Bayesian Quantitative Decision Making for Proof-of-Concept Studies with an Interval-Censored Endpoint

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1. Disclaimer

The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the organizations to which they belong.

2. Background

- Go/no-go decisions in early-phase studies are critical to drug development because they determine whether a program should proceed to costly and time-consuming later-phase studies.
- In oncology development, progression-free survival (PFS) can provide quantitative support for early-phase decisions. A program may advance or stop depending on whether the median PFS or the PFS probability at a prespecified landmark meets a decision criterion.
- PFS is defined as the time to death or disease progression, with progression assessed by diagnostic imaging.
- Death may be observed at an exact time, whereas progression is known only to have occurred between the last progression-free assessment and the first assessment showing progression. Nevertheless, conventional PFS analyses typically assign progression to the date on which it is first detected and treat that date as the exact event time.

3. Objectives

- Develop a go/no-go criterion based on median survival time that (1) accommodates interval censoring and (2) controls the false-go probability.
- Implement the calculation of the correct-go probability and related statistics.
- Compare the operating characteristics in realistic trial settings across (1) the proposed method accounting for interval censoring, (2) a conventional method that uses the detection visit as the event time, and (3) an idealized analysis using the latent exact event times.

4. Method

The proposed method is based on the framework of BOP2 for time-to-event endpoints (Zhou et al., 2020), with modifications to (1) accommodate interval censoring, (2) use a Weibull distribution rather than an exponential distribution, and (3) omit interim analyses.

Survival data are denoted as $\{\delta_i, T_i, L_i, U_i\}$, where δ_i indicates censoring status for the i-th subject with 0 (right censoring), 1 (exact event), 2 (left censoring), and 3 (interval censoring),
T_i indicates the exact event time (observed for death and latent for progression), and L_i and U_i indicate the lower and upper bounds derived from T_i and the visit interval.
The likelihood is

$$L(\boldsymbol{\theta}|\{\delta_i, T_i, L_i, U_i\}) = \prod_{\delta_i=0} S(L_i|\boldsymbol{\theta}) \prod_{\delta_i=1} f(T_i|\boldsymbol{\theta}) \prod_{\delta_i=2} F(U_i|\boldsymbol{\theta}) \prod_{\delta_i=3} \big(F(U_i|\boldsymbol{\theta}) - F(L_i|\boldsymbol{\theta})\big),$$

where $S(\cdot\,|\boldsymbol{\theta})$, $f(\cdot\,|\boldsymbol{\theta})$, and $F(\cdot\,|\boldsymbol{\theta})$ denote the survival, probability density, and cumulative distribution functions, respectively.
The survival time is assumed to follow a Weibull distribution, $T_i \sim \text{Weibull}(\alpha, \sigma)$,
where α and σ are shape and scale parameters.
Weakly informative priors are employed as $\alpha \sim \text{Lognormal}(0,1^2)$ and $\sigma \sim \text{Lognormal}(2,1^2)$.

Algorithm for Determination of Decision Criterion and Go Probability

Step 0

Set $\text{H}_0: \psi = \psi_0$ and $\text{H}_1: \psi = \psi_1 (> \psi_0)$ for an endpoint of interest, i.e., median survival time, and acceptable false-go probability $\text{FGP} = P(\text{go}|\psi_0)$, probability of an incorrect go decision.

Step 1: Find go decision criterion

1-1. Repeat 1-2 to 1-5 R times with the r-th simulation index ($r = 1, \ldots, R$).

1-2. Simulate the r-th study for H_0 with a single survival endpoint and obtain $\{\delta_i^{\text{H}_0}, T_i^{\text{H}_0}, L_i^{\text{H}_0}, U_i^{\text{H}_0}\}_i$.

1-3. Draw posterior samples, $\left(\alpha_r^{(s)}, \sigma_r^{(s)}\right), s = 1, \ldots, S$

1-4. For each s, calculate $\psi\left(\alpha_r^{(s)}, \sigma_r^{(s)}\right)$, the value of the endpoint of interest, such as median survival.

1-5. Calculate $q_{r,k}$ ($k = 1, \ldots, K$), the p_k-quantile of $\left\{\psi\left(\alpha_r^{(s)}, \sigma_r^{(s)}\right)\right\}_s$, where p_k ($k = 1, \ldots, K$) comes from a finely spaced sequence of probabilities, e.g., $0.01, 0.02, \ldots, 0.99$. The quantile at 0.50 (median) can be interpreted as the representative value of the endpoint in the r-th simulation.

1-6. Calculate π_k ($k = 1, \ldots, K$), the proportion of $\{q_{r,k}\}_r$ values that satisfy $q_{r,k} > \psi_0$. This is the estimated false-go probability for k.

1-7. Find the largest k that satisfies $\pi_k \leq \text{FGP}$ and denote it by k^*.

Note: Comparison of the p_{k^*}-quantile of the posterior distribution of $\left\{\psi\left(\alpha_r^{(s)}, \sigma_r^{(s)}\right)\right\}_s$ with ψ estimated from data is used to make the go decision in one study.

Step 2: Determine the go probability under H_1

Same as Step 1 but 1-2 and 1-7 are replaced as follows:

2-2. Simulate the r-th study for H_1 with a single survival endpoint and obtain $\{\delta_i^{\text{H}_1}, T_i^{\text{H}_1}, L_i^{\text{H}_1}, U_i^{\text{H}_1}\}_i$

2-7. Estimate the correct go probability as $\text{CGP}=\pi_{k^*}$.

5. Evaluation Scenarios

Table 1: Parameter settings in evaluation

	Basic scenario	Additional analysis
Diagnosis interval	6 weeks[a]	4 weeks, 8 weeks
Parameter of interest	Median survival of PFS	6-month and 12-month survival probabilities of PFS for further investigation
Median survival	H_0: 24 weeks H_1: 36 weeks[b]	H_0: 24 weeks H_1: 28, 32, 36, 40, 44, 48 weeks
Shape parameter	$\alpha = 1$	α =0.75,1.5
Required number of events	40 events[c]	40
Probability of death (no interval censoring)	20%[d]	050%
Accrual rate	5 persons per month[e]	
False-go probability	0.10[f]	

[a]Six- or eight-week intervals were most common in a pooled analysis of NSCLC and SCLC trials (Qi et al., 2012).
[b]Approximately 6 and 9 months for control and intervention groups in a category in a literature review (Haslam et al., 2022).
[c]Approximate number of events required for a type I error rate of 0.05 and a type II error rate of 0.20.
[d]Approximately 20% in a pooled individual-patient-data analysis (Foster et al., 2015).
[e]Median accrual rate of 5 participants per month among non-randomized phase I/II trials in a literature review (Jenei et al., 2022).
[f]A typical one-sided type I error rate for POC studies is α=0.05 or 0.10 (Roychoudhury et al., 2018)

5. Evaluation Scenarios (Cont.)

Table 2: Censoring in analysis

Interval censoring	The event is treated as having occurred between the previous and current visits. This is the proposed method.
Visit time	The event is assigned to the visit at which it was first detected. This is the conventional approach to PFS analysis.
Exact time	The latent true event time is used. This idealized analysis is included only to evaluate the properties of the other methods.

6. Results

Results were obtained using R 4.6.1 and CmdStan 2.39.0, with the number of simulation replicates R set to 10,000.

Table 3: Correct-go probability in the basic scenario and additional analyses

Parameter setting	Censoring in analysis		
	Interval censoring	Visit time	Exact time
Basic scenario	89.4%	89.0%	90.8%
Diagnosis interval is 4 weeks	88.9%	88.6%	90.1%
Diagnosis interval is 8 weeks	88.9%	88.4%	90.9%
Shape parameter $\alpha = 0.75$	74.3%	74.2%	76.0%
Shape parameter $\alpha = 1.5$	98.9%	98.8%	99.1%
Probability of death is 0.50	89.0%	88.9%	89.8%

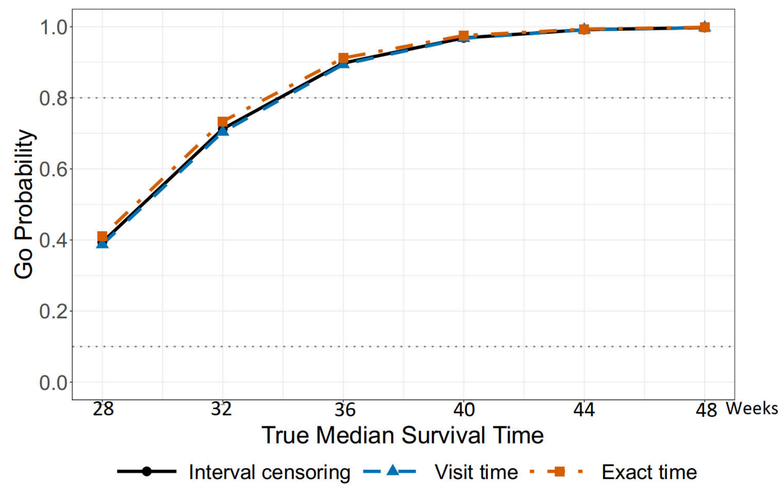


Figure 1: Operating characteristic curve for the correct-go probability across true median survival times

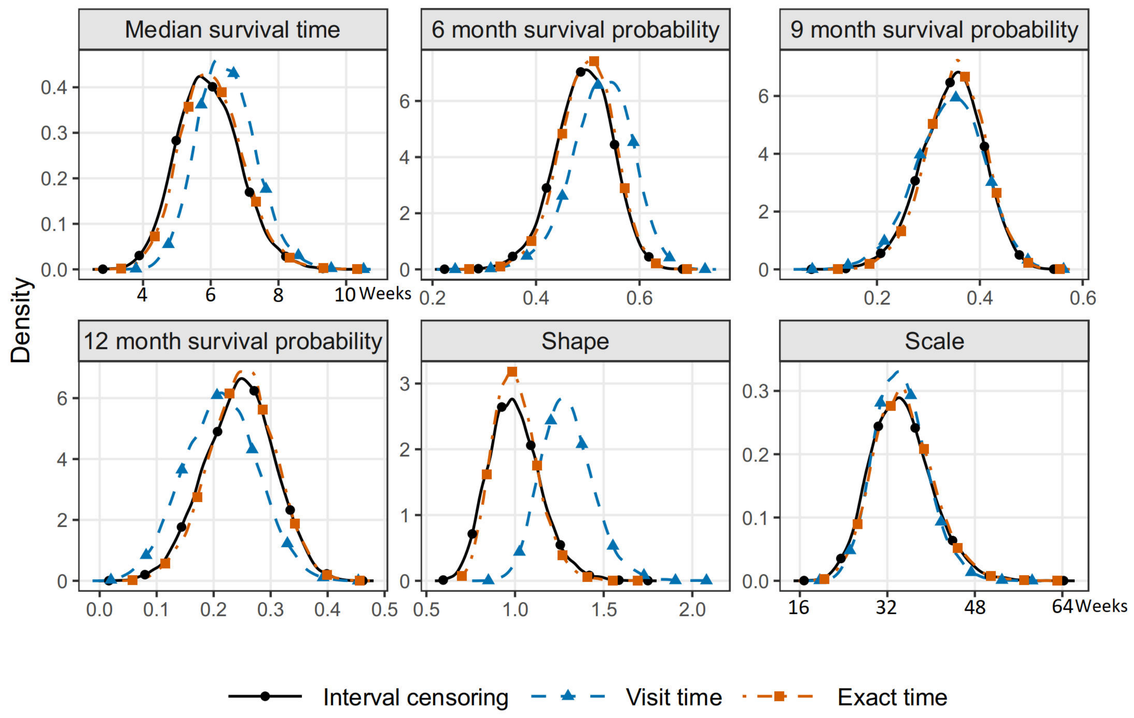


Figure 2: Distribution of the posterior median across simulation replicates in the basic scenario

7. Findings

- In the basic scenario, the correct-go probability was 1.4 percentage points lower with the proposed method than with the exact-time analysis; the corresponding difference for the visit-time method was nearly the same at 1.8 percentage points (Table 3).
- Similar patterns were observed in the additional scenarios (Table 3) and across the range of true median survival times examined (Figure 1).
- The visit-time and exact-time analyses produced visibly different posterior distributions for median survival and for the 6- and 12-month survival probabilities, which may be attributable to bias in estimating the Weibull shape parameter (Figure 2).
- The proposed method may offer advantages over the visit-time analysis when a landmark survival probability is included in the decision criterion or when posterior distributions are used for interpretation.

8. References

Foster, N. R., Renfro, L. A., Schild, S. E., Redman, M. W., Wang, X. F., Dahlberg, S. E., Ding, K., Bradbury, P. A., Ramalingam, S. S., Gandara, D. R., Shibata, T., Saijo, N., Vokes, E. E., Adjei, A. A., & Mandrekar, S. J. (2015). Multitrial Evaluation of Progression-Free Survival as a Surrogate End Point for Overall Survival in First-Line Extensive-Stage Small-Cell Lung Cancer. Journal of Thoracic Oncology, 10(7), 1099–1106. Haslam, A., Gill, J., & Prasad, V. (2022). The frequency of assessment of progression in randomized oncology clinical trials. Cancer Reports, 5(7), e1527. Jenei, K., Haslam, A., Olivier, T., Miljković, M., & Prasad, V. (2022). What drives cancer clinical trial accrual? An empirical analysis of studies leading to FDA authorisation (2015–2020). BMJ Open, 12(10), e064458. Qi, Y., Allen Ziegler, K. L., Hillman, S. L., Redman, M. W., Schild, S. E., Gandara, D. R., Adjei, A. A., & Mandrekar, S. J. (2012). Impact of disease progression date determination on progression-free survival estimates in advanced lung cancer. Cancer, 118(21), 5358–5365. Roychoudhury, S., Scheuer, N., & Neuenschwander, B. (2018). Beyond p-values: A phase II dual-criterion design with statistical significance and clinical relevance. Clinical Trials, 15(5), 452–461. Zhou, H., Chen, C., Sun, L., & Yuan, Y. (2020). Bayesian optimal phase II clinical trial design with time-to-event endpoint. Pharmaceutical Statistics, 19(6), 776–786.