A predictive biomarker enrichment design for Phase II oncology trials

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Biomarkers European Special Interest Group (SIG)

Aim of Enrichment Designs: Enhance trial efficiency by selecting patient subgroups defined by biomarker signatures

Prognostic Enrichment

- Reliably include high-risk and exclude low-risk groups
- Increased absolute effect size (smaller trial)
- Relative effect size similar across groups

Predictive Enrichment

- Reliably include biomarker-positive (responders) and exclude biomarker-negative (non-responders) groups
- Increased absolute effect size (smaller trial)
- Lower relative effect size in patients without enrichment factor

Study vs. Analysis

What patients to study?	What patients to analyse?
Designs including only patients with enrichment factor (Situations where biomarker-negative info not needed or not feasible)	Biomarker-positive
Designs including patients with and without enrichment factor (Situations where there is greater uncertainty in marker cut-off)	Biomarker-positive (?)

FDA: To what extent should biomarker-negative patients be included in the study?

Prognostic Enrichment

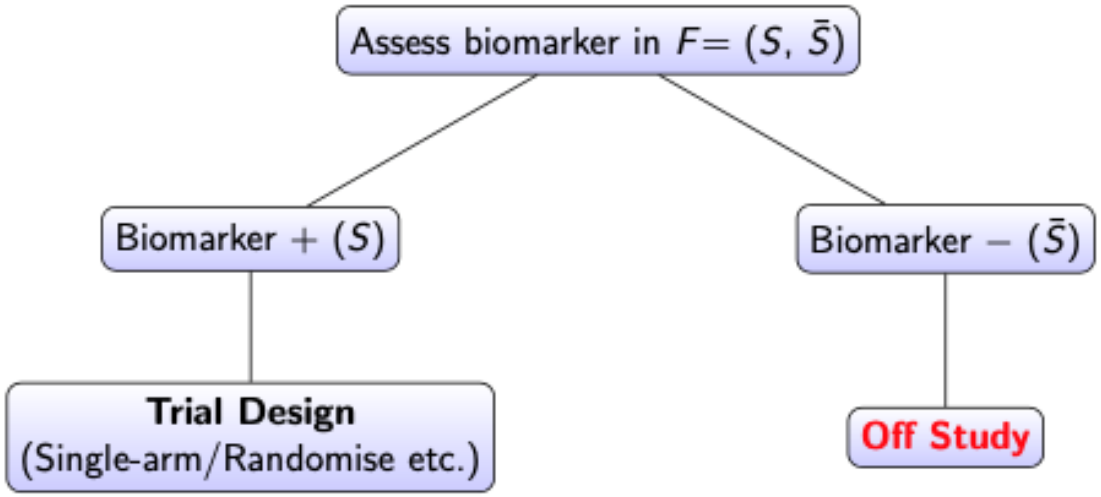
Assumption: Some treatment effect thought to be present in low-risk group

- Impractical due to large sample size.
- Deemed to be less of an issue!

FDA: To what extent should biomarker-negative patients be included in the study?

Prognostic Enrichment	Predictive Enrichment
Assumption: Some treatment effect thought to be present in low-risk group • Impractical due to large sample size. • Deemed to be less of an issue!	Assumption: Some treatment effect thought to be present in biomarker-negative group • Often uncertainty in dichotomising patients into responders and non-responders. • Some info on biomarker-negative population to assess performance is desirable! Focus for this talk!

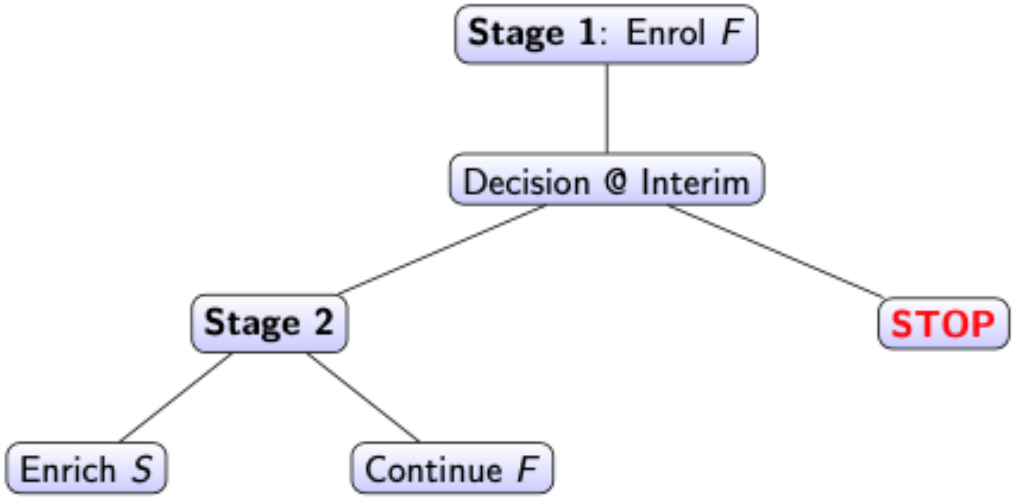
Fixed Enrichment Designs



Goal: Hypothesis test in biomarker $+$ subgroup S only.
Issue: No comparator test in the complementary subgroup $\bar{S}$.

Is the biomarker predictive?

Adaptive Enrichment Designs



Goal: Hypotheses test in S and F.
Issue: While $\bar{S}$ is included in F, no explicit testing in $\bar{S}$.

Is the biomarker predictive?

Biomarker-negatives: To test or not to test?

FDA concerns

- Design may not be efficient if drug has at least some activity in biomarker-negative patients
- Effect in biomarker-negative patients may never be known
- Study would provide no new clinical evidence w.r.t. biomarker negative patients
- Implications for Phase III

Need for testing in biomarker-positive and biomarker-negative subgroups

Example 1: Simon two-stage enrichment design for binary endpoints

Phase II targeted cancer therapy

- Determine whether drug has activity only in target population or the general population
- Outcome is (RECIST) tumour response
- Single-arm trial
- Enrichment adaptation (with testing in biomarker-negative) based on Simon two-stage design

Parashar et. al., Pharmaceut. Statistics 2016

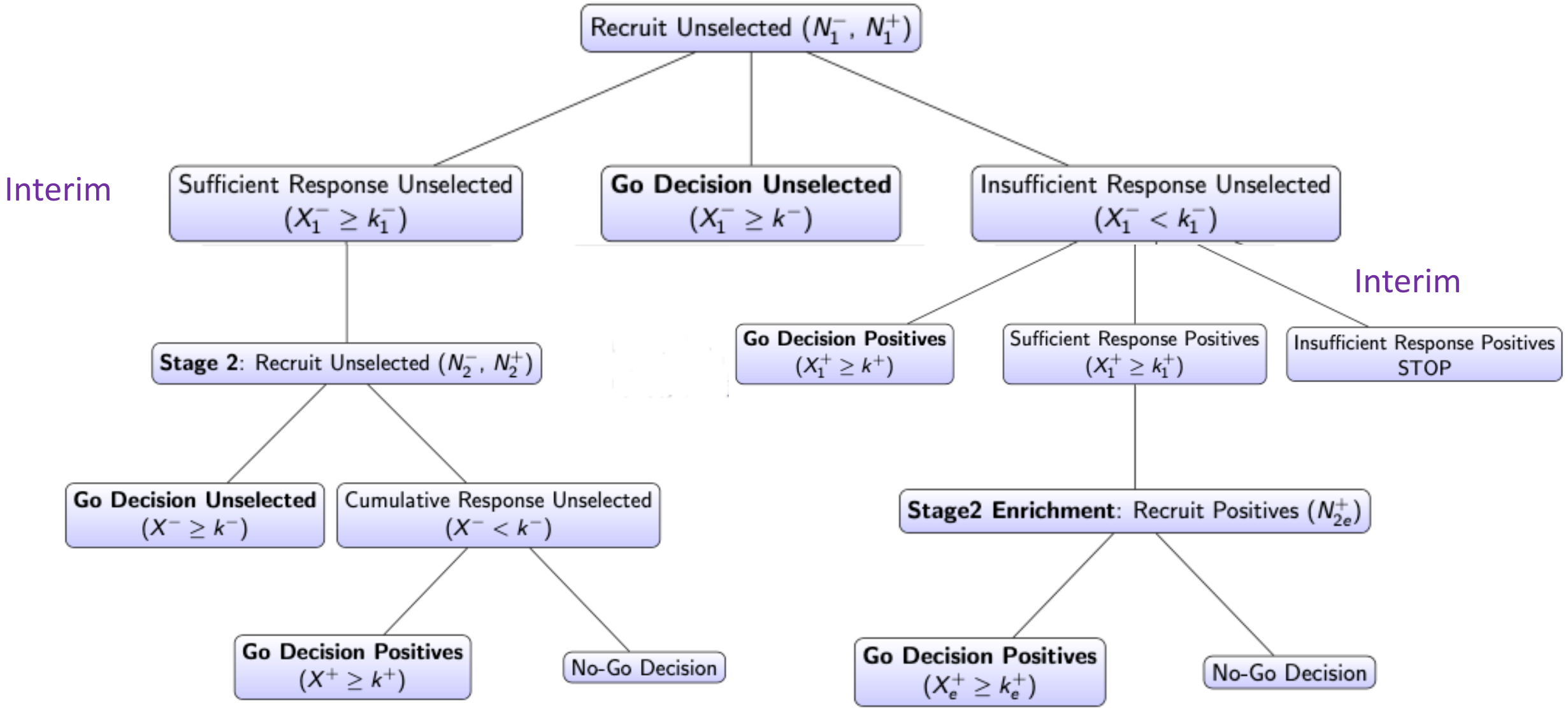
Hypotheses (group-sequential)

$$H_0^- : p^- = p_0^-, \qquad H_0^+ : p^+ = p_0^+$$
$$H_1^- : p^- = p_1^-, \qquad H_1^+ : p^+ = p_1^+$$

Assume $p^- < p^+$

- Conclude efficacy in full population if we reject H_0^-
- Conclude efficacy in biomarker positive if we reject H_0^+

Design Schematic



Treatment effect?

Need randomised clinical trial testing in targeted and non-targeted subpopulations

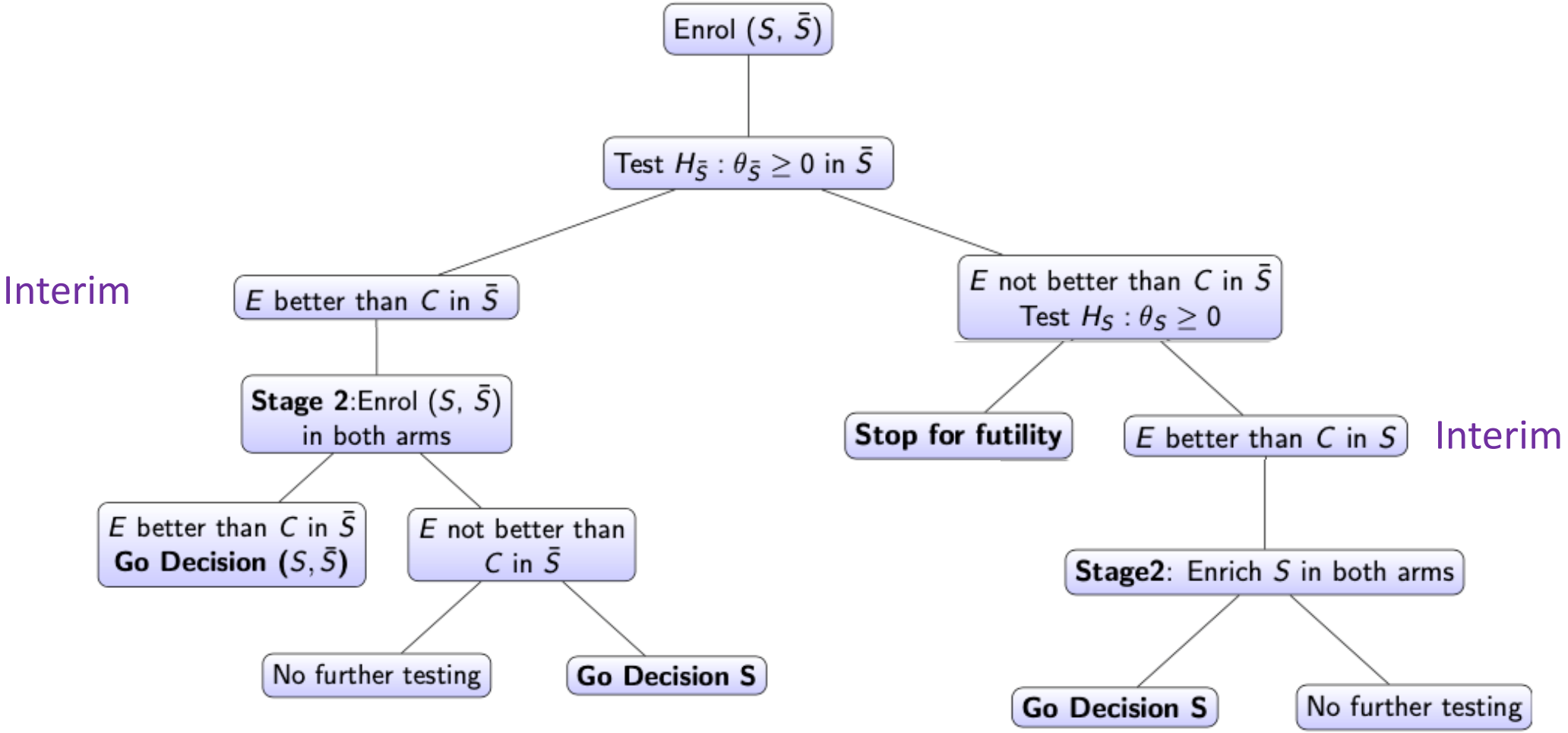
Notation

h_E	hazard using the experimental drug
h_C	hazard using the control drug
θ_S	$\log\left(h_E^S / h_C^S\right)$
$\theta_{\bar{S}}$	$\log\left(h_E^{\bar{S}} / h_C^{\bar{S}}\right)$
HR_S	hazard ratio of S
$HR_{\bar{S}}$	hazard ratio of $\bar{S}$

$$HR_S \ll HR_{\bar{S}}$$

$\boldsymbol{\theta < 0} \Rightarrow$ experimental treatment more efficient than control
$\boldsymbol{\theta \geq 0} \Rightarrow$ no improvement with experimental treatment

Example 2: Randomised Enrichment Design for Time-To-Event Endpoints

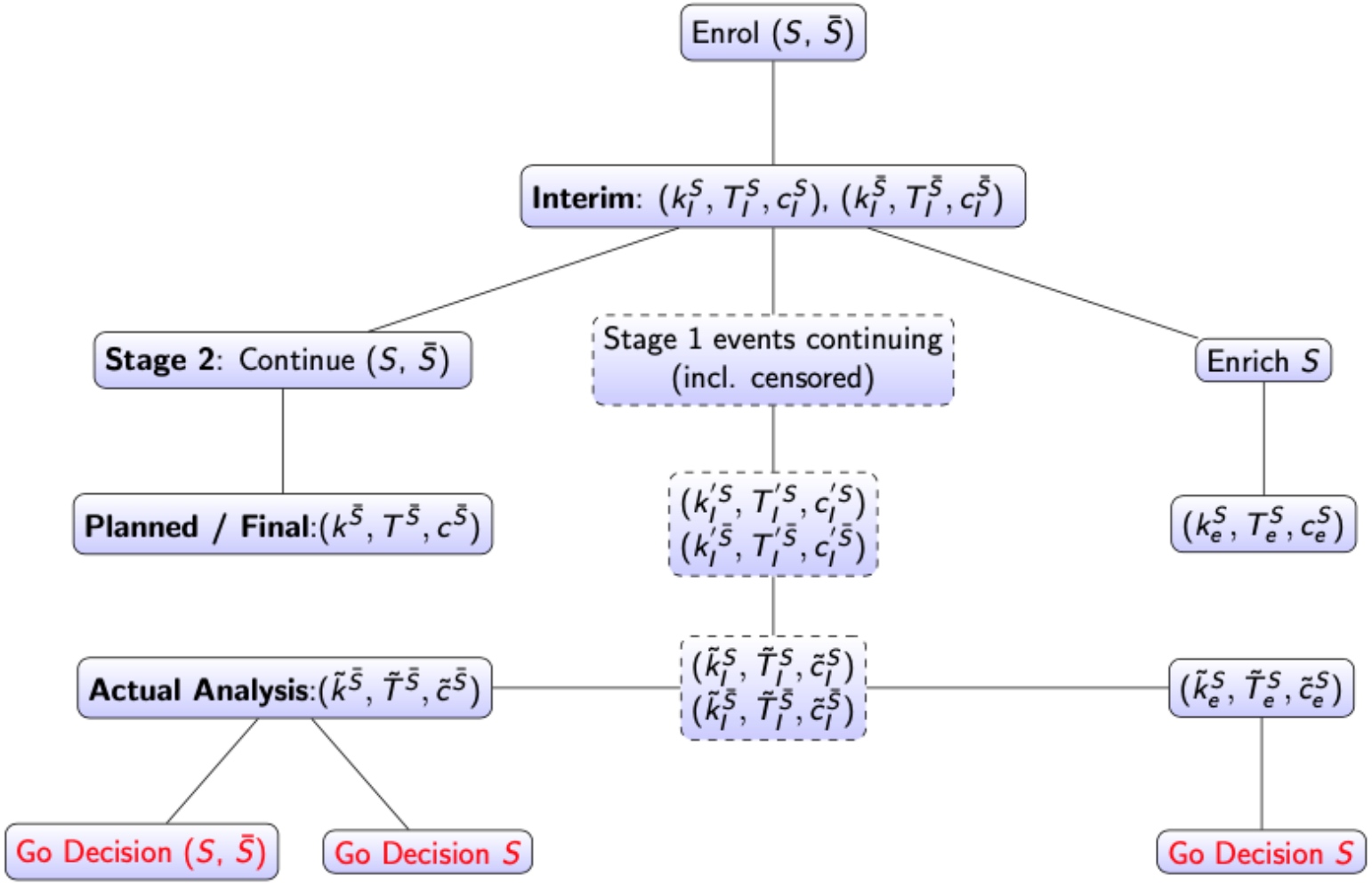


Mehta et. al. (Statist. Med. 2014)

Key points

- Based on CER approach (Müller and Schäfer) guarantees strong control of Type 1 error rate.
- Permits utilisation of all interim data.
- Hypotheses testing in subgroups S and $\overline{S}$ instead of F and S.
- Conditioning event at interim: pair of future logrank test statistic after observing events in S and $\overline{S}$
- Irle and Schäfer: critical value for testing H_S satisfies the CRP principle, and guarantees stochastic independence of the logrank test statistic.
- Triple (k,T,c) $\simeq$ (Events, Logrank test statistic, Critical value for T to reject null)

Methodology sketch (à la Mehta)



CRP Principle

Go Decision S Reject H_S if $\tilde{T}_e^S > \tilde{c}_e^S$ s.t.

$$\underbrace{P(\tilde{T}_e^S > \tilde{c}_e^S | \tilde{T}_I^S)}_{enrichment} + \underbrace{P(\tilde{T}^S > \tilde{c}^S | \tilde{T}_I^S)}_{non-enrichment}$$

$$\leq \underbrace{P(T_e^S > c_e^S | T_I'^S) + P(T^S > c^S | T_I'^S)}_{fixeddesign}$$

Go Decision $(S, \bar{S})$ Reject $H_{\bar{S}}$ if $\tilde{T}^{\bar{S}} > \tilde{c}^{\bar{S}}$ s.t.

$$P(\tilde{T}^{\bar{S}} > \tilde{c}^{\bar{S}} | \tilde{T}_I^{\bar{S}}) \leq P(T^{\bar{S}} > c^{\bar{S}} | T_I'^{\bar{S}})$$

CER of 2-stage design bounded by the error rates of fixed design

Non-small cell lung cancer trial

Clinical Setting:

- endpoint: Progression-free Survival
- sample size: 160 patients
- accrual rate: 15 patients/month
- interim analysis - after recruitment of 40 patients from each subgroup

Target Hazard Ratio: $HR_S = 0.5$

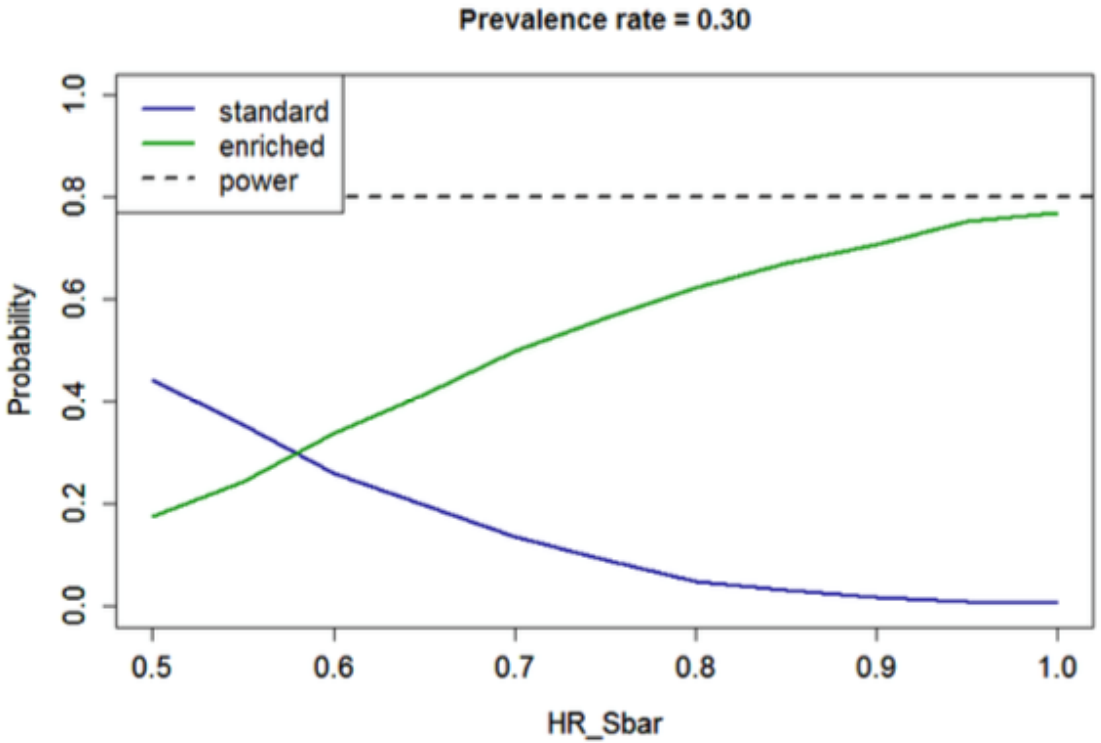
Biomarker prevalence rate: $\{0.30, 0.35, 0.40, 0.45\}$

Familywise error rate: $\alpha = 0.05$

Power: $1 - \beta = 0.80$

$$HR_S \ll HR_{\bar{S}}$$

Probability of concluding efficacy



- Efficient when HR_S is small (0.5 to 0.6) and $HR_{\bar{S}}$ is large (0.8 to 1): Predictive biomarker
- Obtain desired power for recommending an enriched Phase III trial.
- Copes well with slower recruitment rate as well as varying prevalence rates.

Close to the desired power in all cases ⇒ a trial of 160 patients should provide sufficient evidence of efficacy in the biomarker-positive group.

Further regulatory issues on biomarker-negative patients for predictive enrichment

- Even if treatment is a significant advance for biomarker-positive patients, questions still asked on potential effectiveness in biomarker-negative group.
- Physician's choice for critical biomarker-negative patients; important to reliably assess treatment effect in biomarker-negative group
- Our design addresses both issues
- Advanced methods (statistical, machine learning, etc.) to improve precision for biomarker-cutoff.
- Clinical relevance
- Empirical enrichment

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