Economic model of Alzheimer's disease uncertainty associated with measuring efficacy in clinical trials

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Introduction

- The burden of Alzheimer's disease (AD) and related dementias has become a major public health problem. An effective amyloid-targeting therapy would be a great step forward.
- **Lecanemab**: approved by the Food and Drug Administration (FDA) and initially rejected – now approved – by the European Medicines Agency (EMA) related to the imbalance between the clinical relevance of the beneficial effects and the adverse effects.
- Transparent and robust economic evaluations: **IPECAD**
- Based on the effectiveness estimates from cognitive and functional scales used in clinical trials. Extrapolation challenges:
    - Mixed Models for Repeated Measures (MMRM). The incorporation of PSA into models is a challenge that remains to be fully addressed in the economic evaluation of AD treatments
    - Waning Effect

Objective

Incorporate the uncertainty associated with measuring efficacy in clinical trials, and validate the model obtained for the economic evaluation of a generic intervention, in our case, a disease-modifying treatment for patients with AD in the MCI stage.

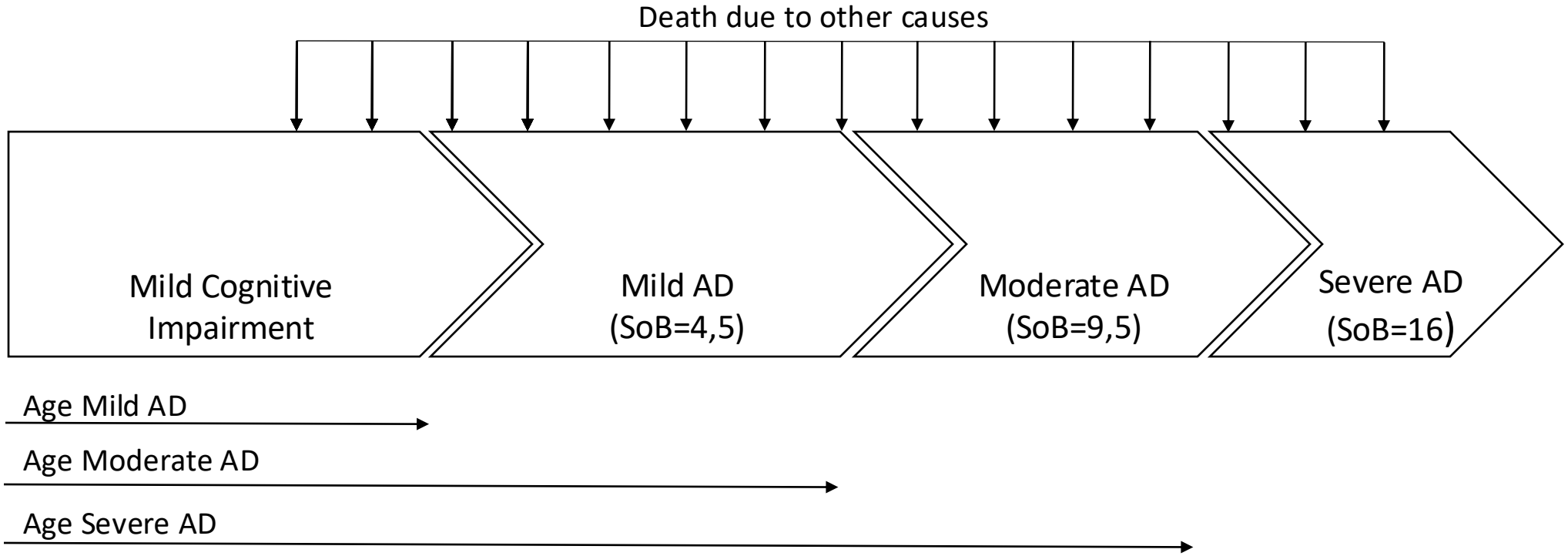
Methods

- The model was build in SimPy and run 1,000 replications of 100,000 patients. We applied the discount rate of 3,5% both for costs and QALYs
- Baseline characteristics
- We tackled the characterization of the population by bootstrapping synthetic data

Baseline population characteristics		Source
Male (%)	60%	ADNI developed for the IPECAD workshop
Age, Mean (sd)	72.72 (6.58)	
Baseline CDR-SB, Mean (sd)	1.70 (0.15)	
Baseline MMSE, Mean (sd)	27.3 (2.40)	
Annual costs ($): Mean (sd)		
Treatment	5,000	Assumption
MCI	29,551 (7,587)	Robinson
Mild AD	38,525 (6,792)	Robinson
Moderate AD	53,920 (8,456)	Gustavsson
Severe AD	74,750 (7,878)	Gustavsson
Utilities		
MCI	0.80	Neumann
Mild AD	0.69	Neumann
Moderate AD	0.53	Neumann
Severe AD	0.38	Neumann

ADNI: Alzheimer's Disease Neuroimaging Initiative

Methods



REMARKS

- To build a target population consistent with amyloid-targeting therapy trials, we reproduced a patient-level natural history by simulating the trajectory of Clinical Dementia Rating-sum of Boxes (CDR-SB) scores from MCI to severe dementia.
- Time to death was assigned using a specific Gompertz function for each sex fitted to the American population in 2019. The increased risk of mortality due to AD was incorporated using hazard ratios from Tahami Monfared et al.

Methods

$$Time\ Until\ AD\ Stage = \frac{CDR\ Cut\ off - bCDR_i - \beta_0 - \beta_2 trt_i - \beta_4 bMMSE_i - b_{i0}}{\beta_1 + \beta_3 trt + b_{i1}},$$

- bCDRi is the baseline CDR-SB score for patient i
- trti indicates whether patient i received the treatment or not (0=no, 1=yes)
- bMMSEi is the baseline MMSE score of patient i, and
- bi0 and bi1 incorporate the random effect.

Methods

CHALLENGE 1: CHOLESKY DECOMPOSITION

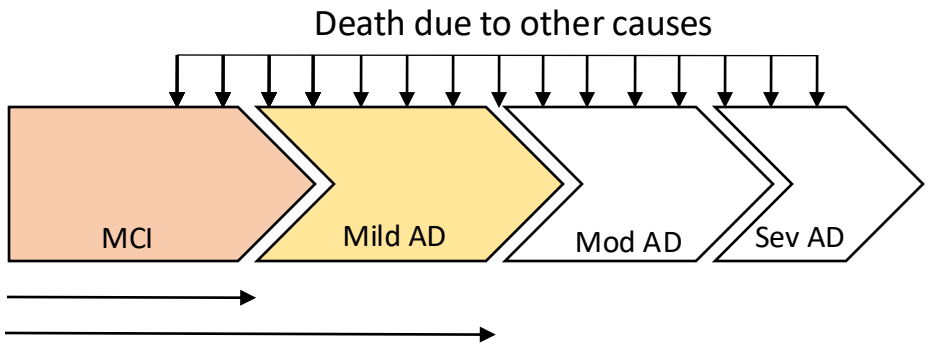
$B' = B + V \times Z$, where

- B is the vector of the betas
- V is the triangular matrix result of Cholesky decomposition of the Var-Cov matrix, and
- Z is a random vector.

Methods

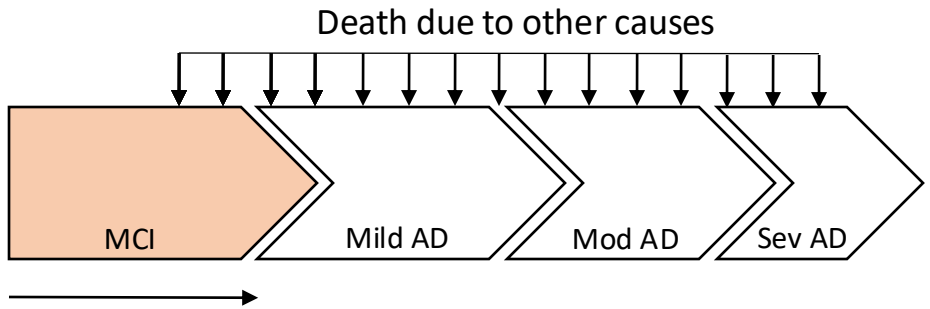
CHALLENGE 2: WANING EFFECT

OPTIMISTIC SCENARIO



Duration Mod AD (control) = Duration Mod AD (interv)

PESSIMISTIC SCENARIO



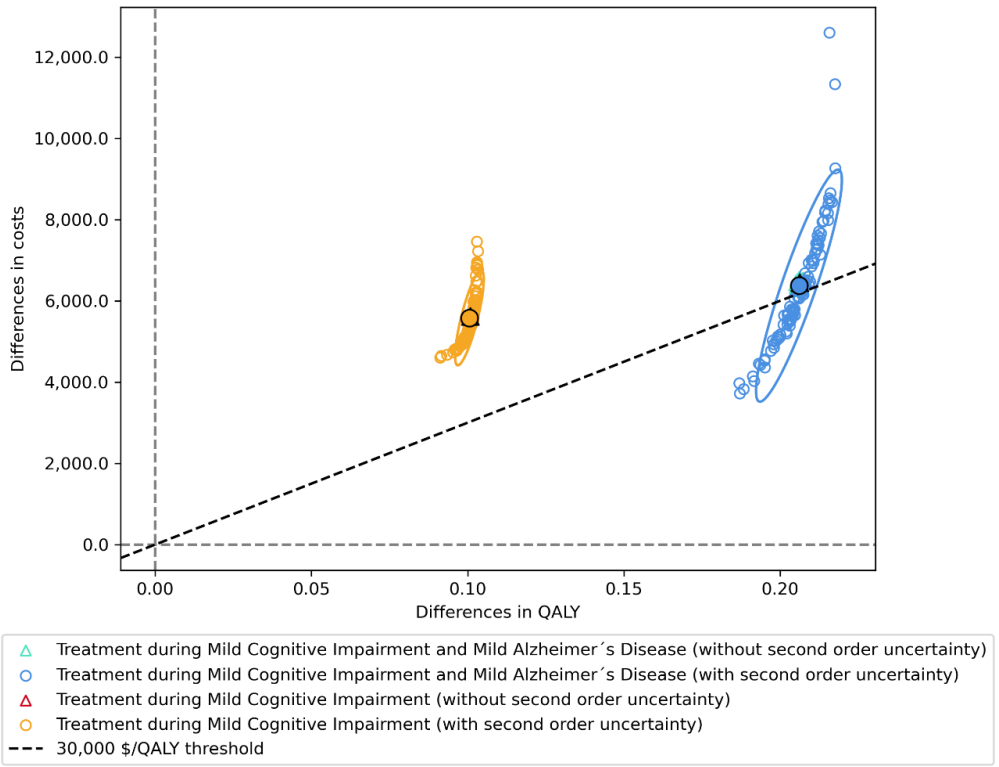
Duration Mod AD (control) = Duration Mod AD (interv)
Duration Sev AD (control) = Duration Sev AD (interv)

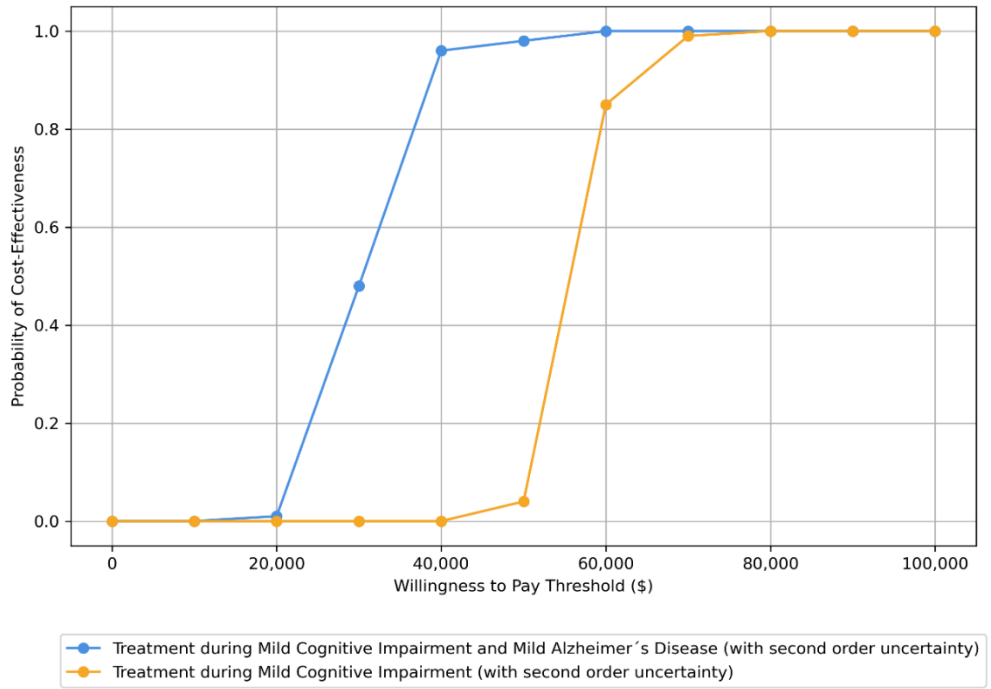
Results

	Pessimistic scenario		Optimistic scenario	
	Control	Interv	Control	Interv
MCI	1.33	1.64	1.33	1.64
Mild AD	5.65	5.55	5.65	6.72
Moderate AD	4.73	4.63	4.73	4.00
Severe AD	3.08	3.02	3.08	2.48
Total time	14.79	14.84	14.79	14.84

	COST ($) mean (standard deviation)		QALYs mean (standard deviation)		ICUR ($/QALY)
	Control	Intervention	Control	Intervention	
Optimistic scenario					
Deterministic	571,316	577,760	7.34	7.55	31,236
Probabilistic: μ(σ)	573,441 (79,294)	579,815 (77,863)	7.36 (0.50)	7.57 (0.49)	30,934
Pessimistic scenario					
Deterministic	571,197	576,815	7.34	7.44	55,698
Probabilistic: μ(σ)	56,3159 (93,028)	568,738 (93,609)	7.29 (0.59)	7.39 (0.58)	55,470

Results


12,000.0
10,000.0
8,000.0
6,000.0
4,000.0
2,000.0
0.0
Differences in costs
0.00
0.05
0.10
0.15
0.20
Differences in QALY
Treatment during Mild Cognitive Impairment and Mild Alzheimer´s Disease (without second order uncertainty)
Treatment during Mild Cognitive Impairment and Mild Alzheimer´s Disease (with second order uncertainty)
Treatment during Mild Cognitive Impairment (without second order uncertainty)
Treatment during Mild Cognitive Impairment (with second order uncertainty)
30,000 $/QALY threshold


1.0
0.8
0.6
0.4
0.2
0.0
Probability of Cost-Effectiveness
0
20,000
40,000
60,000
80,000
100,000
Willingness to Pay Threshold ($)
Treatment during Mild Cognitive Impairment and Mild Alzheimer´s Disease (with second order uncertainty)
Treatment during Mild Cognitive Impairment (with second order uncertainty)

Discussion

- To date, *Lecanemab* and *Donanemab* phase 3 clinical trials have had a follow-up of 18 months. Although new trials with follow-ups of up to 4 years are underway [38,39], models remain a necessary tool for extrapolating results.
  - Probabilistic Sensitivity Analysis (PSA) with Cholevsky
  - Scenario analysis to address waning effect
- In the absence of evidence on the medium-term duration of treatment, we can place the real ICUR somewhere between the averages of the two ellipses of the cost-effectiveness plane.
- Limitations:
  - Application of a linear function in the MMRM model to represent the progression of functional decline in AD. More complex MMRM models using splines would possibly be more accurate in terms of the natural history of AD
  - A further limitation was the utilization of synthetic data for the construction of the MMRM model, which would not be valid for the purpose of making reimbursement recommendations as the treatment effect was implemented by a simple assumption.

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