Outcome Measures used in recent Alzheimer's Disease Phase III Clinical Trials- A Review of ClinicalTrials.Gov

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Objectives

- To investigate the outcome measures used in Alzheimer's Disease (AD) Phase III trials for disease modifying interventions, biomarker studies, cognitive enhancement, and symptomatic relief treatments.

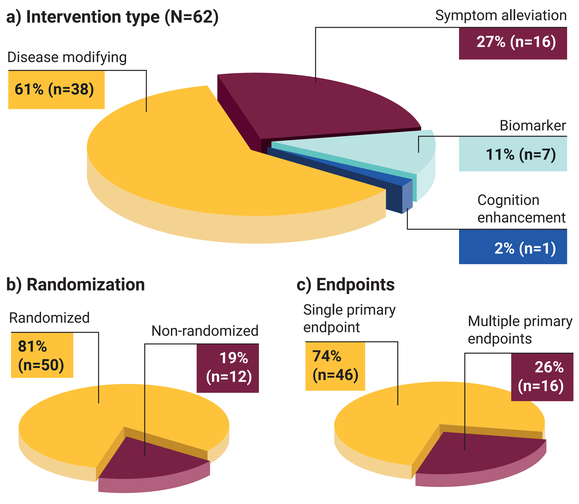
Methods

- Advanced search in clinical trials.gov site was undertaken, using the following words; 'Alzheimer's Disease', 'Interventional studies', 'Phase 3', 'recruiting', 'not yet recruiting', 'active', 'not recruiting studies', 62 studies were identified for inclusion in the analysis. The search was conducted on November 29, 2022.

Results

- Disease modifying interventions were the majority (61%) of the 62 Phase III trials followed by symptom alleviation (26%), biomarker studies (11%), and cognition enhancement (2%) (**Figure 1a**).
- The majority of the trials were randomized (81%) (**Figure 1b**).
- 74% and 26% of trials had single and multiple primary endpoints, respectively (**Figure 1c**).

Figure 1. Phase III trial results: a) Intervention type, b) Randomization of studies, c) Single vs primary endpoints



- Among the single primary endpoints trials, the top four clinical outcome measures used were CDR-SB (19.6%), CMAI (15.2%), ADAS-Cog (6.5%), iADRS, PACC, Amyloid Plaque Clearance, and Time from randomization to agitation relapse (4.3% each) (**Figure 2**). Since the majority of AD Phase III trials are disease modifying, CDR-SB and ADAS-Cog cognitive measures are used frequently to establish treatment efficacy. Also primary endpoint selection, depends on study population, with CDR-SB used preferentially in MCI and early AD. Furthermore, among symptom alleviation trials, treatments to address agitation are the majority and therefore CMAI is also used frequently as a primary endpoint.

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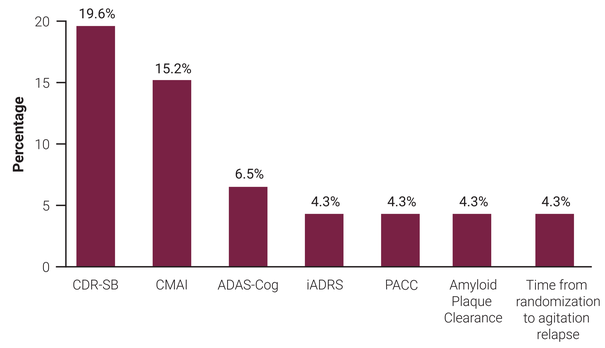
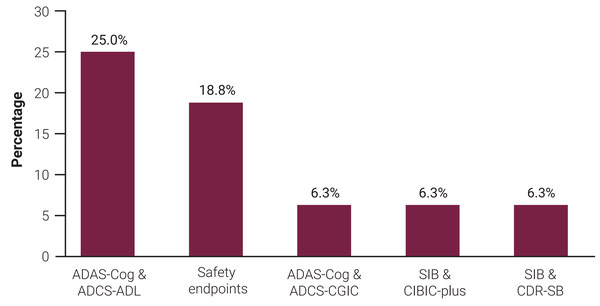
Figure 2. Top 4 clinical outcomes for single primary endpoint AD Phase III trials (n=46)



- Among the multiple primary endpoints trials, the top three combination, clinical outcome measures used were ADAS-Cog & ADCS-ADL (25%), Safety endpoints (18.8%), ADAS-Cog & ADCS-CGIC, SIB & CIBIC-plus, and SIB & CDR-SB (6.3% each) (**Figure 3**). Because AD affects both cognition and function, a quarter of multiple primary endpoint Phase III trials use the ADAS-Cog & ADCS-ADL outcome measures.

Figure 3. Top 3 clinical outcomes for multiple primary endpoints AD Phase III trials (n=16)



ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; **ADCS-CGIC**, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; **ADCS-ADL**, Alzheimer's Disease Cooperative Study - Activities of Daily Living; **CDR-SB**, Clinical Dementia Rating Sum of Boxes; **CIBIC-plus**, The Clinician's Interview-Based Impression of Change Plus caregiver input; **CMAI**, Cohen-Mansfield Agitation Inventory; **MCI,** Mild Cognitive Impairment; **iADRS**, integrated Alzheimer's Disease Rating Scale; **PACC**, Preclinical Alzheimer's Cognitive Composites; **SIB**, Severe Impairment Battery.

Table. A summary of Primary and Secondary endpoints used across 62 AD Phase III trials

Primary endpoints			
Cognition enhancement trial (n=1, randomized)	• Changes in Neuropsychological Test Battery scores		
Biomarker clinical trials (n=7, non-randomized)	• Regional Standardized Uptake Values Ratio (SUVR) values • Whole brain SUVR values • PET Imaging		• Drug uptake • Volume, and thickness of medial temporal lobe subregion
Symptom alleviation trials (n=16, 15 randomized, 1 non-randomized)	• CMAI (7) • Time from randomization to relapse (2) • Mini Mental State Examination • ADAS-Cog	• Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change • Insomnia Severity Index	• Total Standardized Daily Doses • Incidence of Mild Cognitive Impairment or Dementia • Treatment Emergent Adverse Events (1 each)
Disease modifying trials (n=38, 34 randomized, 4 non-randomized)	Top five primary endpoints • ADAS-Cog (9) • CDR-SB (9) • ADCS-ADL (4) • Safety (4) • PACC (3)		
Secondary endpoints			
Cognition measures	• Mini Mental State Examination • Peanut Butter Smelling Test • International Shopping List Test • Continuous Paired Associate Learning • International Daily Symbol Substitution Test-Medicines • Category Fluency • Face Name Association Test	• Behavioral Pattern Separation-Object test • Cogstate Brief Battery • Cognitive Function Index • Montreal Cognitive Assessment • Verbal Fluency Task Score • Tests of Attention-Trails A and B • Digit-symbol substitution	• Test of Everyday Attention • Free and Cued Selective Reminding test • Category Naming Test • Choice reaction time • Simple Reaction Time • Hopkins Verbal Learning Test • Lure discrimination index-objects, spatial, temporal
Activities of Daily Living (ADL) and dependence measures	• Lawton Activity of Daily Living scale • Caregiver Activity Scale • Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)	• Autonomy Scale on daily activities • ADCS-ADL-MCI • Amsterdam-Instrumental Activities of Daily Living Questionnaire-Short Version	• Functional Activities Questionnaire score • Dependence Scale • Disability Assessment for Dementia
Patient/Caregiver focused measures	• Quality of Life-AD • EQ-5D-5L • Dementia Quality of Life • Health Utilities Index Mark 3	• Zarit Burden Interview • Geriatric Depression Scale • Epworth Sleepiness Scale • Sleep Maintenance Efficiency	• Total Sleep Time • Patient Global Impression of Change score • Pain Assessment Checklist for Seniors with Limited Ability to Communicate-II
HCRU measures	• Resource Utilization in Dementia	• Number of participants using concomitant medicines	
Biomarker measures	• Amyloid Plaque Clearance • Tau PET imaging • Amyloid brain burden • Cerebrospinal fluid (CSF) biomarkers of AD pathology, neurodegeneration, and neuroinflammation • Brain volume via MRI • Homeostatic assessment of insulin resistance • Fasting blood glucose	• Postprandial glucose excursions • Brain Tau Load • Blood biomarkers • Ventricle Volume via MRI • Hippocampal Volume via MRI • Annualized rate of whole brain atrophy • SUVR • Annualized rate of temporal and parietal lobe atrophy	• CSF ptau217/total tau • CSF neurofilament light chain • Entorhinal cortical thickness • Perforant path integrity • Tau spatial distribution • Cortical Thickness • White matter hyper intensity volume
Time to events	• Time to severe dementia • Time to progression to dementia	• Time to progression in disease stage • Time to first occurrence of stroke	• Time to first occurrence of Major Adverse Cardiovascular Event

Conclusion

- **Alzheimer's Disease Phase III trials are complex, heterogeneous, and use several outcome measures for primary and secondary endpoints to capture cognitive decline, functional decline, neuropsychiatric symptoms, biomarkers, time to events, patient and caregiver QoL, and healthcare resource utilization.**
- **This leads to challenges in performing comparative clinical effectiveness and cost-effectiveness assessments required by payers and HTAs for market access and reimbursement decision making.**

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