interests

- Narrow biomarker enrollment criteria (e.g., A+, T+)
  - May increase sensitivity
  - Afford smaller, shorter trials
  - Produce greater rates of ineligibility
  - Limit generalizability
- Broad enrollment criteria with biomarker characterizations
  - Limited in appropriateness (non-specific MOA)
  - Require larger trials
  - May be most inclusive

Racial and Ethnic Disparities in Biomarkers/Eligibility

Relative Amyloid Eligibility



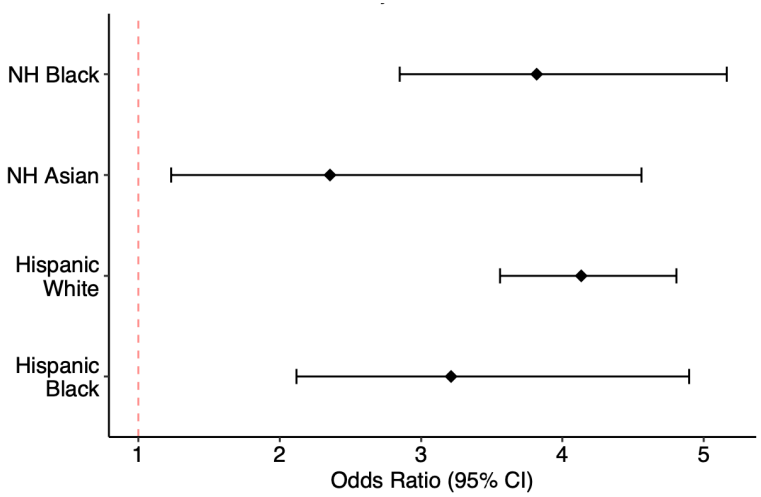
Raman et al., JAMA Netw Open 2021

Relative Amyloid Positivity

Race and ethnicity		
Asian	0.47 (0.37-0.59)	<.001
Black	0.71 (0.60-0.84)	<.001
Hispanic	0.68 (0.59-0.79)	<.001
White	1 [Reference]	NA

Wilkins et al., JAMA Neuro, 2022

Relative Amyloid Ineligibility



Grill et al., AAIC 2022

New Approaches to Trial Screening?

Safety and Modulation of ABCC9 Pathways by Nicorandil for the Treatment of Hippocampal Sclerosis of Aging (SMArT-HS)

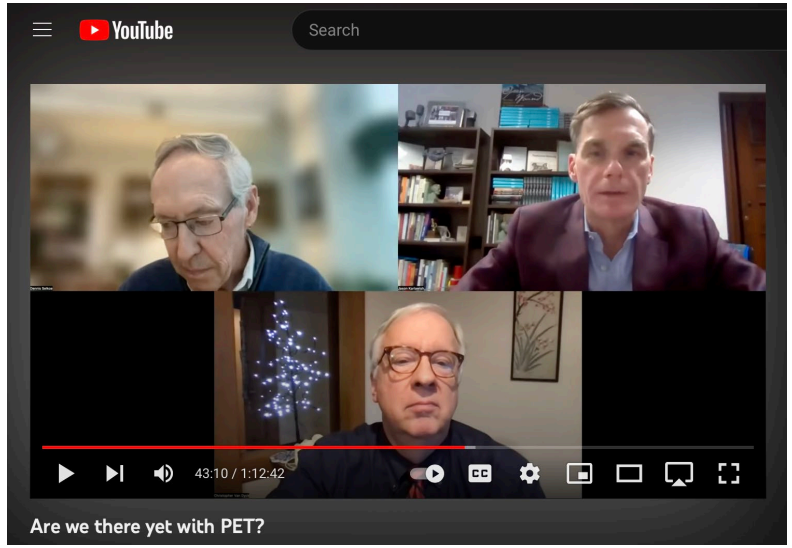
Inclusion Criteria:

- Men or women at least age 75 years
- UPDRS ≤ 7
- Hachinski Ischemic Score ≤ 4
- CSF profile of **"A-T-N+"** defined as Aβ(1-42)>250pg/ml; Total Tau>50pg/ml; Phospho-tau<30pg/ml within 24 months, Aβ PET scan negative for Alzheimer's disease within 24 months, or plasma profile of Phospho-tau181 negative for Alzheimer's disease; hippocampal volume ≤ 1 s.d. below age and gender adjusted mean

https://clinicaltrials.gov/ct2/show/NCT04120766?term=SMArT-HS&draw=2&rank=1

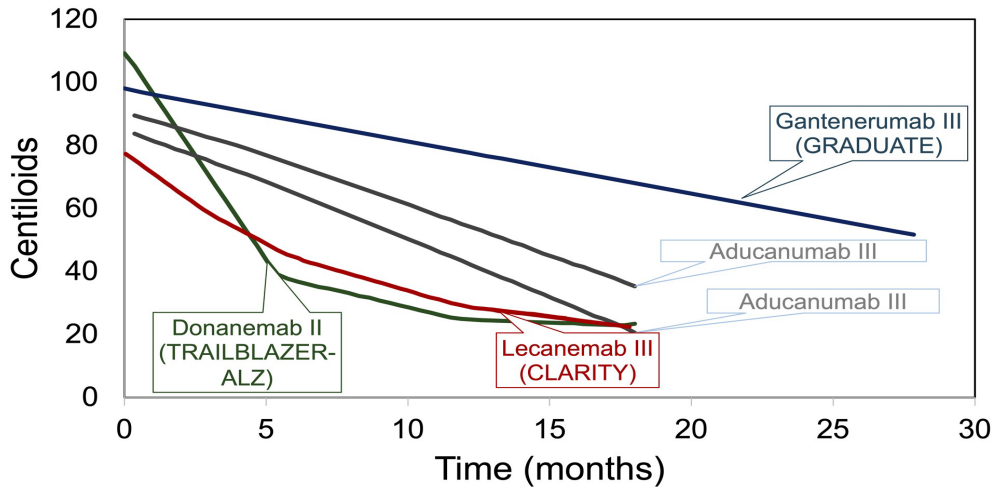
Surrogate Outcome Measures

- There remains no validated surrogate outcome for AD/ADRD
  - AD ≠ HIV/AIDS
  - Amyloid PET measures fibrillar amyloid only
  - Amyloid PET still has variation within and across tracers
  - As yet, no clear threshold for surrogacy for clinical outcomes



[Chris van Dyck, ACTC Ethics Webinar (https://www.youtube.com/watch?v=hrUd_ppMU6w)](https://www.youtube.com/watch?v=hrUd_ppMU6w)

Fleming and DeMets, Ann Intern Med 1996



Hardy and Mummery, Brain 2023

Consideration of trial designs in the setting of an approved disease-modifying therapy

	Scientific and ethical considerations	
Trial designs	**Pros**	**Cons**
New drug versus placebo: approved therapy not allowed		
New drug versus placebo: approved therapy as "background therapy"		
New drug versus approved: equivalency or superiority designs		

Grill and Karlawish, Neurology 2021

Consideration of trial designs in the setting of an approved disease-modifying therapy

	Scientific and ethical considerations	
Trial designs	**Pros**	**Cons**
New drug versus placebo: approved therapy not allowed	Optimal efficiency and validity of the effect of Rx on the disease	Creates potentially difficult cross-study comparisons Risk of delayed benefits of approved therapies
New drug versus placebo: approved therapy as “background therapy”	Valuable information for clinical practice	Potential challenges to validity Added risks related to drug interactions
New drug versus approved: equivalency or superiority designs	Valuable information for clinical practice	Potential challenges to feasibility Potential challenges to validity

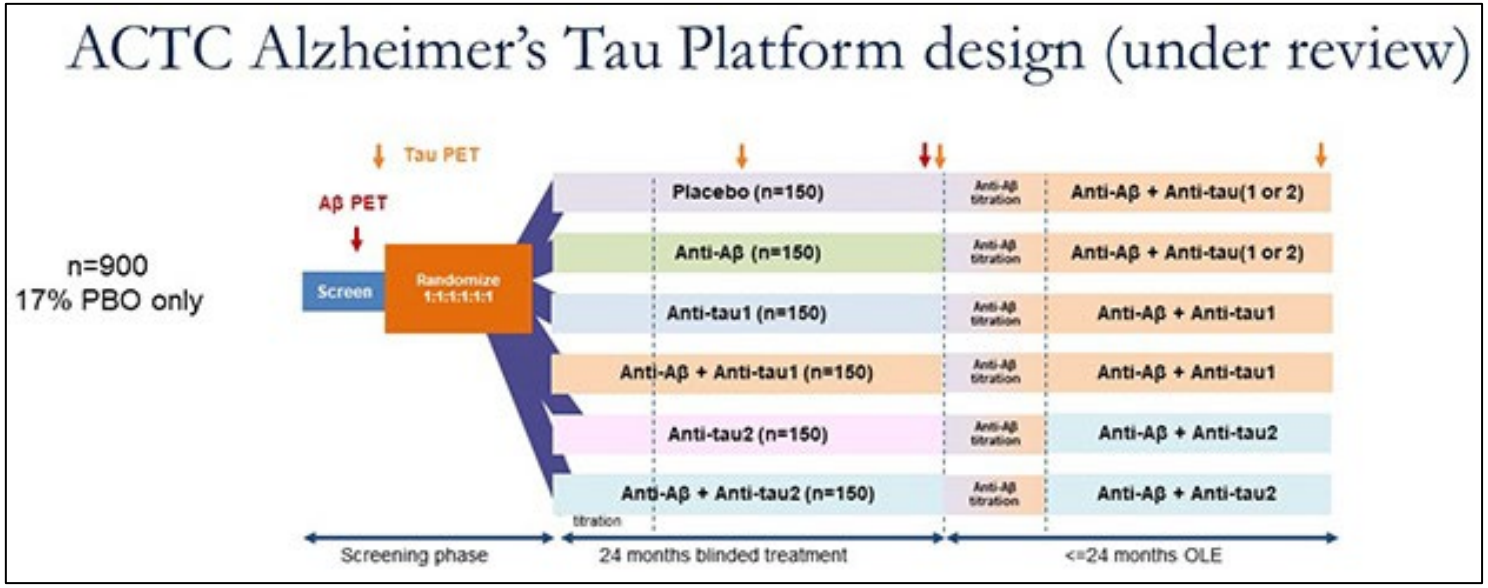
Grill and Karlawish, Neurology 2021

Factorial Designs Answer Important Questions

2 X 2 Design

- 1:1:1:1 Randomization
- N=250/arm
- Early disease or subjective complaint + AD biomarker population
- Biomarker or cognitive outcome measures

Drug A + Drug B	**Placebo + Drug B**
Drug A + Placebo	**Placebo + Placebo**



Salloway et al., Alz & Dem TRCI 2020. Boxer, Johnson et al. ACTC

Standard of Care

- ***Widescale agreement that a therapy is effective (not efficacious) and that withholding therapy results in lasting harm to participants (and placebo is therefore exploitative)***

- No new drug has achieved full clinical approval or widescale coverage by payers
- Efficacy does not equal effectiveness
- Numerous patient populations have been left out of the trials of the newly approved agents
- Limited evidence of disease-modification for new treatments
- Earlier and longer duration treatment may result in increased benefit to patients, but few data to instruct this

Practical Examples

- “Better” amyloid-lowering therapies
  - Head-to-head in early-to-middle phases
  - Placebo-controlled in late phase
- Drugs targeting amyloid from a small molecule approach
  - Factorial design could answer whether agents are better than placebo and whether agents synergize with amyloid-lowering drugs
- Tau-lowering therapies
  - Placebo-controlled trials could enroll only patients who have been demonstrated to have amyloid lowered below 20CL

Opportunities for ADRCs

- Greater synergy with trials and trial networks
- Educating participants, specific communities, and public at large about importance of trials and need for participation
- Phenotyping/staging and referring participants to appropriate trials
- Long-term follow-up of trial participants, including to autopsy

AD Trials in 2023 and Beyond

- Every trial must answer a scientific question
- What question is being asked and at what stage of development are likely to impact the best choice of control group
- Placebo controlled trials remain the most efficient and effective means to answer scientific questions and, at present, remain an ethically viable choice for AD investigators
- Other designs, especially factorial designs, may be key to the field's ultimate therapeutic goals
- The field will need more trials and more alignment with observational research to address the most pressing needs in practice