Simulation scenario

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Simulation Scenario: Treatment Discontinuation, Stroke, and Death in Continuous Time

We simulate a cohort of patients who initiate treatment at time $t = 0$, denoted by $A(t) = 1$ for all $t \geq 0$, and who are initially stroke-free, $L(0) = 0$. All individuals are followed for up to 2 years (730 days) or until death. During follow-up, patients may experience a stroke, stop treatment (irreversibly), and die. The primary outcome is the **risk of death within 2 years**.

Key Event Processes We model the following time-to-event processes in continuous time:

- **Stroke occurrence**: Hazard depends on current treatment status.
- **Treatment discontinuation**: Allowed only at scheduled visits, influenced by stroke status.
- **Death**: Hazard depends on treatment and stroke history.

Model Notation and Structure

Let:

- T_{stroke}: time to stroke
- T_{stop}: time of treatment discontinuation
- T_{death}: time of death
- $C = 730$: administrative censoring at 2 years
- $A(t) \in \{0, 1\}$: treatment status at time t
- $L(t) \in \{0, 1\}$: stroke status (1 = stroke has occurred)

Initial conditions:

$$A(0) = 1, \quad L(0) = 0$$

1. Stroke Process

Stroke occurs at hazard:

$$\lambda_{\text{stroke}}(t) = \lambda_0^{\text{stroke}} \cdot \exp\left(\beta_A \cdot A(t)\right)$$

- $\lambda_0^{\text{stroke}}$: baseline hazard
- β_A: treatment effect on stroke

2. Doctor Visit Process

- If no stroke: visit at $t \sim \text{Uniform}(335, 395)$
- If stroke occurs first:

$$t_{\text{visit}} \sim \text{Gamma}(\alpha_{\text{stroke}}, \theta_{\text{stroke}}) + T_{\text{stroke}}$$

3. Treatment Discontinuation Process

Can only occur at visit time. Probability of stopping depends on stroke status:

$$\Pr\left(A(t_{\text{visit}}^+) = 0 \mid A(t_{\text{visit}}^-) = 1\right) = \begin{cases} p_{\text{no-stroke}}, & \text{if } L(t_{\text{visit}}) = 0 \\ p_{\text{stroke}}, & \text{if } L(t_{\text{visit}}) = 1 \end{cases}$$

Treatment is irreversible: once stopped, $A(t) = 0$ for all $t > T_{\text{stop}}$.

4. Death Process

Hazard of death depends on stroke and treatment:

$$\lambda_{\text{death}}(t) = \lambda_0^{\text{death}} \cdot \exp\left(\gamma_L \cdot L(t) + \gamma_A \cdot A(t)\right)$$

- λ_0^{death}: baseline hazard
- γ_L: effect of stroke
- γ_A: effect of treatment

Censoring and Outcome

Define:

$$T = \min(T_{\text{death}}, C), \quad \Delta = I(T_{\text{death}} \leq C)$$

$$Y = I(T_{\text{death}} \leq 730)$$

Our outcome is the indicator for death within 2 years.

Suggested Parameters for Sensitivity/Estimation

Parameter	Description	Example Values
$\lambda_0^{\text{stroke}}$	Baseline stroke hazard	0.002 per day
β_A	Treatment effect on stroke	-0.5, 0, 0.5
$p_{\text{no-stroke}}$	Stop prob. at visit (no stroke)	0.3
p_{stroke}	Stop prob. at visit (post-stroke)	0.05
λ_0^{death}	Baseline death hazard	0.001 per day
γ_L	Effect of stroke on death	1.5
γ_A	Treatment effect on death	-0.5, 0, 0.5
α, θ	Post-stroke visit delay (Gamma params)	(2, 7)
Jitter window	Timing of first visit	$\pm$30 days

Plain Language Summary (for Clinical Audience)

We simulate patients who all begin treatment and are initially healthy. Over two years, they may have a stroke, stop treatment (only at doctor visits), or die. A routine doctor visit is scheduled about a year after treatment begins, unless a stroke happens first, in which case a visit is likely to occur soon after. Doctors are less likely to stop treatment after a stroke. The chance of dying depends on whether the patient has had a stroke and whether they are still on treatment.