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An Industry Viewpoint on Clinical Trials Designed for Demonstrating Disease Progression in Alzheimer's Disease: Current Approaches

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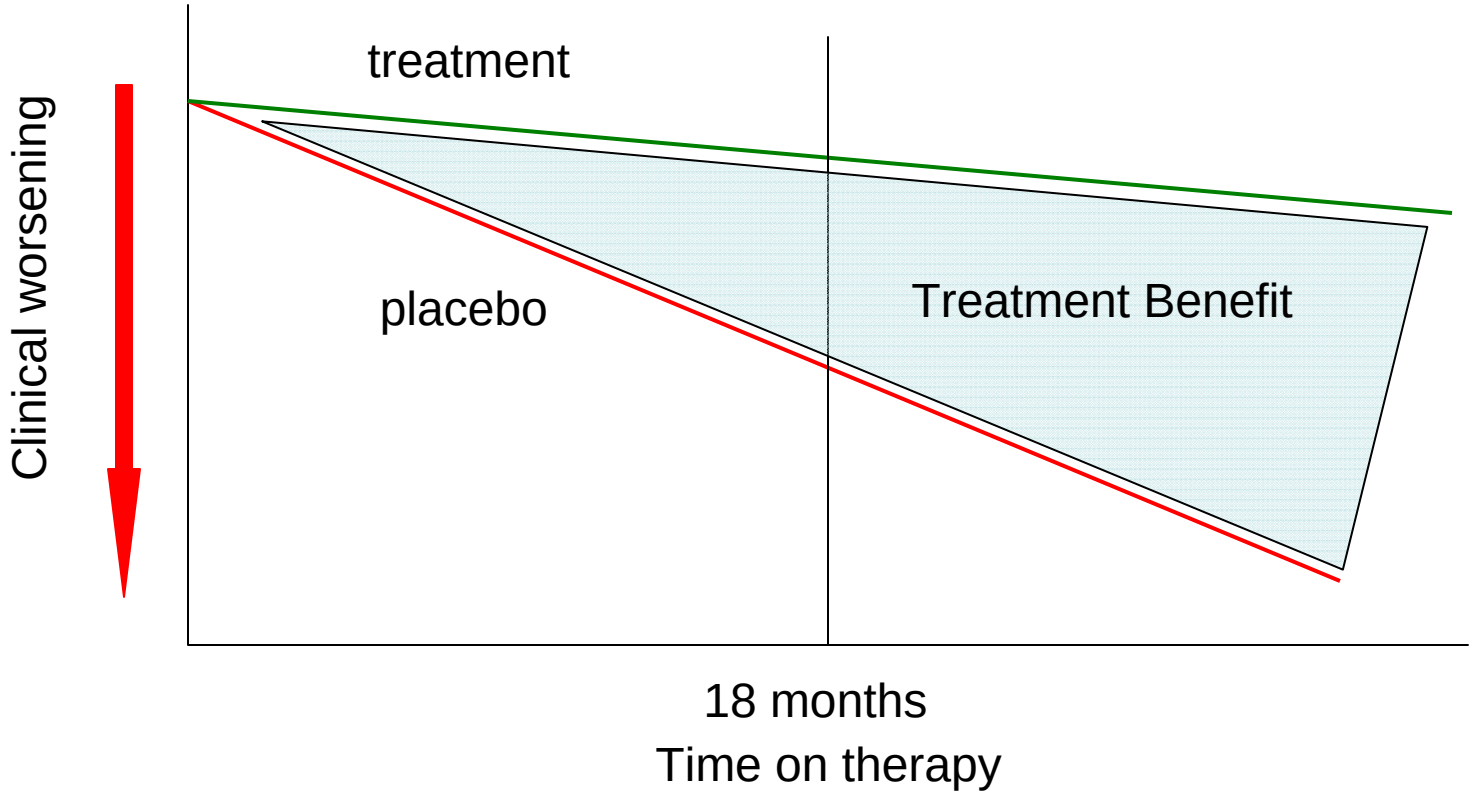
Disease Modification in AD

Q: Why distinguish between symptomatic and disease-modifying (DM) AD treatments ?
A: Because DM treatment benefit should increase over time



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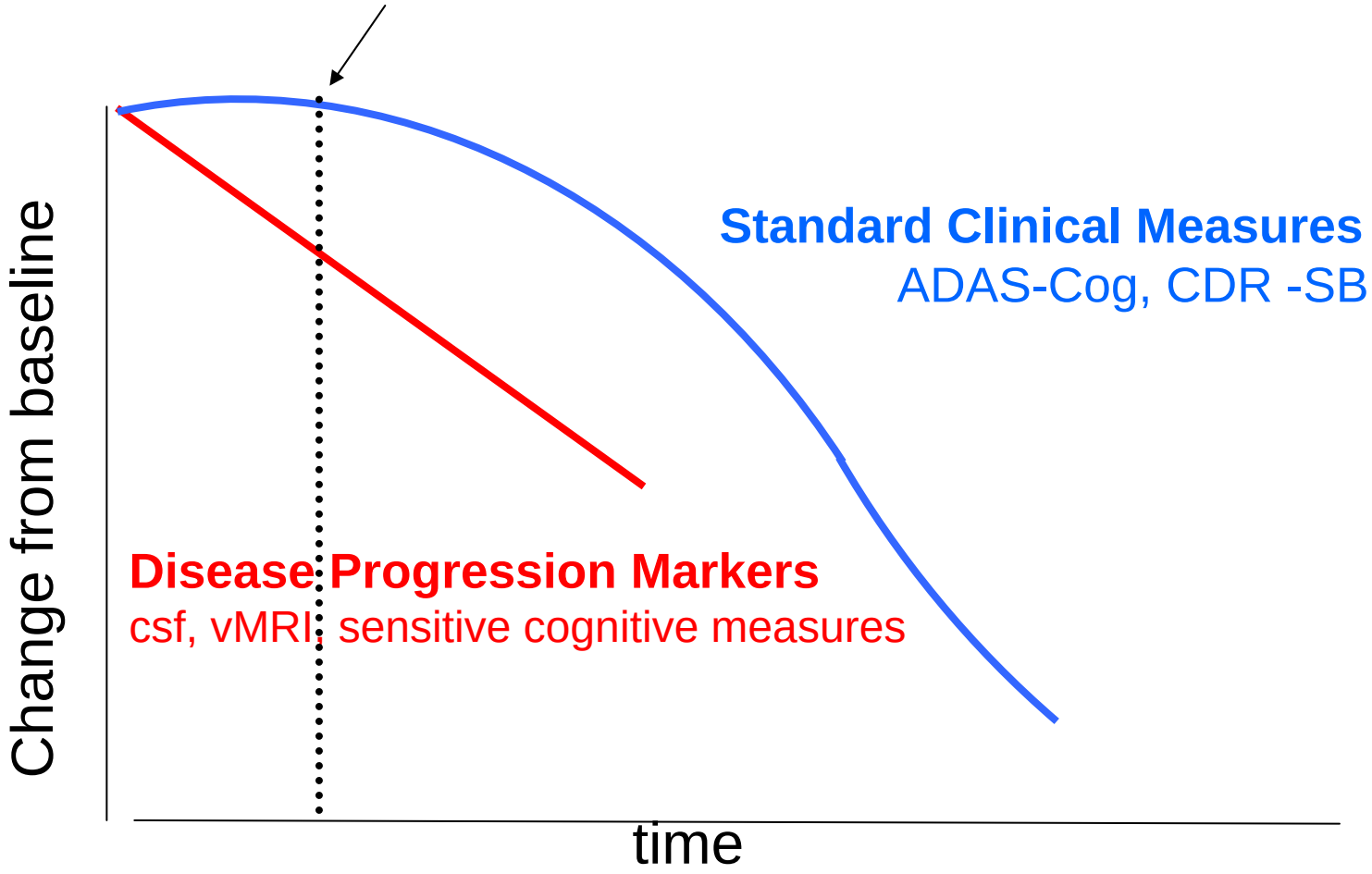
Clinical Expression vs. Disease Progression

Evaluation early in disease

Signal Strength: Progression Marker > Clinical Expression



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Endpoints for trials in Alzheimer's disease: a European task force consensus

*Bruno Vellas, Sandrine Andrieu, Cristina Sampaio, Nicola Coley, Gordon Wilcock, for the European Task Force Group**

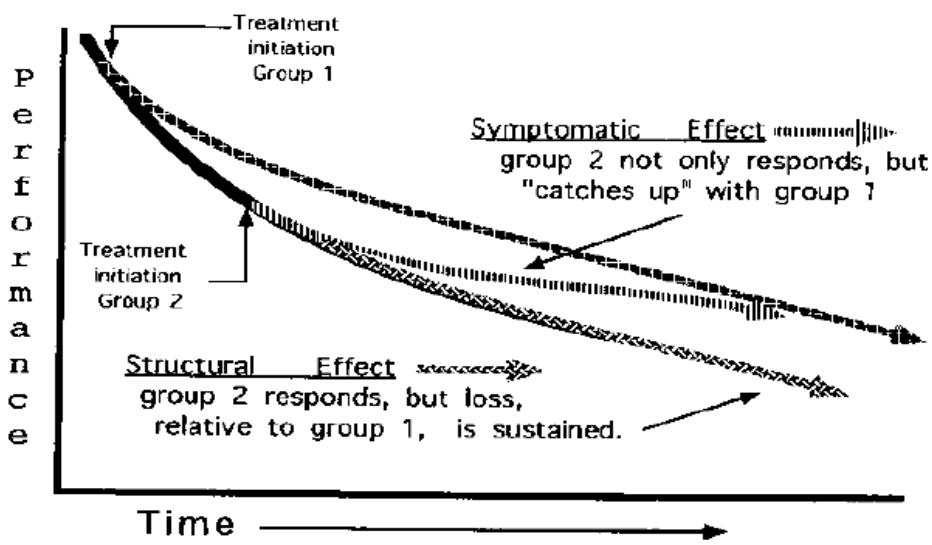
	Strengths	Limitations
Prevention trials		
Conversion to dementia or AD[10–14]	Most clinically relevant outcome	Relatively subjective; difficult to determine the precise moment of conversion; incidence can remain low in healthy older patients; independent committee necessary to validate diagnoses
Cognitive decline (eg, memory testing with cued recall)[15–16]	More sensitive and objective than conversion outcome; can detect small cognitive changes; individual cognitive domains can be studied separately	No standardised cognitive test battery for prevention trials; some well known instruments (eg, MMSE) might not be sensitive enough to detect early signs of cognitive decline; clinical relevance and suitability of cognitive decline as a surrogate marker for dementia still to be established
Symptomatic trials: mild to moderate AD		
ADAS-cog[17,18–19]	Widely used and standardised; can show some symptomatic effects in trials of cholinesterase inhibitors; sensitive to change in moderate AD	Inadequate assessment of some cognitive domains, especially in very early AD; unclear definition of what constitutes a clinically important change, especially in mild AD
NTB[20,21]	More sensitive than the ADAS-cog and covers more cognitive domains	Requires further validation in therapeutic trials
CIBIC-plus[22–23,18]	Significant change reported in clinical trials*	High inter-rater variability hinders comparison between different studies
Symptomatic trials: moderate to severe AD		
Cognition: SIB[105,106,108,111,127–130]	Adapted for patients with severe AD who might not be able to complete other measures (eg, MMSE or ADAS-cog); scoring based on correct responses rather than errors, and partial responses are credited	Might be difficult to show clinically important differences
Function: ADCS-ADL-sev[106,111,128]	Adapted for patients with severe dementia	Might be difficult to show clinically important differences
ADCS-ADL[108,111]	Significant change reported in clinical trials*	Not adapted for severe dementia
CGI-C[107]	Global assessment	Might be subject to inter-rater variability, thus hindering comparison between different studies
CIBIC-plus[105,110–111,116,118]	Global assessment	High inter-rater variability hinders comparisons between different studies
Disease-modifying trials: mild to moderate AD		
ADAS-cog[23–203]	Widely used in symptomatic trials	No significant differences between groups in trials so far.* Only evidence for disease-modifying effects comes from long trial duration
NTB	More sensitive than the ADAS-cog and covers more cognitive domains	Requires further validation in therapeutic trials†
ADCS-ADL[98,203]	Widely used in symptomatic trials	Negative in trials so far*
CDR[83–87,120]	Suggested as a co-primary outcome (global outcome)	No behavioural component
CIBIC	Global assessment	Difficult to interpret in long-term trials

*Most of these trials were carried out several years ago versus placebo. However, significant changes now seem more difficult to detect in add-on trials with patients who have milder AD. †There is still discussion about the clinical relevance of changes in scores on this assessment.

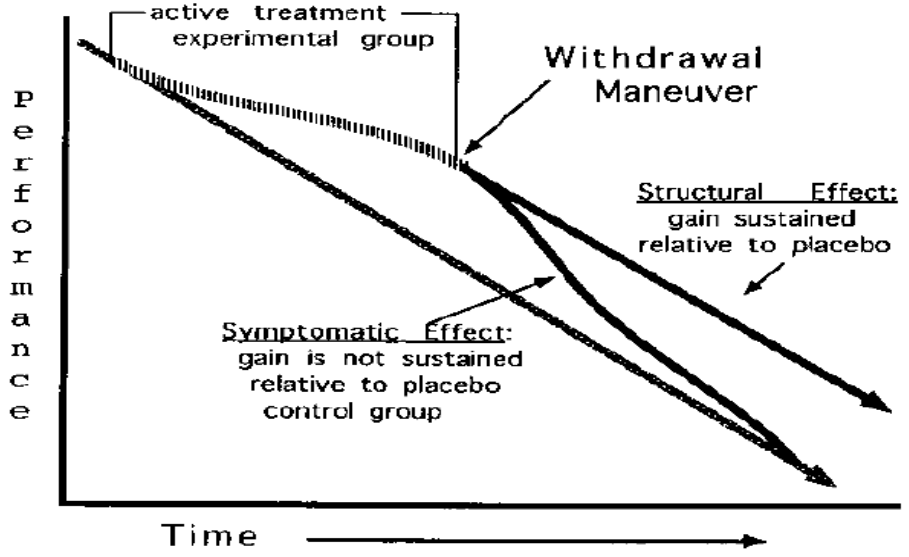
Lancet Neurol 2008; 7: 436–50

Randomized Start/Withdrawal

- 2 sequential treatment segments
- Variation on crossover design



Randomized Start (RS)



Randomized Withdrawal (RW)

Leber, *Alzheimer Disease and Associated Disorders* (1997)

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RS/RW: Issues

- Treatment effects likely differ across severity stages of AD
  - 2 period dichotomy accentuates impact of treatment by time interactions
- Optimal duration of the withdrawal /staggered start segment is unknown
  - 3 months ? 6 months ?
  - PK/PD/clinical relationships
- Negative impact of dropouts is amplified
- Non-linear change in clinical outcomes
- Result→ RS/RW infrequently used in long AD trials

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Biomarkers

- Leading candidates: vMRI, CSF Aβ, CSF tau, PET and ratios/combinations
- For a particular compound, can be used now to justify dose selection in “Learn” phase of development
- For a particular compound, can be used now in “Confirm” trials as supportive data if treatment benefit demonstrated on primary clinical outcomes
- To achieve surrogate status, will likely need replication across multiple compounds and trials

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EMEA Guidance 2008

- "Lack of agreement on the appropriate methodology to demonstrate slowing or arrest of the dementing process"
- "Ideally, proof of a disease-modifying effect would require demonstration of clinically relevant changes in key symptoms of the dementia syndrome and in addition supportive evidence for a change in the underlying disease process based on biological markers"
- Qualification and validation of proposed biomarkers not addressed
- 2-step approach to disease modification claim
  - Step 1: "delay of disability" based solely on clinical outcomes
  - Step 2: "full claim for disease modification" if convincing biomarker package also supports the clinical outcomes

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Apolipoprotein E (ε2, ε3, ε4)

- APOE is a 299 aa polymorphic protein w/ diverse roles in neurobiology
- APOE stimulates the degradation of brain Aβ *
  - isoform-dependent activity → ε4 being least effective
- Greater Aβ burden among patients with ε4
  - Including greater vascular Aβ deposition
- APOEε4 carrier status confers ↑ risk of developing AD
- APOE ε4 status may alter course of disease progression
- ~ 60 % of AD trial participants are APOE ε4 carriers
- APOE genotype may modify treatment response

* Jiang et al, Neuron 2008

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Missing Data

- Missing data severely undermines ability to demonstrate disease modification in long AD trials
- Missing not at random (MNAR) ?
  - AE profile of drug, patient factors, etc.
- Preventing missing data is better than using statistical methods at study completion
- Operational aspects of study conduct:
  - Detailed manual for scoring clinical outcomes
  - Intensive training of study personnel
  - Frequent monitoring of missing data at the site level
  - Strategies to enhance subject retention
  - Ongoing sponsor/site communication to explain “lessons learned”
  - Early termination visits

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Disease-modifying trials in Alzheimer's disease: a European task force consensus

Bruno Vellas, Sandrine Andrieu, Cristina Sampaio, Gordon Wilcock for the European Task Force group

Panel 3: The European Alzheimer's Disease Consortium's recommendations for disease-modifying trials

Target population

- Early Alzheimer's disease
- Mild to moderate Alzheimer's disease

Study design

- Randomised, parallel, two-arm, placebo-controlled trial

Follow-up

- 18 months

Statistical analysis proposed

- Slope analysis

Primary and secondary outcomes

- Endpoints should be clinically relevant and include cognitive functions (composite measures), functional status (activities of daily living), neuropsychiatric symptoms (NPI) and cost-effectiveness (RUD, Zarit)[19]
- Biomarkers (biological and neuroimaging)

Surrogate markers

- Not recommended for primary outcome at this time

NPI=neuropsychiatry inventory; RUD=resource utilisation in dementia.

Vellas et al, Lancet Neurol 2007

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Conclusions

- Approach to AD DM trials in 2008
  - Placebo-controlled, parallel – group design
  - Power sample size conservatively
  - Consider APOE genotype stratification
  - Minimum 18-month treatment duration
  - Primary outcomes: cognition + function or global
  - Consider a biomarker as key secondary outcome if “Learn” phase data are convincing and biologically plausible
  - If decline on clinical outcomes is linear, compare treatment effect on slope of decline
  - Need robust methods to deal with missing data