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A Time-to-Event Framework for Quantifying Clinical Significance of Effect in Alzheimer's Disease Clinical Trials

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Background

- Alzheimer's Disease (AD) is a progressive neurodegenerative disease associated with significant costs.[1,2]
- Many AD therapeutic trials fail to demonstrate clinical significance.[3]
- Therefore, alternative ways of looking at clinical significance are needed.

Objective

To present a method for reframing clinical significance in terms of a meaningful delay in time to the level of cognitive functioning associated with substantial new costs (e.g., increased home care needs [HCN] or care facility admission [CFA]).

Methods

We propose employing a time-to-event (TTE) model to evaluate AD treatment benefit in the context of cognitive functioning.

1. First, an event is defined, such as as the threshold of cognitive functioning associated with new financial costs.
2. Second, statistical significance is determined: a TTE model evaluates the significance of the association between treatment and TTE delay.

Methods (Cont'd)

3. Lastly, clinical significance is determined: the calculated TTE delay is presented to an appropriate audience to evaluate clinical meaningfulness of the estimated effect.

- **For example, an estimated 4-month delay in time to CFA is presented to AD caregivers;**
- **Caregivers then rate the extent to which this delay would be meaningful to them;**
- **If an acceptably high percentage agrees it's meaningful, then a clinical significance criterion has been generated and validated.**

Illustrative Example

- Data from the AMBAR trial evaluating plasma exchange with albumin replacement (PE-A) is used to illustrate this method.[4]
- The Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) and the Mini-Mental State Exam (MMSE) were included to assess cognitive functioning.[5,6]
- Literature-based mean MMSE scores associated with a substantial HCN increase were used to create a dichotomous threshold.
- Threshold was predicted by ADAS-Cog scores and receiver operator characteristic (ROC) curves; Youden's index were used to derive corresponding ADAS-Cog thresholds.

Results

- An ADAS-Cog score of ≥31.92 was associated with a substantial HCN increase and defined as an event.
- Assumptions were met, and a Cox model was fit; AD treatment significantly reduced the hazard of increased HCN by 27.4%, *p=0.04*. **(Table 1).**

Table 1 | Cox PH Model for Cognitive Functioning Home Care

	Hazard Ratio	95% CI	p-Value
PE-A Treatment	0.726	(0.536, 0.985)	0.040*
Age	1.016	(0.996, 1.036)	0.129
Baseline ADAS-Cog	1.156	(1.113, 1.201)	<0.001*
AD Severity	2.640	(1.713, 4.070)	<0.001*
AD Stage	0.825	(0.591, 1.152)	0.258

Note: asterisk (*) indicates p < 0.05

Abbreviations: AD = Alzheimer's Disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; Plasma exchange with albumin replacement; CI = Confidence Interval

- AD treatment delayed median TTE 3 months compared to placebo. **(Table 2).**

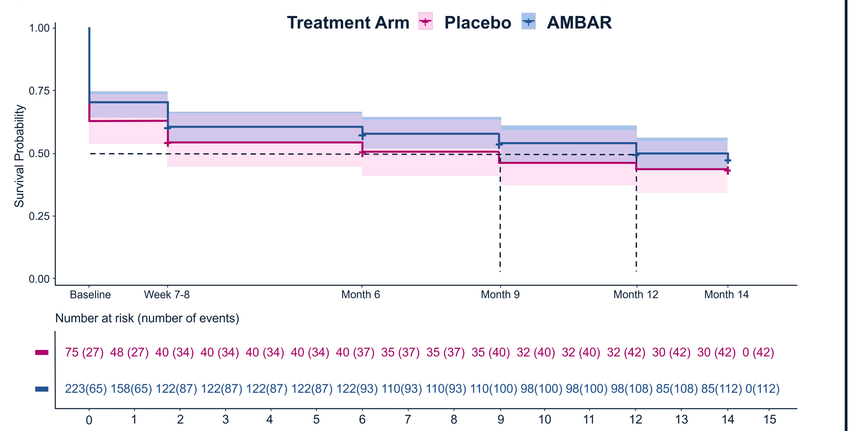
Table 2 | Median TTE for Cognitive Functioning Home Care Threshold

	Median TTE (Time Post-Baseline)	95% CI
Placebo	9 Months	(7-8 Weeks, Not Reached)
PE-A Treatment	12 Months	(9 Months, Not Reached)

Abbreviations: PE-A = Plasma exchange with albumin replacement; CI = Confidence Interval; TTE = Time-to-event

Figure 1. Illustrates the Kaplan-Meier plot and associated risk table for this event definition and TTE analysis, stratified by treatment arm. The dashed lines represent the median TTE for each arm.

Figure 1 | Kaplan-Meier Plot and Risk Table for Cognitive Functioning Home Care Threshold



Conclusions

This analysis can be seen as a proof-of-concept for an approach characterizing treatment effect in terms of delays to pre-defined cognitive thresholds.

This approach provides objective valuation information by linking AD therapy value to avoided costs that would otherwise occur in the absence of treatment.

Next steps include presenting the estimated TTE delay to AD caregivers to determine clinical meaningfulness.

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