A Decision Theoretic Approach to Optimize Clinical Trial Designs for Targeted Therapies

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Joint work with Thomas Ondra, Sebastian Jobjörnsson, Robert Beckman, Carl-Fredrik Burman, Franz König, Nigel Stallard

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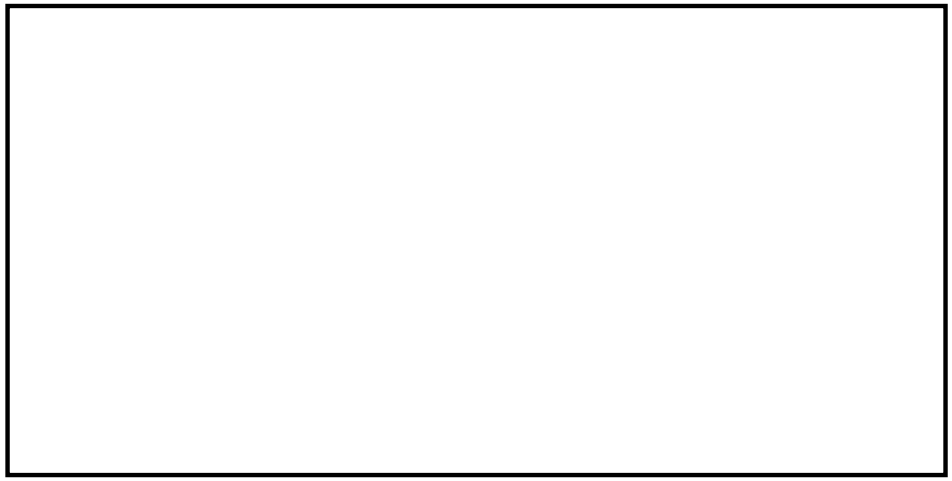
Patient Populations

Full Population F



- Assume the treatment effects in the subgroups satisfy $\delta_S \geq \delta_{S'}$.
- The treatment effect in F is

$$\delta_F = \lambda_S \delta_S + (1 - \lambda_S)\delta_{S'}$$

  where λ_S is the prevalence of subgroup S.
- Test of hypotheses $H_F : \delta_F \leq 0$ and $H_S : \delta_S \leq 0$.

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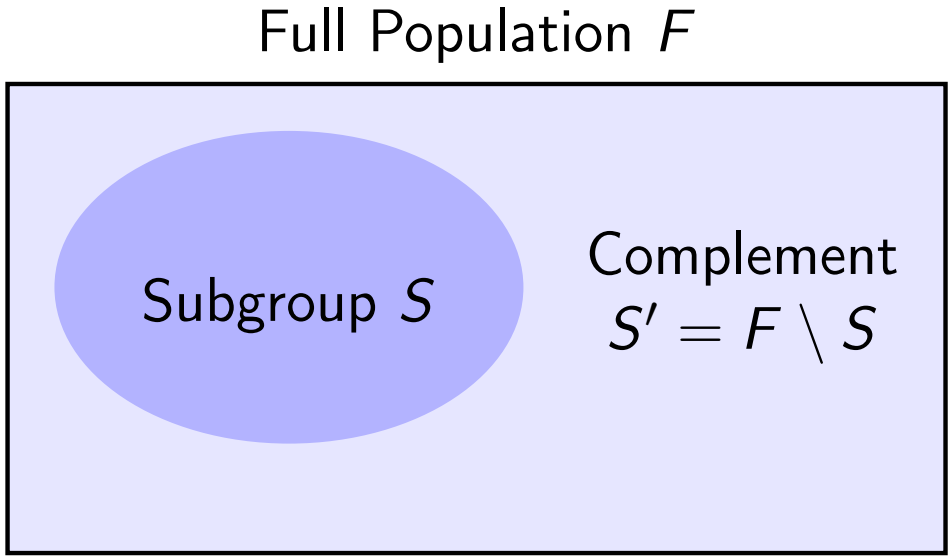

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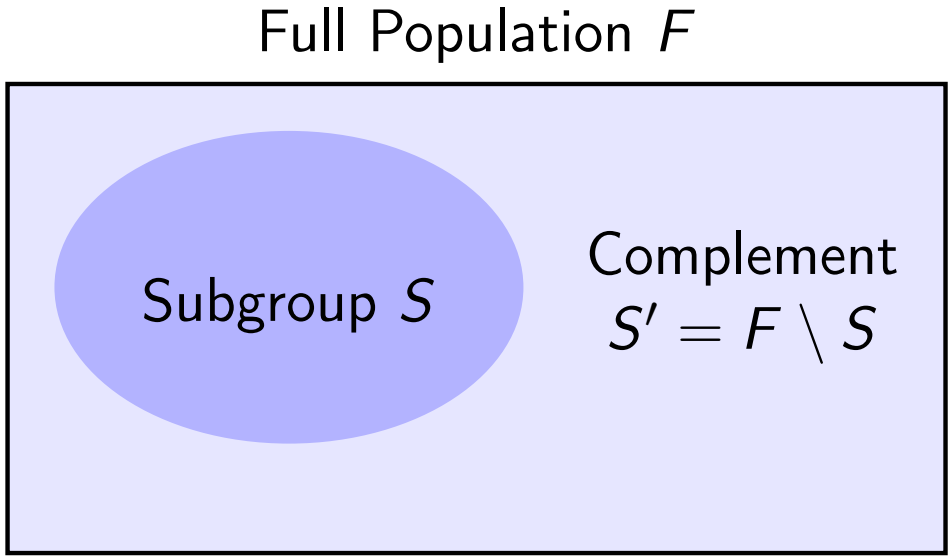

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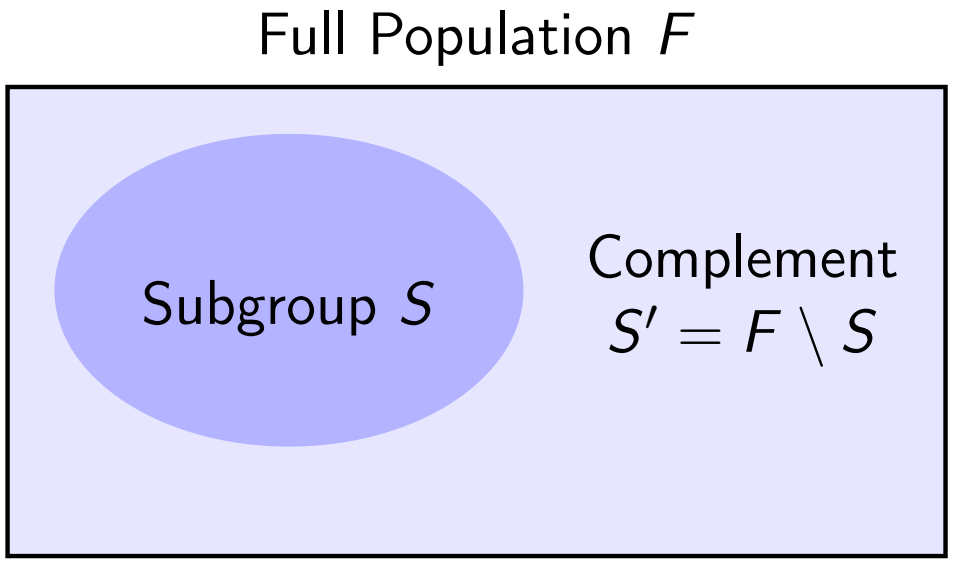

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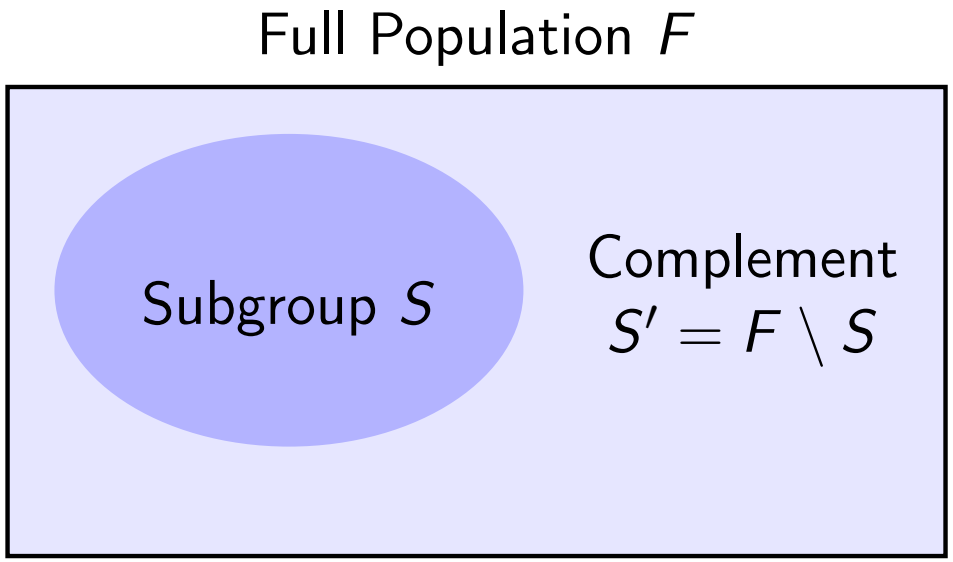

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Which clinical trial design to choose?

Classical Design:

Recruitment from population F.
No Biomarker is determined.
Test of H_F.

Stratification Design:

Recruitment from population F.
Stratified randomization by Biomarker.
Test of H_F and H_S.

Enrichment Design:

Recruitment only from population S.
Test of H_S

Biomarker Designs

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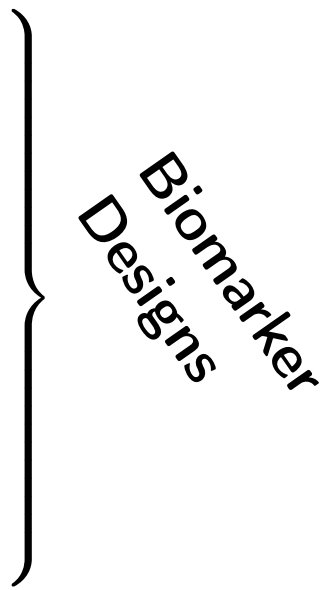

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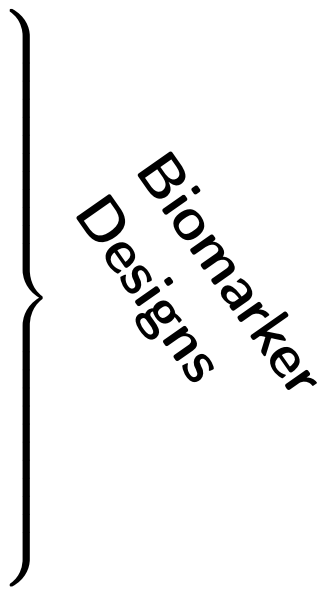

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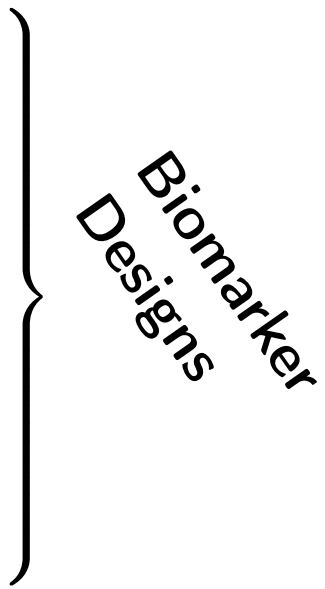

Testing Procedures for Parallel Group Comparison of Means

Classical Design:

H_F is tested with a z-test.

Stratification Design:

- H_S and H_F are tested with a closed Spiessens-Debois (2010) test at levels α_S, α_F. If a hypothesis is rejected, the other is tested at level α.
- To reject H_F, also the consistency condition

$$p_S \leq \tau_S \text{ and } p_{S'} \leq \tau_{S'},$$

for parameters $\tau_S, \tau_{S'}$, must be satisfied.

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Optimizing Clinical trial designs

- When is a biomarker (BM) design beneficial compared to a classical design?
- When to choose stratified, when an enrichment design?
- Which sample size?
- Which significance levels α_F and α_S for H_F and H_S in the weighted multiple test for the stratified design are optimal?

We apply a utility based approach, (cf. Beckman et al., 2011; Rosenblum et al., 2014; Graf et al., 2015), to model the expected utilities of a particular trial design from a sponsor's and a public health view.

The Utility for a design d

$$U(d) = \underbrace{-\,C(d)}_{\text{Cost}} + \underbrace{\begin{cases} \varphi_{F,d} & \text{if } H_F \text{ is rejected} \\ \varphi_{S,d} & \text{if only } H_S \text{ is rejected} \\ 0 & \text{if no hypothesis is rejected} \end{cases}}_{\text{Reward}} .$$

The Rewards

Sponsor view

$$\varphi_{F,d} = N \cdot r_F \cdot (\hat{\delta}_{F,d} - \mu_F)^+$$
$$\varphi_{S,d} = \lambda_S \cdot N \cdot r_S \cdot (\hat{\delta}_{S,d} - \mu_S)^+$$

- N ... number of future patients (market size).
- r_F, r_S ... revenue parameters.
- $\hat{\delta}_{F,d}, \hat{\delta}_{S,d}$ ... efficacy estimates.
- μ_F, μ_S ... clinically relevant thresholds.

Public health view

$$\varphi_{F,d} = N \cdot r_F \cdot (\delta_F - \mu_F)$$
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- δ_S, δ_F ... true effect sizes.

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Trial Costs $C(d)$

- Classical Design

$$c_{\text{setup}} + 2n\, c_{\text{per-patient}}.$$

- Stratified Design

$$c_{\text{setup}} + c_{\text{BM development}} + 2n(c_{\text{per-patient}} + c_{\text{BM determination}}).$$

- Enrichment Design

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The Expected Utility of Trial Designs in the Planning Stage

Identifying optimized trial designs

Expected Utility:

$$E_\pi \{E_\Delta[U(d)]\}$$

The expectation is taken over

- the prior π on the effect sizes $\Delta = (\delta_S, \delta_{S'})$ and
- the sampling distribution

Optimal design: Choose the design with maximal expected utility optimizing over

- Type of design (classical/stratified/enrichment)
- Sample size
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Prior Distributions π On the Effects $\delta_S, \delta_{S'}$

δ_S	0	θ	θ	θ
$\delta_{S'}$	0	0	$\theta/2$	θ
Weak Biomarker Prior	0.2	0.2	0.3	0.3
Strong Biomarker Prior	0.2	0.6	0.1	0.1

$\theta > 0 \ldots$ effect size parameter.

Scenario

- **Effect size parameter in the prior**
  $\theta = 0.3$
- **Reward parameters**
  $Nr_F = Nr_S = 1000\text{MUSD}$
  $\mu_F = \mu_S = 0.1.$
- **Cost Parameters in (MUSD)**
  $c_{\text{setup}} = 1$
  $c_{\text{per-patient}} = 0.05$
  $c_{\text{BM development}} = 1$
  $c_{\text{BM determination}} = 0.005.$
- **Consistency parameters** $\tau_S = \tau_{S'} = 0.3.$

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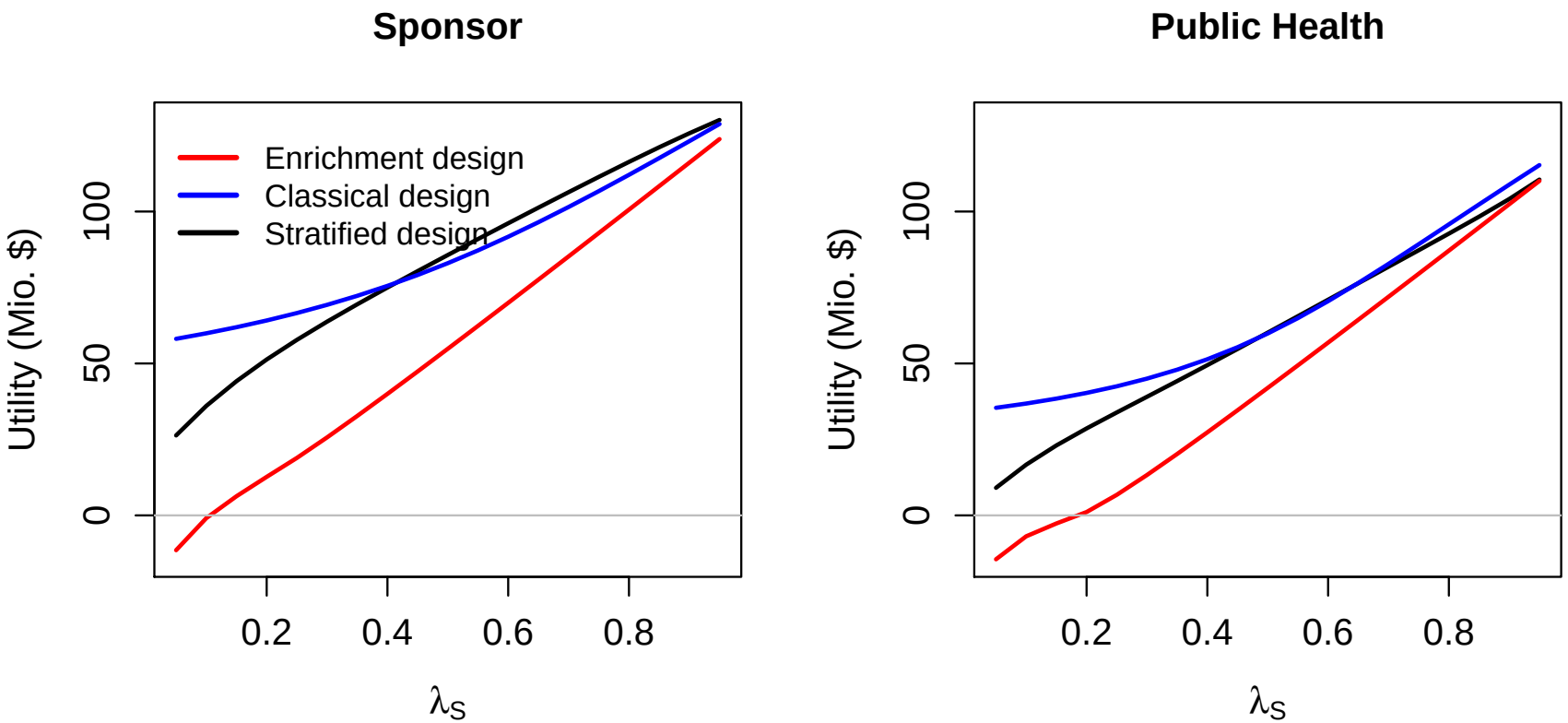
Optimized Expected Utilities

Weak Biomarker Prior



Optimized Sample Size

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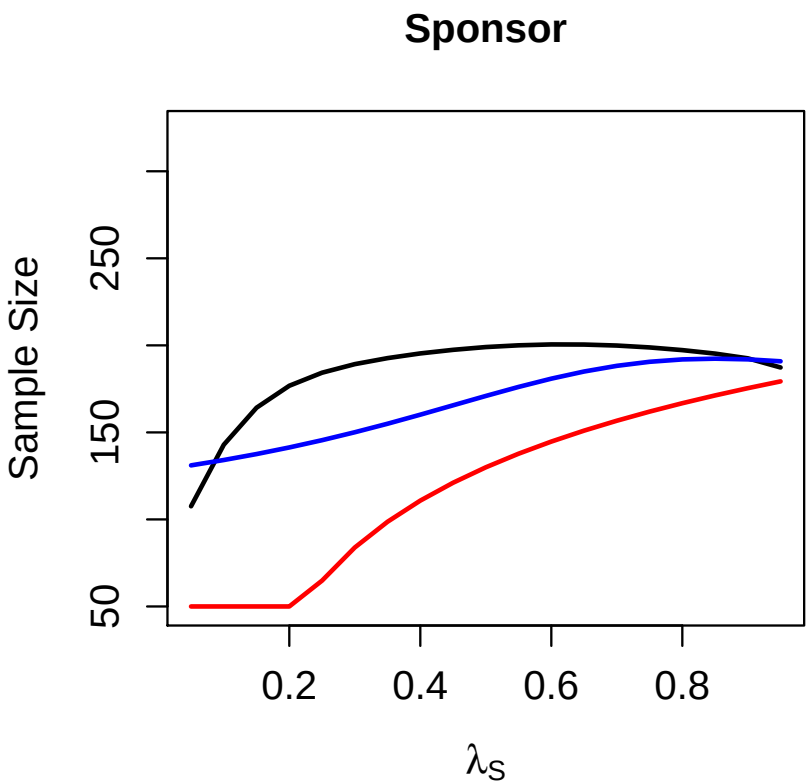

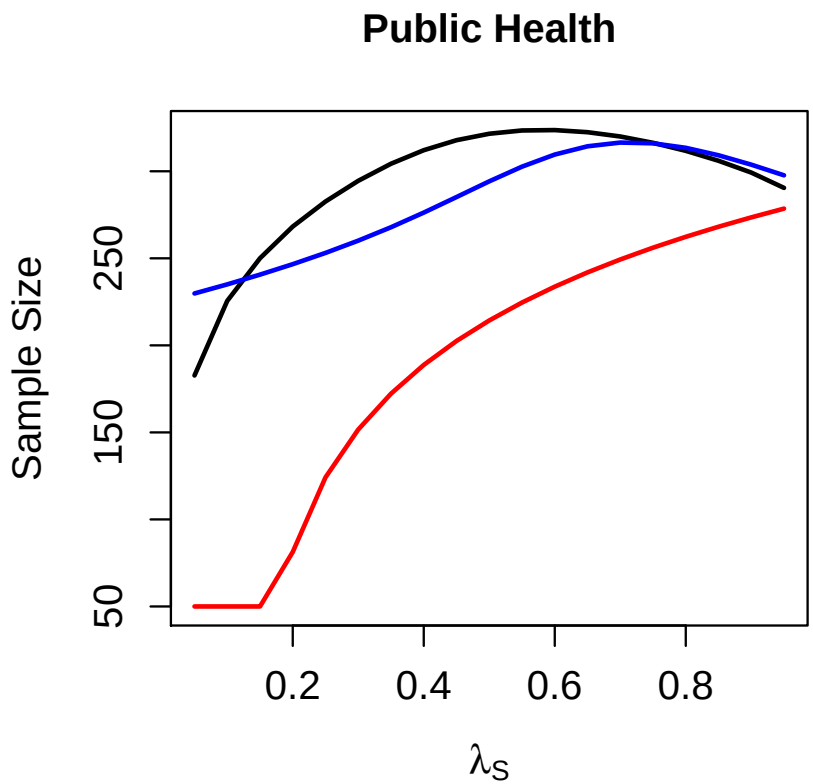

Optimized Alpha Allocation

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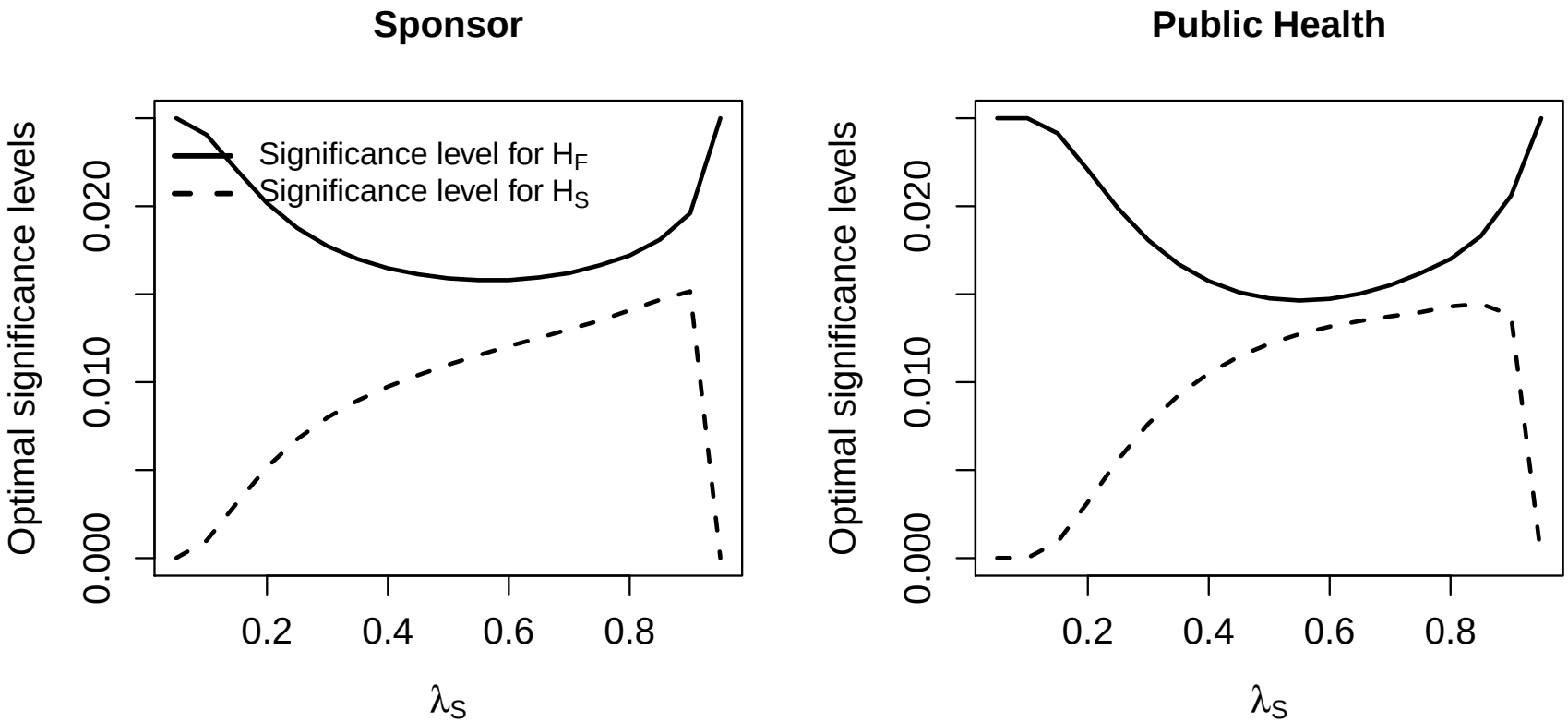
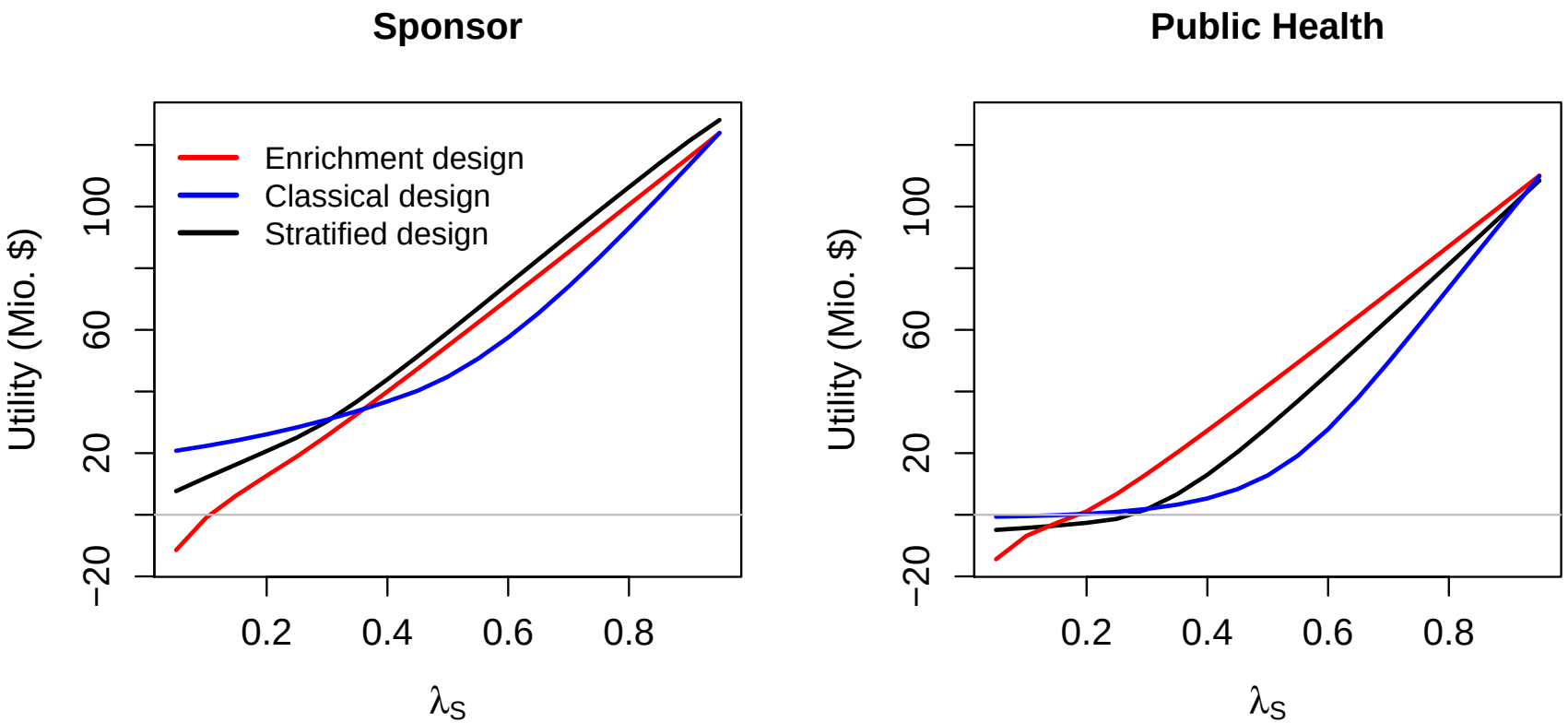


Optimal Designs for the Strong Biomarker Prior



Optimal Trial Designs

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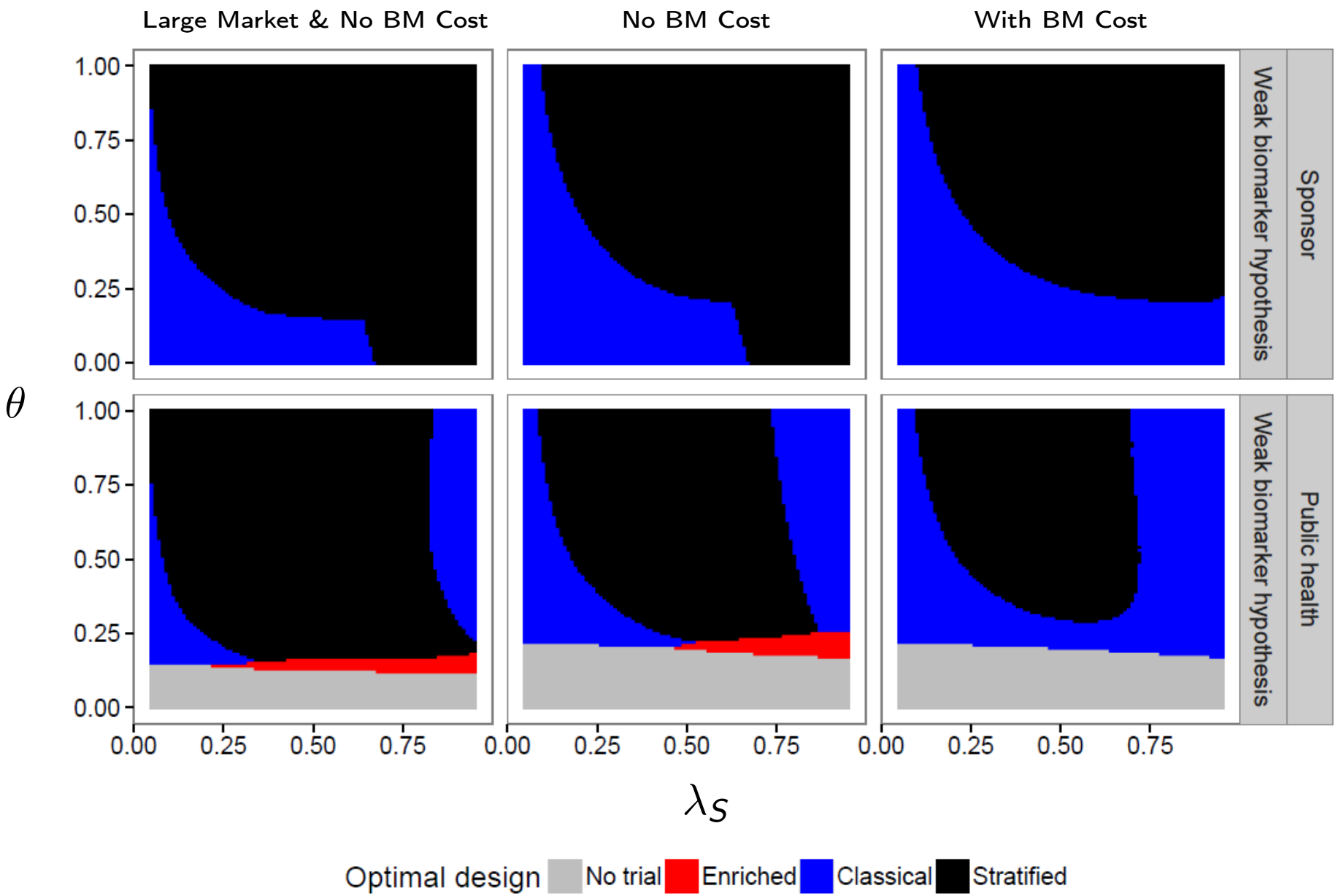

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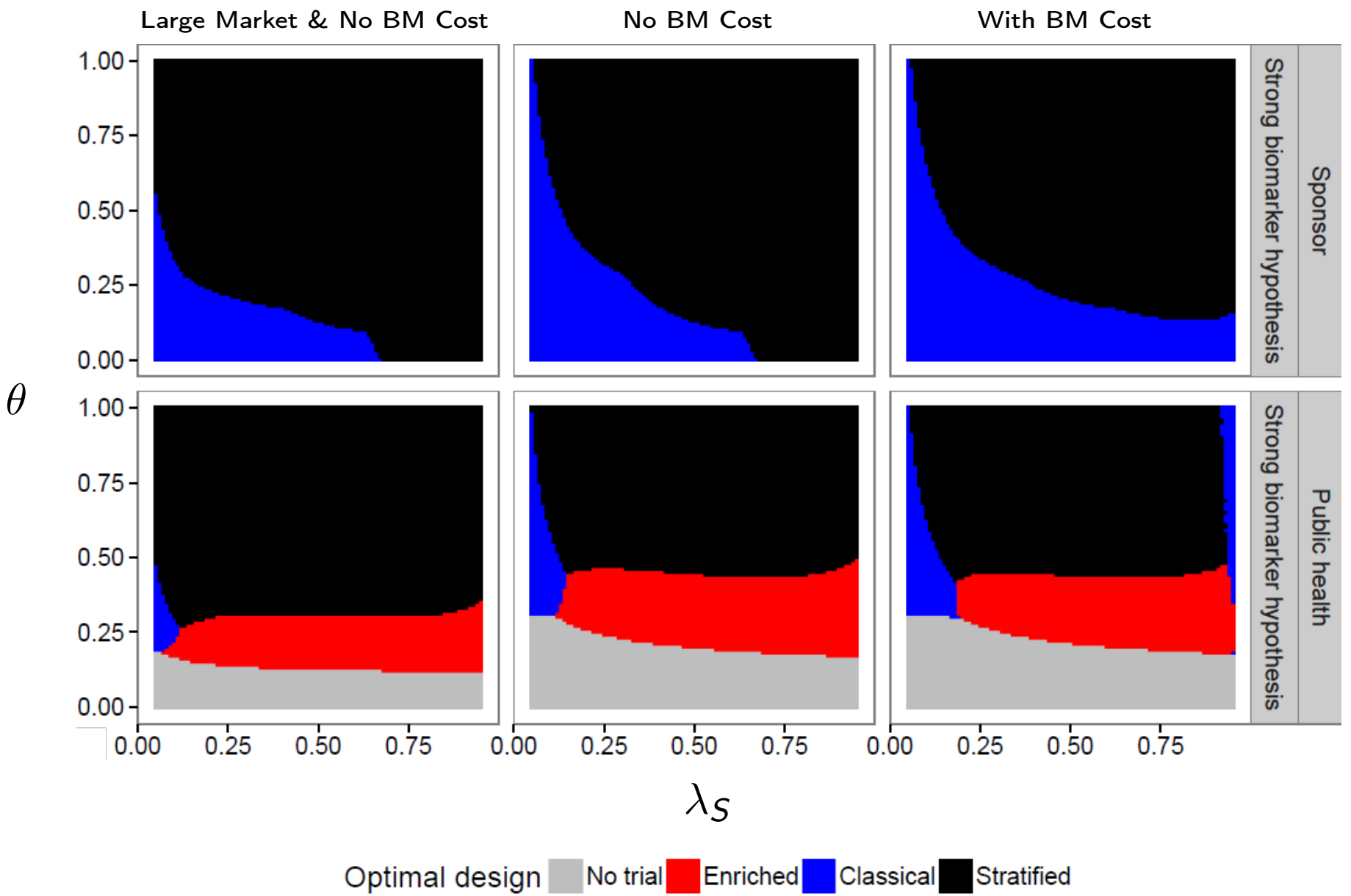


Discussion

- The optimal sample size under the public health view is typically larger than in the sponsor view.
- For the considered priors, the enrichment design is never optimal for the sponsor view
- The optimal design depends strongly on the particulars of the situation: Subgroup prevalence, trial costs and initial beliefs.

Two Extensions of the Trial Designs

Partial Enrichment Design

The prevalence of the subgroup in the trial λ_T is a design parameter and may differ from λ_S, the prevalence in the population.
Special cases are the stratified design ($\lambda_T = \lambda_S$) and the (full) enrichment design ($\lambda_T = 1$).

E.g., Zhao et al. (2010)

Adaptive Enrichment Designs

Two stage design, where the second stage sample size and second stage trial prevalence may depend on the first stage outcome.

E.g., Brannath et al. (2009); Beckman et al. (2011); Jenkins et al. (2011); Friede et al. (2012); Simon and Simon (2013); Krisam and Kieser (2015); Graf et al. (2015); Fisher and Rosenblum (2016)

For simplicity we use as multiple testing procedure a single step unweighted Bonferroni test.

Partial Enrichment Design: Hypothesis test of H_F

Because trial and population prevalence do not match, the standard z-test is not a valid test for H_F.

- H_F is tested with a reweighted z-statistics

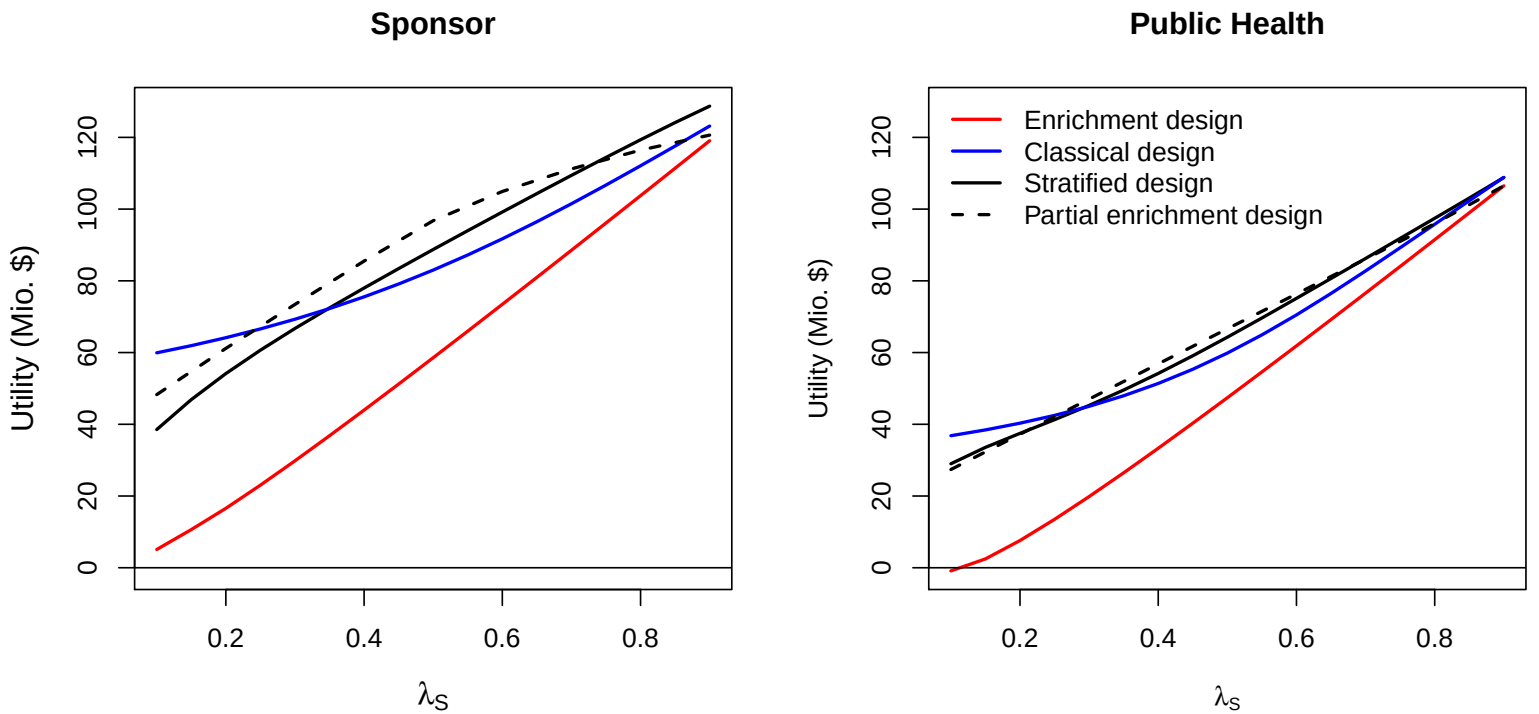
$$\tilde{Z}_F = \xi \left(\frac{\lambda_S}{\sqrt{\lambda_T}} Z_S + \frac{1-\lambda_S}{\sqrt{1-\lambda_T}} Z_{S'} \right),$$

  where $Z_S, Z_{S'}$ denote the z-statistics for the subgroups S, S' and ξ is a normalizing constant.

  e.g., Zhao et.al. 2010

- As above, to reject H_F, in addition the consistency condition needs to be fulfilled.

Optimized Utilities
Weak Biomarker Prior



$(Nr_F = Nr_S = 1000, c_{\text{setup}} = c_{\text{BM development}} = 1, c_{\text{per-patient}} = 0.05, c_{\text{BM determination}} = 0)$

Optimal Subgroup Prevalence λ_T

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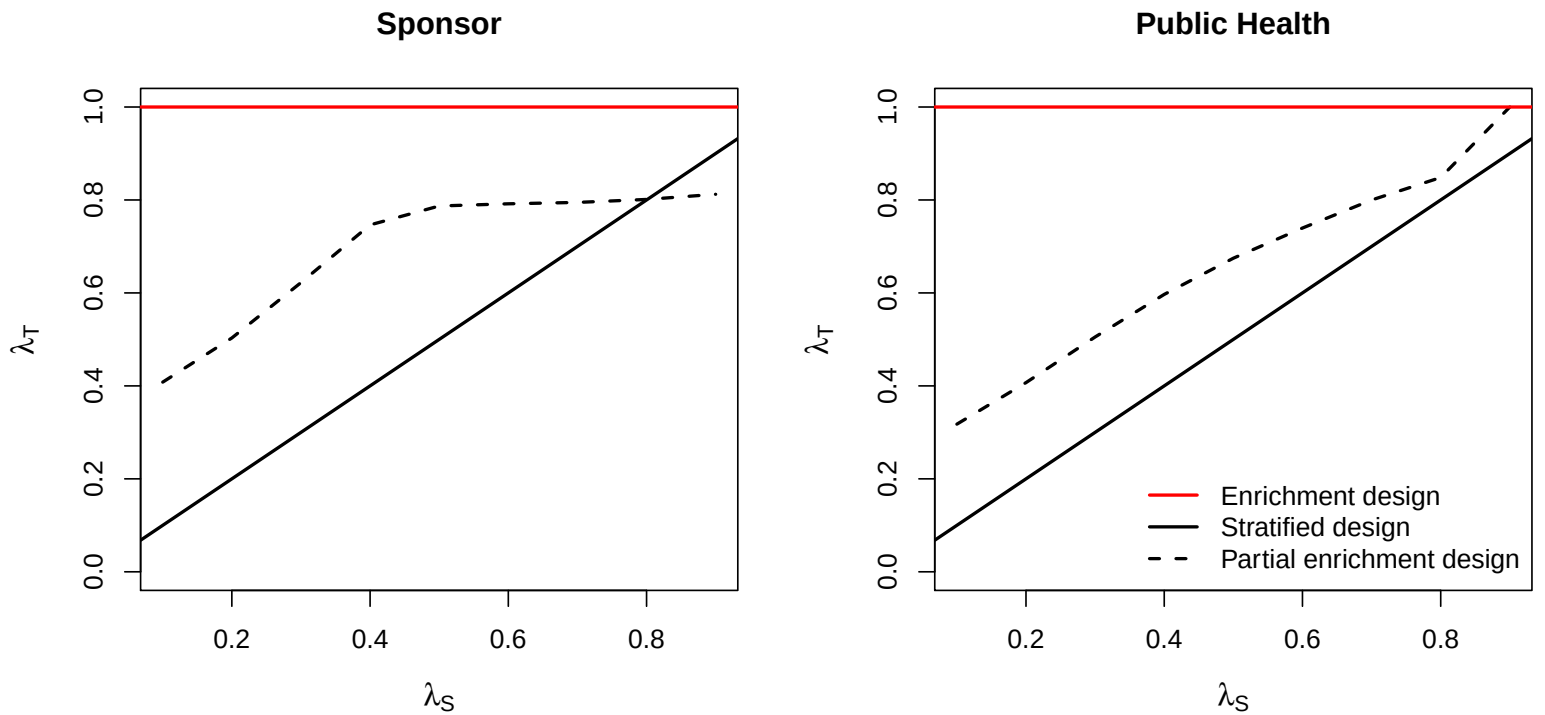
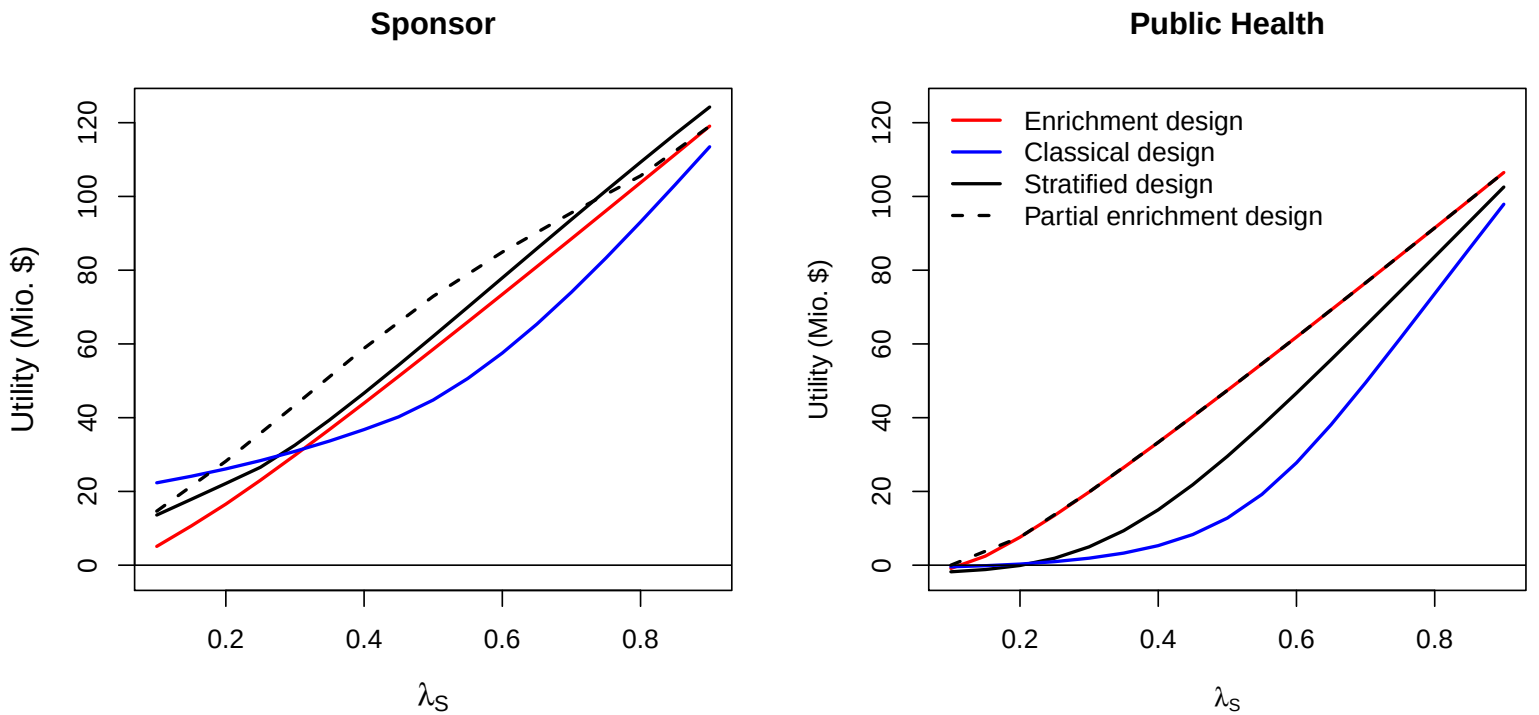


Optimized Utilities
Strong Biomarker Prior



Adaptive Design

First stage

Sample size n_1, subgroup trial prevalence λ_T^1

Second Stage

Second stage sample size n_2 and subgroup trial prevalence λ_T^2
are chosen based on first stage data.

Testing procedure

- Overall test statistics computed with combination function:

$$\begin{aligned} Z_S &= \sqrt{\tfrac{1}{2}}\, Z_S^1 + \sqrt{\tfrac{1}{2}}\, Z_S^2 \\ \tilde{Z}_F &= \sqrt{\tfrac{1}{2}}\, \tilde{Z}_F^1 + \sqrt{\tfrac{1}{2}}\, \tilde{Z}_F^2 \end{aligned}$$

  where Z_S^1, Z_S^2 and $\tilde{Z}_F^1, \tilde{Z}_F^2$ are stage wise z-statistics.
- Unweighted Bonferroni test boundaries applied to Z_S and $\tilde{Z}_F$ (if $\lambda_T^2 < 1$).

Optimal Adaptive Design
Based on Backwards Induction

Optimal Adaptation Rule

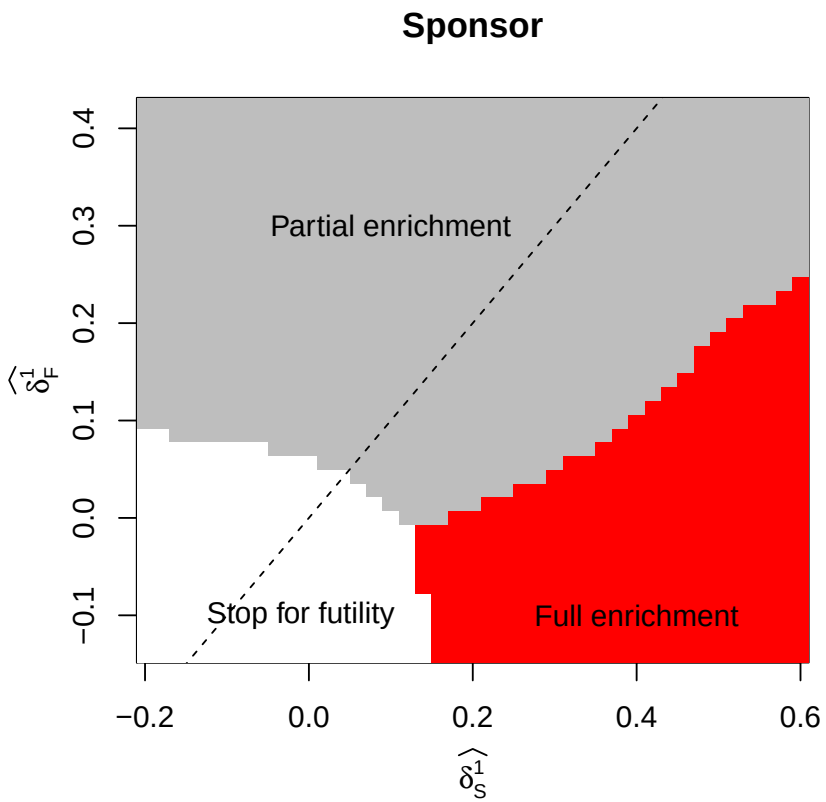
- In the interim analysis choose n_2, λ_T^2 such that the expected utility conditional on the first stage data is maximized.
- Especially, $n_2 = 0$ corresponds to stopping for futility, $\lambda_T = 1$ to a second stage enrichment design.

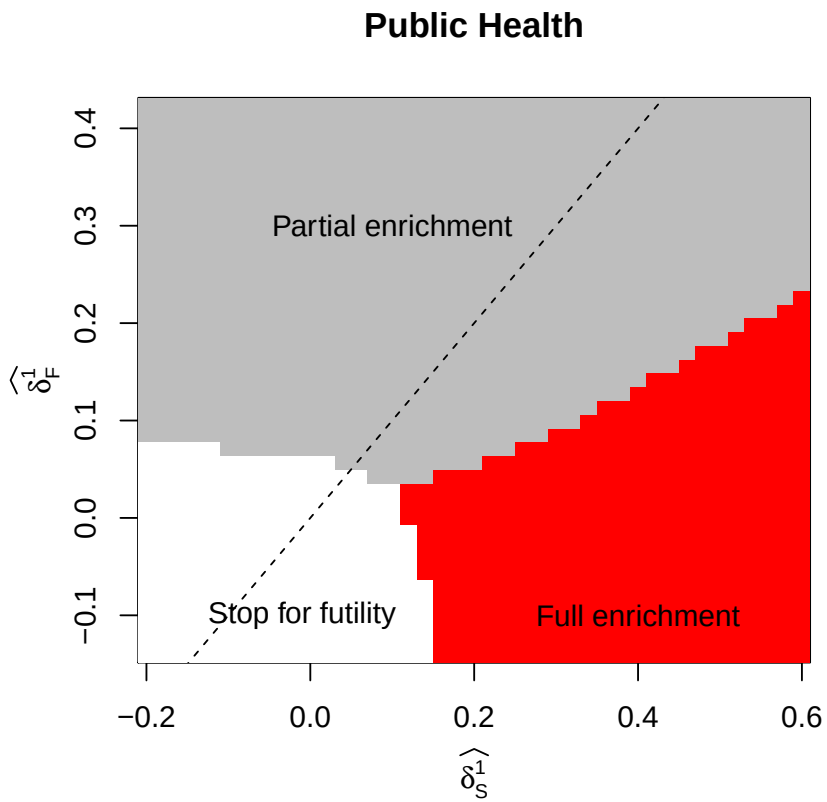
Optimizing first stage parameters

- Choose n_1, λ_T^1 such that the expected utility (given the optimal adaptation rule is applied at interim) is maximized.

Example for the Optimal Decision Rule

Weak Biomarker Prior ($n_1 = 100, \lambda_S = \lambda_T^1 = 0.5$)





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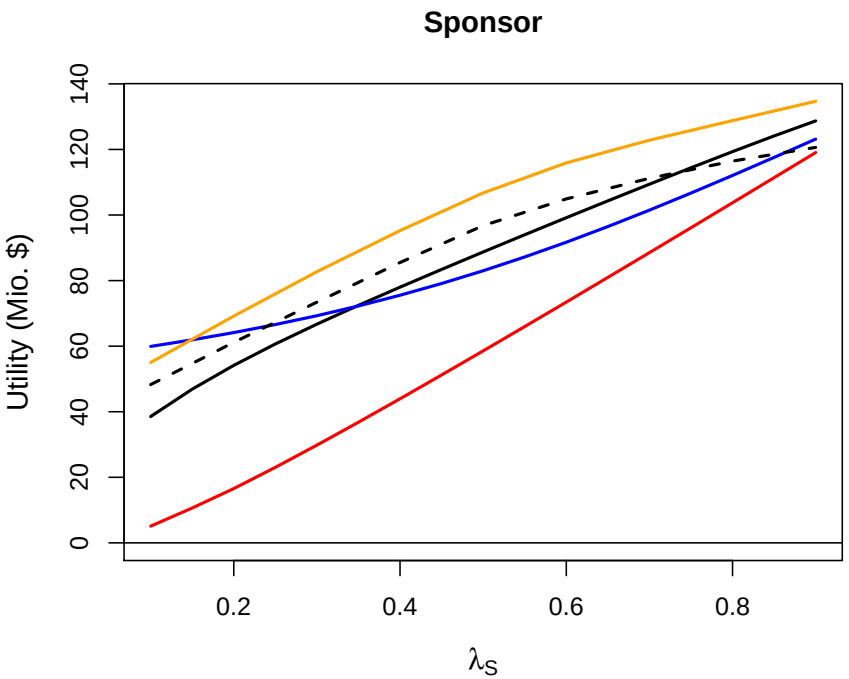

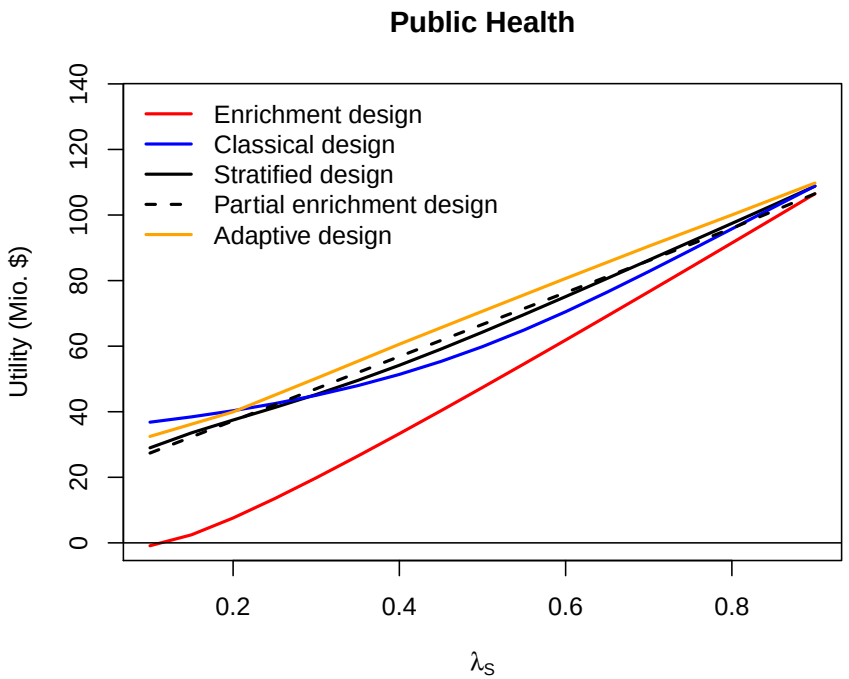

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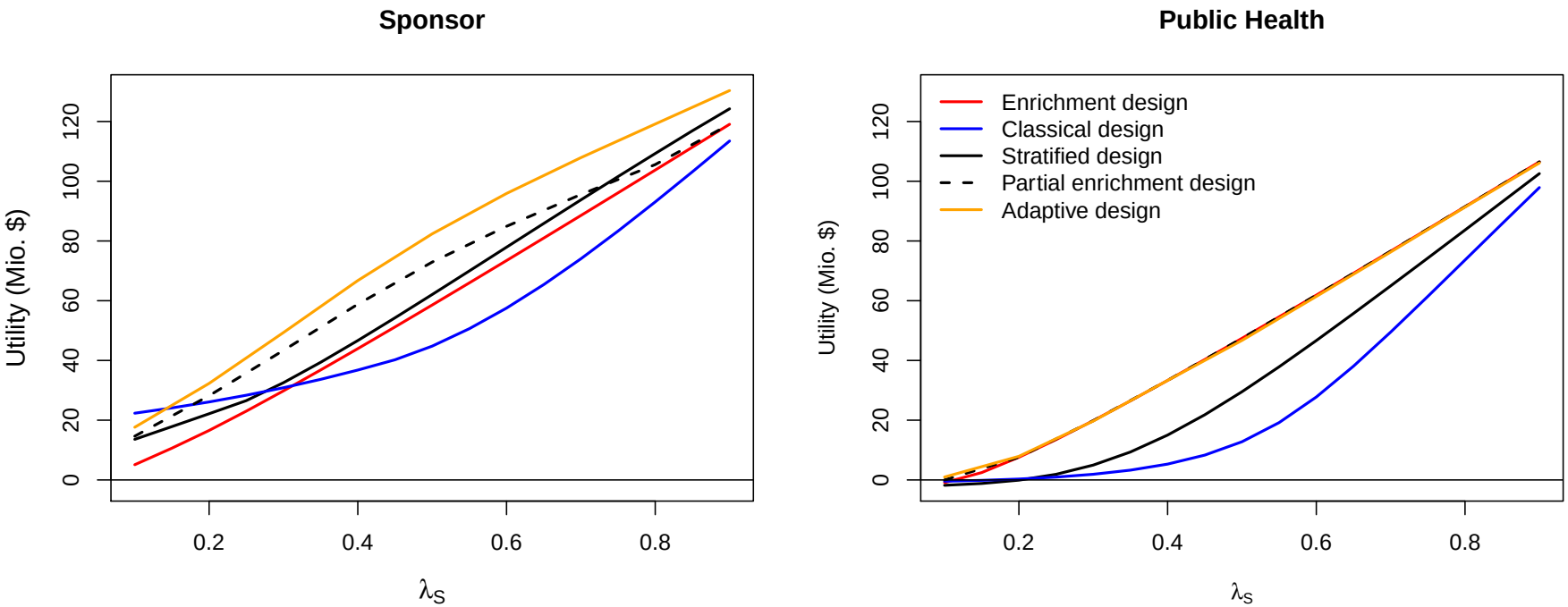
Strong Biomarker Prior



Summary

- Partial Enrichment Designs can increase the utility mainly for the sponsor utility function.
- Adaptive Enrichment Designs further increase the expected utility, also for the public health utility function.
- Extensions: weighted, stepwise Spiessens Debois test for the partial enrichment design, optimized weights in combination function...

Ondra, T., Jobjörnsson, S., Beckman, R. A., Burman, C. F., König, F., Stallard, N., Posch, M. (2016). Optimizing Trial Designs for Targeted Therapies. arXiv preprint arXiv:1606.03987.

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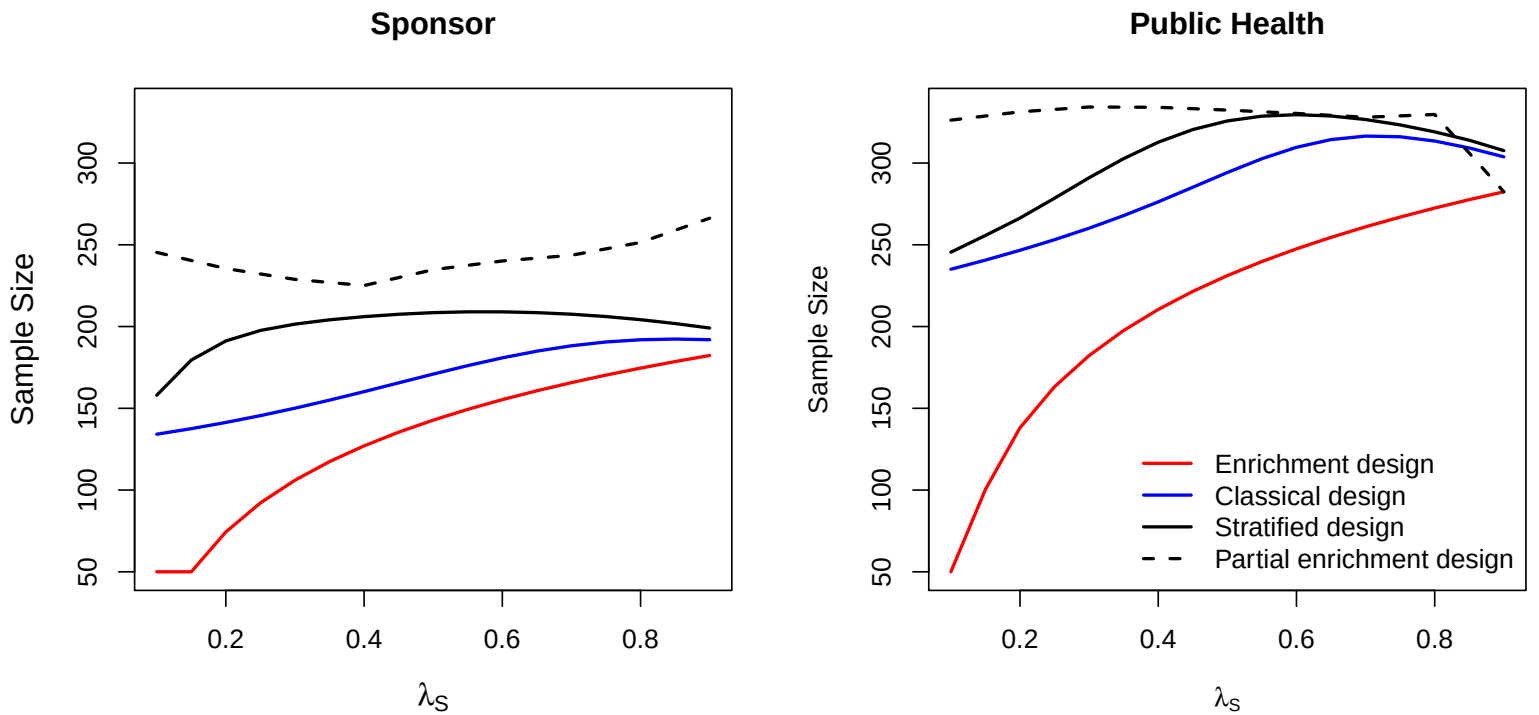
Backup Slides

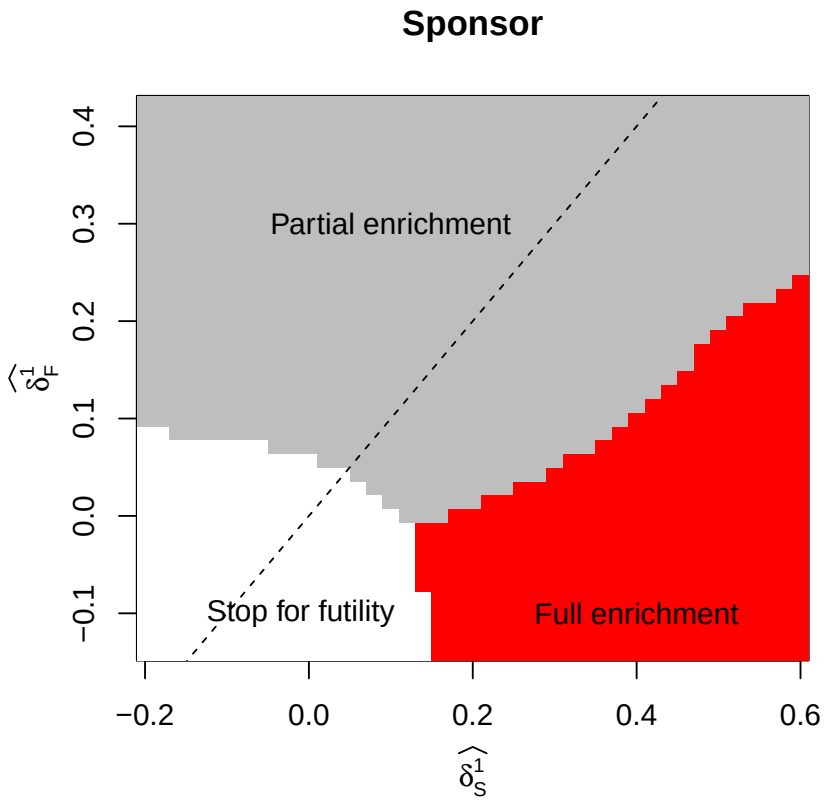
Optimal Sample Size of the Partial Enrichment Design

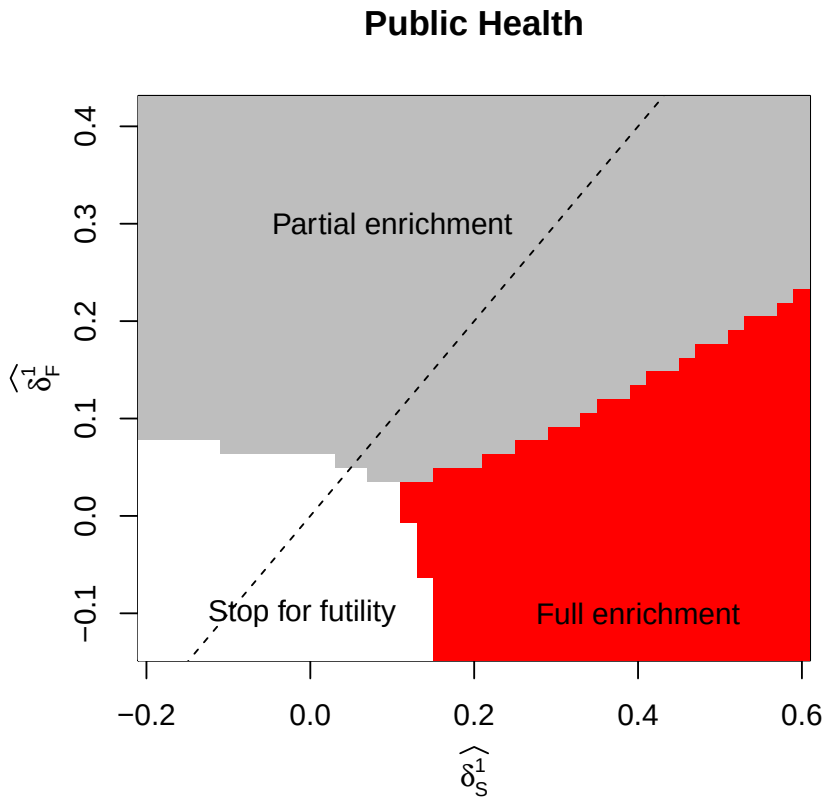
Weak Biomarker Prior



Example for the Optimal Decision Rule

Weak Biomarker Prior ($n_1 = 100, \lambda_S = \lambda_T^1 = 0.5$)





Example for the Optimal Decision Rule

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