Time Delay – A Meaningful Outcome of Disease Modification in Alzheimer's Disease

ISPOR Europe 2023 - Educational Symposia

Tuesday, 14 November Bella Center Copenhagen

We would like to start with an introduction to our panel speakers today

Time Delay: A Meaningful Outcome of Disease Modification in Alzheimer's Disease – *ISPOR 2023 Educational Symposium*

Max Schlueter - *Moderator*

Affiliation: Real World Solutions, IQVIA

Role: Principal

Birgitta Martensson

Affiliation: Person Living with AD, Alzheimer Schweiz Suisse Svizzera

Role: Former CEO

Time Delay - Educational Symposia

Anja Schiel

Affiliation: Norwegian Medicines Agency (NoMA)

Role: Lead Methodologist in Regulatory and Pharmacoeconomic Statistics

Julie Hviid Hahn-Pedersen

Affiliation: Novo Nordisk A/S

Role: Global Associate Director, Global Payer Evidence

Linus Jönsson

Affiliation: Karolinska Institutet

Role: Professor / Health Economics Expert

The symposia includes a broad set of perspectives outlining why a novel approach measuring time delay is of value

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Agenda for the Educational Symposia

Panel title: Time Delay - a meaningful outcome of disease modification in Alzheimer's disease		
Speakers (in order)	**Section Title**	**Duration (minutes)**
Max Schlueter, IQVIA	• Agenda and topic introduction • Why benefit to persons living with AD has been challenging to demonstrate in early disease stages	**10**
Birgitta Martensson, person living with AD	• Perspective of what's important to someone living with AD (and their care partners), and specifically what the value/impact of a time delay could represent to someone with AD	**10**
Julie Hahn-Pedersen, Novo Nordisk	• A novel method for assessing outcomes in AD, focusing on a potential slowing of progression and the resulting increased time in earlier, less severe phases of the disease	**10**
Linus Jönsson, Karolinska Institute	• The novel method Vs. other commonly used outcome measures in AD and the potential for application to health economic evaluation of novel technologies in AD	**10**
Anja Schiel, NoMA	• The novel approach in the context of an evolving HTA landscape where the topic of surrogate outcomes remains controversial	**10**
NA	Q&A with audience	**10**

Firstly, we will discuss why the benefit of AD therapies in early AD has been difficult to quantify to date

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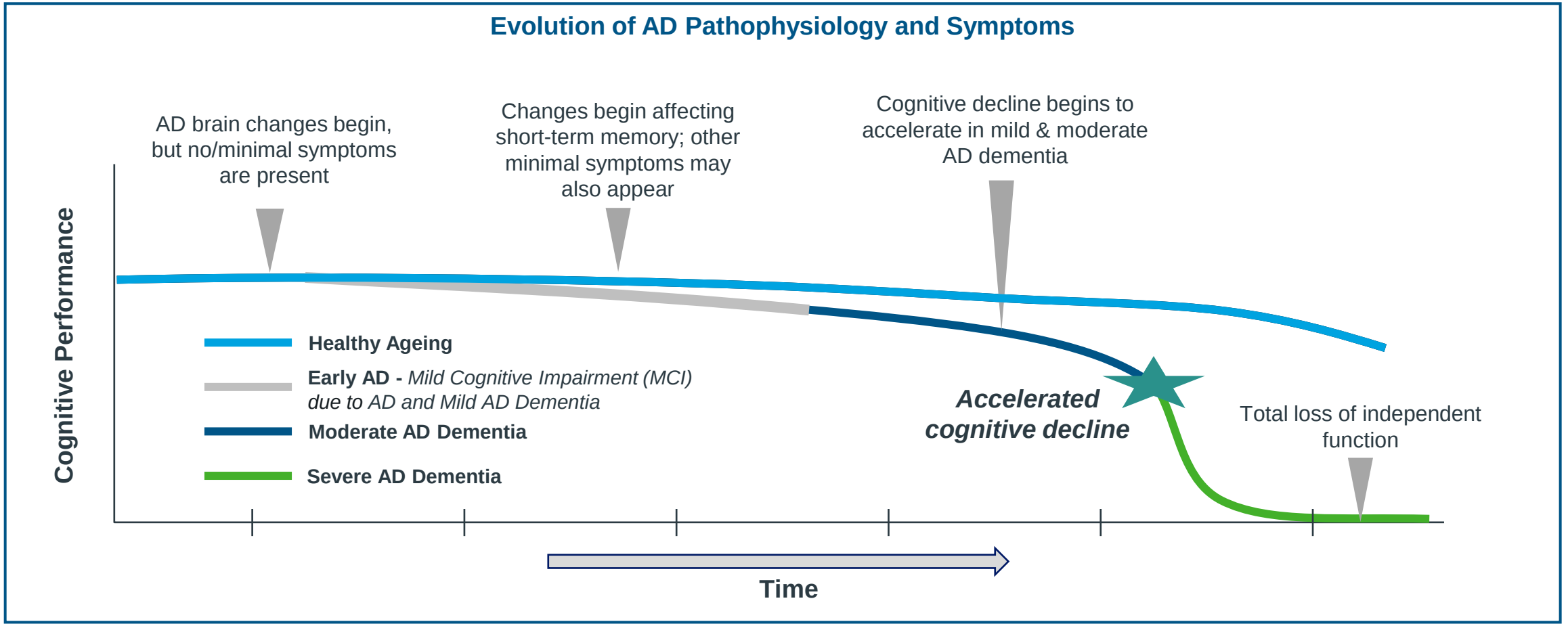
Disclosures

IQVIA Disclosures

- IQVIA have been commissioned by Novo Nordisk to facilitate this educational symposium

AD development is progressive, with only moderate decline in cognitive functioning in the early stages of disease

Staging of AD Development

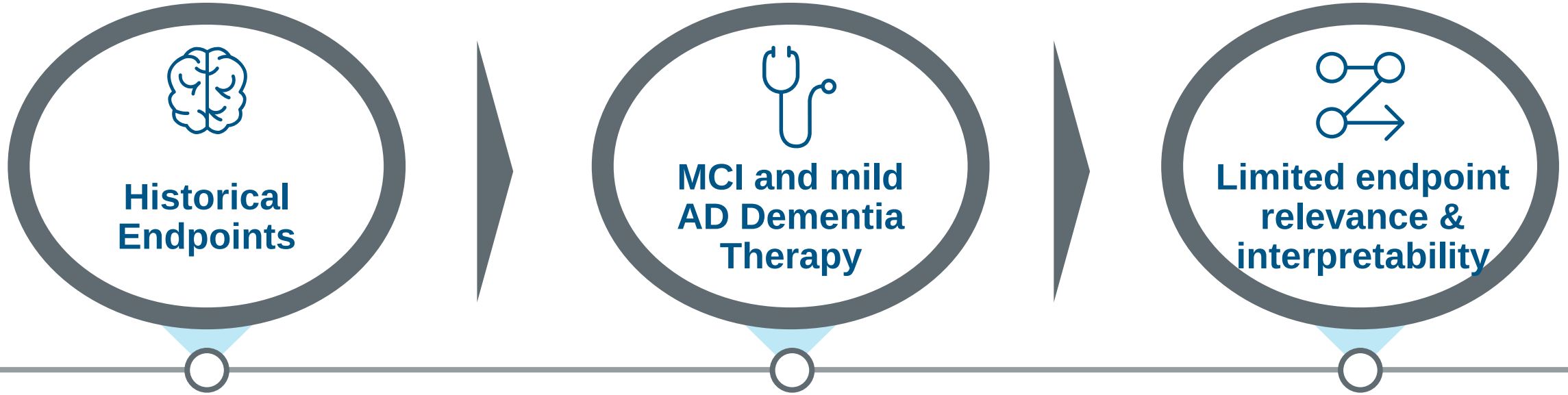


Adapted from Sperling, et al. Alzheimer's Dementia. 2011

Abbreviations: AD = Alzheimer's Disease

Outcome measures designed for more progressed AD struggle to quantify potential treatment effect in MCI and Mild AD

Endpoint Appropriateness in MCI and mild AD Dementia



Endpoints Designed for moderate or severe AD Dementia

- Memory and functional **deficits more obvious**
- Clinical scales (e.g. CDR & Global Deterioration) traditionally work as objective measures of cognitive function[1]

Shift Towards Therapeutics Targeting MCI and mild AD Dementia

- **High variability** in trial participant baseline functioning and cognitive abilities[2]
- Slower decline in early disease means **cohort differences are likely to be less pronounced** in clinical trials[3]

Need for new methods to quantify treatment effect in MCI due to AD

- The subtle point differences between cohorts become more **difficult to translate into meaningful outputs** with existing endpoints

1 – Schmitt F, et al. Alzheimer Dis Assoc Disord. 1997; 2 – Sabbagh M, et al. J Prev Alzheimer's Dis. 2020; 3 – Insel, et al. Neurology. 2019

Abbreviations: MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; CDR – Clinical Dementia Rating Scale

Point-in-time changes in endpoints such as the CDR-SB offer little interpretability and relevance

The CDR Sum of Boxes (CDR-SB) - Sum Score (0-18) of Six Cognitive & Functional Domains

Domain	0	Questionable cognitive impairment	Mild dementia	Moderate dementia	Severe dementia
Memory	…	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	…	…
Orientation	…	Fully orientated except for slight difficult with time relationships	Difficulty with time relationships; oriented for place at exam; geographic disorientation elsewhere	…	…
Judgement & problem solving	…	Slight impairment in solving problems, similarities and differences	Moderate difficult handling problems, similarities and differences; social judgement maintained	…	…
Community affairs	…	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some	…	…
Home and hobbies	…	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of home function; more difficult chores 7 hobbies abandoned	…	…
Personal care	…	Fully capable of self-care	Needs prompting	…	…

Total – Sum of Boxes				
0: Normal	**0.5-4.0:** Questionable cognitive impairment / MCI		**4.5-9.0:** Mild dementia	**9.5-15.5:** Moderate dementia	**16.0-18.0:** Severe dementia
	0.5-2.0: Questionable impairment	*2.5-4.0: Very mild dementia*			

Traditional endpoints (e.g. CDR-SB) offer limited utility in translating results from MCI and mild AD Dementia clinical trials into outcomes that are meaningful and easily interpretable

E.g. What does a treatment-induced improvement of 0.2 in CDR-SB mean for a person living with AD?

Abbreviations: AD = Alzheimer's Disease; MCI = Mild cognitive impairment

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Example Scoring

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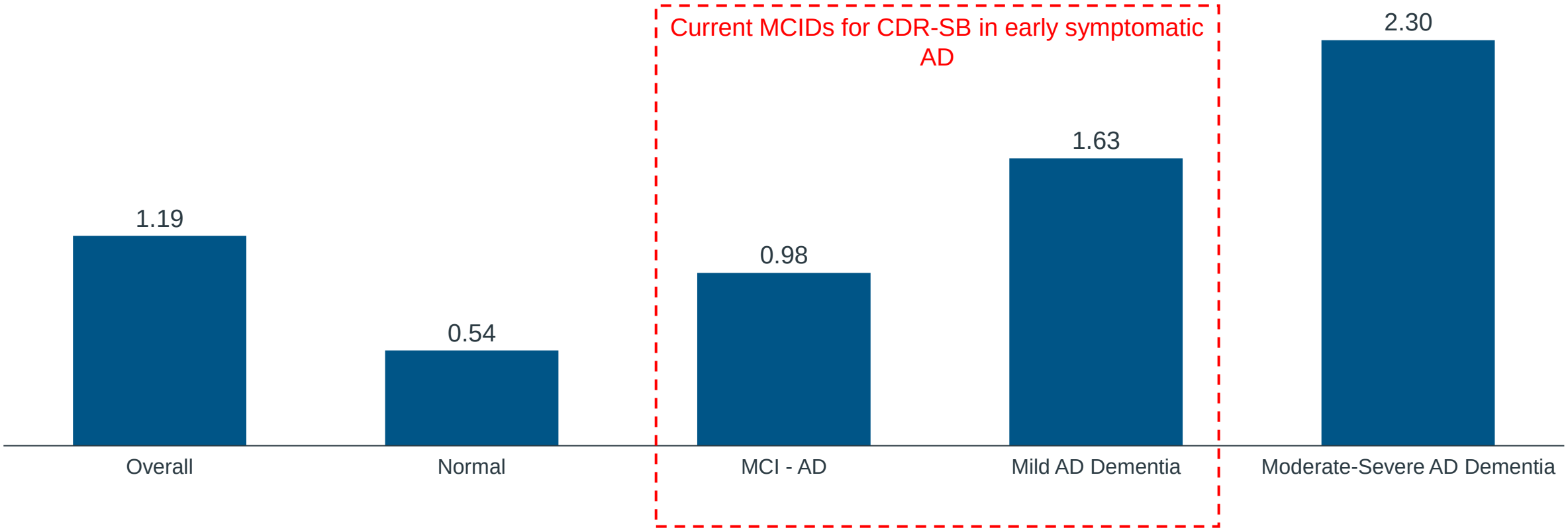
E.g. What does a treatment-induced improvement of 0.2 in CDR-SB mean for a person living with AD?

Abbreviations: AD = Alzheimer's Disease; MCI = Mild cognitive impairment

Additionally, MCIDs for point differences in CDR-SB are defined based on clinical assessment with no patient involvement

Minimal Clinically Important Differences (MCIDs) – CDR-SB

MCIDs (CDR-SB) – Clinicians assessment



Andrews J, et al. Alzheimer's Dement (N Y). 2019

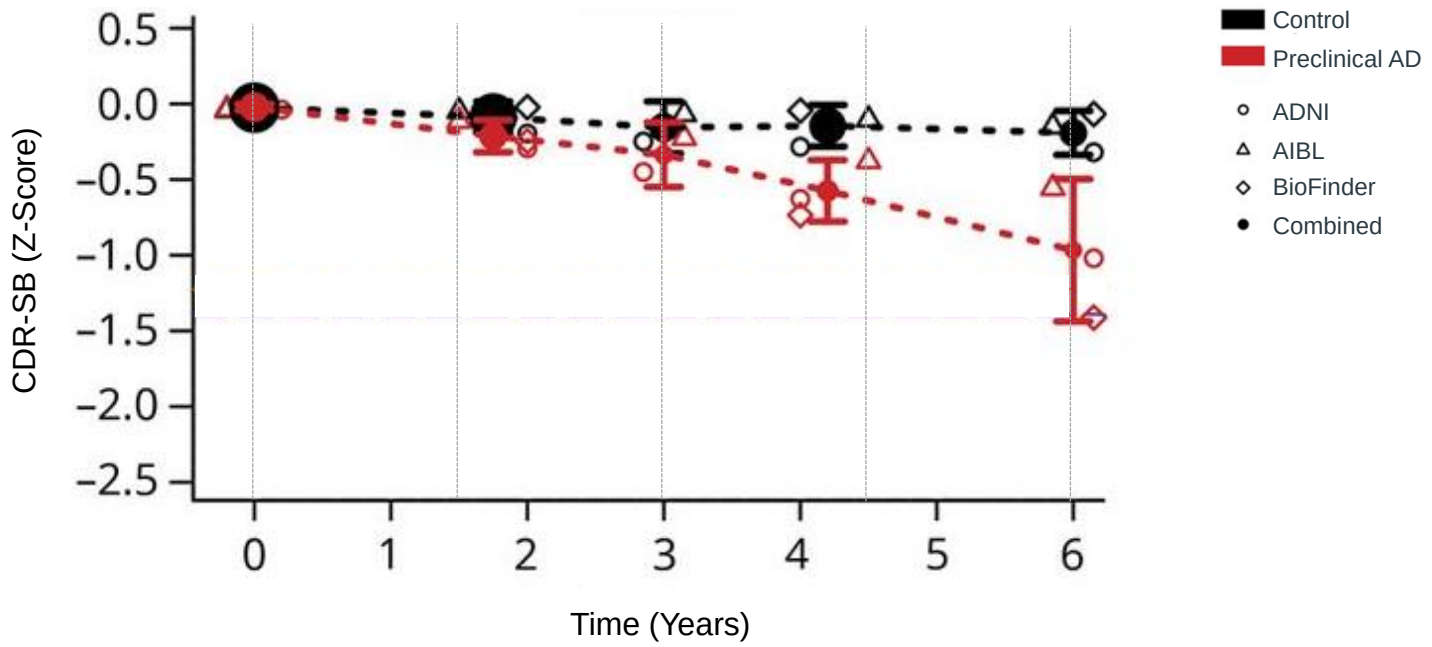
Abbreviations: MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease

In early phases of AD, we can expect point differences to not be “meaningful” when we implement typical trial designs

Time to Reach a Meaningful Decline in Preclinical AD

Starting a potential disease modifying therapy early in the disease process and assessing a meaningful effect during the relatively brief (e.g., 18-month) clinical trial period is essential to capture the value of a treatment

Decline in CDR-SB scores for Preclinical AD participants over a 6-year period



Preclinical AD groups take **~6-years to average a decline in CDR-SB of ~1.0**

Changes in the CDR-SB are minimal between epochs of 18-months (typical / realistic trial durations)

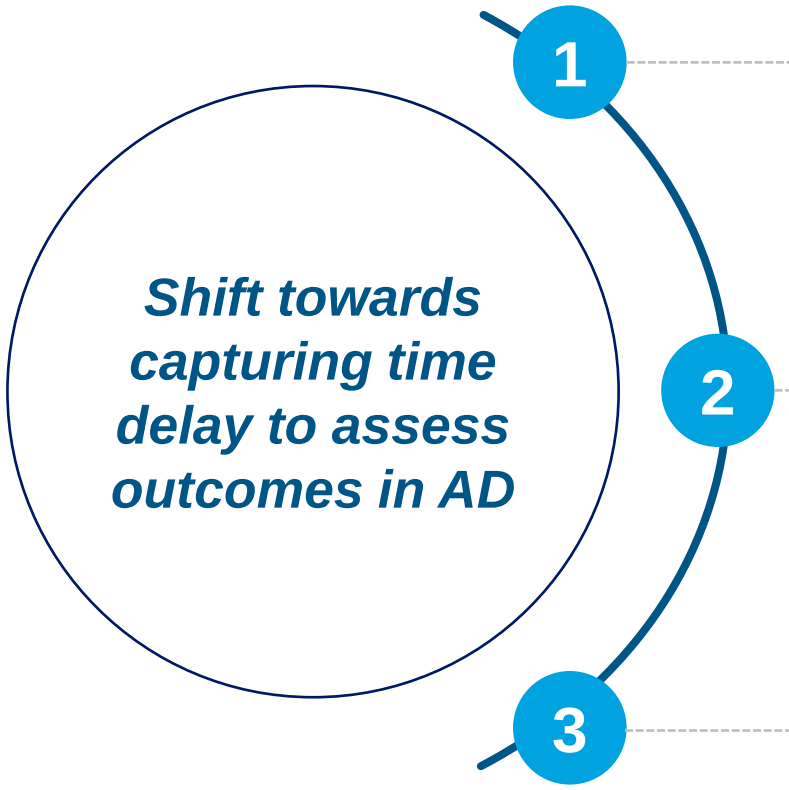
Either trials of excessive duration are required…or **we need a new way to assess treatment benefit in MCI and mild AD**

Adapted from Insel, et al. Neurology. 2019

Abbreviations: AD = Alzheimer’s Disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging, Biomarkers & Lifestyle; CDR-SB = Clinical Dementia Rating Sum of Boxes; MCI = Mild Cognitive Impairment

As standalone, traditional point differences have limited value in early AD given the challenges in showing meaningful benefit

Section Summary



Traditional endpoints for moderate & severe AD dementia lack suitability for assessing potential treatment benefit in early AD, mainly due to limited divergence between groups, thus limiting interpretability

Trials using such endpoints would typically **require extensive follow-up periods** for a meaningful point-difference to be observed between placebo and treatment arms

However, a potential slowing of disease progression is of **high importance for people living with early AD**, even if not deemed “clinically meaningful”, requiring alternative methods to quantify this in a meaningful way

We will now pass over to Birgitta Martensson to provide perspective as a person living with AD

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NA	Q&A with audience	10

Next, we will present the time delay method as a meaningful outcome of disease modification in AD

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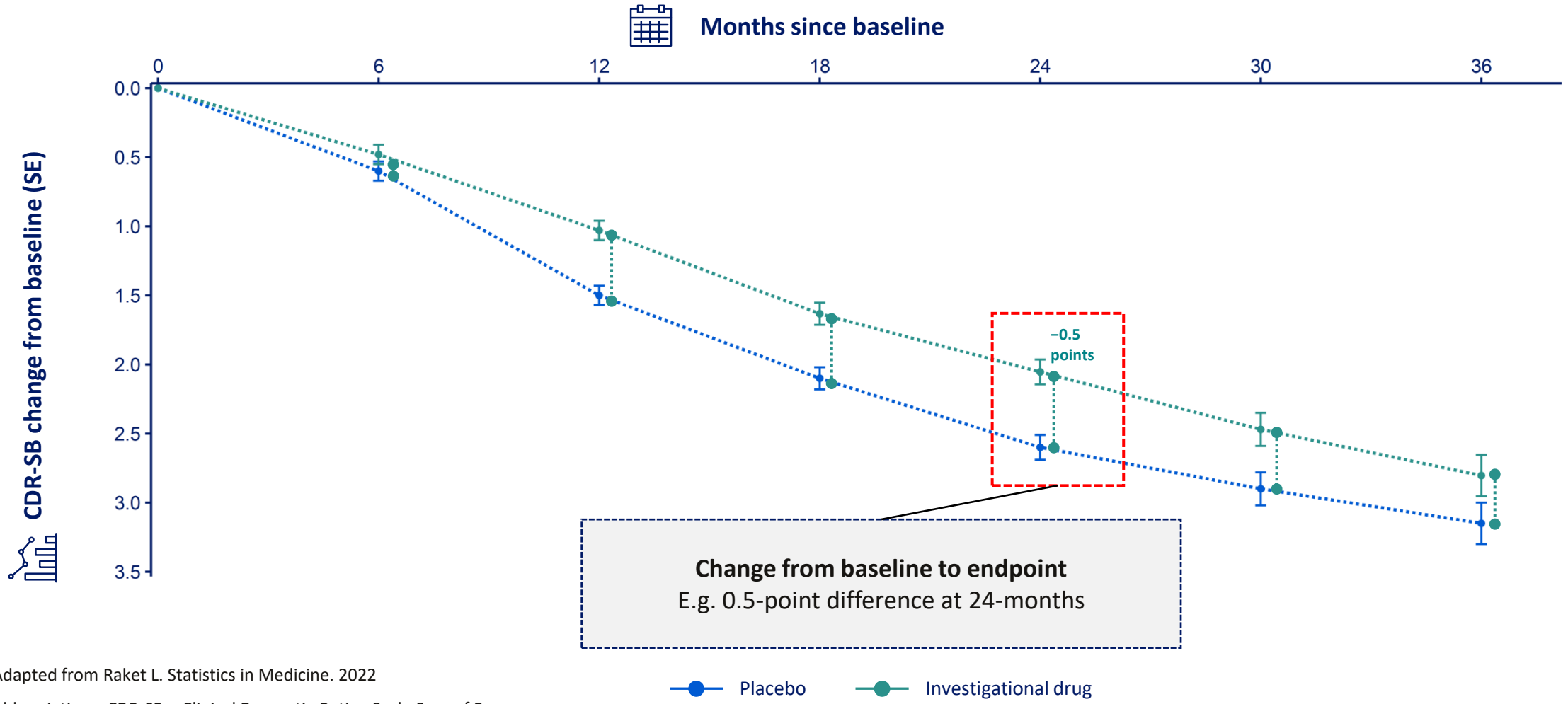
Traditional methods focus on the potential treatment-induced change in the outcome measure from baseline at a fixed time point

Mixed Model for Repeated Measures - "Traditional"



Adapted from Raket L. Statistics in Medicine. 2022

Abbreviations: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes

The time delay allows quantification of treatment outcomes for potential DMTs that aim to slow disease progression

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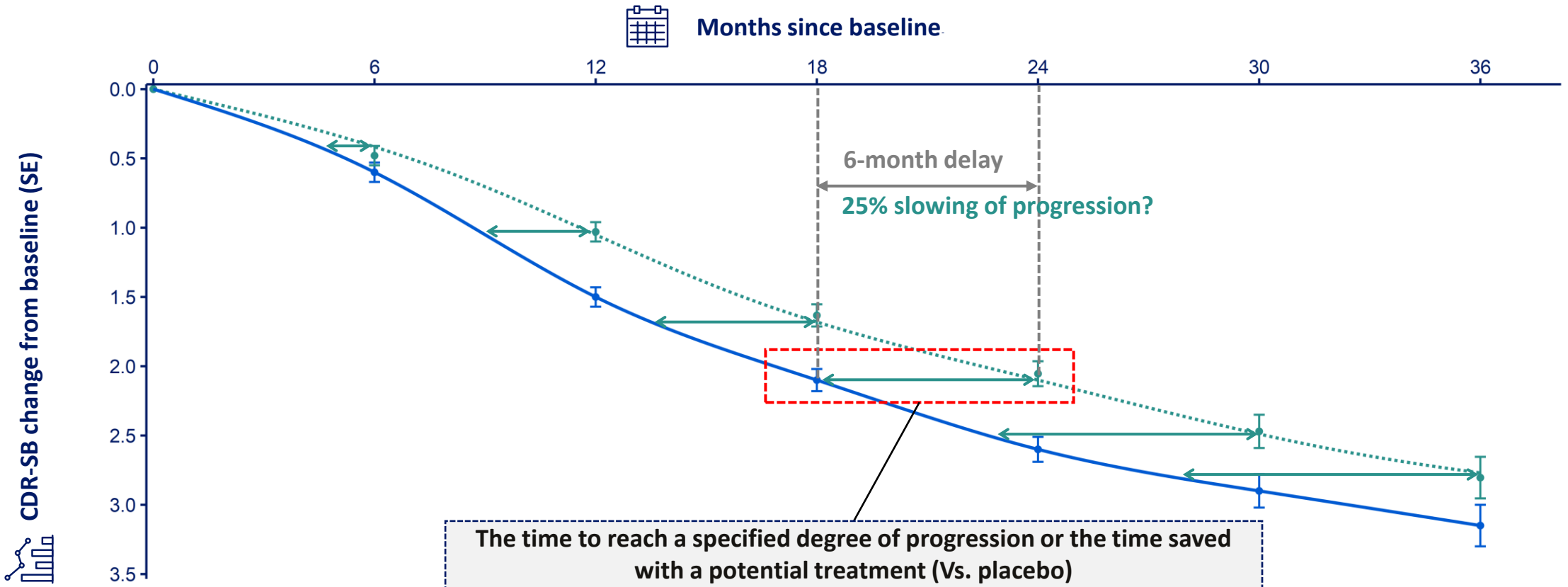
Progression Model for Repeated Measures - "Novel"



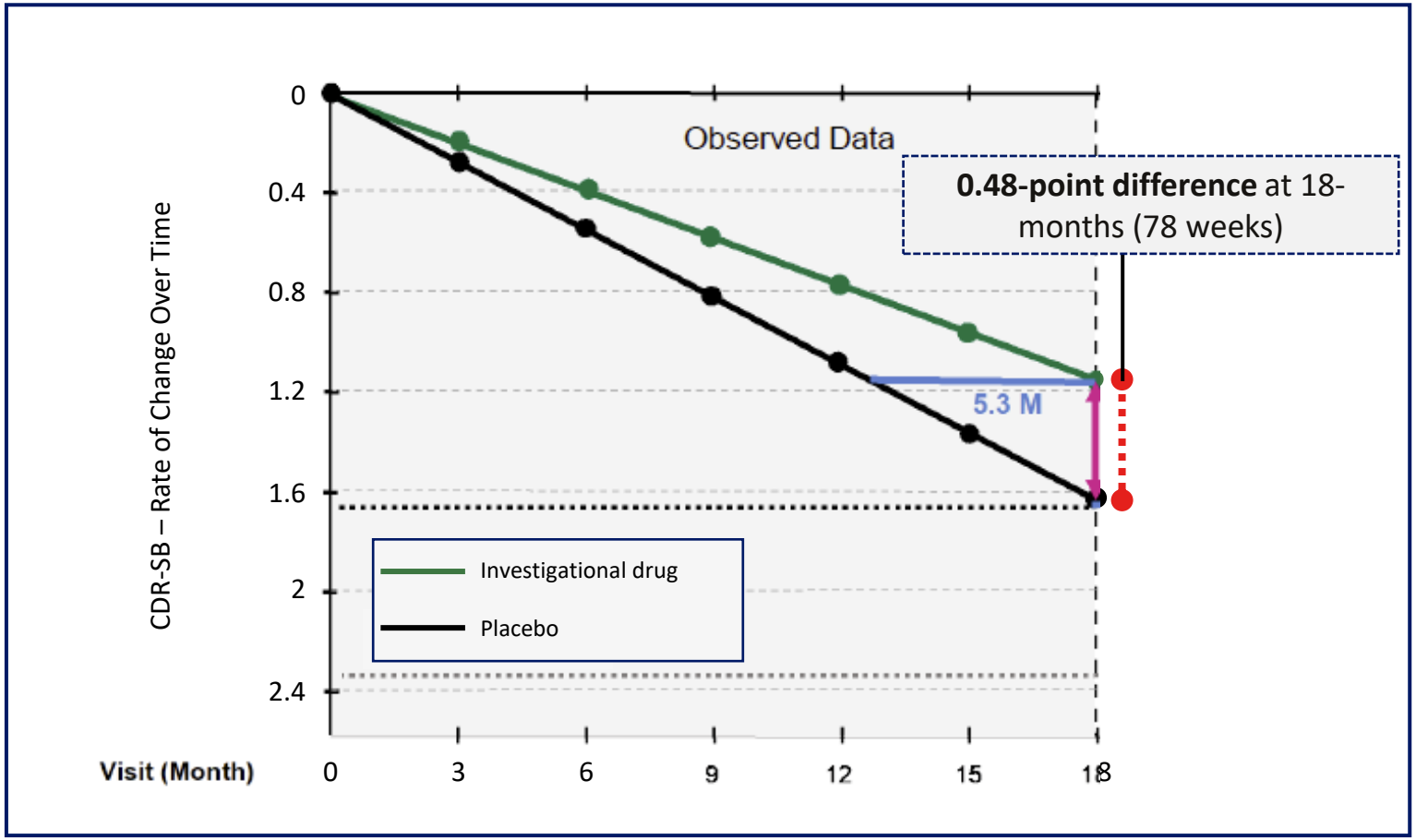
Adapted from Raket L. Statistics in Medicine. 2022

Abbreviations: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes

Time Delay Applied to Recent Clinical Trial Examples

A recent phase III trial showed a delayed decline in CDR-SB by 5.3-months after 18-months

Time Delay Applied to Recent Clinical Trial Examples (1/2)



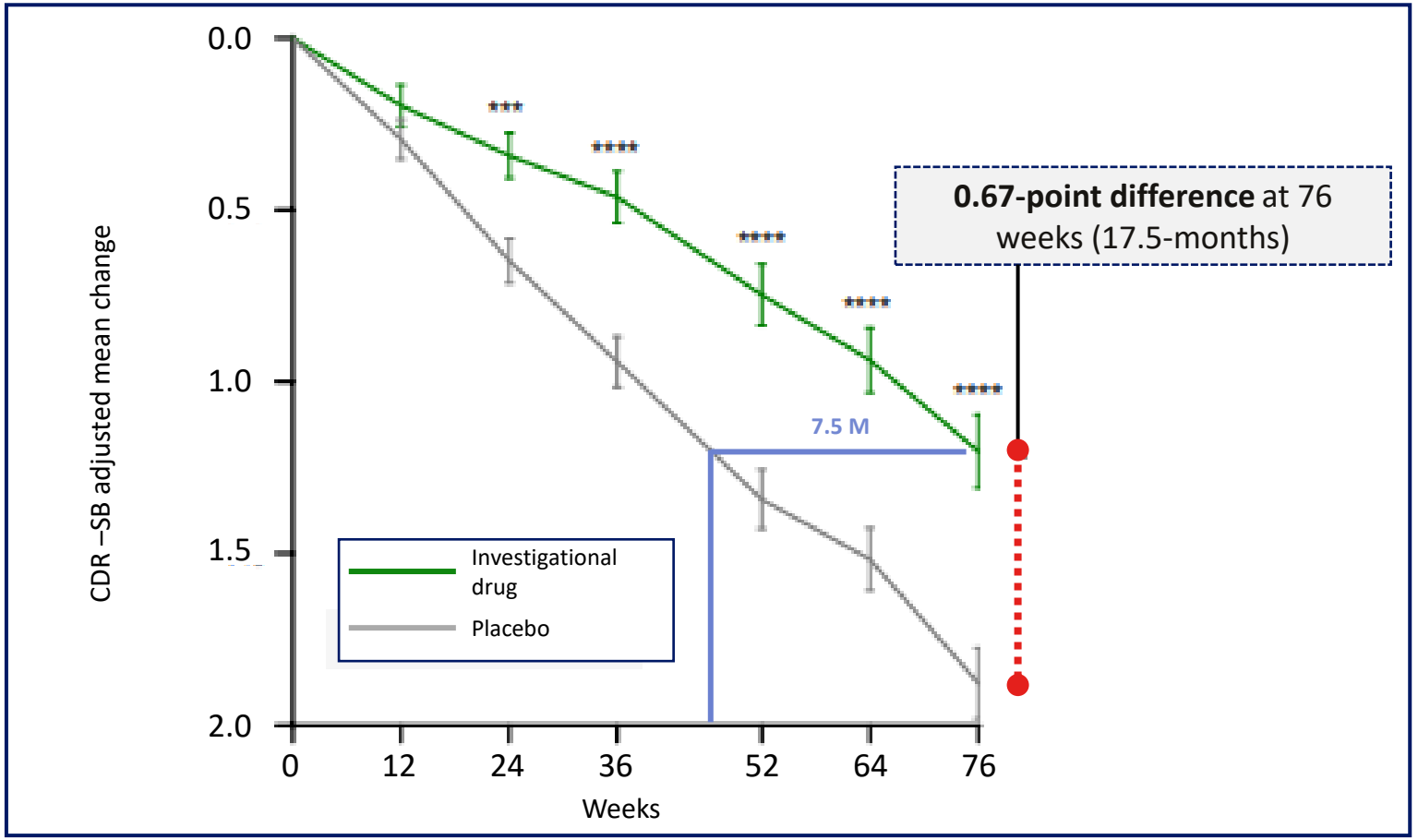
The investigational arm took 18 months (78.2 weeks) to reach the same CDR-SB level as placebo at 12.7 months (55.2 weeks)
=
5.3-month (23.0-week) delay in disease progression

Adapted from Van Dyck, et al. NEJM. 2023

Abbreviations: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes

For another phase III trial, the time delay method showed a delay in CDR-SB decline by ~7.5-months

Time Delay Applied to Recent Clinical Trial Examples (2/2)



The investigational arm took 17.5 months (76.0 weeks) to reach the same CDR-SB level as placebo at 10.0 months (43.4 weeks)*

=

7.5-month (32.6 week) delay in disease progression*

Adapted from Sims J, et al. JAMA. 2023

*When assessed with PMRM; ***P<0.001; ****P<0.0001; Abbreviations: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; PMRM = Progression Models for Repeated Measures; AD = Alzheimer's Disease; PMRM = Progression Model for Repeated Measures

Current Minimal Clinically Important Differences (MCID)

Current MCIDs are based on clinician assessment and unlikely to reflect what is meaningful to people with AD

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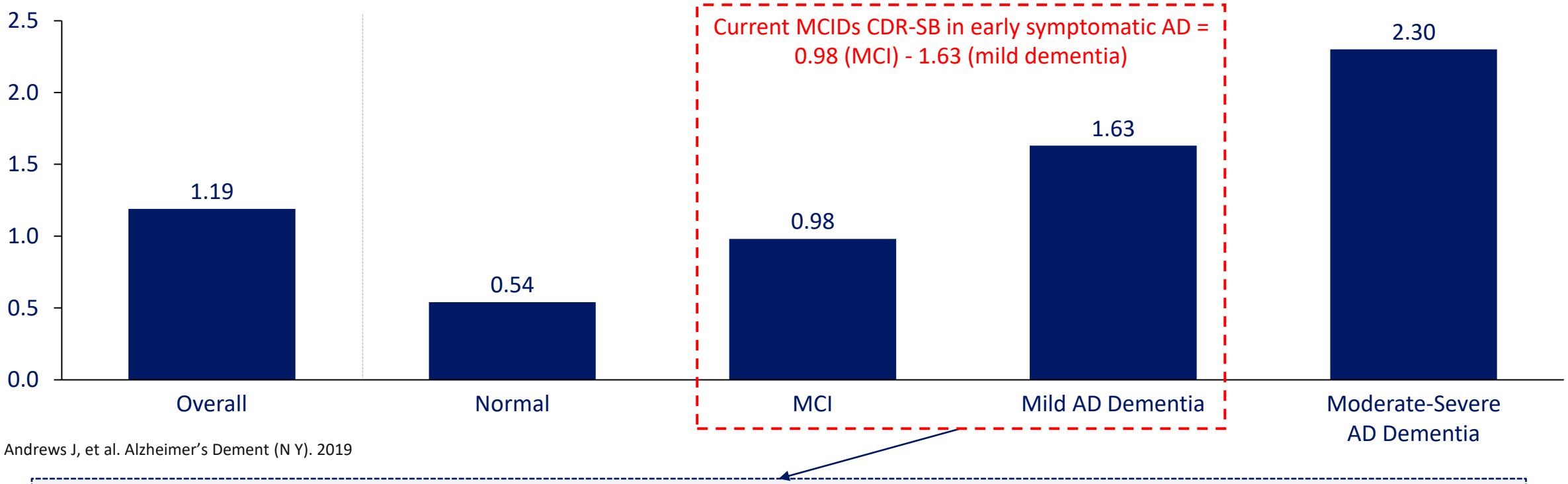
MCIDs in CDR-SB

MCID for CDR-SB—Overall and by Disease Severity as per clinicians' assessment of meaningful decline



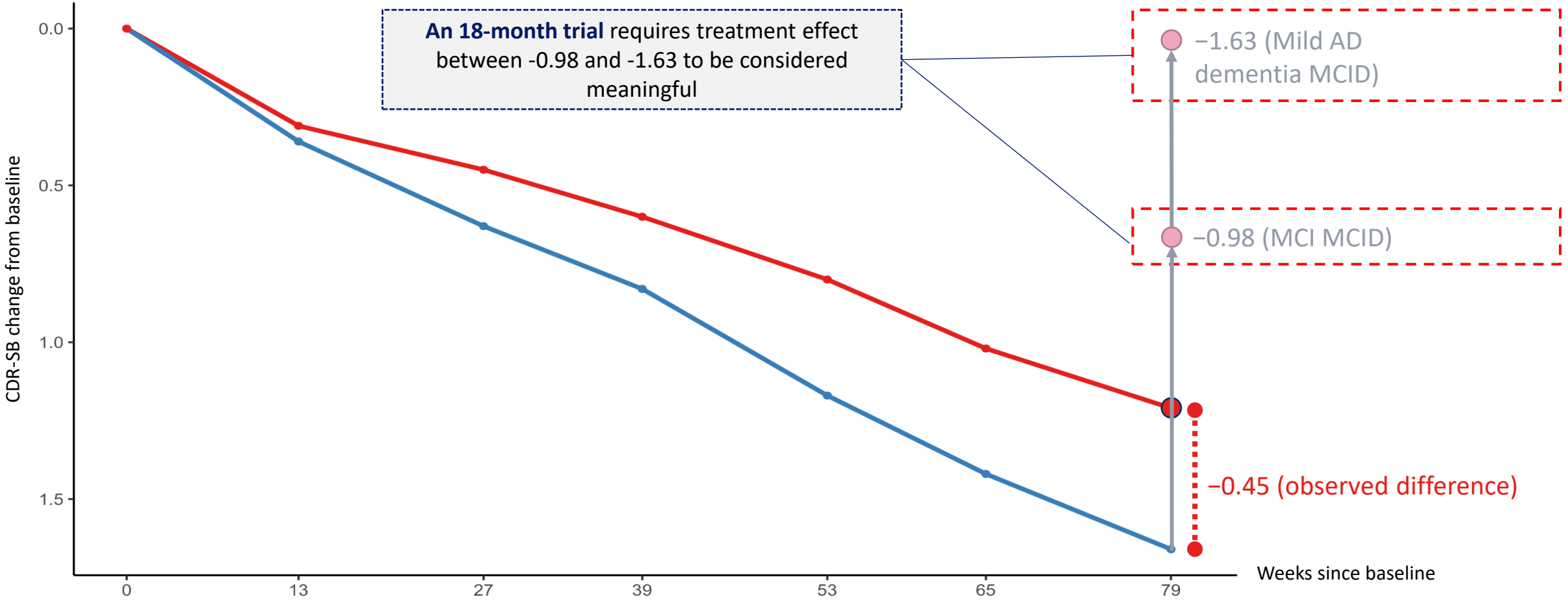
Andrews J, et al. Alzheimer's Dement (N Y). 2019

Such anchor-based estimates from clinicians of **MCIDs are unlikely to resemble what is meaningful to people living with AD** and are **not likely to be reached in MCI and Mild AD Dementia over typical trial durations**

Abbreviations: MCID = Minimal Clinically Important Difference; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease

In a key recent clinical trial example, the investigational arm did not reach half of what would be considered clinically meaningful

Observed Difference for Recent Clinical Trial Examples and MCIDs

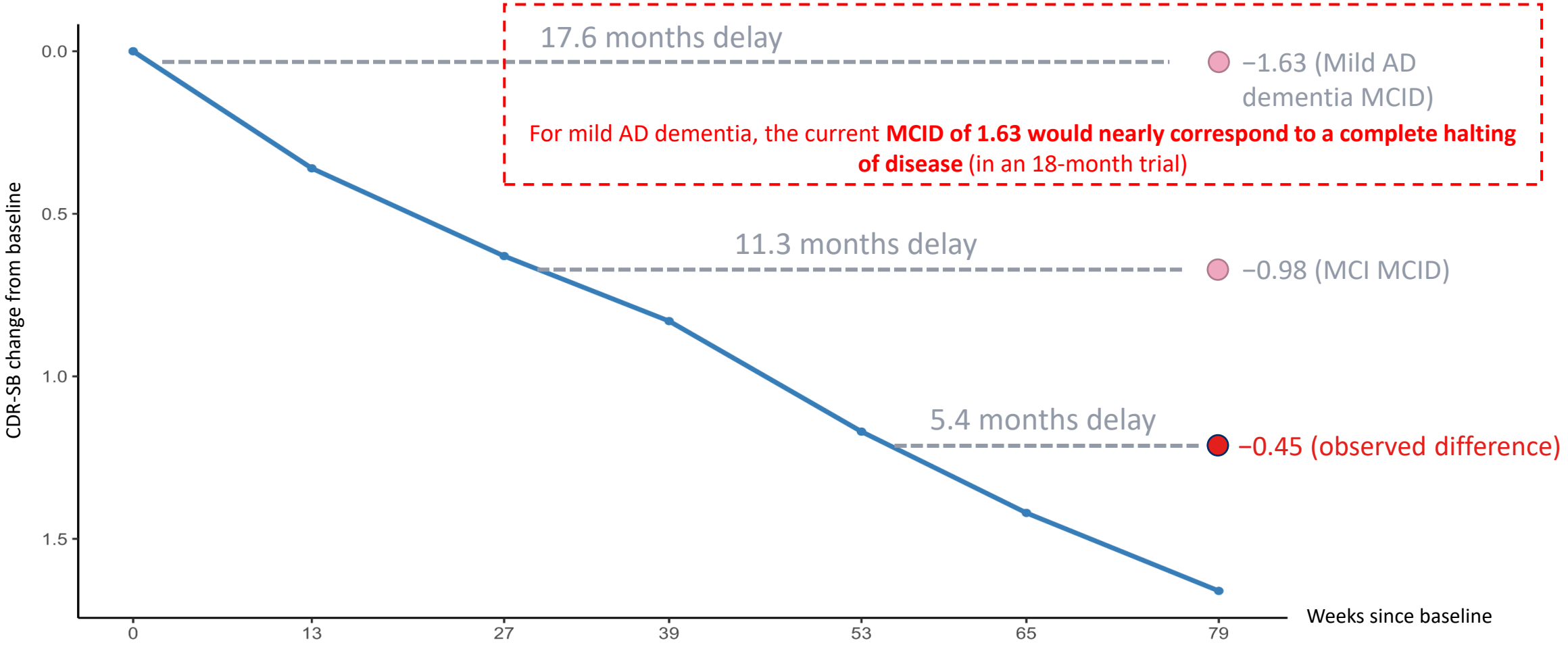


Adapted from Lanctôt K, et al. Alzheimer's Association International Conference (Featured Research Symposium). 2023

Abbreviations: MCID = Minimal Clinically Important Difference; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease

Over 18-months, the example would have had to effectively halt disease progression to reach mild AD dementia MCID

Placebo Trajectory for Recent Clinical Trial Examples and Corresponding Time Delay MCIDs



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Abbreviations: MCID = Minimal Clinically Important Difference; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease

Example: Given current MCID thresholds, a 67% slowing of disease progression may not have been considered meaningful

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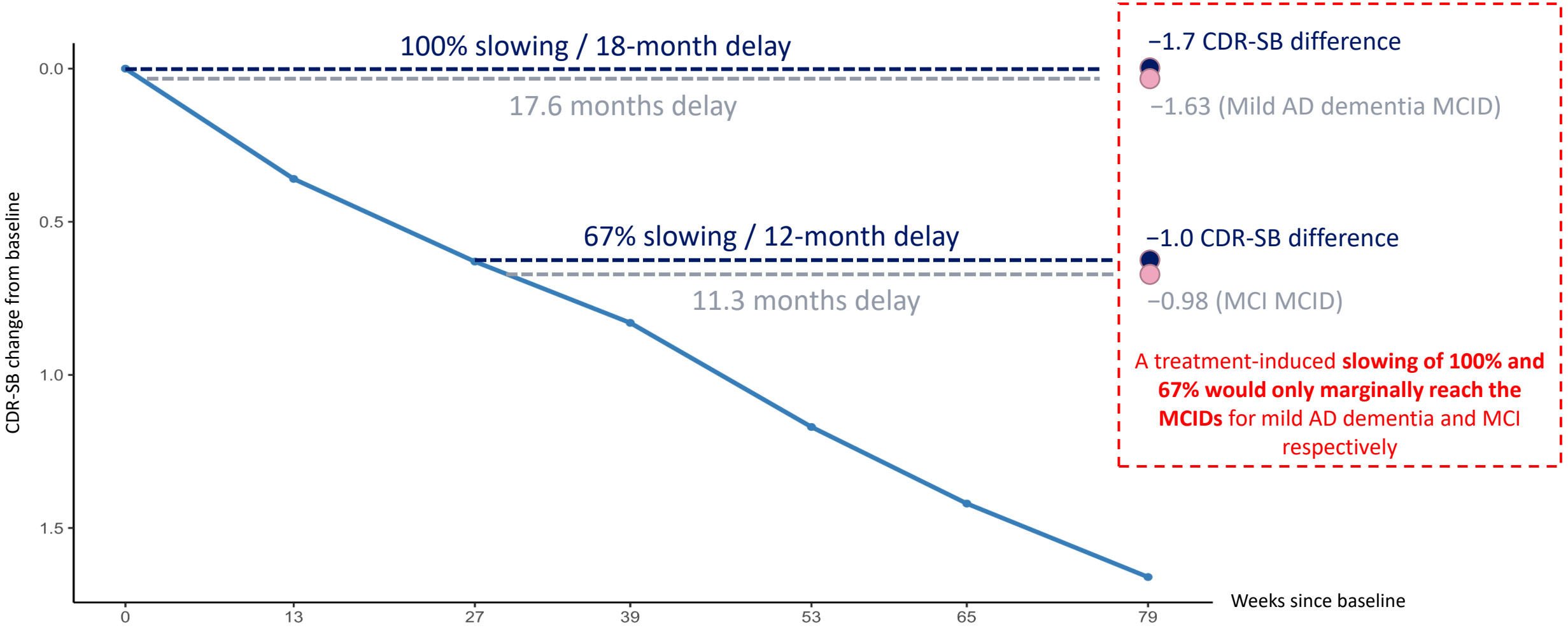
Placebo Trajectory for Recent Clinical Trial Examples and Corresponding Time Delay MCIDs



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Section Summary

The time delay method offers a potentially more intuitive method to quantify slowing of progression in clinical trials

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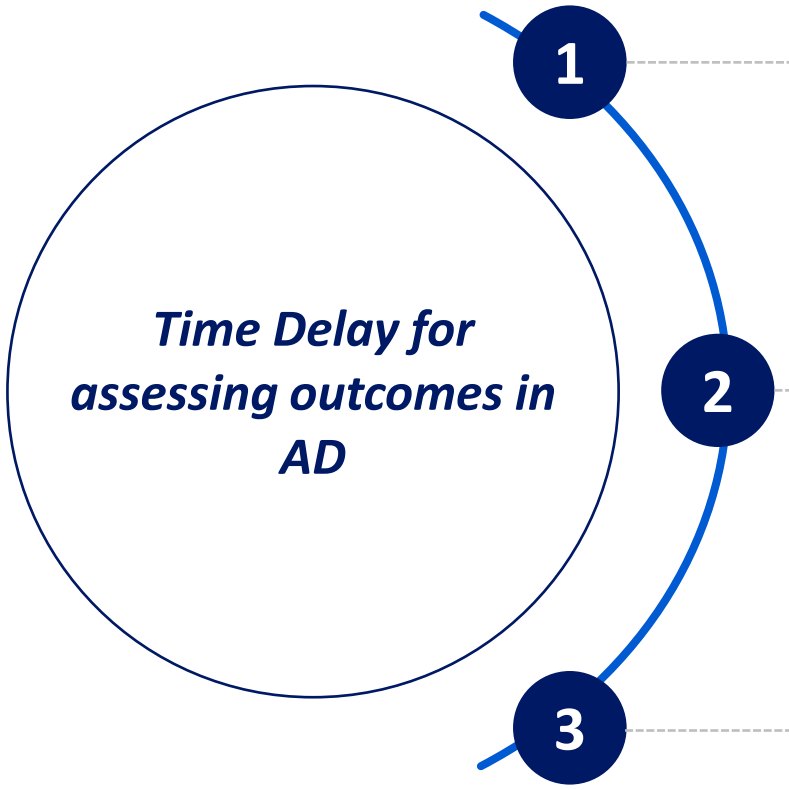
Section Summary



1. The novel approach of **quantifying delay** focuses on time to reach a specified degree of disease progression and **enables treatment effect for potential DMTs to be quantified** in AD

2. The time delay method for quantifying outcomes **can be applied to examples of recent clinical trials to show potential meaningful delays in disease progression** for investigational drugs over trial durations

3. However, for the full benefit in AD DMT trials to be realised, **further research is required to establish the MCID for time delay from people living with AD's perspective**

Abbreviations: AD = Alzheimer's Disease; DMT = Disease Modifying Therapy; MCID = Minimal Clinically Important Difference

We will now consider the time delay method in the context of health economic modelling and evaluation

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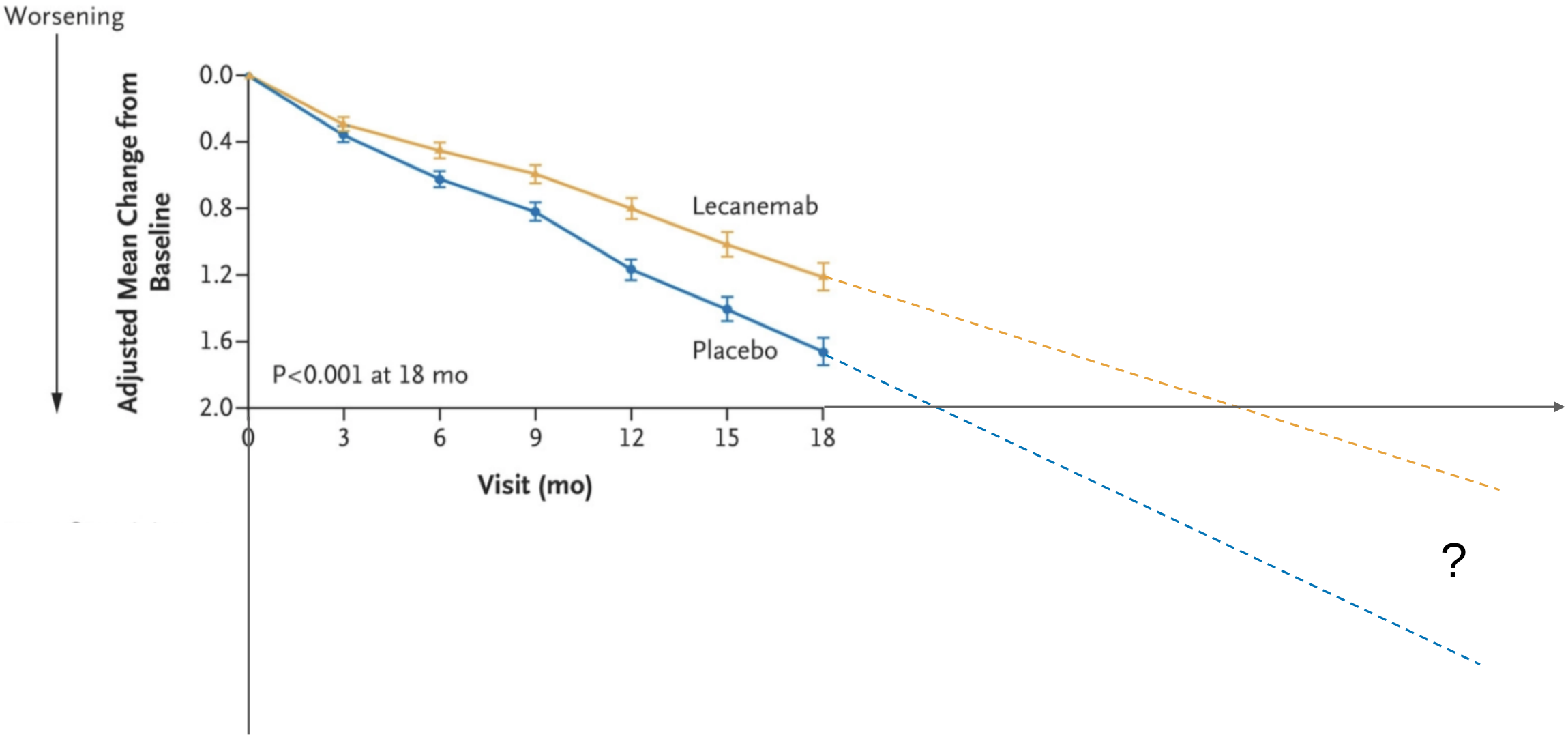
Time delay – the right outcome for economic evaluations of disease modification in Alzheimer's disease?

Linus Jönsson MD MSc PhD
Professor of Health Economics
Section for Neurogeriatrics, Department of Neurobiology, Care Sciences and Society

Disclosures

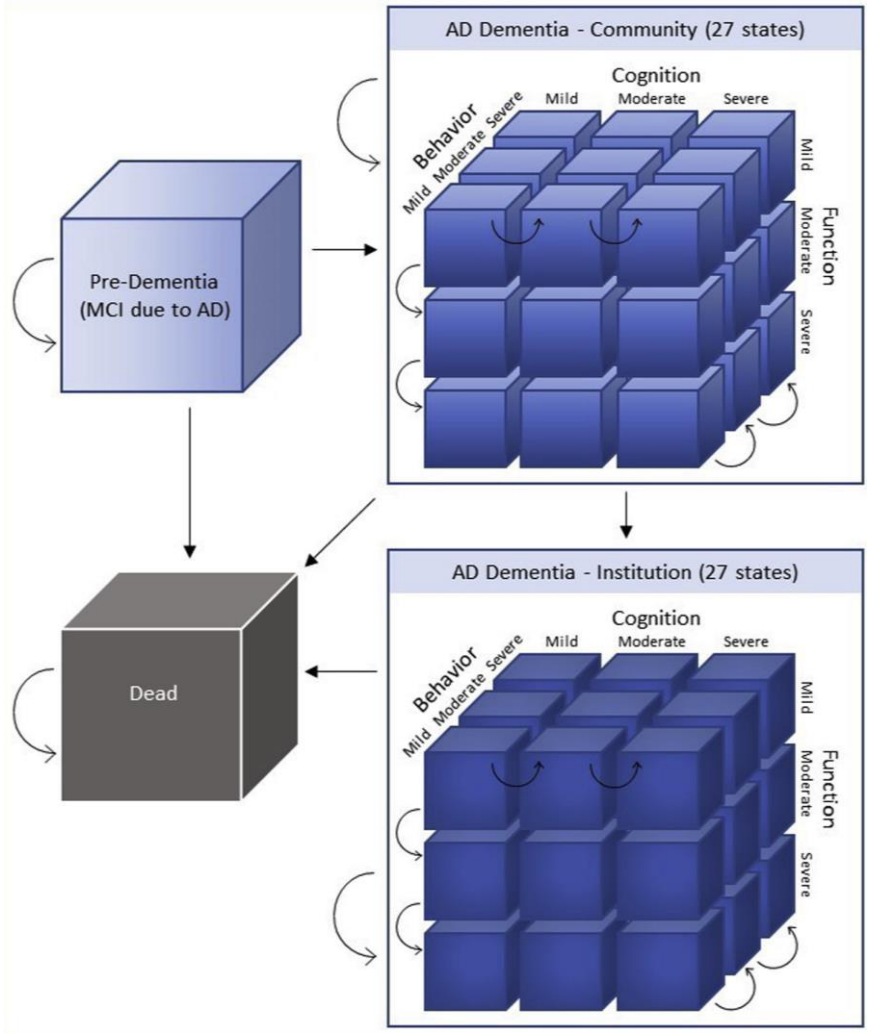
- Lundbeck A/S
- Novo Nordisk A/S
- Eli Lilly & Co.
- Janssen-Cilag Ltd.



Source: van Dyck, NEJM 2023

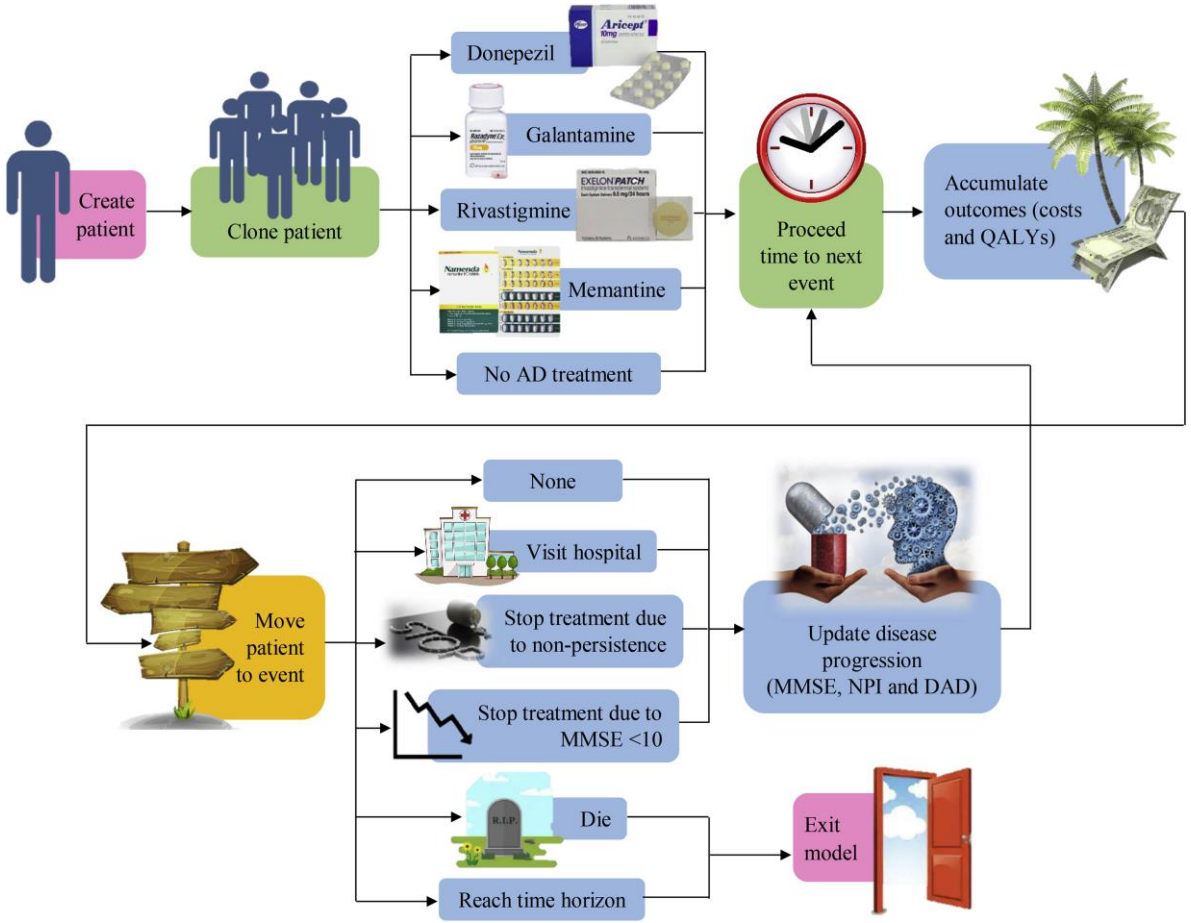
Health Economic models of Alzheimer's disease

Markov state-transition models

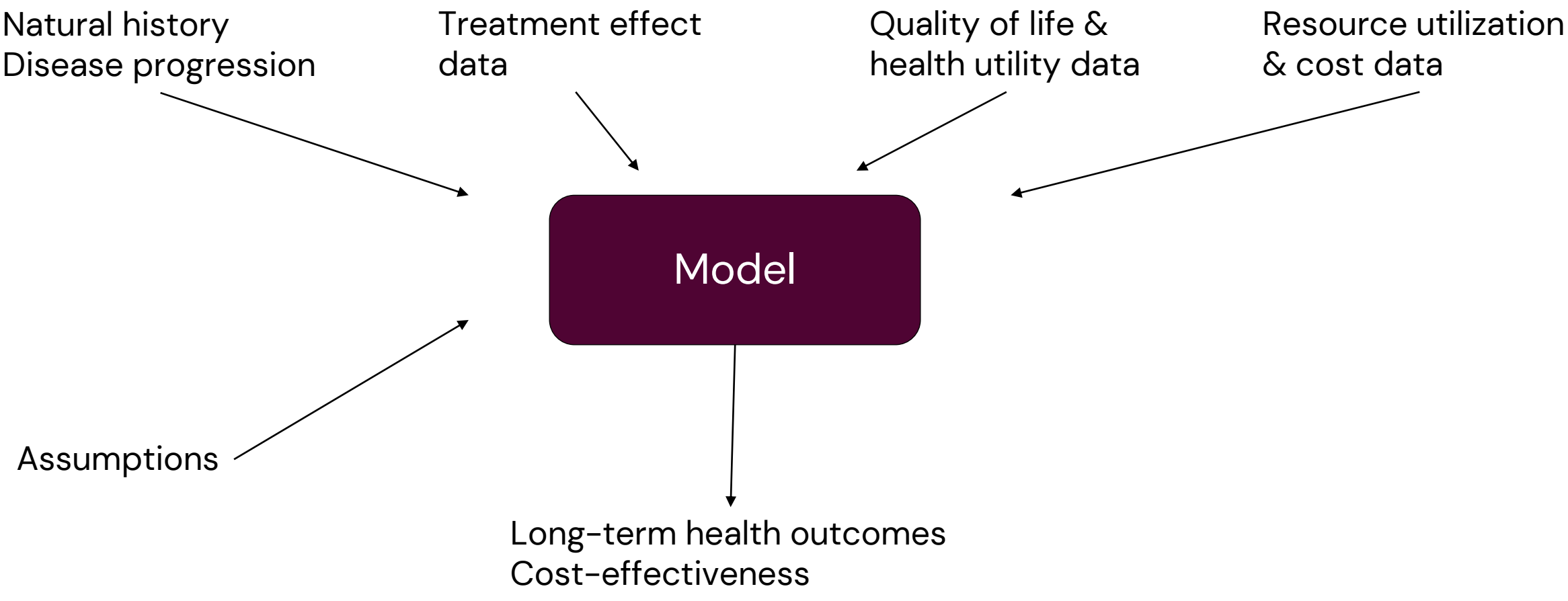


Green et al (2019)

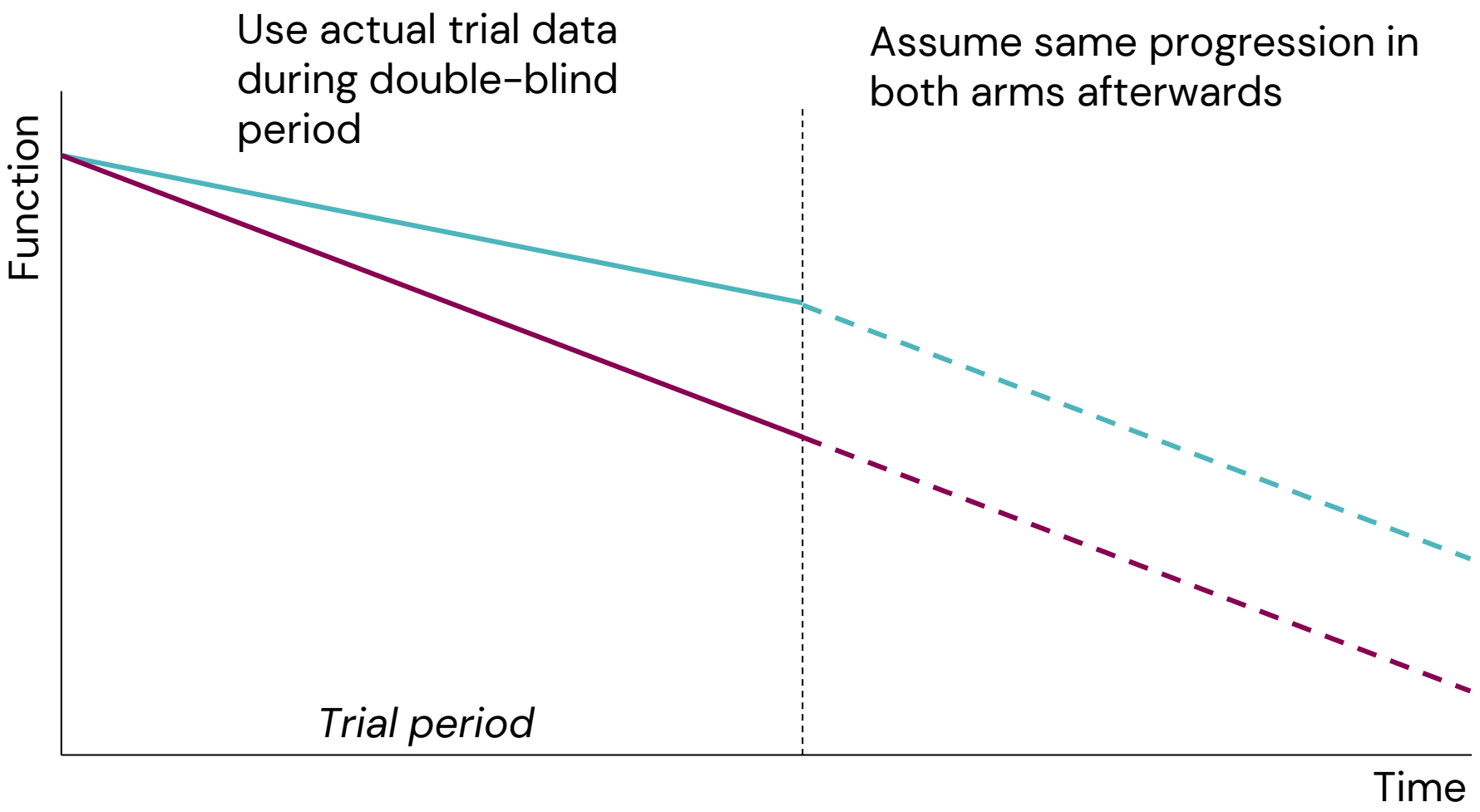
Discrete event / microsimulation models



Kongpakwattana et al (2020)

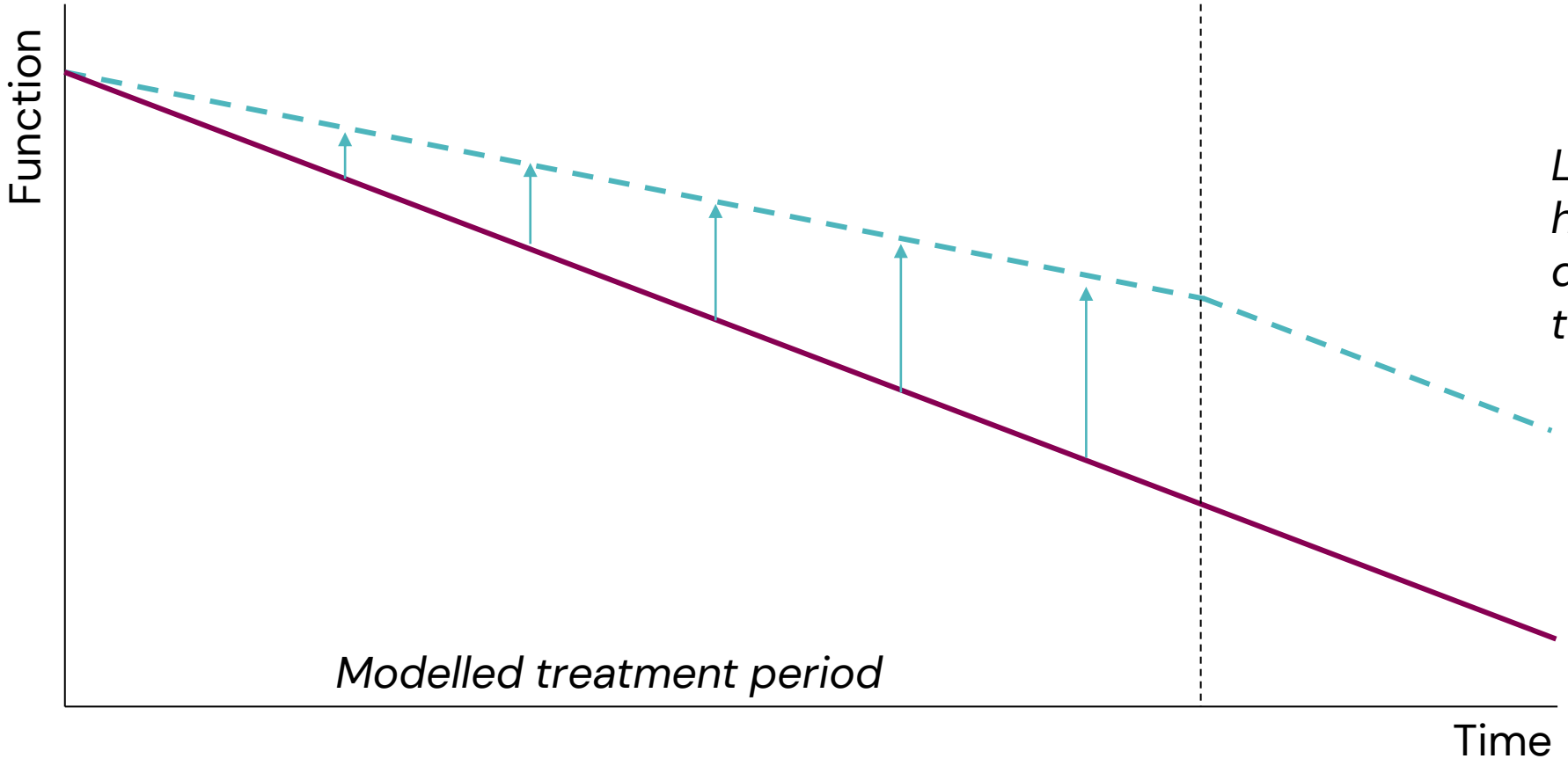

Natural history
Disease progression
Treatment effect
data
Quality of life &
health utility data
Resource utilization
& cost data
Model
Assumptions
Long-term health outcomes
Cost-effectiveness

Approach 1: minimum assumptions



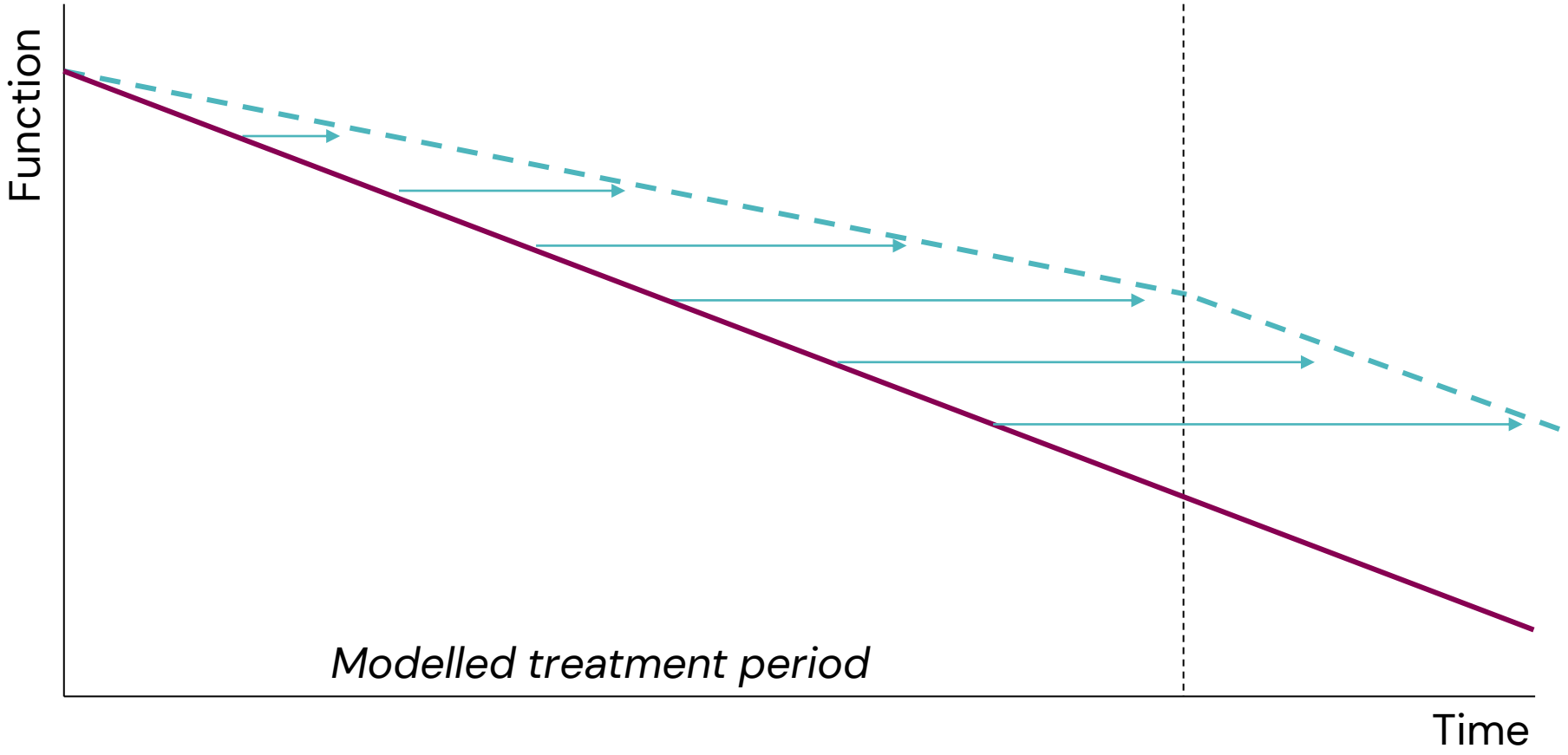
Limitation: cannot test different treatment duration assumptions

Approach 2: estimate treatment effect with conventional methods (change from placebo)

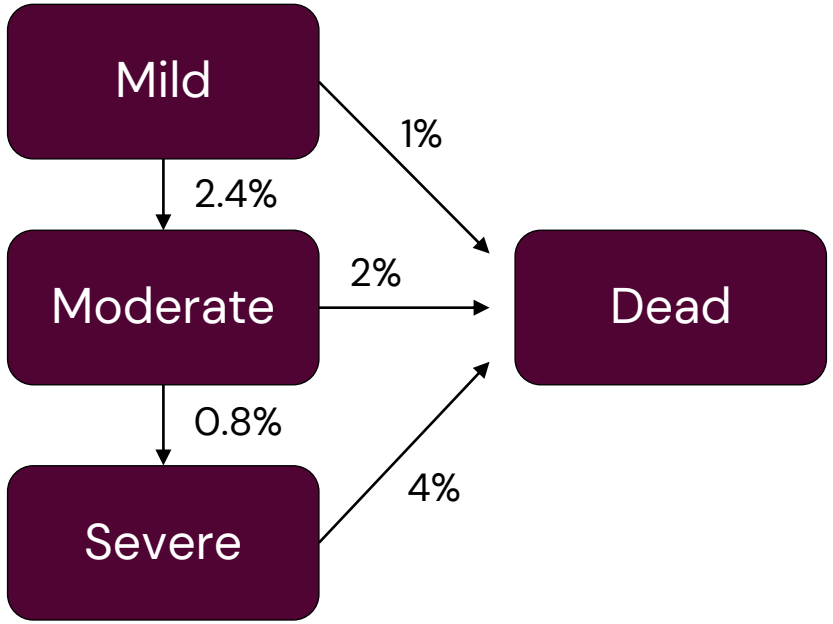


Limitation: model needs to have the same measure of disease severity as clinical trial

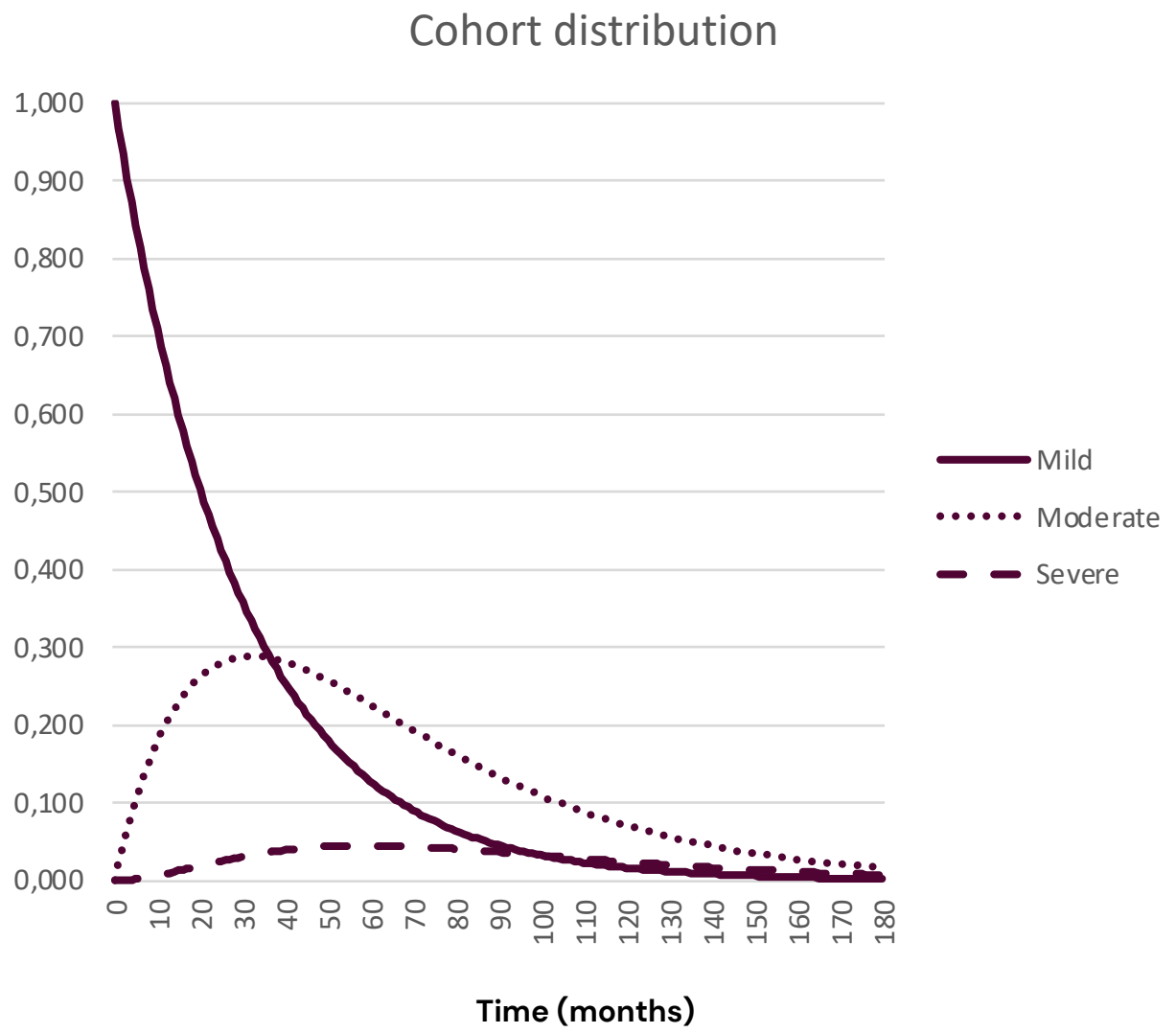
Approach 3: estimate treatment effect as time delay, apply in model



Example for illustration

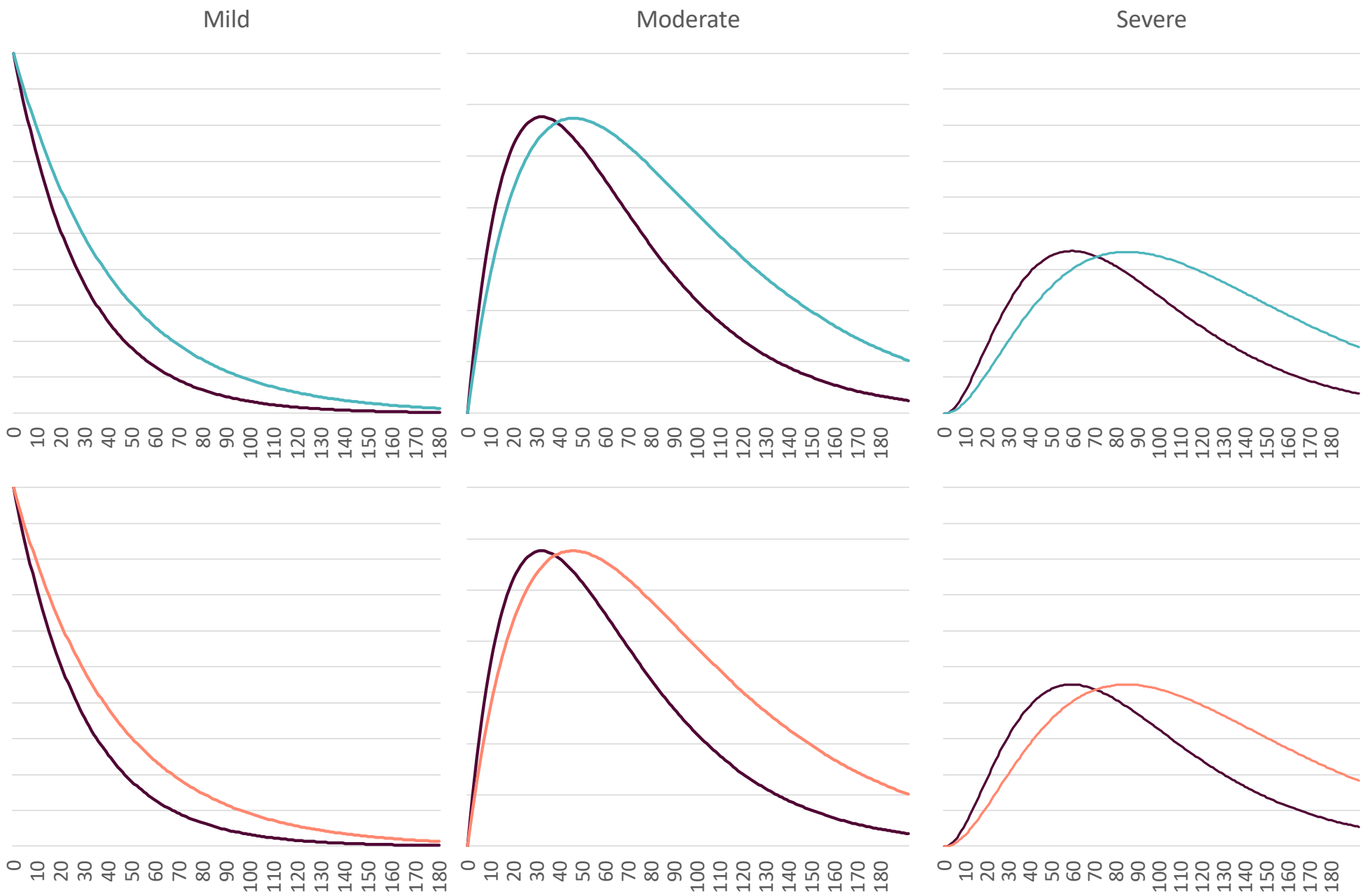


Constant monthly transition probabilities
Data from Swedish Dementia Registry

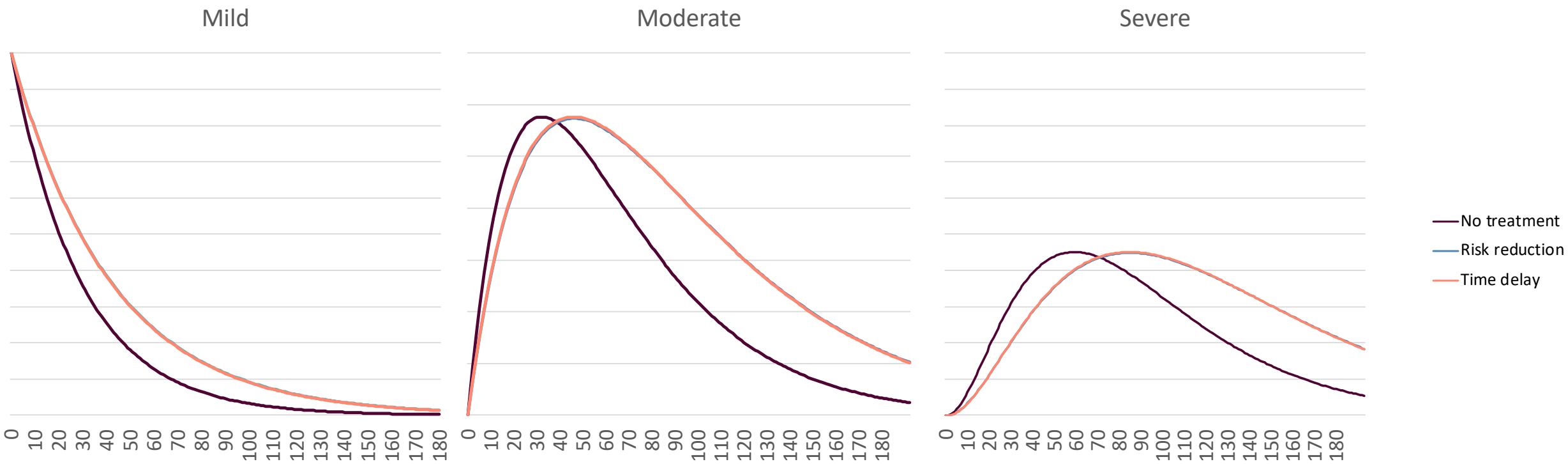


Reduced risk of progression by 30%

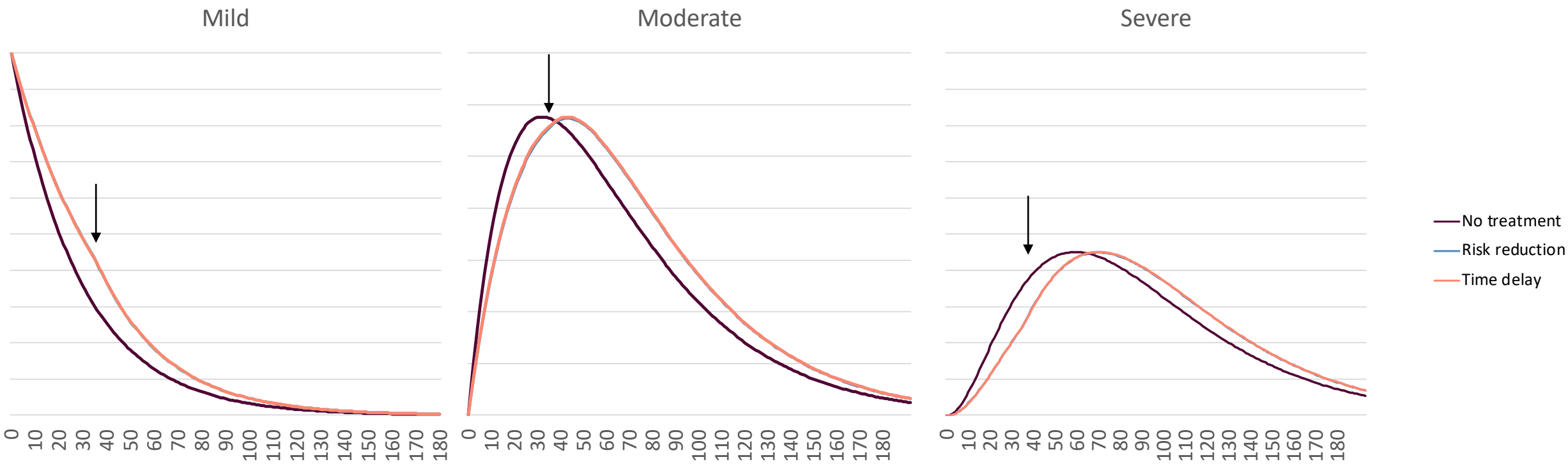
Time delay by 30%



Treatment effect: risk reduction or time delay



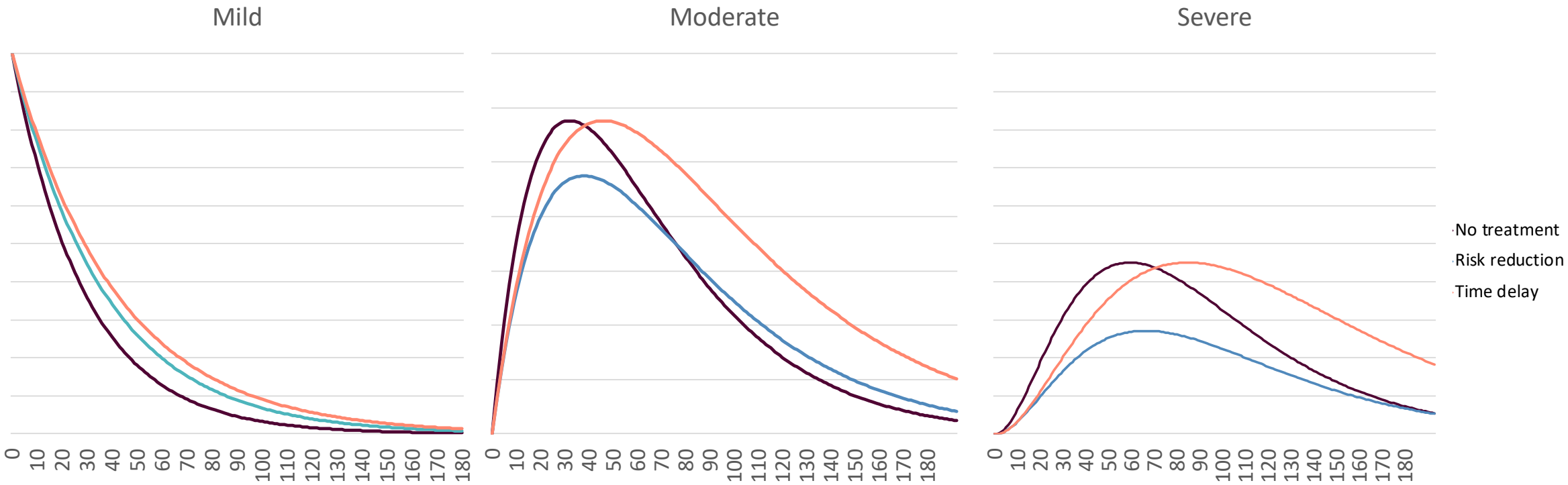
Stopping treatment after 36 months



Mortality

- Potential effect of treatment on mortality
  - → Direct effect
  - → Indirect effect: lower mortality due to less time in severe states
- Time delay by default affects all transitions, including mortality
  - → Only effect on ‘attributable mortality’?

Consequences of alternative mortality assumptions



No direct treatment effect on mortality with ‘risk reduction’ method

Conclusions

- Treatment effects can be implemented in health economic models as a time delay.
- In a simple Markov model framework with constant transition probabilities, a time delay effect is identical to a reduction of transition probabilities
  - → This will not hold for more complex models
- Advantages:
  - → less dependent on choice of outcome measure
  - → intuitive interpretation
- Limitations:
  - → Cannot model improvements with treatment
- Specific handling of mortality effects required

Acknowledgements

- Lars Lau Raket
- Anders Gustavsson
- Ron Handels
- Alireza Atri
- Milana Ivkovic
- Julie Hviid Hahn-Pedersen

Karolinska Institutet

And finally, we will consider the applicability of the time delay method to the HTA assessment process

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Agenda for the Educational Symposia

Panel title: Time Delay - a meaningful outcome of disease modification in Alzheimer's disease (AD)		
Speakers (in order)	**Section Title**	**Duration (minutes)**
Max Schlueter, IQVIA	• Agenda and topic introduction • Why benefit to persons living with AD has been challenging to demonstrate in early disease stages	10
Birgitta Martensson, person living with AD	• Perspective of what's important to someone living with AD (and their care partners), and specifically what the value/impact of a time delay could represent to someone with AD	10
Julie Hahn-Pedersen, Novo Nordisk	• A novel method for assessing outcomes in AD, focusing on a potential slowing of progression and the resulting increased time in earlier, less severe phases of the disease	10
Linus Jönsson, HE expert	• The novel method Vs. other commonly used outcome measures in AD and the potential for application to health economic evaluation of novel technologies in AD	10
Anja Schiel, NoMA	• The novel approach in the context of an evolving HTA landscape where the topic of surrogate outcomes remains controversial	**10**
NA	Q&A with audience	10

Surrogate endpoints – controversial and context dependent

ISPOR / 14-11-2023, Copenhagen

Anja Schiel, PhD, Special Adviser / Lead Methodologist in Regulatory and Pharmacoeconomic Statistics

- Scientific Advice Working Party member
- Methodology Working Party member
- Member HTACG JSC sub-group

Norwegian Medicines Agency

Disclaimer

The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of the Norwegian Medicines Agency (NoMA), the European Medicines Agency (EMA) or its scientific committees, nor the European Commission's Health Technology Assessment Coordination group (HTACG).

There are many guidelines.....

PharmacoEconomics (2020) 38:1055–1070
https://doi.org/10.1007/s40273-020-00935-1

REVIEW ARTICLE

Check for updates

Surrogate Endpoints in Health Technology Assessment: An International Review of Methodological Guidelines

Bogdan Grigore[1] · Oriana Ciani[1,2] · Florian Dams[3] · Carlo Federici[2] · Saskia de Groot[4] · Meilin Möllenkamp[5] · Stefan Rabbe[5] · Kosta Shatrov[3] · Antal Zemplenyi[6,7] · Rod S. Taylor[1,8]

Published online: 23 June 2020

There are many guidelines.....

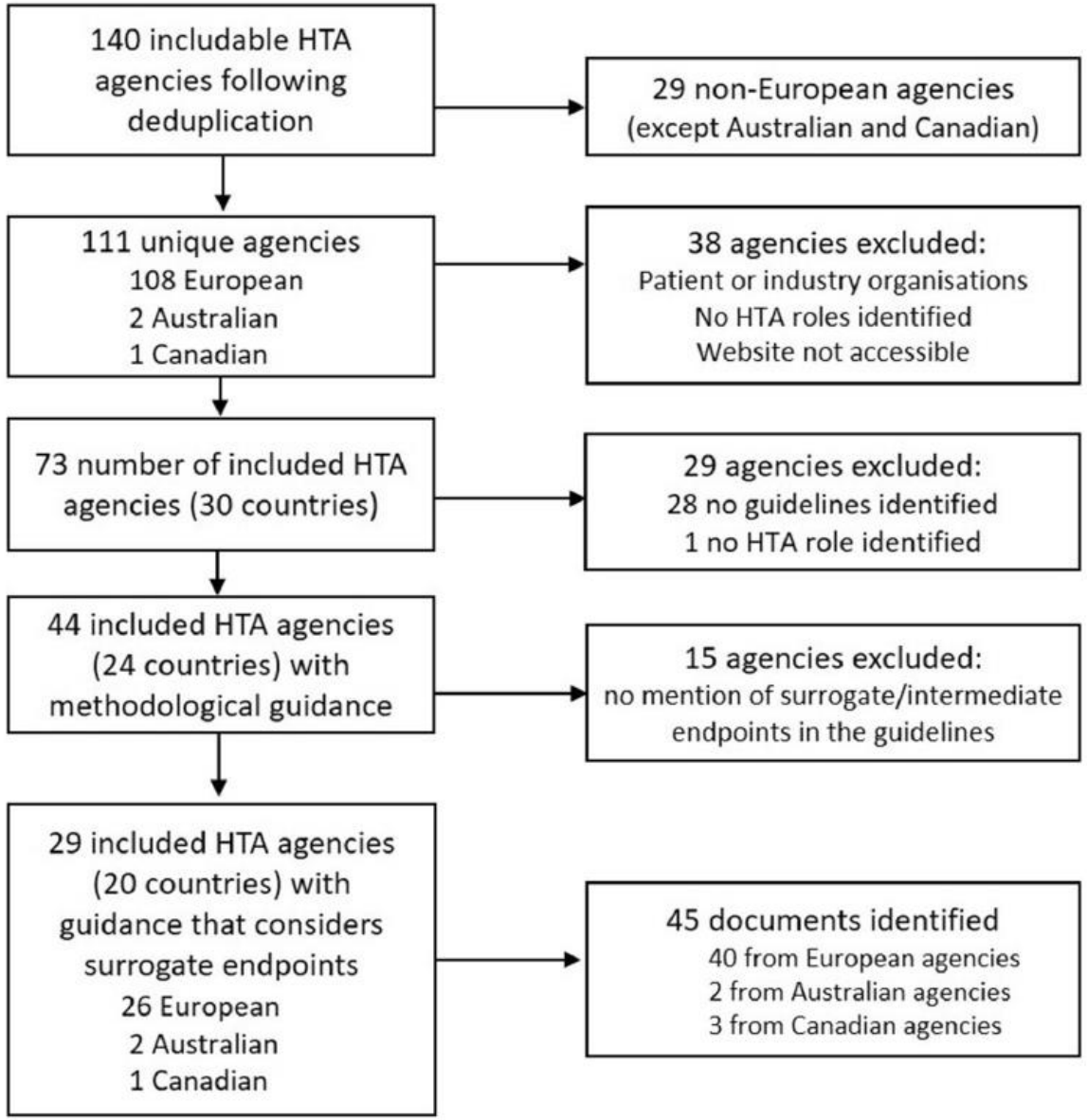
Key Points for Decision Makers

Although surrogate endpoints enable faster trials and therefore faster access to treatment, they increase the uncertainty of coverage decisions on health technologies

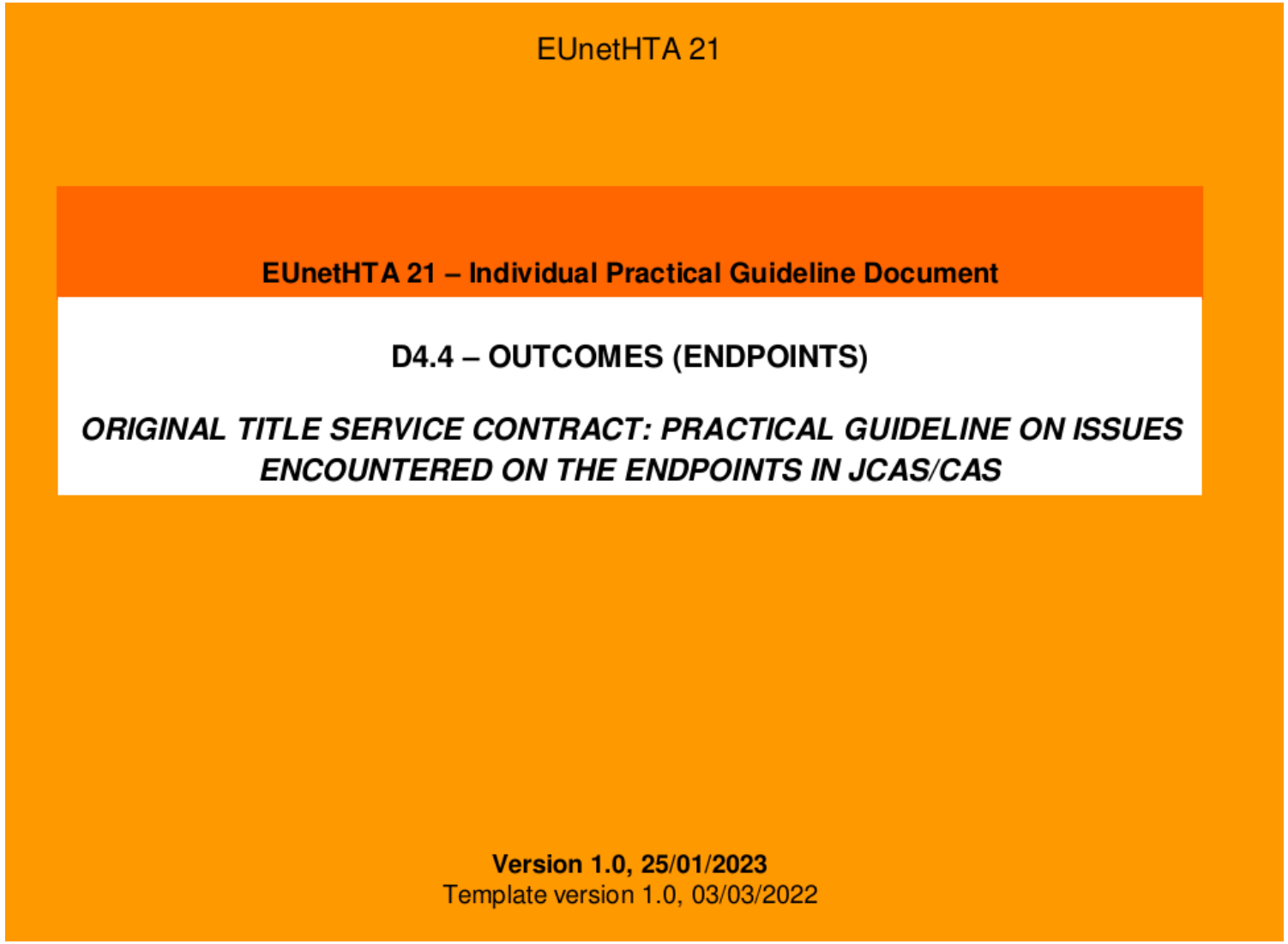
Our survey shows that many international health technology assessment (HTA) agencies currently lack detailed guidance for the evaluation of health technologies that rely on surrogate endpoint evidence

HTA agencies need to provide more detailed and prescriptive guidelines for the consistent qualification and incorporation of surrogate endpoint evidence in the decision processes where the evidence on patient-relevant endpoints is lacking

Current best knowledge suggests that adequate approaches include evidence hierarchy frameworks, meta-regression analytical techniques and economic modelling methods that explicitly explore the uncertainty in the surrogate-to-final endpoint relationship



There are many guidelines but this one is important



There are many guidelines but this one is important

EUnetHTA 21

EUnetHTA 21 – Individual Practical Guideline Document

D4.4 – OUTCOMES (ENDPOINTS)

ORIGINAL TITLE SERVICE CONTRACT: PRACTICAL GUIDELINE ON ISSUES ENCOUNTERED ON THE ENDPOINTS IN JCAS/CAS

Version 1.0, 25/01/2023

Template version 1.0, 03/03/2022

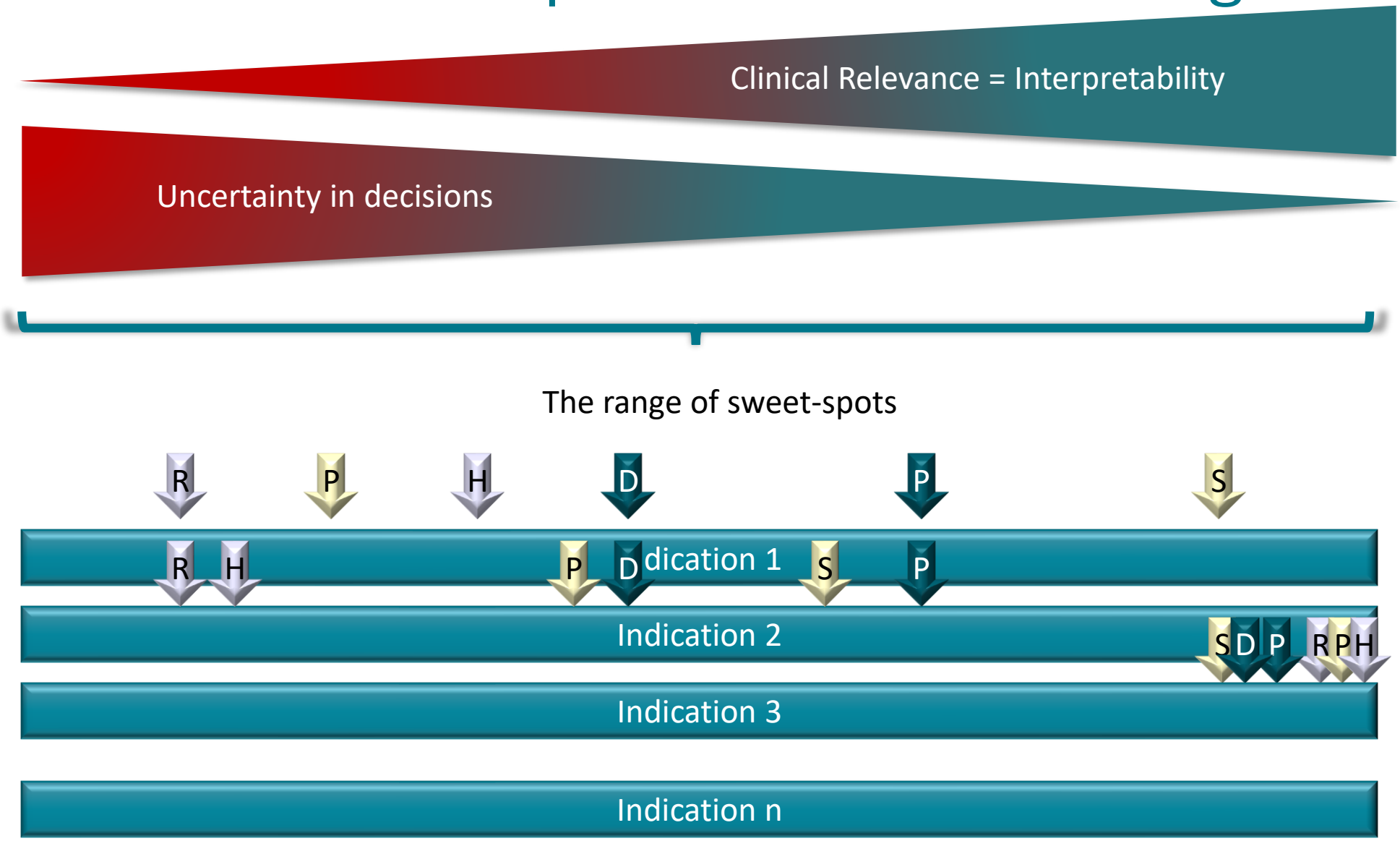
The HTA definition of a surrogate outcome

- Outcome that is intended to replace an outcome of interest that cannot be observed in a trial
- Provides an indirect measurement of effect in situations in which direct measurement of a patient-centred effect is not feasible or practical
- May be a biomarker that is intended to substitute for a patient-centred outcome, or it may be an intermediate outcome
- Is expected to only predict the treatment effect
- The use of surrogate outcomes in assessment of the clinical added benefit of a health technology can be controversial since the validity of surrogate outcomes has rarely been fully established in a rigorous manner
- Only a few surrogate outcomes have been shown to be true measures of tangible clinical benefit

It is all about decision making

- Endpoints have different ‘value’ to those that need to make a decision
- Benefit/Risk → is there enough signal for efficacy to outweigh safety risks
- Cost/Effectiveness → is there proven causality, precision and likelihood to translate in a clinical relevance experience for ‘my’ patients
- Physicians and patients → is the surrogate meaningful on the individual level, is that information enough to make me choose one treatment over another

The sweet-spot of decision making



Pink: Regulators and HTAs Green: Doctors and Patients Yellow: Payers and the Societal

It is all about decision making

- Benefit/Risk → is there enough signal for efficacy to outweigh safety risks
  - Is changing the estimator going to influence the Benefit/Risk?
  - As a Statistician the proposal is still derived from the same data and hence not intuitively preferred (regulators like to have a benchmark)
- Cost/Effectiveness → is there proven causality, precision and likelihood to translate in a clinical relevance experience for ‘my’ patients
  - There is the problem with no MCID established and the lack of validation (study level / individual level)
  - We still don’t address the weighting of domains by patient preference

It is all about decision making

- Physicians and patients → is the surrogate meaningful on the individual level, is that information enough to make me choose one treatment over another
  - The more intuitive approach is an argument here
  - Again, it does not help with patient preference per se
  - Still, also the message conveyed on ‘nicer numbers’ must be objective and meaningful

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Please feel free to now share any questions you may have for the panel

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