Event-Driven Trial Design for Recurrent Event Outcomes: A Blinded Monitoring Approach

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1. BACKGROUND

➢ **Event-Driven Design for Time-to-First-Event Data**

$$\hat{\beta} \sim \left(\beta_0, \left(\frac{L}{4}\right)^{-1}\right)$$

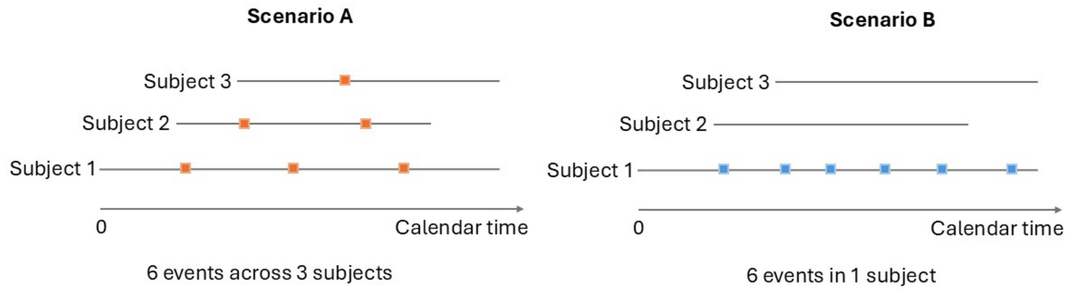
1: 1 randomization

$\hat{\beta}$: the estimated treatment effect (e.g. hazard ratio), with β_0 being the true value.

- The required number of events L is determined **at the design stage** based on the prespecified minimum clinically relevant treatment effect β_0.
- The final analysis is conducted when L events are observed.
- Misspecifying the underlying survival distribution primarily impacts trial duration (timing), while statistical power and Type I error remain protected.

➢ **Recurrent Events: With-Subject Correlation of Event Times**

Repeated occurrences of the same type of events over time in the same patient.
Examples: cancer recurrence, repeated hospitalizations due to adverse events, skeletal-related events, recurrent infections, etc.



Same total events ≠ same statistical information

The within-subject correlation matters when calculating the required number of events for trials with recurrent events → applying the event-driven design for time-to-first-event data to recurrent events data (**by assuming independent increment structure**) may lead to underpowered studies.

2. EXISTING METHOD FOR SAMPLE SIZE PLANNING & ISSUES

➢ **Ingel & Jahn-Eimermacher (2014):** frailty-based inflation factor, assuming a common follow-up $\bar{\tau}$, relatively small variability in individual rates, and $\beta_0 \approx 0$.

- The frailty model for individual event rate: $\mu_i(t) = \eta_i \cdot \mu_0(t) \cdot \exp(\beta_0 Z)$, where the frailty term η_i *is i.i.d with* $\boldsymbol{E(\eta_i) = 1}$ *and* $\boldsymbol{Var(\eta_i) = \theta}$; $\mu_0(\mathrm{t})$ is the baseline mean function of recurrent events.
- The required number of events L and sample size n calculated **at the design stage**:

$$L = 4 \cdot \left(1 + \theta\mu_0\,(\bar{\tau})\,\frac{1+\exp(2\beta_0)}{1+\exp(\beta_0)}\right) \cdot \left(\frac{z_{1-\alpha/2}+z_{1-\gamma}}{\beta_0}\right)^2, \quad n = \frac{2L}{\mu_0(\bar{\tau})\cdot(\exp(\beta_0)+1)}$$

➢ Strong assumptions on treatment effect, follow-up durations, and the individual rates.
➢ Frailty variance θ is hardly known at the design stage → misspecification of parameters would lead to a poor estimate of power.

3. STATISTICAL FRAMEWORK & PROPOSED PROCEDURE

➢ **Setting and Notation**

$\boldsymbol{Z}$: randomized treatment allocation (1/0).
$\boldsymbol{N^*(t)}$: the underlying counting process for events of interest.
$\boldsymbol{C}$: censoring time; $\boldsymbol{N(t) = N^*(t \wedge C)}$ being the observed number of events.
$\boldsymbol{Y(t) \equiv I(C \geq t)}$: at-risk process.
The follow-up duration is supposed to be subject-specific; denote $\boldsymbol{\tau}$ the maximum follow-up duration.

➢ **Marginal rate model and the robust variance:** modeling the marginal rate of recurrent events (Lawless and Nadeau, 1995; Pepe and Cai, 1993),

$$E\{\mathrm{d}N^*(t)|Z\} = \exp(\beta_0 Z)\mathrm{d}\mu_0(t),$$

$\mu_0(\cdot)$: an unknown continuous baseline marginal mean function of recurrent events.

- A robust sandwich estimator is used to account for within-subject correlation when estimating the variance of $\hat{\beta}$: Lin et al. (2000) showed that $n^{1/2}(\hat{\beta} - \beta_0)$ is asymptotically zero mean normal with variance $A^{-1}\Sigma A^{-1}$, where

$$A \equiv E\left[\int_0^\tau (Z - \bar{z}(\beta_0, u))^2 Y(u) \exp(\beta_0 Z)\,\mathrm{d}\mu_0(t)\right],$$
$$\Sigma = E\left[\int_0^\tau (Z_1 - \bar{z}(\beta_0, u))\mathrm{d}M_1(u) \int_0^\tau (Z_1 - \bar{z}(\beta_0, v))\mathrm{d}M_1(v)\right],$$

and

$$M_i(t) = N_i(t) - \int_0^t Y_i\,(u)\exp(\beta_0 Z_i) d\mu_0(u).$$

➢ **Power formula and blinded estimator of the robust variance**

Consider H_0: $\beta_0 = 0$ H_1: $\beta_0 = \delta/\sqrt{n}$ (**local alternative**, δ is a constant).
Denote $v^2 = n^{-1}A^{-1}\Sigma A^{-1}$. For a two-sided significance level α, the power is given by

$$power = \Phi(-z_{1-\alpha/2} - \beta_0/v) + 1 - \Phi(z_{1-\alpha/2} - \beta_0/v).$$

By Slutsky's theorem, rewrite the robust variance estimator of $\hat{\beta}$ (Zhang & Hattori, 2026):

$$\widehat{\boldsymbol{v}}^2_{\boldsymbol{blind}} = \left(\frac{\boldsymbol{L}}{\boldsymbol{4}}\right)^{-1} \cdot \left(\frac{\boldsymbol{1}}{\boldsymbol{4}}\sum_{\boldsymbol{i=1}}^{\boldsymbol{n}} [\,\boldsymbol{N_i(\tau) - \widehat{\mu}_0(\tau \wedge C_i)}]^{\boldsymbol{2}}\right) \cdot \left(\frac{\boldsymbol{L}}{\boldsymbol{4}}\right)^{-1},$$

$\widehat{\boldsymbol{\mu}}_{\boldsymbol{0}}(\cdot)$: the Nelson-Aalen estimator calculated from pooled data.

✓ **Pooled event data**
No treatment codes are required to calculate the proposed statistic.

✓ **Subject-level variation**
The squared residual contributions capture variability beyond a simple event count.

➢ **Proposed procedure: blinded monitoring of variance**

1. Set α, target power $1-\gamma$, and β_0
2. Set the number of subjects n
3. $1 - \gamma = \Phi(-z_{1-\alpha/2} - \beta_0/v) + 1 - \Phi(z_{1-\alpha/2} - \beta_0/v) \rightarrow v^2_{target}$. — **Design stage**
4. Monitor $\hat{v}^2_{blind}$ in a blinded manner continuously as the study proceeds. — **Blinded monitoring**
5. Once $\hat{v}^2_{blind} \leq v^2_{target}$, conduct the final analysis fitting the marginal rate model. — **Final analysis**

4. SIMULATION DESIGN

➢ **Calculation of sample size at design stage:** Ingel & Jahn-Eimermacher (2014)'s formulas
➢ **Model for data generation:** mixed Poisson process with Weibull baseline mean $\mu_0(t) = \lambda t^\nu$ and gamma frailty with variance θ.
➢ **Methods compared**

Method	Final-analysis criterion
Fixed design	The prespecified target number of events at the design stage
Re-estimation	The updated the target number of events: using re-estimated $\hat{\theta}$ from interim analysis
Proposed	Monitoring $\hat{v}^2_{blind}$ until reach the threshold v^2_{target}

➢ **Settings**: Correct specified parameters to calculate (L, n) at the design stage (**Setting 1**); misspecified parameters to calculate (L, n) at the design stage (**Setting 2**).
➢ **Evaluation**: empirical power, Type I error, analysis time, and the number of events at the final analysis.

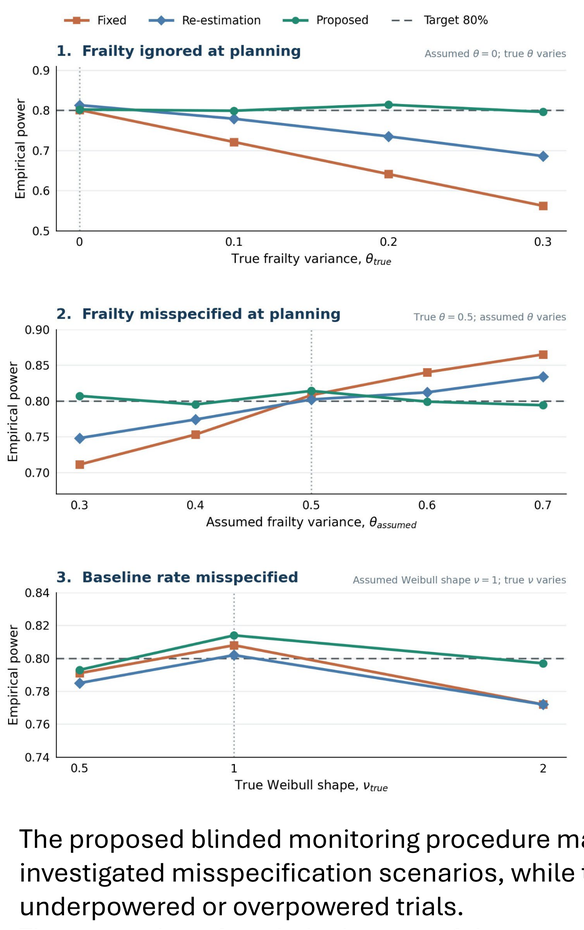
5. SIMULATION RESULTS

➢ **Setting 1**

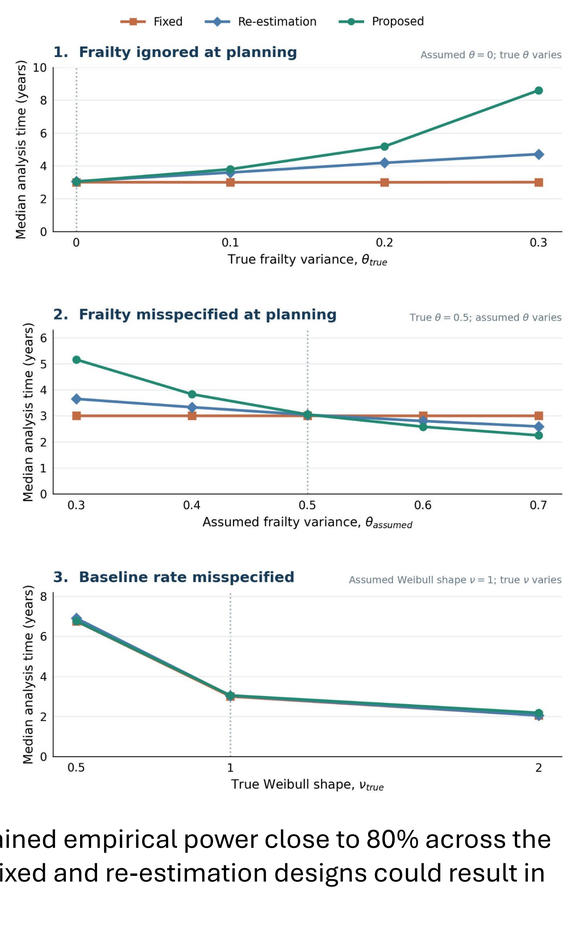
All three methods achieved approximately 80% empirical power and maintained Type I error rates near the nominal 5% level.

➢ **Setting 2**

- **Empirical power**



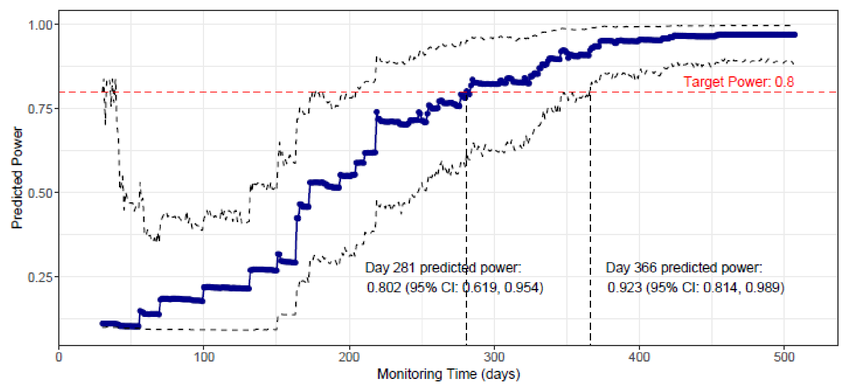
- **Calendar time for final analysis (median)**



- The proposed blinded monitoring procedure maintained empirical power close to 80% across the investigated misspecification scenarios, while the fixed and re-estimation designs could result in underpowered or overpowered trials.
- The protection of statistical power of the proposed method is achieved by adjusting follow-up durations; sometimes requires prolonging trial durations.

6. CLINICAL EXAMPLE

➢ **Chronic granulomatous disease (CGD) data**: a randomized, double-blind trial ($n = 128$) to evaluate the efficacy of interferon gamma in preventing **recurrent severe infections** in patients with CGD, a primary immunodeficiency disorder.
➢ **Application**: targeting 80% power, the proposed blinded monitoring procedure was retrospectively applied to determine the timing of final analysis; the result was compared with the fixed design.
➢ **Key findings**



The predicted power and corresponding bootstrapped upper and lower bounds over monitoring time.

281	**306**	**0.294**
Analysis day: proposed	Analysis day: fixed	Rate ratio: both designs

7. DISCUSSION

➢ **Assumptions & practical considerations**: the method assumes a marginal proportional rate model and independent, treatment-independent censoring. To avoid excessive follow-up, appropriate initial sample size planning is important.
➢ **Implications for oncology trials**: the proposed procedure may be useful to recurrent oncology endpoints, although informative terminal events (e.g., death) may require further consideration.
➢ **Future topics**: sample-size planning strategies for the proposed method; framework to combine the proposed method with group sequential studies, etc.

CONCLUSION

We proposed an event-drive type design for trials with recurrent events, which explicitly accounts for within-subject correlation through blinded monitoring of the sandwich variance under a semiparametric marginal rate model. The proposed method performed well under various scenarios, maintaining the statistical power at a desirable level without inflation of Type I error rates.

1. J. Zhang and S. Hattori, " *Event-Driven Type Design for Clinical Trials With Recurrent Events*," *Statistics in Medicine* 45, no. 20-22 (2026): e70742, https://doi.org/10.1002/sim.70742.
2. K. Ingel and A. Jahn-Eimermacher, "Sample-Size Calculation and Reestimation for a Semiparametric Analysis of Recurrent Event Data Taking Robust Standard Errors Into Account," *Biometrical Journal* **56** (2014): 631–648, https://doi.org/10.1002/BIMJ.201300090.
3. M. S. Pepe and J. Cai, "Some Graphical Displays and Marginal Regression Analyses for Recurrent Failure Times and Time Dependent Covariates," *Journal of the American Statistical Association* **88**, no. 423 (1993): 811–820, https://doi.org/10.1080/01621459.1993.10476346.
4. J. F. Lawless and C. Nadeau, "Some Simple Robust Methods for the Analysis of Recurrent Events," *Technometrics* **37** (1995): 158–168, https://doi.org/10.1080/00401706.1995.10484300.
5. D. Y. Lin, L. J. Wei, I. Yang, and Z. Ying, "Semiparametric Regression for the Mean and Rate Functions of Recurrent Events," *Journal of the Royal Statistical Society, Series B: Statistical Methodology* **62** (2000): 711–730, https://doi.org/10.1111/1467-9868.00259.

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