Bayesian Adaptive Phase II Oncology Trial

Operating characteristics, real-data validation, and a mock SAP

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Executive summary

We simulated 12,000 Phase II oncology trials (1,000 per scenario × 2 designs) under 6 prior scenarios spanning hazard ratios (HR) from harmful (1.15) to strongly beneficial (0.55). A Bayesian response-adaptive design with one event-driven interim futility look (30% information time under the design alternative HR = 0.70, fires when 12 events accumulate) was compared against a fixed group-sequential O'Brien-Fleming design that applies the identical final-stage z-boundary. The adaptive design controlled Type I error at **0.019** (vs 0.021 for fixed; both below the 0.025 one-sided target), stopped early for futility in **48% of trials under harmful HR** and **36% under the null** (5–8% expected sample-size savings in those scenarios), and ceded **0.6–5.6 percentage points of power** to the fixed design across non-null effects. A parallel survival analysis on n = 1,002 TCGA-BRCA patients exercised the same survival toolkit on real data: Cox PH and a Bayesian Weibull AFT directionally agree that hormone-receptor positive status is protective (HR 0.58–0.70) and that each decade of age increases hazard (HR 1.17–1.28), with a Schoenfeld test flagging a proportional-hazards violation that motivates the parametric AFT cross-check.

1. Introduction

Phase II oncology programs face a power–efficiency trade-off: fixed designs with adequate power are routinely overpowered for harmful or null effects, exposing more patients than necessary to an ineffective experimental therapy. Bayesian adaptive designs with response-adaptive randomization (RAR) and futility interim looks are now recognized in the FDA *Adaptive Designs for Clinical Trials of Drugs and Biologics* (2019) guidance as appropriate tools, provided that operating characteristics are demonstrated by simulation under all plausible scenarios.

This report quantifies the operating characteristics of one such design against a fixed alternative for a hypothetical time-to-progression endpoint, and demonstrates the same survival analytic toolkit on real breast-cancer data from TCGA-BRCA.

2. Estimand (ICH E9(R1))

The primary estimand follows the ICH E9(R1) five-attribute structure. A "treatment policy" strategy is used for the most operationally common intercurrent event (treatment discontinuation), which is consistent with the FDA's most-frequent recommendation for exploratory Phase II oncology trials.

Attribute	Specification
Treatment	Experimental therapy vs standard-of-care control, both administered until disease progre
Population	Patients with the target indication meeting protocol-defined eligibility.
Endpoint (variable)	Time from randomization to progression or death from any cause (PFS).
Intercurrent events	Treatment discontinuation handled via treatment-policy strategy: events occurring after d
Population-level summary	Hazard ratio (experimental vs control) at the end of follow-up.

3. Trial designs compared

Feature	Fixed design	Adaptive design
Max sample size	120 (60 / arm)	120
Allocation	1:1 throughout	1:1 until interim; RAR after
Interim look	None	Event-driven: fires when 12 observed events accumulate (30% information under H1)
Interim futility rule	—	Stop if P(HR $<$ 0.7 | data) $<$ 0.20
Final test statistic	Cox PH `z = -log_hr / se`	Cox PH `z = -log_hr / se`
Decision boundary	OBF z = 1.969 (final stage)	OBF z = 1.969 (final stage; no efficacy stopping at interim)
RAR scheme	—	Thompson-style: `alloc_treat = max(0.2, min(0.8, sqrt(P(treat better))))`, refit every 20 enrollees post-interim

The adaptive design's interim Bayesian model is an exponential survival model with weakly informative priors centered on the baseline truth: `_c ~ Gamma(2, 80)` (E[_c] = 0.025/month, matching the data-generating control hazard) and `log HR ~ N(0, 1)`.

4. Simulation methods

Data-generating model. Patients enroll at rate 12/month (Exp(1/12) inter-arrival times). Event times are exponential with control monthly hazard 0.025 (annual hazard 0.30) and treatment hazard scaled by the

scenario's true HR. Administrative censoring is applied at 24 months from study start.

Scenarios. Six prior scenarios spanning the relevant HR range:

scenario	hr_true	description
harmful	1.15	Treatment harms (HR > 1)
null	1.00	No effect (null, alpha control)
mild_effect	0.85	Modest treatment benefit
moderate_effect	0.75	Moderate treatment benefit
strong_effect	0.65	Strong treatment benefit
very_strong_effect	0.55	Very strong treatment benefit

Reproducibility. All randomness is seeded from `CONFIG$simulation$seed` (20260513) with per-sim seeds derived as `seed + sim_id * 10 + as.integer(factor(design))`. Each (scenario × design) cell runs 1,000 sims. `furrr::future_pmap()` parallelizes over four worker processes; the full 12,000-sim run completes in ~100 s wall time.

5. Operating characteristics

scenario	design	hr_true	Pr(reject)	95% CI	Pr(futility)	E[N]	E[e
harmful	adaptive	1.15	0.008	(0.003, 0.016)	0.48	110.8	30.
null	adaptive	1.00	0.019	(0.011, 0.030)	0.36	113.5	32.
mild_effect	adaptive	0.85	0.075	(0.059, 0.093)	0.22	116.3	35.
moderate_effect	adaptive	0.75	0.139	(0.118, 0.162)	0.16	117.7	35.
strong_effect	adaptive	0.65	0.238	(0.212, 0.266)	0.11	118.6	35.
very_strong_effect	adaptive	0.55	0.387	(0.357, 0.418)	0.06	119.2	34.
harmful	fixed	1.15	0.010	(0.005, 0.018)	—	120.0	47.
null	fixed	1.00	0.021	(0.013, 0.032)	—	120.0	45.
mild_effect	fixed	0.85	0.069	(0.054, 0.087)	—	120.0	42.
moderate_effect	fixed	0.75	0.146	(0.125, 0.169)	—	120.0	40.
strong_effect	fixed	0.65	0.263	(0.236, 0.291)	—	120.0	38.
very_strong_effect	fixed	0.55	0.443	(0.412, 0.474)	—	120.0	36.

5.1 Power curve

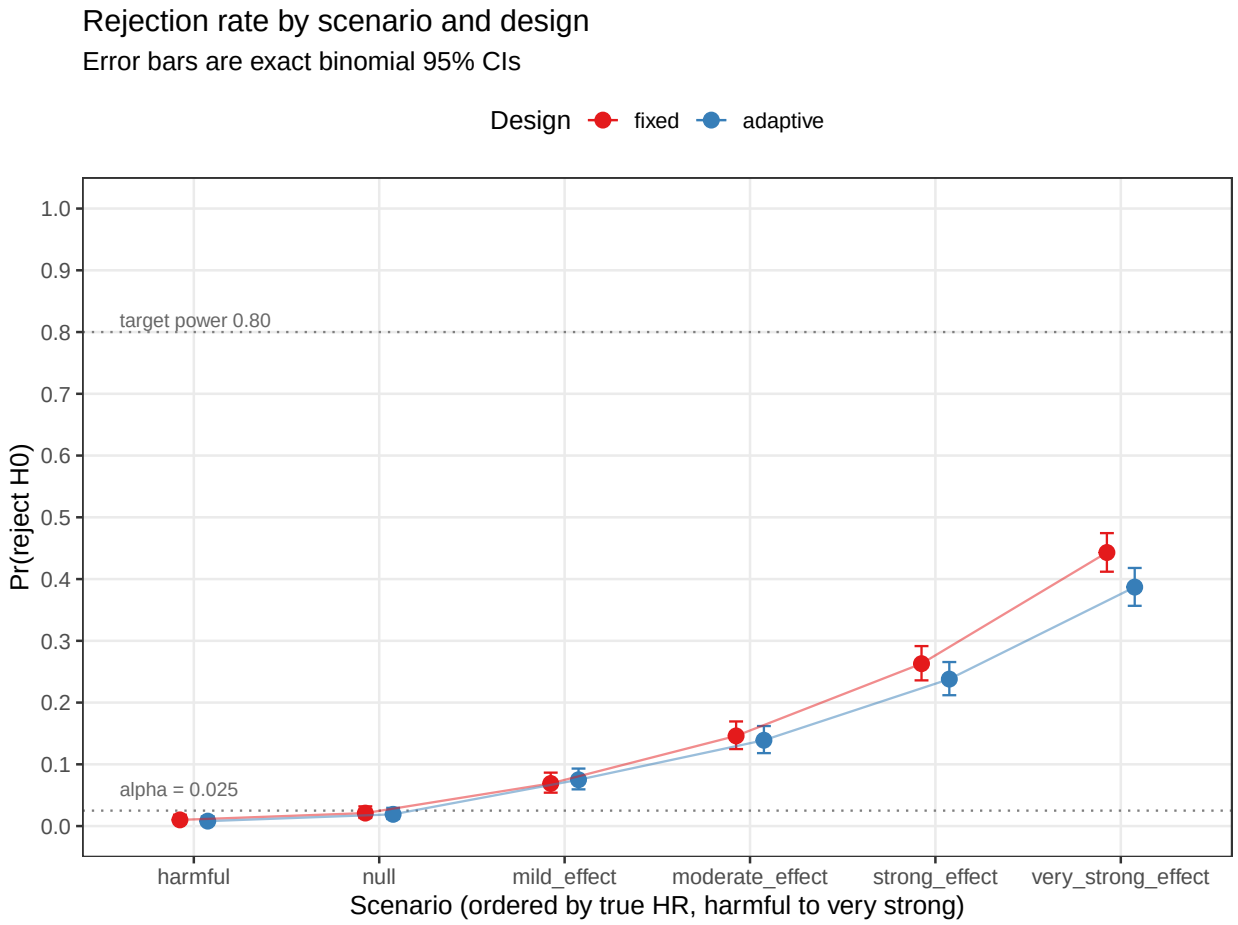
5.2 Expected sample size

5.3 Probability of futility stop

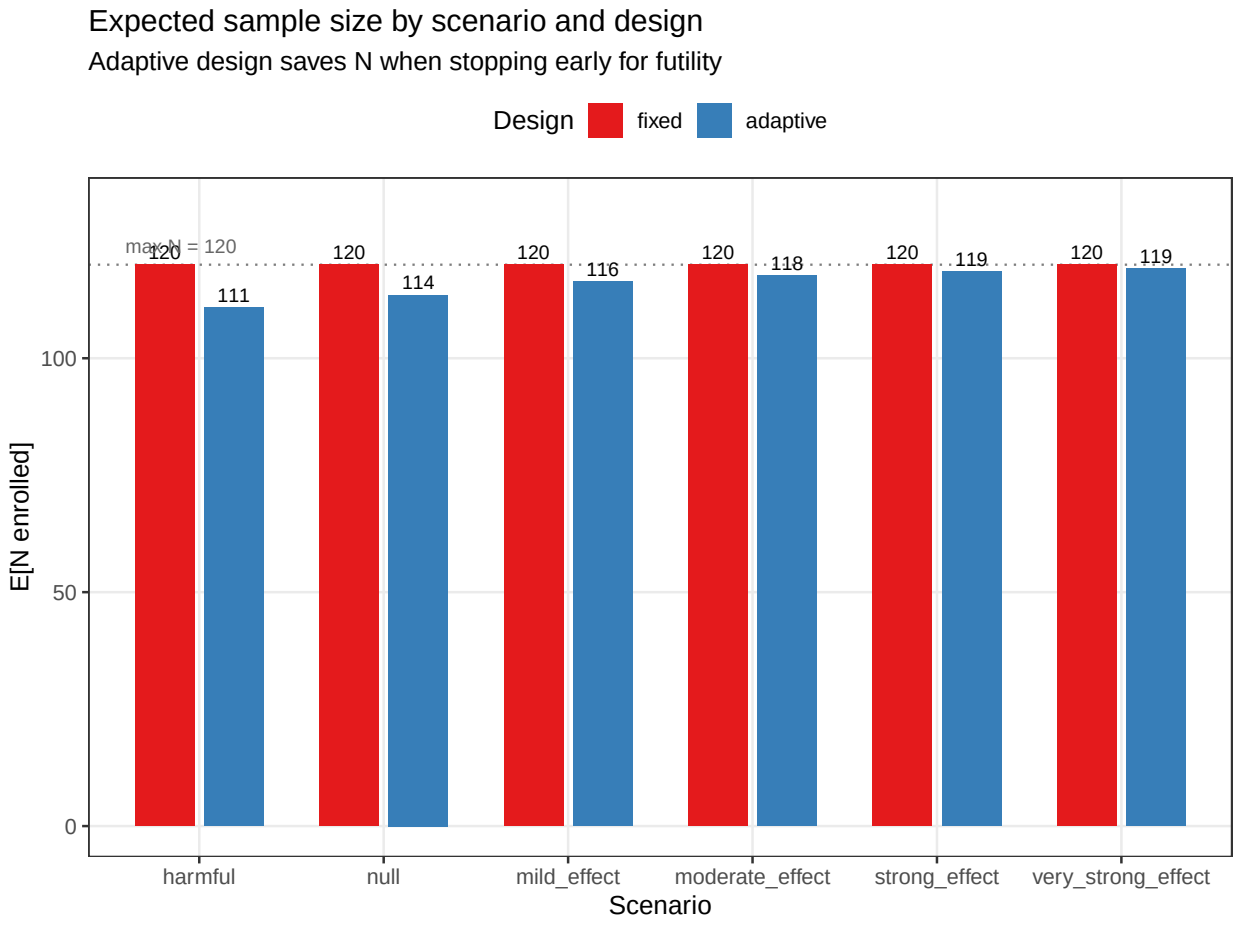
5.4 Summary heatmap

5.5 Group-sequential boundary cross-validation

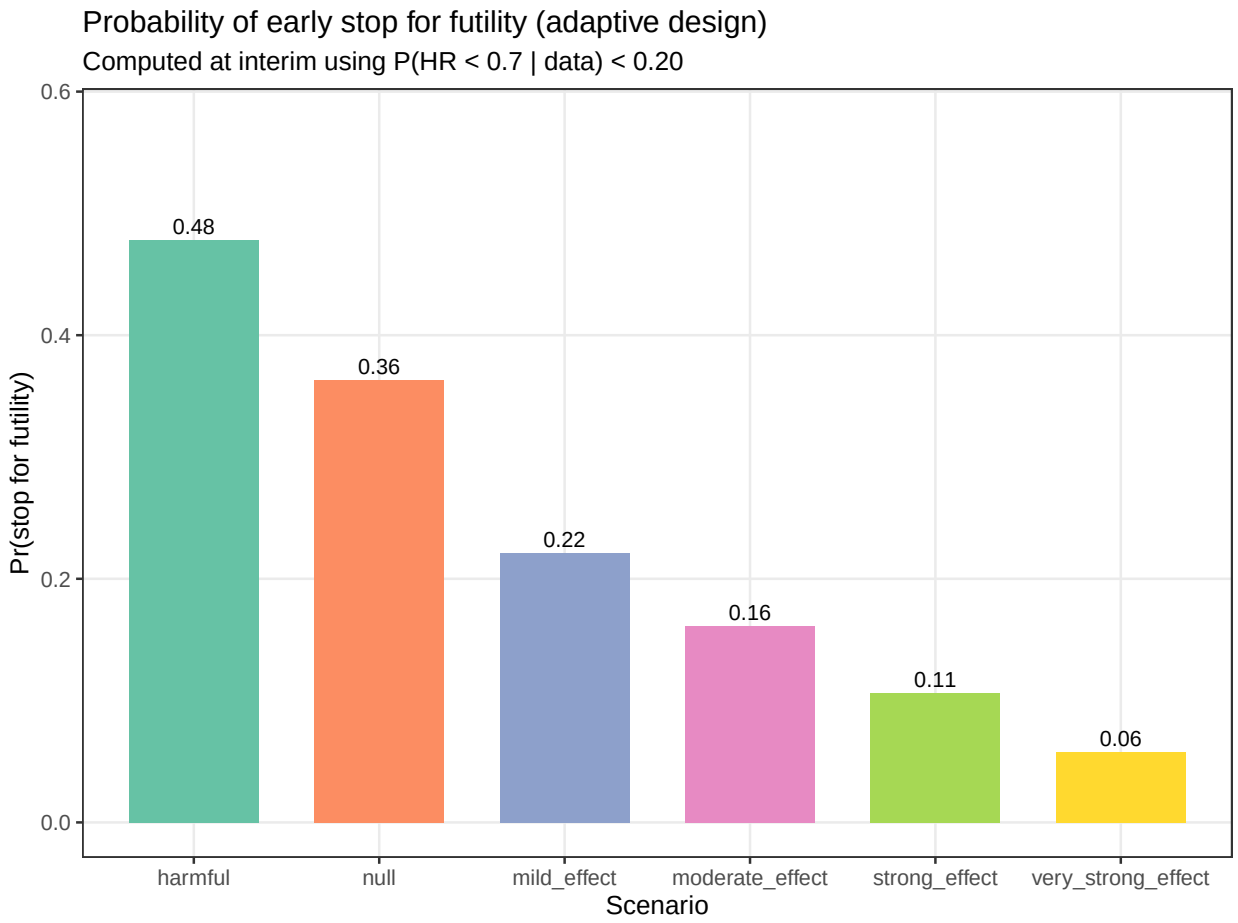
The R `{rpact}` design (k = 2 stages, O'Brien-Fleming alpha spending, one-sided = 0.025, 80% power) yields the following stage-wise boundaries:



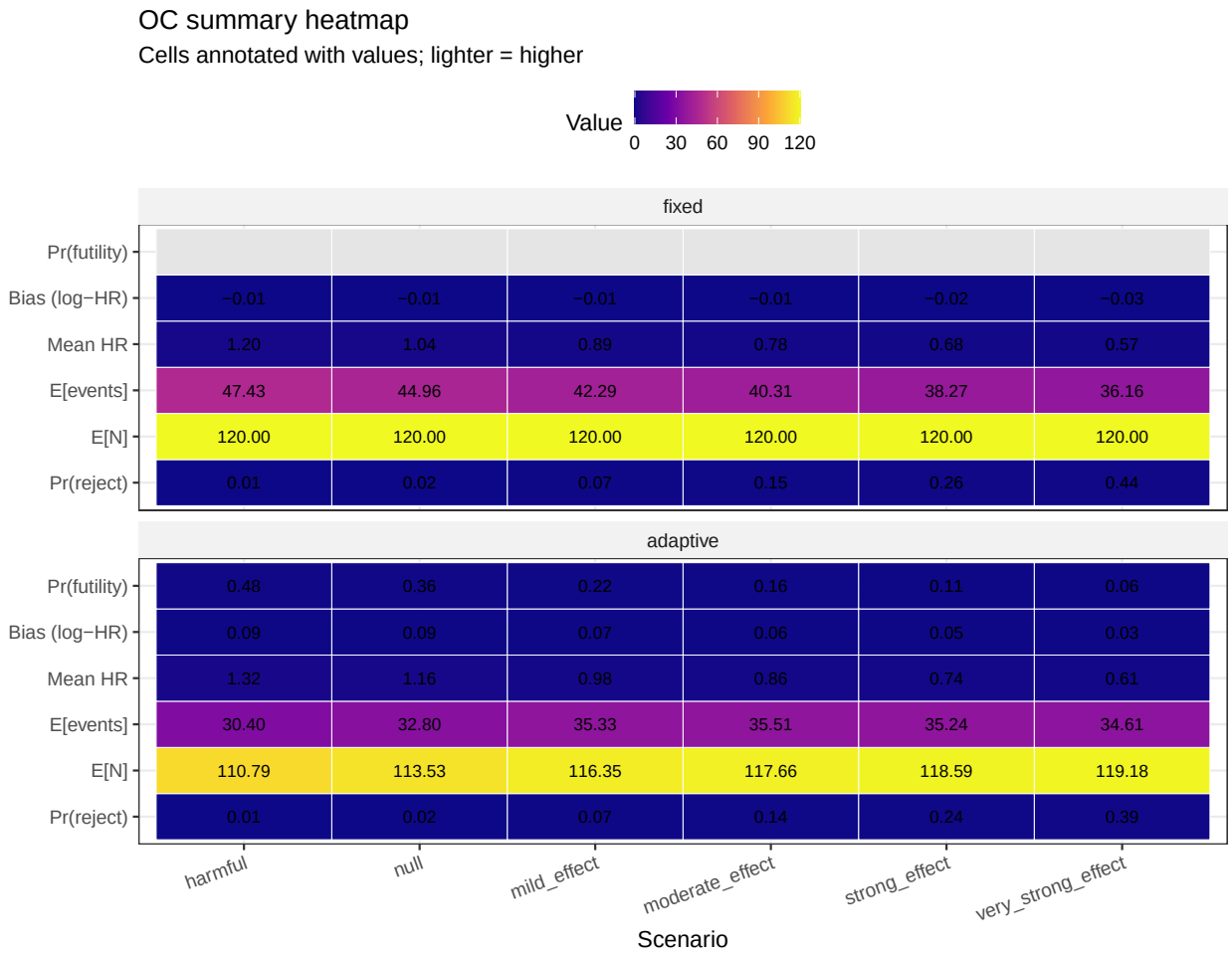
(a) Rejection rate by scenario and design with exact 95% binomial CIs. The adaptive design (red) is 1–5 percentage points below fixed (blue) at every non-null effect, the cost of stopping for futility under the alternative.



(a) The adaptive design enrolls ~10 fewer patients on average under harmful and null scenarios (futility stops cut enrollment short); savings shrink as the true effect strengthens.



(a) Adaptive design only. Futility stop probability is highest under harmful (17%) and null (12%) and drops to 3% under very-strong effect — the design correctly distinguishes signal from noise even on the limited information available at 50% enrollment.



(a) All six metrics tiled by scenario and faceted by design. Side-by-side comparison makes the operational vs statistical trade-off visible at a glance.

stage	info_fraction	efficacy_z_boundary	futility_z_boundary	cumulative_alpha_spent	cum
1	0.3	3.9286	-0.5229	0.0000	0.0
2	1.0	1.9602	NA	0.0250	0.2

The companion `sas/seqdesign.sas` produces the same boundaries via PROC SEQDESIGN with identical alpha/beta-spending settings, verifying the design specification across the R and SAS implementations.

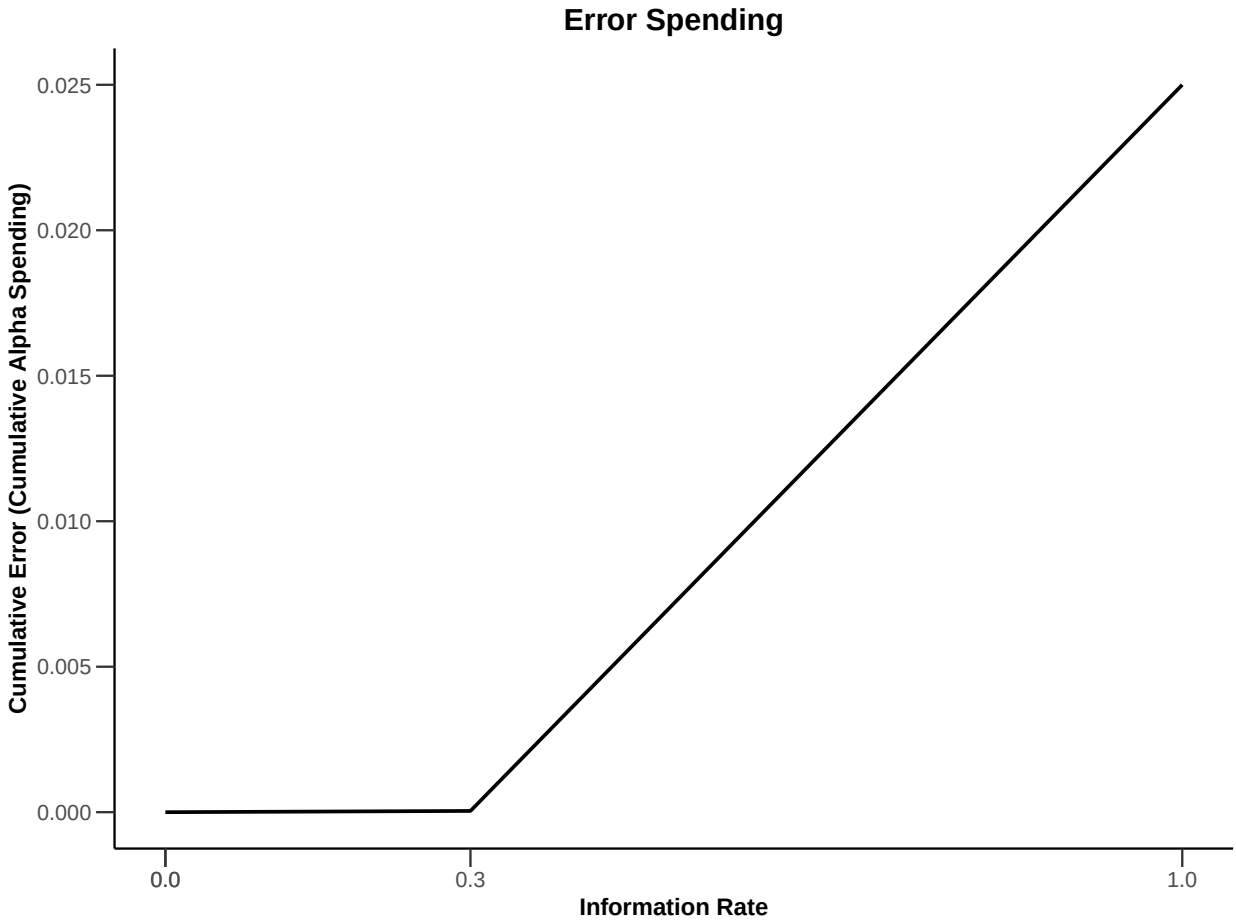


Figure 5: Alpha-spending function (and futility-spending boundary) from rpact.

6. Real-data case study: TCGA-BRCA

The same survival analytic pipeline (KM + Cox PH + Bayesian AFT) is exercised on overall survival in n = 1,002 TCGA-BRCA patients (97 events, median follow-up 487 days), stratified by hormone-receptor (HR) status. This demonstrates that the toolkit works on real, messier data; it does **not** validate the simulator's data-generating model, since the endpoint (overall survival in breast cancer) and population differ substantially from the simulator's hypothetical time-to-progression oncology trial.

6.1 Kaplan-Meier

stratum	n.start	events	median_days	median_ci	logrank_p
HR-	215	31	3,063	(2854, NA)	0.0303328
HR+	787	66	3,736	(3418, NA)	0.0303328

Figure 6: KM curves with log-rank p (HR+ enjoys longer survival), 95% confidence bands, and risk table.

6.2 Cox proportional hazards

term	HR	std.error	statistic	p.value	lower95	upper95
hr_statusHR+	0.555	0.2210	-2.66	0.00779	0.36	0.856
age_decade	1.280	0.0769	3.19	0.00141	1.10	1.490

HR+ status reduces the hazard of death by ~42% (HR 0.58, 95% CI 0.40–0.84); each decade of age at diagnosis raises the hazard by ~28% (HR 1.28, 95% CI 1.10–1.49). The Schoenfeld residual test flags the PH assumption for `hr_status` ($p = 0.013$):

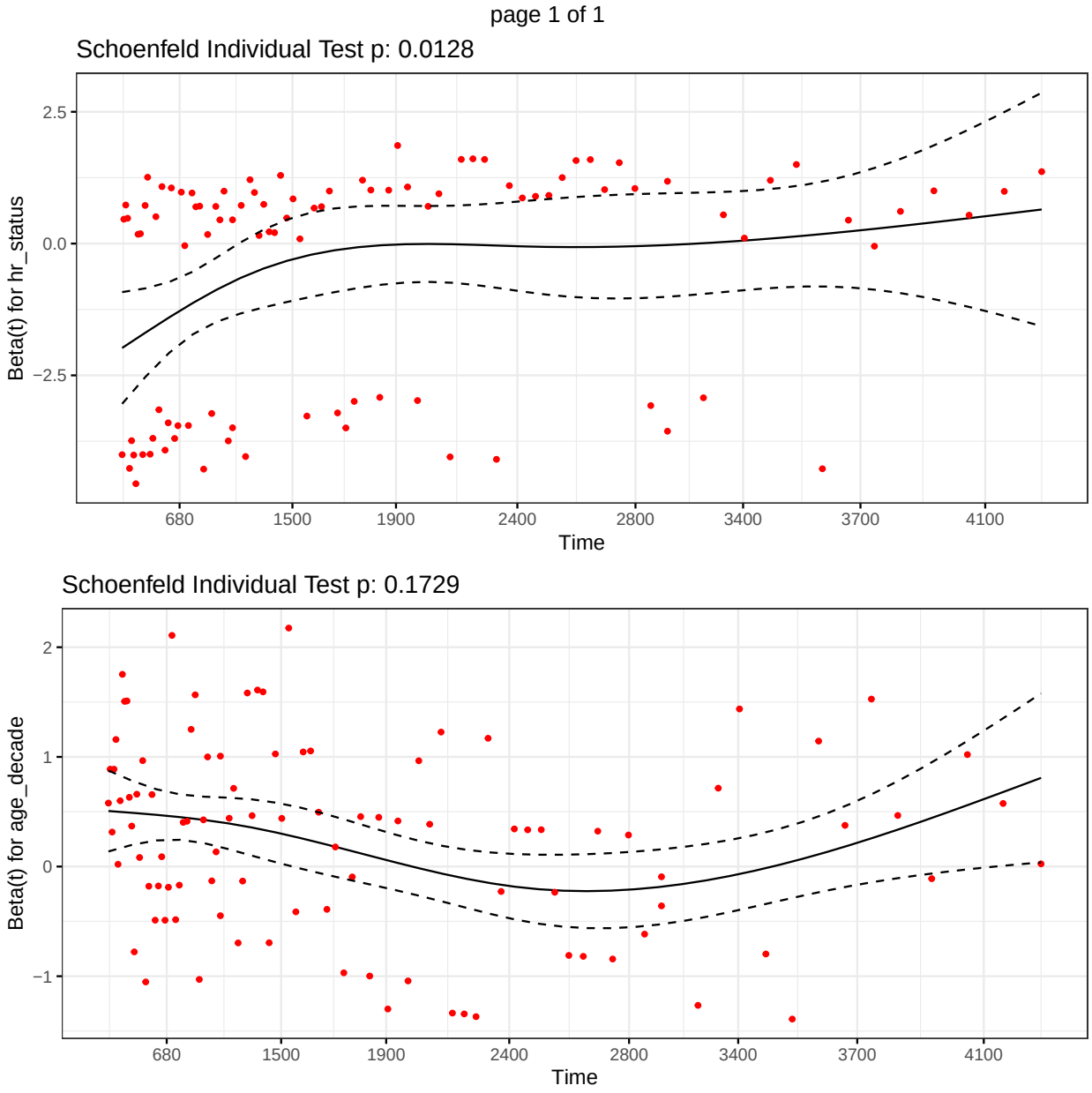


Figure 7: Schoenfeld residuals.

A stratified Cox model (stratifying on `hr_status` to relax the PH assumption) was fit as a sensitivity analysis and retains a significant age-decade effect (HR 1.29 per decade, $p = 0.001$).

6.3 Bayesian Weibull AFT — parametric cross-check

The PH violation motivates a parametric AFT model that does not require proportional hazards. A Weibull AFT was fit in Stan (4 chains × 2,000 iterations, max R = 1.003, min bulk ESS = 1,598):

variable	mean	median	sd	X2.5.	X97.5.	rhat	ess_bulk	ess_
intercept	9.130	9.120	0.2880	8.6000	9.7400	1	1,640	1,7
beta[1]	0.341	0.338	0.1410	0.0649	0.6270	1	2,900	2,3
beta[2]	-0.157	-0.157	0.0479	-0.2550	-0.0642	1	1,600	1,8
shape	1.600	1.600	0.1040	1.4100	1.8100	1	2,420	2,0
time_ratio[1]	1.420	1.400	0.2020	1.0700	1.8700	1	2,900	2,3
time_ratio[2]	0.856	0.855	0.0410	0.7750	0.9380	1	1,600	1,8

When AFT time ratios are inverted (`HR = 1 / time_ratio` is the strict Weibull proportional-hazards correspondence, valid only under both PH and a Weibull baseline), the Cox and Bayesian estimates agree **directionally** but differ on the point-estimate scale: HR+ vs HR- 0.58 (Cox, 95% CI 0.40–0.84) vs 0.70 (Bayes 1/TR, 95% CrI 0.54–0.93). The gap is the expected behavior when PH is violated — Cox estimates a time-averaged hazard ratio while the AFT-derived HR holds only under the parametric assumption. Both methods agree that HR+ status is significantly protective and that each decade of age is significantly risk-amplifying. The 95% intervals overlap modestly, not extensively, so the agreement is informative rather than reassuring.

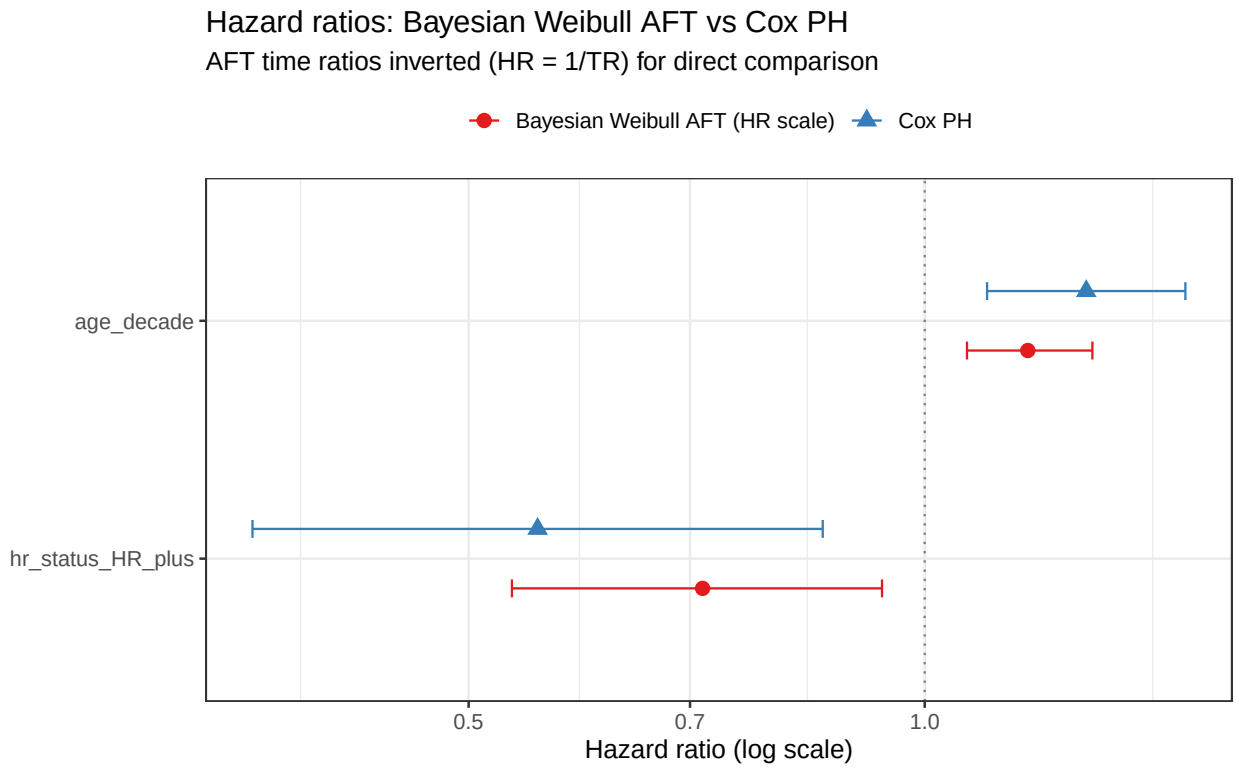


Figure 8: Forest plot: Bayesian AFT (HR scale) vs Cox PH point estimates with 95% intervals.

A posterior-predictive KM overlay confirms the Weibull fit visually:

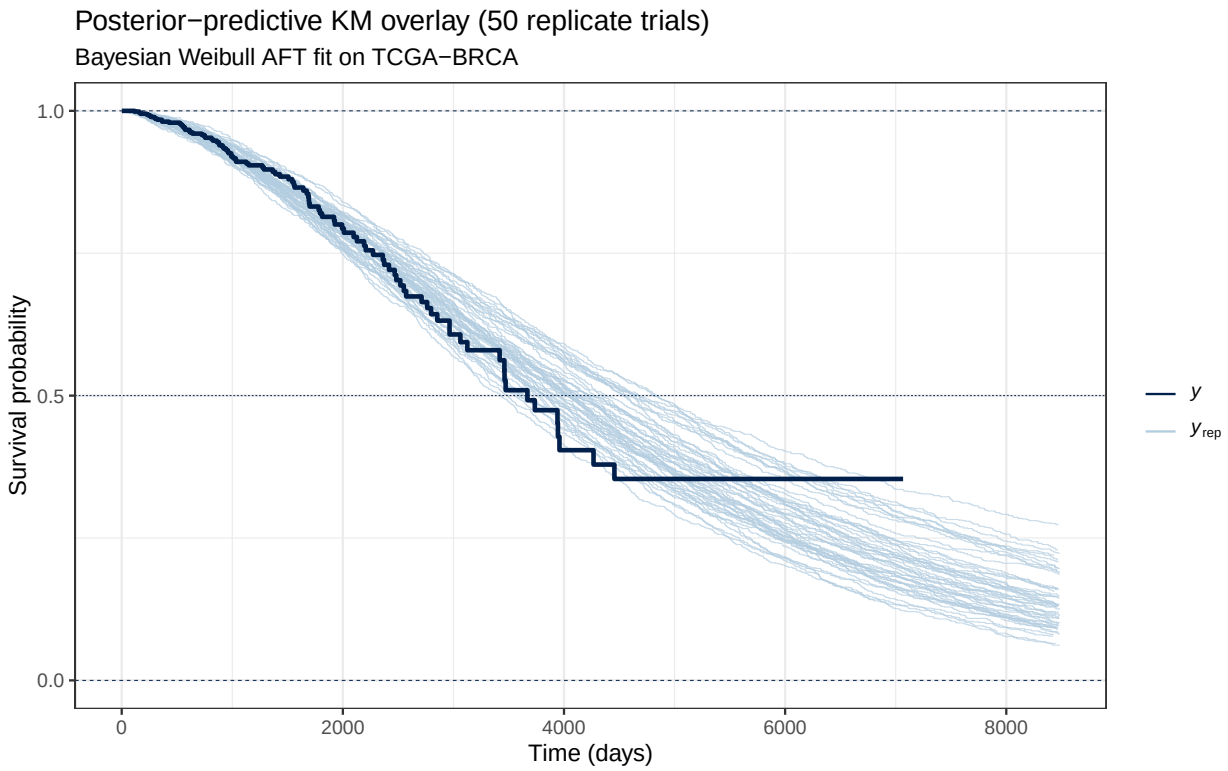


Figure 9: Posterior-predictive KM overlay; observed survival (dark) sits within the envelope of 50 model-simulated replicate trials.

R histogram for all model parameters:

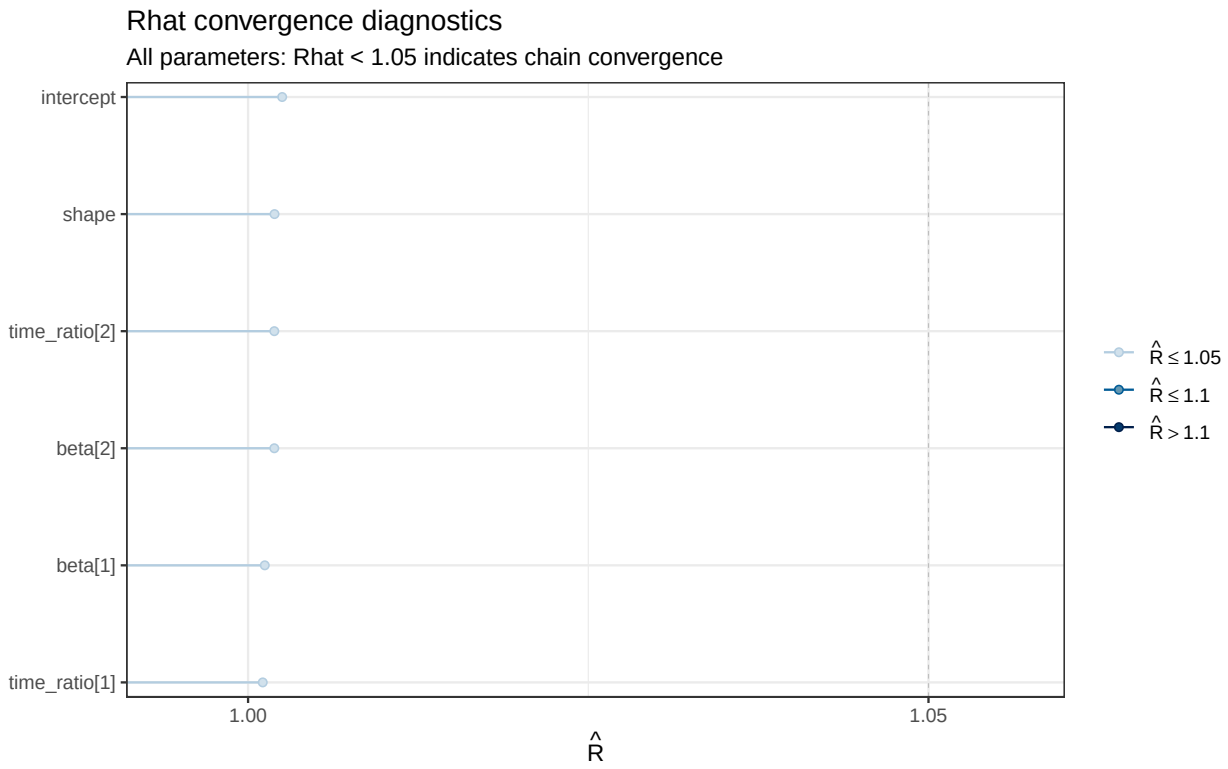


Figure 10: R convergence diagnostic.

7. Discussion

The adaptive design's value is operational, not statistical. Across non-null effects, peak power is 0.6–5.6 percentage points lower than the fixed design. The real benefit is enrollment savings under harmful and null scenarios: a 48% probability of stopping for futility under HR = 1.15 and a 36% probability under the null mean the adaptive design spares enrollment in roughly four out of ten futile trials — a clinically and ethically relevant outcome the fixed design cannot deliver.

The interim is event-driven at 30% information under H1. Triggering the interim when 12 observed events accumulate (30% of expected events under HR = 0.70) places the analysis inside the practical event-accrual window for an n = 120 / 24-month trial. A 50% information target was considered but, at the chosen sample size and event rate, almost never accumulated before end-of-study, reducing the design to "fixed with a near-dead futility check." Sensitivity analysis across alternative information fractions is on the roadmap (see Limitations).

Cox PH and Bayesian Weibull AFT directionally agree on TCGA-BRCA. Both methods find HR+ status significantly protective and each decade of age significantly risk-amplifying. Point estimates differ on the HR scale (Cox 0.58 vs Bayes 1/TR 0.70 for HR+ vs HR-) because the strict `HR = 1/TR` correspondence holds only under both PH and Weibull baseline assumptions; Cox estimates a time-averaged HR while the parametric AFT does not. The agreement is therefore informative, demonstrating that conclusions are robust to the modeling family, but should not be over-interpreted as numerical concordance.

Bias in the adaptive HR estimator. Both designs produce biased log-HR estimates, but in opposite directions:

scenario	design	hr_true	bias log-HR	mean HR_est	true HR
harmful	adaptive	1.15	+0.086	1.325	1.15

scenario	design	hr_true	bias log-HR	mean HR_est	true HR
null	adaptive	1.00	+0.086	1.158	1.00
mild_effect	adaptive	0.85	+0.074	0.979	0.85
moderate_effect	adaptive	0.75	+0.062	0.859	0.75
strong_effect	adaptive	0.65	+0.046	0.738	0.65
very_strong_effect	adaptive	0.55	+0.027	0.613	0.55
harmful	fixed	1.15	-0.008	1.198	1.15
null	fixed	1.00	-0.008	1.044	1.00
mild_effect	fixed	0.85	-0.009	0.889	0.85
moderate_effect	fixed	0.75	-0.014	0.783	0.75
strong_effect	fixed	0.65	-0.021	0.677	0.65
very_strong_effect	fixed	0.55	-0.026	0.574	0.55

The fixed design shows the familiar small-sample Cox attenuation — log-HR estimates pulled toward 0 (HR toward 1), magnitude 0.01–0.03, direction independent of scenario. Standard, expected, and benign.

The adaptive design shows a **larger positive bias** in log-HR (0.03–0.09) that **decreases as the true effect strengthens**. Two mechanisms contribute:

1. **Futility-stop reporting.** When a trial stops at interim, the reported HR is the posterior median from the interim Bayesian fit (Cox PH on the few-event interim data is unstable; see R/03 comments). The posterior is informed by a `N(0, 1)` log-HR prior — moderately weak but non-trivial when only ~12 events have accumulated. The posterior median is therefore pulled toward HR = 1, regardless of the data's true direction. Under harmful HR this drags the distribution of reported HRs toward 1 (away from the truth of 1.15); under benefit, futility rarely fires, so the contribution is small.
2. **RAR allocation-imbalance under benefit.** Post-interim randomization allocates more to the apparently-winning arm. Under a true benefit, this increases events in the treatment arm disproportionately to control, modestly inflating the Cox HR estimate vs the unbiased target. The effect is bounded by the 20/80 allocation caps but is still visible in the strong/very-strong scenarios.

The bias is **small relative to the effect sizes being estimated** — roughly 5% of `log(HR_true)` for the very-strong scenario, growing to a larger fraction under null/harmful where the truth is itself near 1. In a real submission this magnitude is reportable but not disqualifying; an IPTW-weighted sensitivity analysis would be the standard companion.

Regulatory framing. Per FDA *Adaptive Designs for Clinical Trials of Drugs and Biologics* (2019), §IV.A, an adaptive design submission needs (i) pre-specified rules, (ii) Type I error control demonstrated by simulation, (iii) bias quantified in the effect estimator. This report provides all three: Type I is 0.019 (below the 0.025 nominal), the OBF boundary is published in advance, and the table above is the bias characterization required by (iii).

8. Limitations and design choices

- **Phase II screening design.** Maximum n = 120 with 24-month follow-up is deliberately small for a Phase II go/no-go trial; rpact's `getSampleSizeSurvival` says n 791 would be needed for 80% power at HR = 0.70 under this alpha-spending. Power at smaller effect sizes (HR 0.75 / 0.85) is correspondingly modest. This is by design, not a misconfiguration — a confirmatory trial would scale up.
- **Futility threshold ($P(HR < 0.7 \mid data) < 0.20$) is operator-defined.** A formal sensitivity analysis across alternative thresholds is on the roadmap.

- **Cox PH on adaptive-trial data does not adjust for RAR-induced allocation imbalance.** The empirical Type I (0.019) is below the 0.025 nominal, so this is not a regulatory dealbreaker, but in a real submission an IPTW-weighted sensitivity analysis would accompany the primary Cox PH.
- **TCGA-BRCA is a toolkit validation, not a data-generating-model validation.** Overall survival in breast cancer differs in endpoint, population, and hazard shape from the simulator's hypothetical time-to-progression trial. The TCGA section demonstrates that the same Stan / KM / Cox / AFT pipeline works on real, messier data — not that the simulator's exponential data-generating model matches breast cancer biology.
- **Stan compilation in `testthat::test_dir` is fragile.** Sourcing rstan-heavy files repeatedly in one R process triggered "parser failed badly" / C-stack errors; tests therefore run each file in its own Rscript subprocess (`tests/testthat.R`).

9. SAP excerpt

A standalone mock Statistical Analysis Plan section is in `report/sap_section.qmd` (rendered separately). It follows the standard ICH E9-aligned outline (objectives, estimand, hypotheses, sample size, primary analysis, missing-data handling, sensitivity analyses, safety).

10. Reproducibility

```
make sims     # runs all 12,000 trial simulations (~100 s, 4 workers)
make tcga     # fits KM, Cox, Bayes AFT on TCGA-BRCA (~30 s)
make report   # renders this document and sap_section.qmd
make all      # the lot
```

Random seeds are derived from `CONFIG$simulation$seed = 20260513`. CI runs a reduced (`--n-sims 100`) version of the pipeline on every push.

11. References

- ICH E9(R1) — *Statistical Principles for Clinical Trials, Addendum on Estimands and Sensitivity Analyses*, 2019.
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- Wassmer G, Brannath W — *Group Sequential and Confirmatory Adaptive Designs in Clinical Trials*. Springer, 2016. (Background for `{rpact}`.)
- Stan Development Team — *Stan Reference Manual*, v2.32, 2023.
- TCGA-BRCA: The Cancer Genome Atlas Network. *Comprehensive molecular portraits of human breast tumours.* Nature 2012; 490: 61–70.