Impact of Time-Varying Relapse Risk on Long-Term Cost-Effectiveness Outcomes in Chronic Relapsing Diseases

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The Status Quo

- Chronic relapsing diseases are characterized by a fluctuating and non-linear disease trajectory. Relapse risk varies with treatment exposure, disease progression, and patient heterogeneity, and is not a fixed constant
- Real-world evidence consistently shows relapse rates are highest in early treatment periods and decline progressively with sustained treatment and disease stabilization
- Despite this, most cohort-based Markov models apply a constant transition probability to relapse, a simplifying assumption that fails to capture time-dependent disease dynamics
- This introduces systematic bias in long-term estimates of relapse frequency, healthcare costs, and QALYs - directly distorting cost-effectiveness outcomes
- For HTA decision-making, structural assumptions around transition probabilities represent a key, frequently underexplored source of uncertainty in economic models
- Flexible parametric survival models and smoothing-based hazard estimation now make time-varying approaches both technically feasible and methodologically transparent, yet applied evidence on their quantitative impact on ICERs remains limited

What We Set Out to Solve

- To evaluate the quantitative impact of incorporating time-varying relapse risk compared to a constant hazard assumption - on long-term cost-effectiveness outcomes in a cohort-based Markov model for chronic relapsing disease

How We Solved It

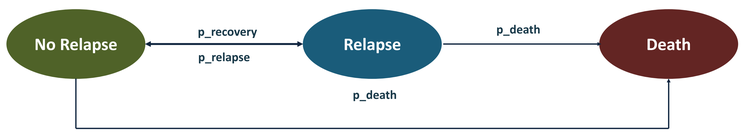
Relapse Definition

- A clinically meaningful worsening event resulting in increased healthcare resource utilization and temporary reduction in health-related quality of life (disutility)
- Captured as a discrete transition event within each monthly model cycle

Model Structure

- A cohort-based state-transition (Markov) model was developed to simulate disease progression over a lifetime horizon using monthly cycles. The model included three mutually exclusive health states
- All patients entered the model in the "no relapse" state and could transition between states based on defined probabilities

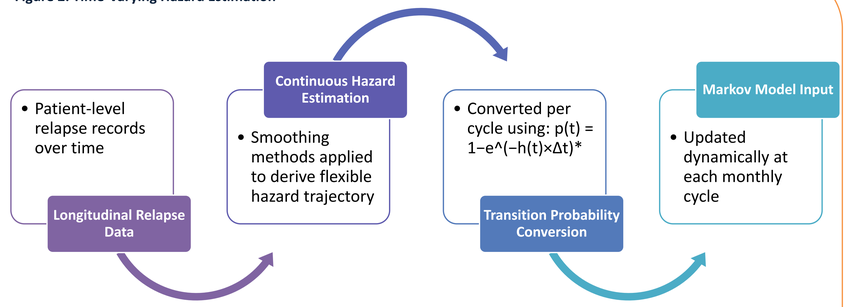
Figure 1: Transition Diagram



Model Assumptions

- Background age-specific mortality incorporated from general population life tables
- Relapse events associated with increased direct medical costs and HRQoL disutility
- Under time-varying approach, a sustained long-term treatment effect assumed - relapse risk highest in early cycles, declining with continued exposure
- A monthly cycle length and lifetime time horizon were used to adequately capture long-term disease progression, relapse occurrence, survival outcomes, and accumulation of healthcare costs and QALYs over time

Figure 2: Time-Varying Hazard Estimation



***Transition Probability Conversion**

$P(t)=1-e^{-h(t)\Delta t}$

Where:
$P(t)$:transition probability
$h(t)$:time-varying hazard
Δt: cycle length

- Longitudinal relapse data were used to estimate relapse trajectories over time
- Flexible smoothing methods were applied to derive continuous hazard estimates
- Smoothed hazards were converted into cycle-specific transition probabilities
- Transition probabilities were updated dynamically at each monthly cycle

Table 1: Comparison of Constant vs. Time-varying modeling approach

	Approach 1: Time-Varying	Approach 2: Constant
Hazard	Declines over time	Fixed throughout
Data Source	Longitudinal patient data	Single summary estimate
Cycle update	Dynamic, per-cycle	Static
Assumption	Reflects real-world trajectory	Simplification
HTA transparency	Higher	Lower

Model Inputs

- Costs sourced from published literature and national reference costs, applied from a payer perspective
- Utility values derived from published HRQoL evidence; disutility decrements applied during relapse states
- Background mortality incorporated using age-specific general population life tables

Limitations

- Time-varying hazard estimates derived from available longitudinal data - may not fully capture all patient subgroups, treatment lines, or very long-term relapse trajectories beyond the observed follow-up period
- Disease-agnostic model structure limits direct applicability to specific conditions without disease-specific calibration of transition probabilities, costs, and utilities
- Probabilistic sensitivity analysis (PSA) not presented - characterization of parameter uncertainty around the ICER is a planned extension
- Model assumes homogeneous cohort - does not account for patient-level heterogeneity in treatment response or disease severity

What We Got

- The constant hazard model projected 7.08 and 13.99 cumulative relapses at years 10 and 20 respectively
- The time-varying model projected 3.39 and 5.21 - representing a 2.15-fold overestimation at year 10 and 2.68-fold at year 20 under the constant assumption (Figure 3)
- Relapse overestimation under the constant hazard assumption compounds over time - the divergence between models widens progressively, with the gap nearly doubling between year 10 and year 20

Figure 3: Cumulative relapses over time

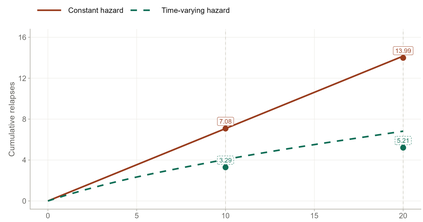
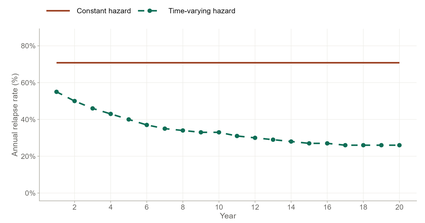


Figure 4: Annual relapse rate over time



- Annual relapse rate under the time-varying model was highest in year 1 (55%) and declined progressively, stabilizing at approximately 26% by year 20. In contrast, the constant hazard model assumed a fixed annual rate of 70.8% throughout the entire time horizon.
- This declining risk pattern - consistent with long-term treatment effect, is not captured under the constant hazard assumption (Figure 4)

Healthcare Costs

- Total costs were £312,450 (time-varying) vs £328,200 (constant hazard) for the intervention arm - a difference driven entirely by overestimated relapse management costs under the constant assumption
- Constant hazard resulted in £15,750 higher incremental costs, inflating the economic burden through artificially elevated relapse frequency

QALY Outcomes

- Intervention arm accrued 14.82 QALYs (time-varying) vs 14.46 QALYs (constant) — comparator QALYs were more substantially affected at 12.00 vs 10.03 respectively
- Constant hazard artificially suppressed comparator QALYs through overestimated relapse-associated disutility, inflating incremental QALY gain by 57% (2.82 vs 4.43)

Table 2: ICER Comparison

	Approach 1: Time-Varying	Approach 2: Constant
Incremental Cost	£87,650	£103,400
Incremental QALYs	2.82	4.43
ICER	£31,080/QALY	£23,340/QALY
vs. £30k threshold	Above - not cost-effective	Below - cost-effective

- The modelling assumption alone changes the reimbursement decision - constant hazard produces an ICER £7,740 below threshold, while time-varying places it £1,080 above
- This represents a £7,740/QALY difference in ICER driven entirely by structural assumption, not clinical data

Why It Matters to You

One assumption.
One reimbursement decision. Changed.

- Assuming a constant relapse risk oversimplifies disease dynamics and introduces meaningful bias into long-term cost-effectiveness estimates - resulting in a 2.68-fold overestimation of cumulative relapses at year 20
- Incorporating time-varying relapse risk produces more realistic disease trajectories, with the modelling assumption alone shifting the ICER across the £30,000/QALY reimbursement threshold
- Structural assumptions around transition probabilities represent a key, frequently underexplored source of uncertainty in HTA submissions - and should be subject to explicit scenario analysis
- Future analyses should explore flexible parametric survival approaches as a transparent, reproducible alternative for modelling time-dependent risks in NICE, CADTH, and EU HTA dossiers

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