# The role of trials in health-economic evaluation of anti-amyloid treatment for early Alzheimer's disease

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# Disclosure

**Related to current work**

- No funding

Maastricht University

Karolinska Institutet

**Unrelated to current work (past 36 months)**

- Consulting fees from Lilly Nederland (paid to institution)
- Consulting fees from the Institute for Medical Technology Assessment (paid to institution)

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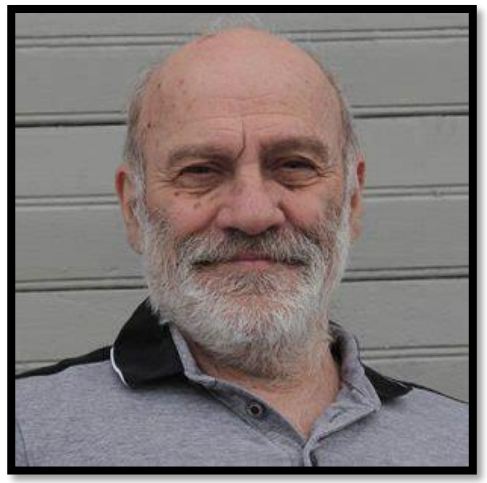

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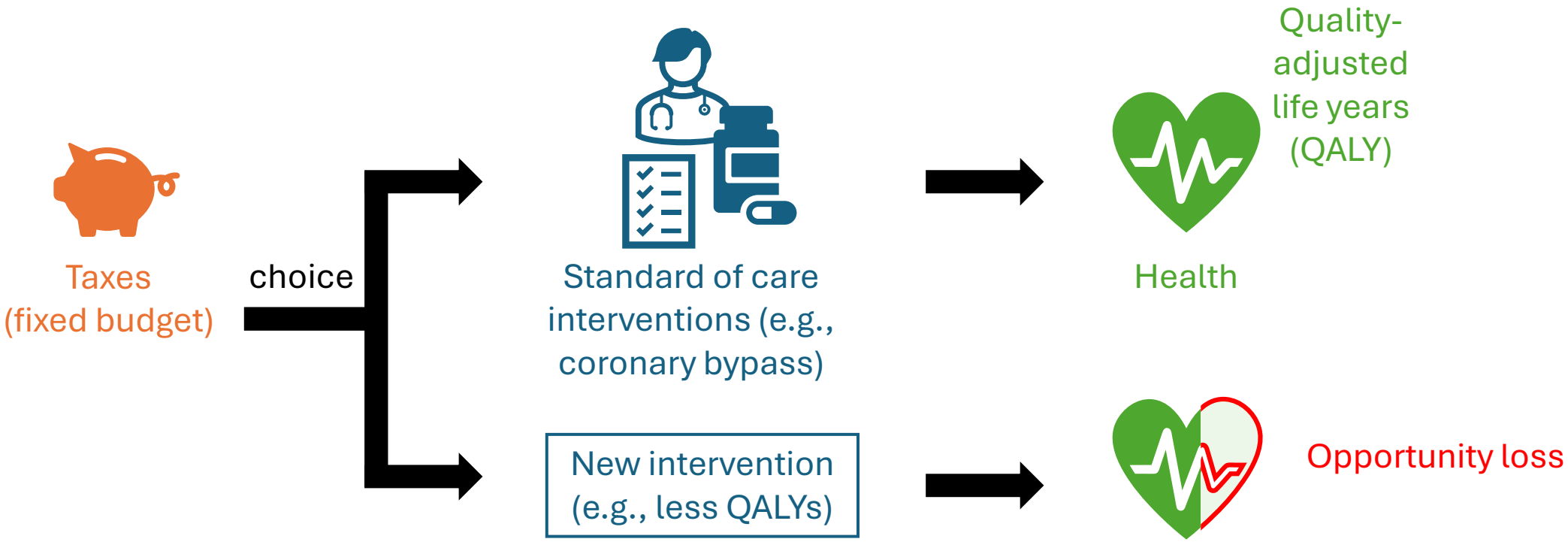
# Background: why health-economic evaluation?




Common maximum willingness to pay for new intervention ~$100,000 per QALY gained

# Aim

**Estimate the cost-effectiveness of amyloid targeting treatment (ATT) for early AD in a US setting**

Example: lecanemab

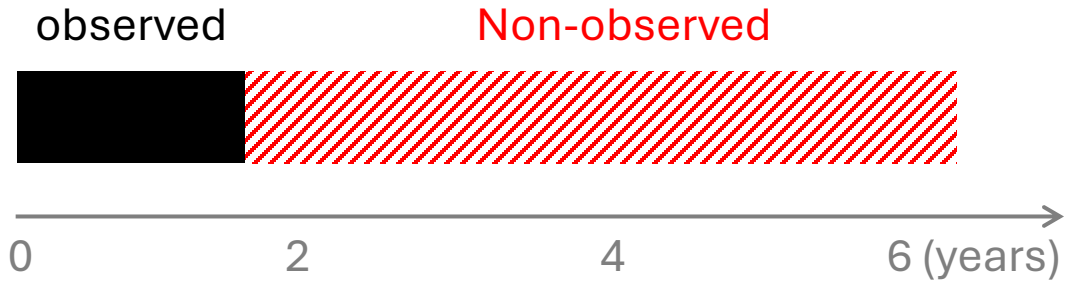
# Challenges

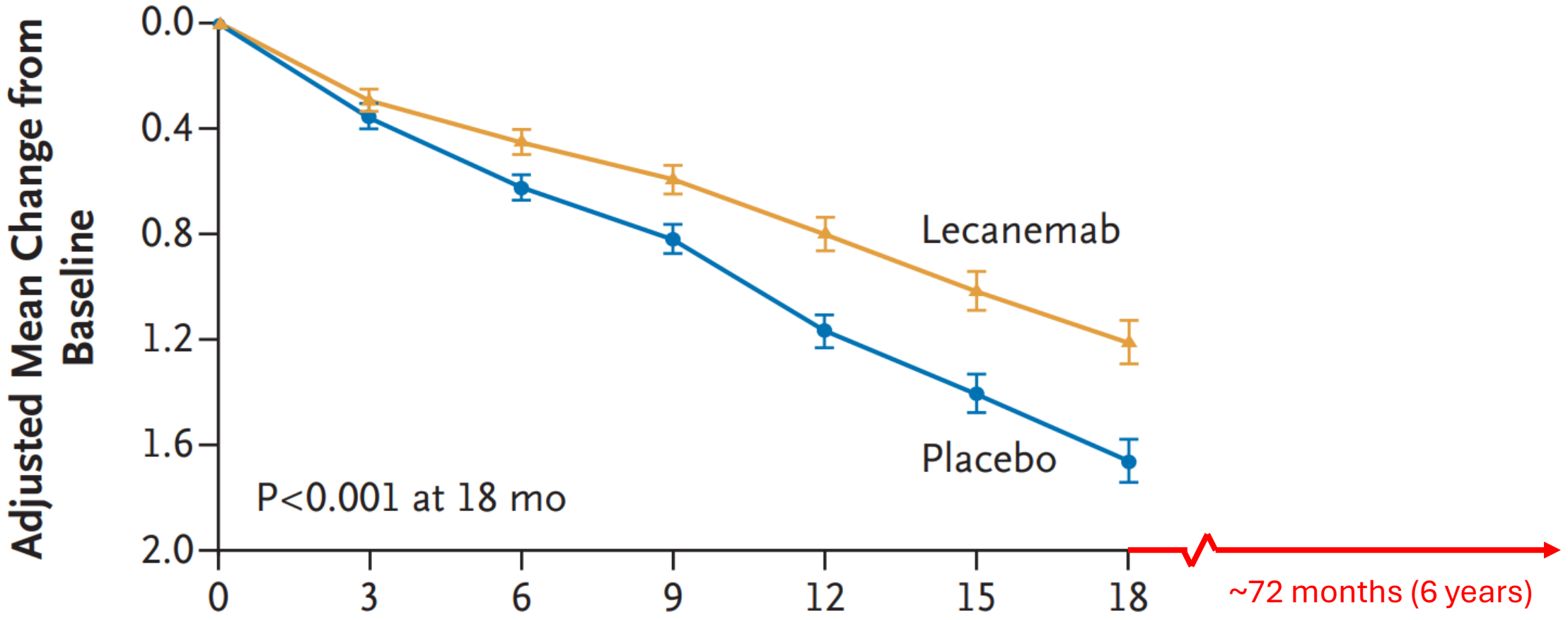
| | Trial | Health-economic model |
|---|---|---|
| Time horizon | 18 months | **Lifetime (~6 years)** |

# Challenges

| | Trial | Health-economic model |
|---|---|---|
| Time horizon | 18 months | Lifetime |
| Endpoint | • Amyloid pathology<br>• Clinical outcomes | • Quality-adjusted life years (QALY)<br>• Costs<br>• Clinical outcomes |
| Endpoint type | CDR-SB **continuous** | CDR-SB **categorized** as MCI, mild, moderate, severe |
| Statistic | Significance (mixed model) | Effect size (progression-free survival) |
| Reflected population | Trial exclusion criteria | Real-world population |
| Primary effect outcome | Prespecified | Post-hoc (limitation) |

# Lifetime horizon



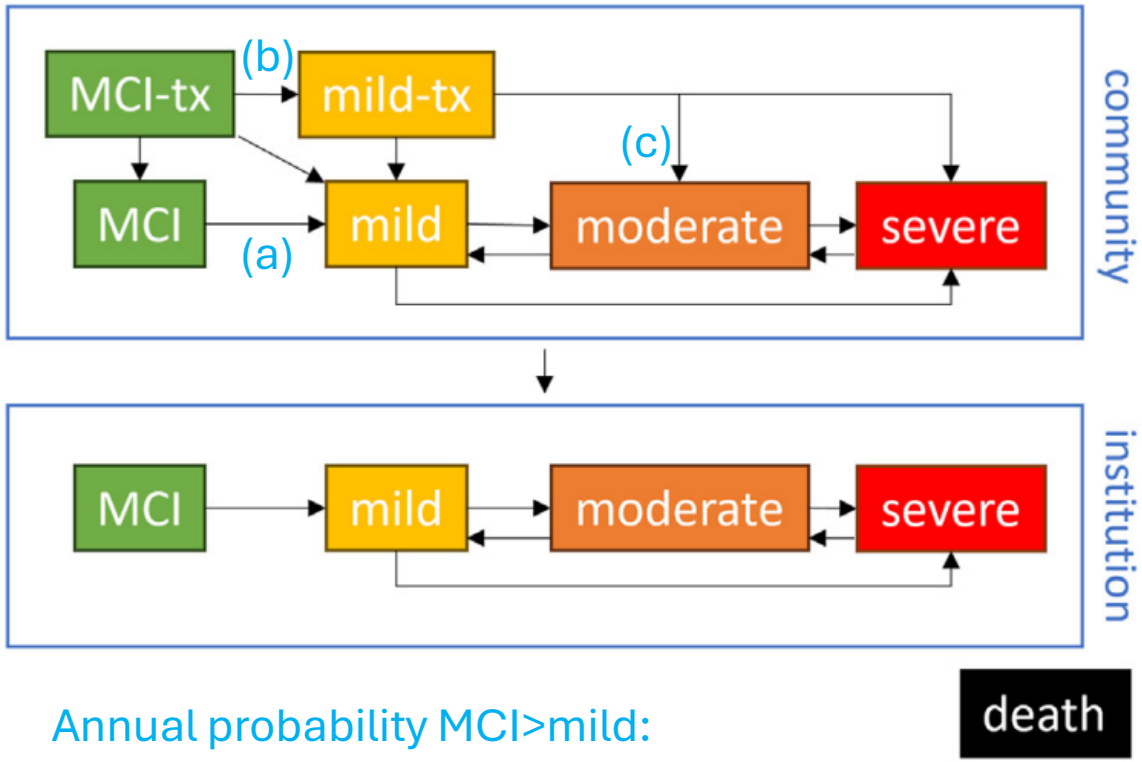

*Copied from Van Dyck et al. (2022) DOI: 10.1056/NEJMoa2212948 (CLARITY-AD trial)*

# Methods

- **Simulation model:** IPECAD open-source health-economic model
- Target population: MCI or mild dementia with abnormal amyloid
- Treatment effect:
  - 31% reduction risk of transition to (more severe) dementia (RR=0.69) from non-prespecified post-hoc analysis
  - Assumption: treatment continued and treatment effect sustains after lecanemab trial follow-up period (18m)
- Treatment costs: €26,500 (US list price) per year
- Quality of life and care use: by disease severity state
- Model freely available: https://github.com/ronhandels/ipecad

*Handels et al. https://doi.org/10.1016/j.jval.2024.07.009; partly based on Whittington et al. https://icer.org/*

# Simulation model




Annual probability MCI>mild:

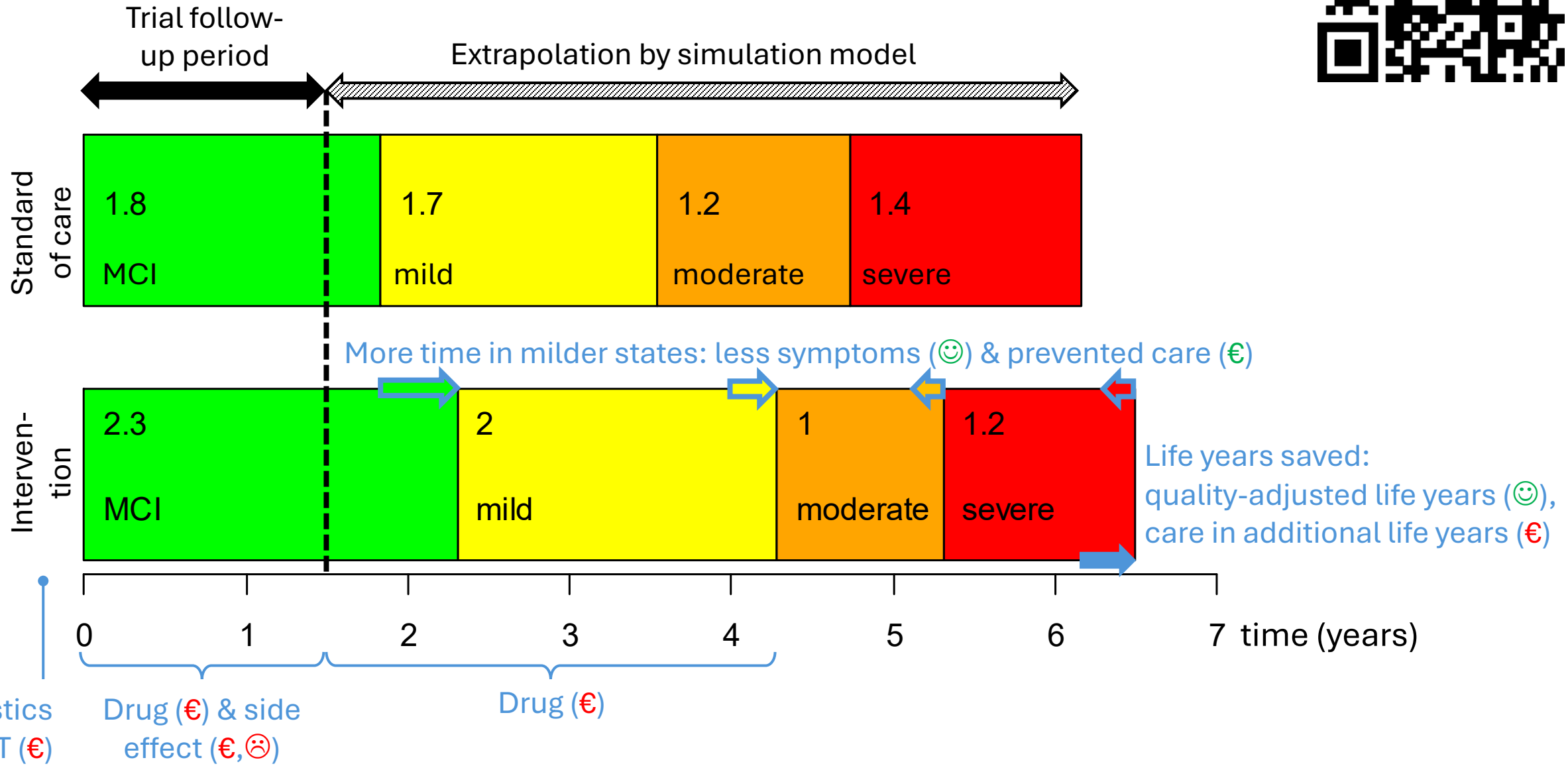
a) Standard of care = 0.23
b) Amyloid targeting treatment: ~0.23 * 0.69 = 0.17
c) Amyloid targeting treatment: idem

Proportion in state by year

| Year | MCI | Mild | Moderate | Severe | Death |
|---|---|---|---|---|---|
| 0 | 0.55 | 0.45 | 0 | 0 | 0 |
| 1 | 0.46 | 0.38 | 0.11 | 0.01 | 0.05 |
| 2 | 0.37 | 0.32 | 0.15 | 0.06 | 0.10 |
| 3 | 0.30 | 0.26 | 0.16 | 0.11 | 0.16 |
| 4 | 0.25 | 0.22 | 0.15 | 0.15 | 0.24 |
| 5 | 0.20 | 0.18 | 0.13 | 0.17 | 0.32 |
| 6 | 0.16 | 0.14 | 0.11 | 0.18 | 0.41 |
| 7 | 0.13 | 0.11 | 0.09 | 0.17 | 0.50 |
| 8 | 0.10 | 0.09 | 0.07 | 0.15 | 0.59 |
| 9 | 0.08 | 0.07 | 0.06 | 0.12 | 0.67 |
| 10 | 0.06 | 0.05 | 0.05 | 0.10 | 0.74 |
| Total | 2.66 | 2.27 | 1.08 | 1.22 | 3.78 |

***MCI** = mild cognitive impairment; **tx** = on treatment*

# Results: mean person-years in state



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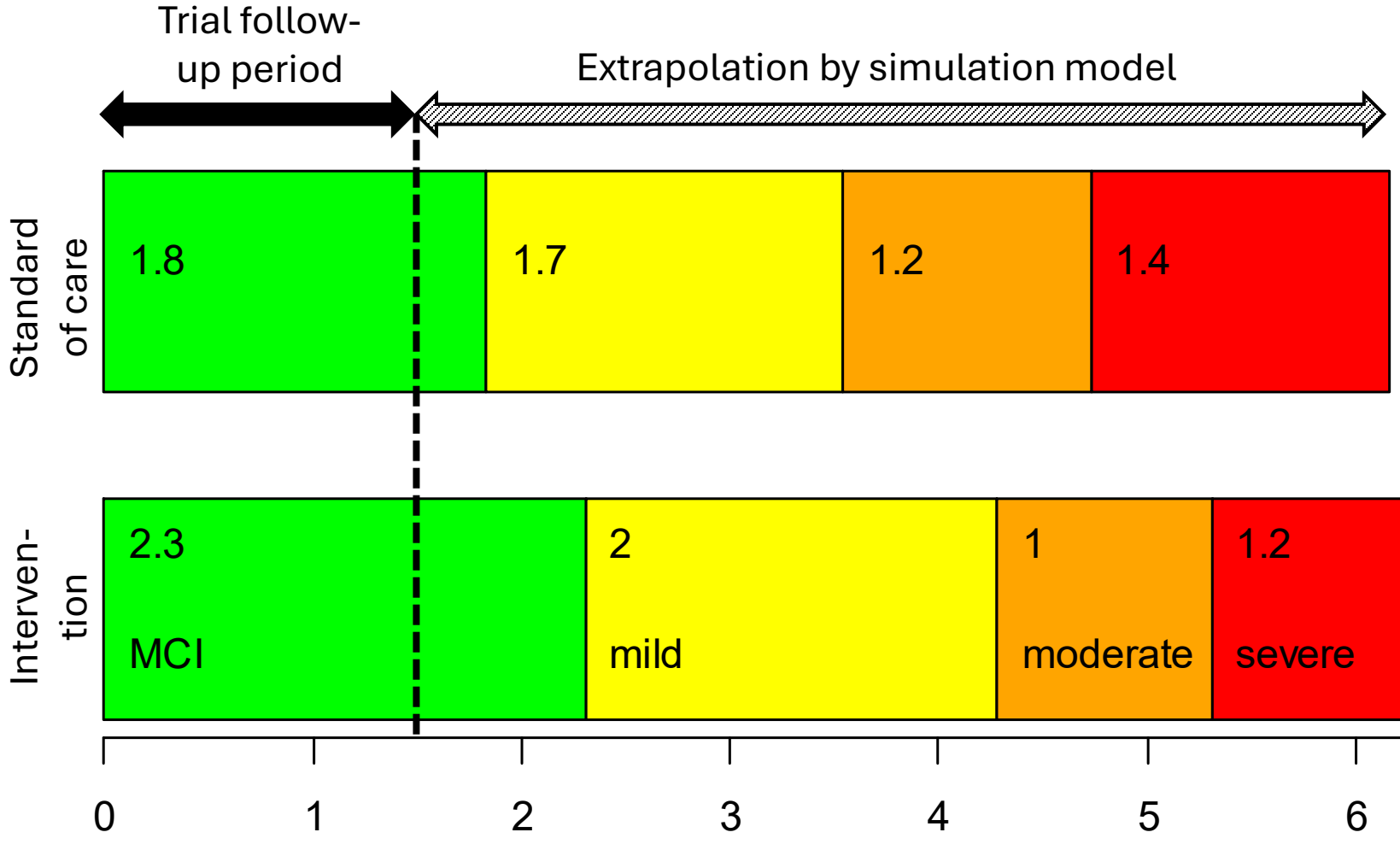



QALY = 2.94
Costs = $485,000

QALY = 3.29
Costs = $588,000

QALY difference = 3.29 - 2.94 = 0.35
Costs difference = $588,000 - $485,000 = $103,000

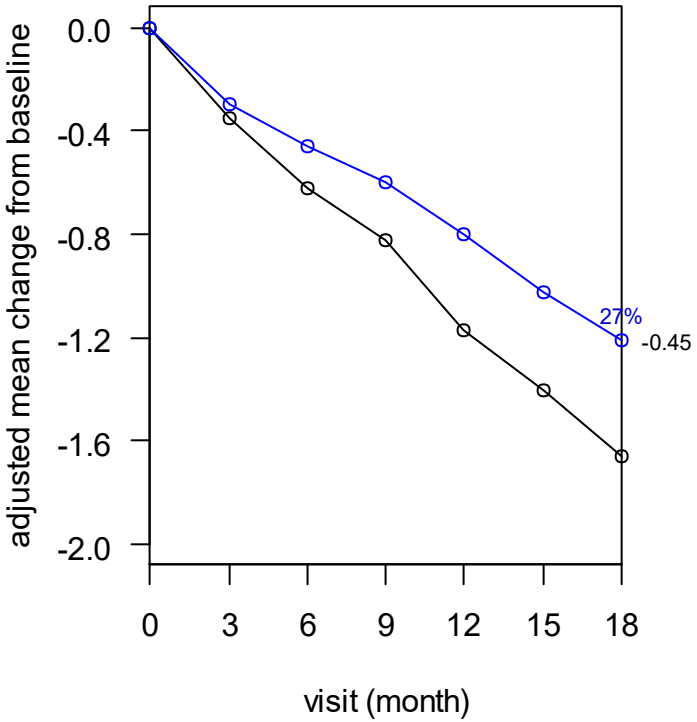
Incremental cost-effectiveness ratio:
+$103,000 / +0.35 = $293,000/QALY

# Cost-effective at willingness to pay of $100,000/QALY?

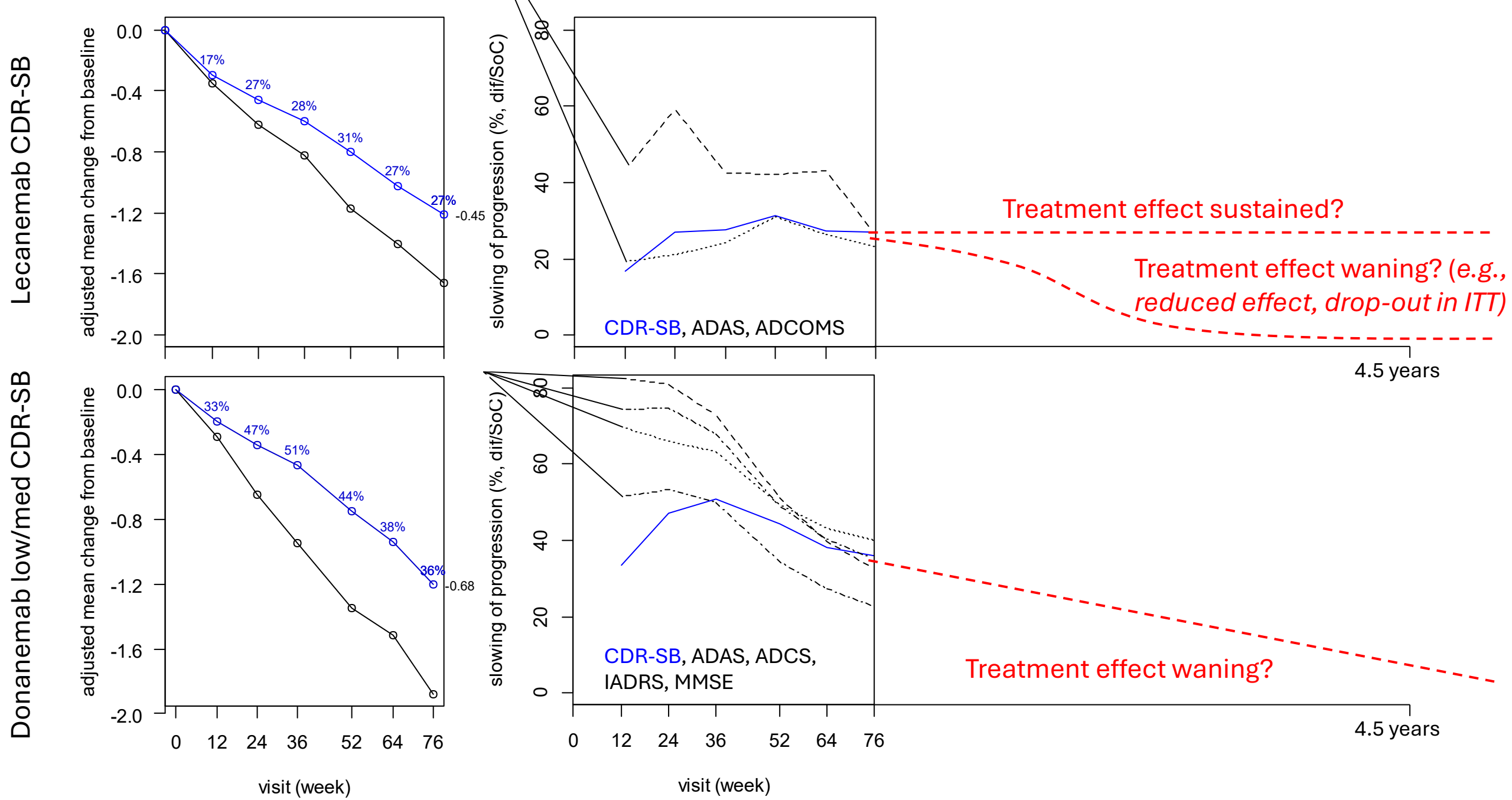
- At $26,500 US list drug price: not cost-effective
- At ~$10,000: potentially cost-effective

- However, extrapolation from 18-months to ~6 years:
  - No randomized evidence on clinical outcomes
  - Rely on assumptions
  - Make health-economic result highly uncertain

Lecanemab CDR-SB




*Data from Van Dyck et al. (2022) DOI: 10.1056/NEJMoa2212948 (CLARITY-AD trial) and Sims et al. (2023) doi:10.1001/jama.2023.13239 (TRAILBLAZER-ALZ 2)*

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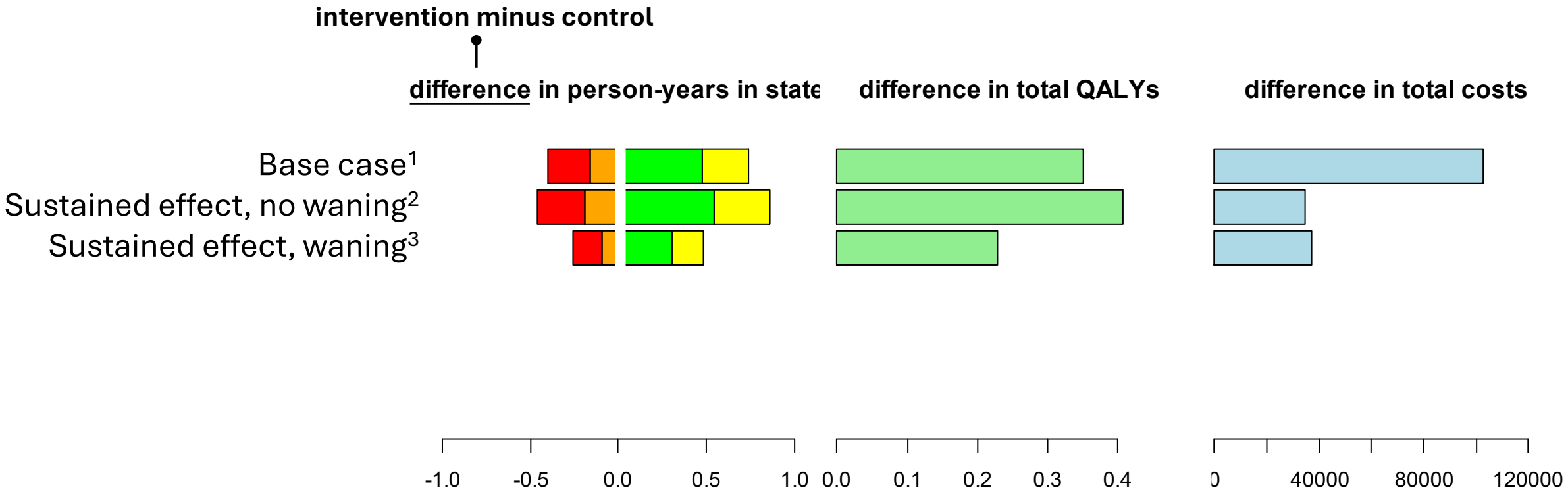
# Impact on health-economic outcomes



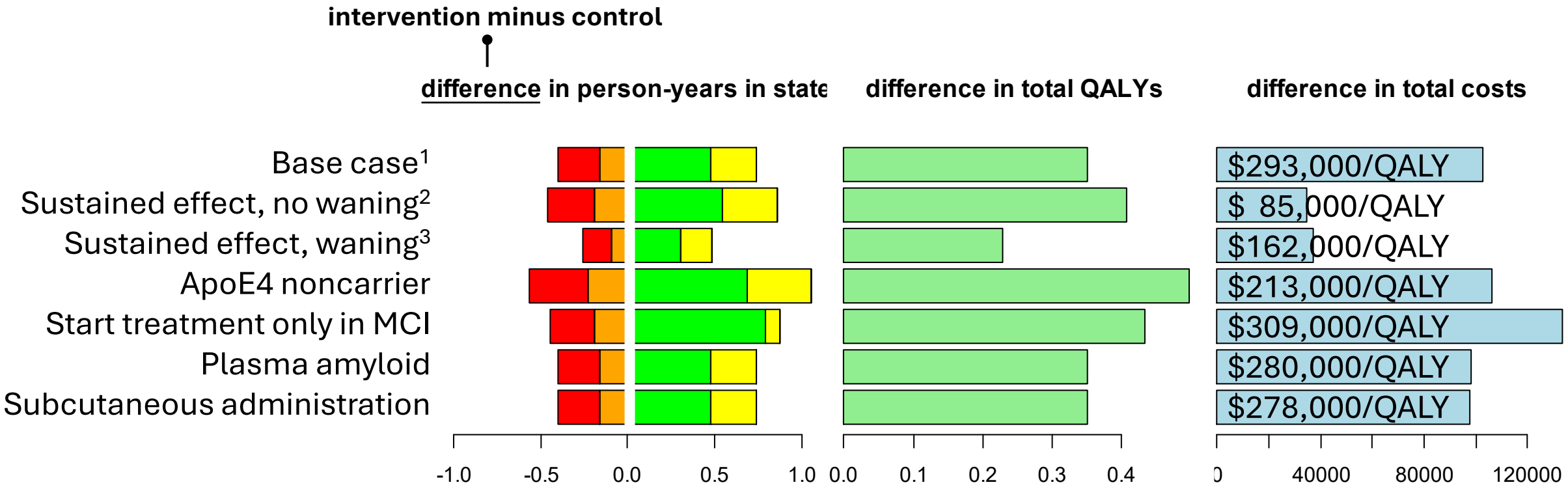

Assumptions:

[1] = treat in MCI and mild for 10+ years, effect only while treated, assume no effect waning

[2] = treat in MCI and mild max. 2 years, sustained effect after stopping treatment, assume no effect waning

[3] = treat in MCI and mild max. 2 years, sustained effect after stopping treatment, assume 30% effect waning per year

# Impact of population, diagnostics, drug administration

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# Need for long-term empirical evidence, which setting?

| | **Research setting** (countries without market access) | **Real-world setting / registry** (countries with market access) |
|---|---|---|
| Risk of biased effect estimate | Low (randomization) | High (selection, drop-out) |
| Population | Narrow / selected | Broad / unselected |

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| Population | Narrow / selected | Broad / unselected |
| Availability to patients | Only in trials | Memory clinics with sufficient (diagnostic) facilities |
| If long-term effect is present/high | Opportunity loss for patients | |
| If long-term effect is absent/low | | Opportunity loss for other care |
| Sample size | • MCI (MCID 0.98): n = 230<br>• Mild dementia (MCID: 1.63): n = 85 | Easily reachable |

# Conclusions

- Short-term (18m) trial outcomes are extrapolated to lifetime health-economic outcomes using a simulation model (QR-code)
- Anti-amyloid treatment lecanemab for early AD at the current US price exceeds common willingness-to-pay thresholds (also in Europe, data not shown)
- Cost-effectiveness improves by:
  - Lower drug price
  - Narrow target population to treatment responders (ApoE4 noncarrier)
  - Plasma screener
  - Subcutaneous
- Need for empirical evidence on long-term effectiveness