Sample Size Under the Additive Hazards Model

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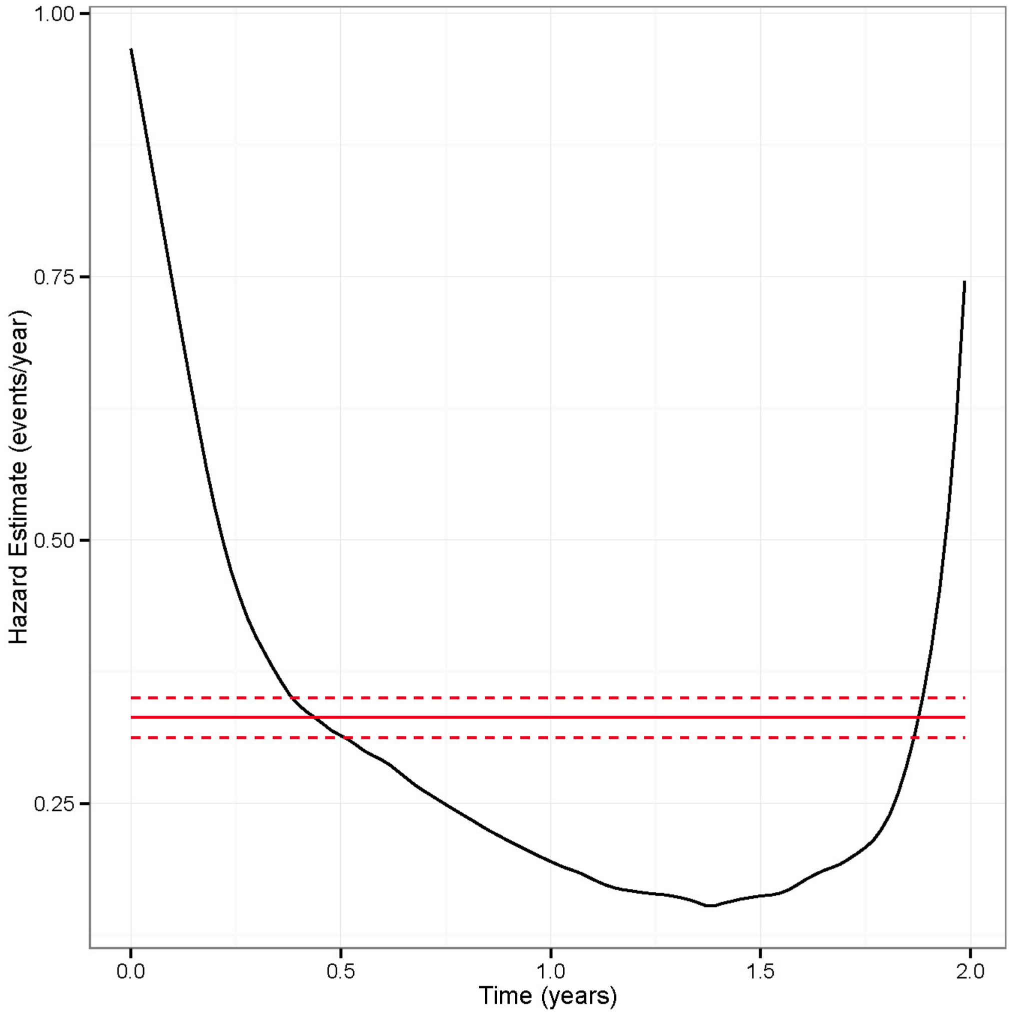
Motivation - SPORTIF III

- Non-inferiority trial with margin as **hazard difference**
- Warfarin vs. ximelagatran
- Exponential distribution assumed
- Low primary event rate (stroke, systemic embolic event, death), about 3% per year

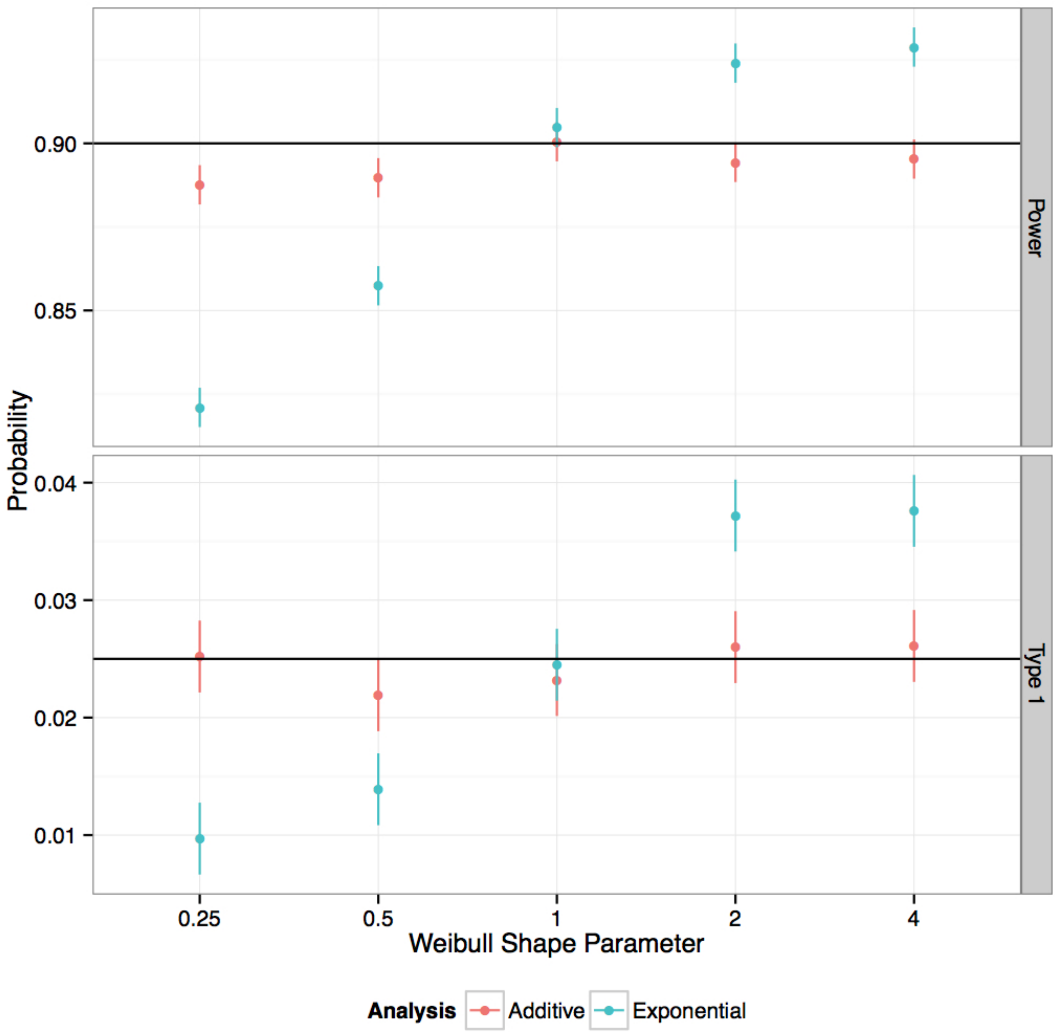
What if endpoint had included bleeding?

- 35% event rate per year
- Cannot appeal to exponentiality
- (At least not if hazard rate is non-constant)

Estimated Hazard



Consequences of Analysis



Selection of Hypotheses

Two candidates for time to event hypotheses

$$
\begin{aligned}
H_0 &: \lambda_B(t) - \lambda_A(t) \geq \delta \\
H_1 &: \lambda_B(t) - \lambda_A(t) < \delta \\
&\text{or} \\
H_0 &: \lambda_B(t)/\lambda_A(t) \geq \delta \\
H_1 &: \lambda_B(t)/\lambda_A(t) < \delta
\end{aligned}
$$

We want to design clinical trials based on a hazard difference without distributions.

Additive Hazards

Aalen's original model

$$\lambda_i(t) = \lambda_0(t) + \gamma(t)'\mathbf{Z}_i(t)$$

Lin and Ying model

$$\lambda_i(t) = \lambda_0(t) + \gamma'\mathbf{Z}_i(t)$$

Treatment indicator: $Z_i = 1$

$$\lambda_i(t) = \lambda_0(t) + \gamma Z_i$$

So model reduces to

$$\lambda_B(t) - \lambda_A(t) = \gamma$$

Superiority Trials

Superiority - Setup

Events are bad.

We want to test

$$
\begin{aligned}
H_0 &: \lambda_B(t) - \lambda_A(t) = 0 \\
H_1 &: \lambda_B(t) - \lambda_A(t) \neq 0
\end{aligned}
$$

Further define

- T = failure time
- C = censoring time
- $X = \min(T, C)$

Superiority Assumptions

- Subjects are independent
- $\lambda_B(t) = \lambda_A(t) + \gamma$
- Assignment to B completely random w.p. p
- Independent censoring
- Censoring distribution common (surv. function = $G(t)$)
- Local alternative:

$$\lambda_B^{(n)}(t) = \lambda_A(t) + \gamma^{(n)}$$

$$\sqrt{n}\gamma^{(n)} \to \phi$$

Superiority Sample Size

$$n = \frac{(z_\alpha + z_\beta)^2 d}{p(1-p)\gamma^2 E(X)^2}$$

Non-Inferiority Trials

Non-inferiority Setup

Test:

$$H_0 : \lambda_B(t) - \lambda_A(t) \geq \delta$$
$$H_1 : \lambda_B(t) - \lambda_A(t) < \delta$$

Same assumptions as superiority

Alternative is equivalence (not local)

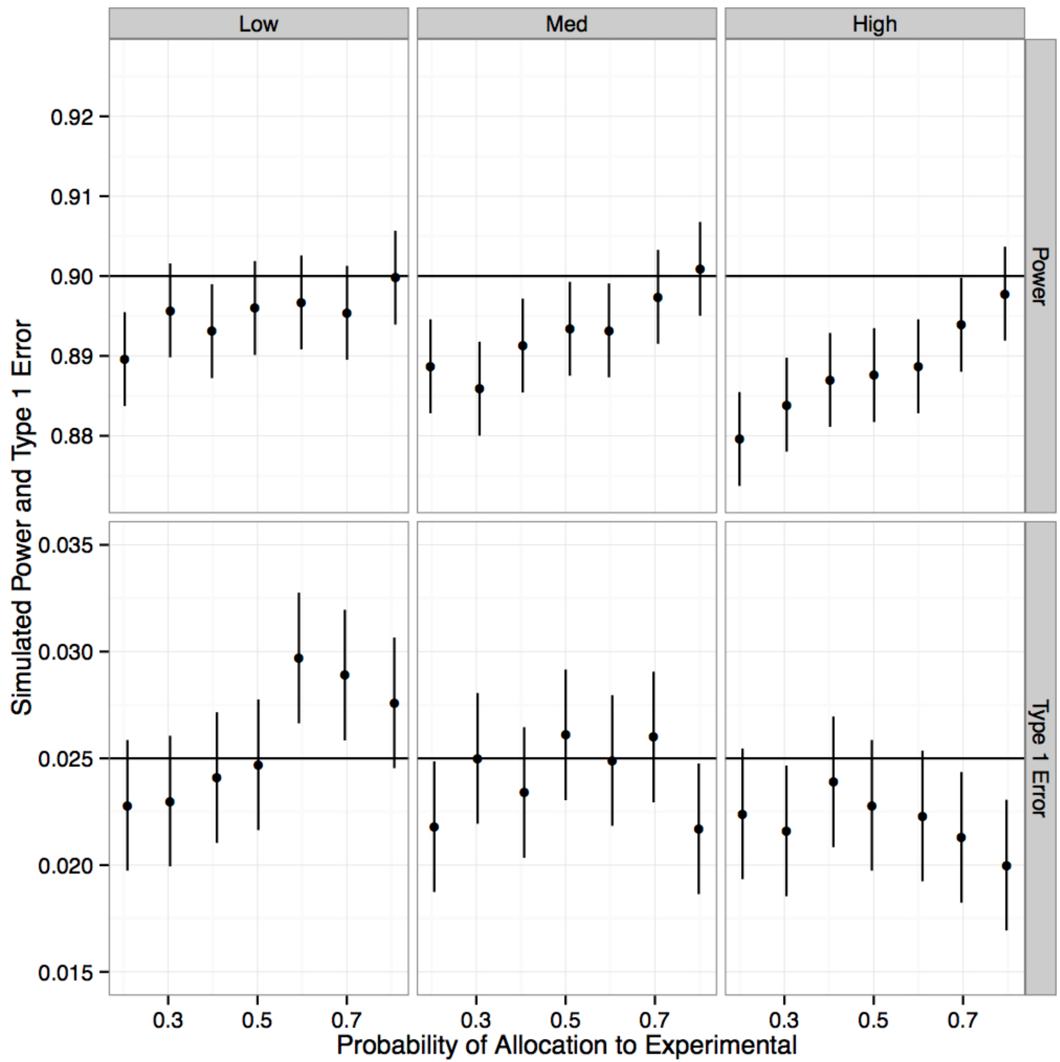
NI Sample Size

$$n = \frac{z_\beta^2 d + z_\alpha^2 \left\{ d + \delta E(X)(1-2p) \right\} + 2 z_\alpha z_\beta \sqrt{d} \sqrt{d + \delta E(X)(1-2p)}}{p(1-p)\delta^2 E(X)^2}$$

Equal Allocation

$$n = \frac{(z_\alpha + z_\beta)^2 d}{p(1-p)\delta^2 E(X)^2}$$

Simulations



Comparison to Logrank

$$n = \frac{(z_\alpha + z_\beta)^2 d}{p(1-p)\gamma^2 E(X)^2} \quad \text{vs.} \quad n = \frac{(z_\alpha + z_\beta)^2}{p(1-p) d \log \Delta^2}$$

Margin or Hazard Difference: Event Probability: Expected Follow-up Time:

Type 1: 0.025

Power: 0.9

Trial Type: Non–Inferiority

Calculate

Margin or Difference:

Event Probability:

Expected Follow-up:

Thank you!