Optimizing Confirmatory Clinical Trial Designs for Targeted Therapies

A Decision Theoretic Approach

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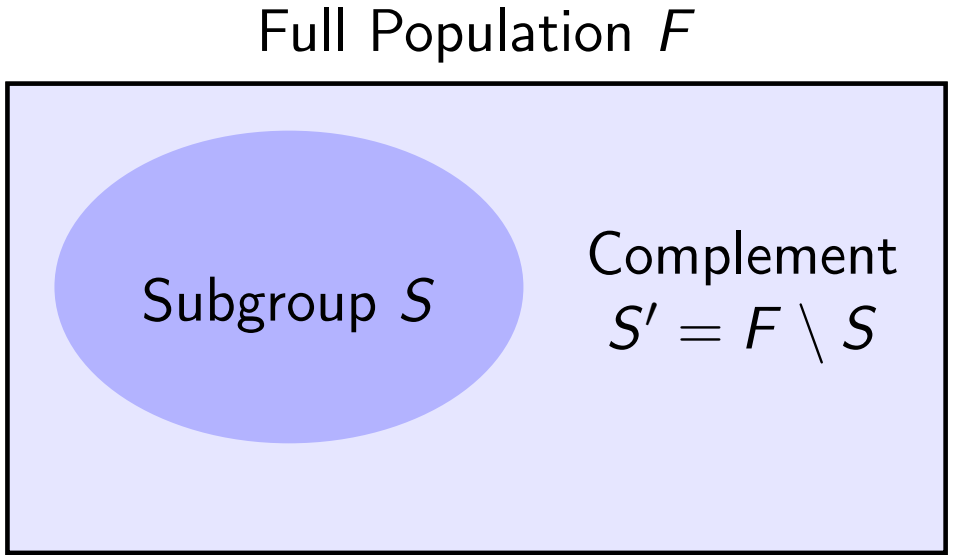
Patient Populations



- The overall treatment effect is

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

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

Which clinical trial design to choose?

Classical Design:

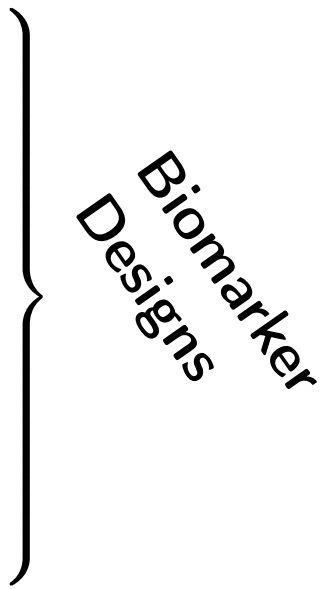
Recruitment from population F.
No Biomarker is determined.
Test of H_F.

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



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.

Enrichment Design:

H_S is tested with a z-test.

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; 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 Function

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

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

$$\varphi_{F,d} = N \cdot r_F \cdot (\delta_F - \mu_F)$$
$$\varphi_{S,d} = \lambda_S \cdot N \cdot r_S \cdot (\delta_S - \mu_S)$$

- δ_S, δ_F ... true effect sizes.

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

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

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
- α allocation (for the stratified design)

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

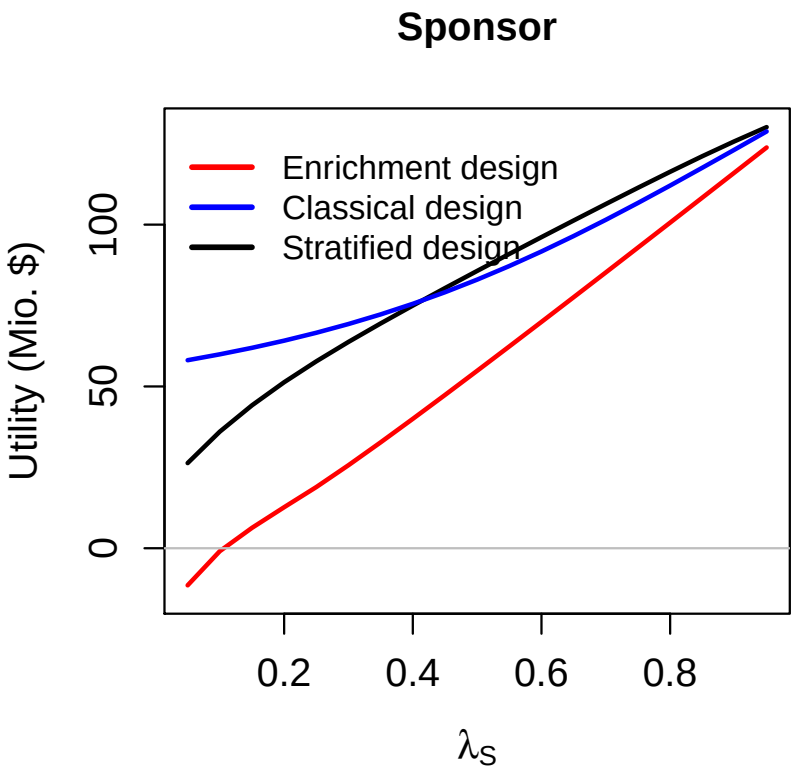
where $\theta > 0$ is an effect size parameter.

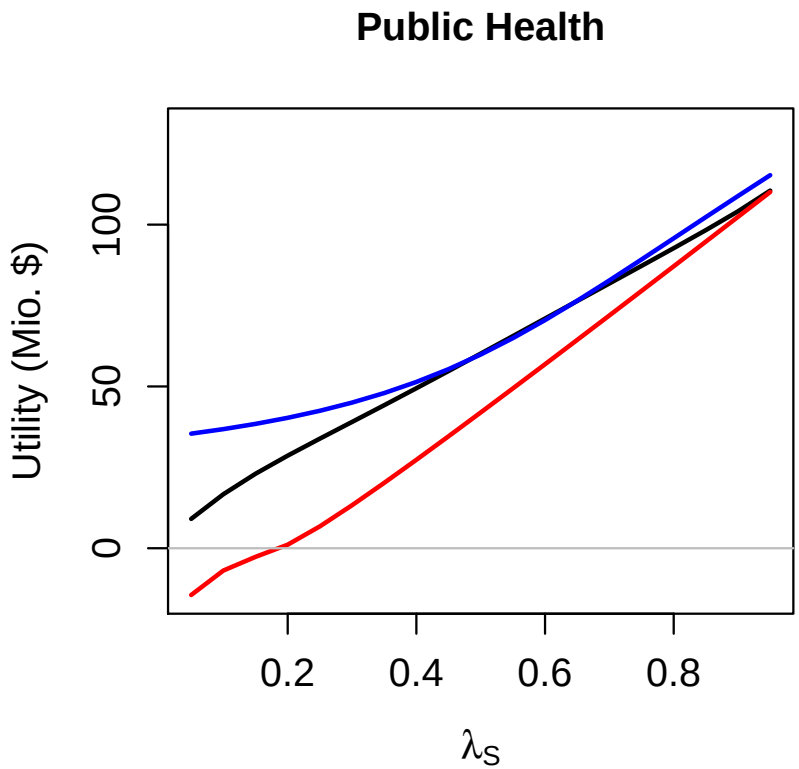
Scenario

- **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** $\tau_S = \tau_{S'} = 0.3.$

Optimized Expected Utilities

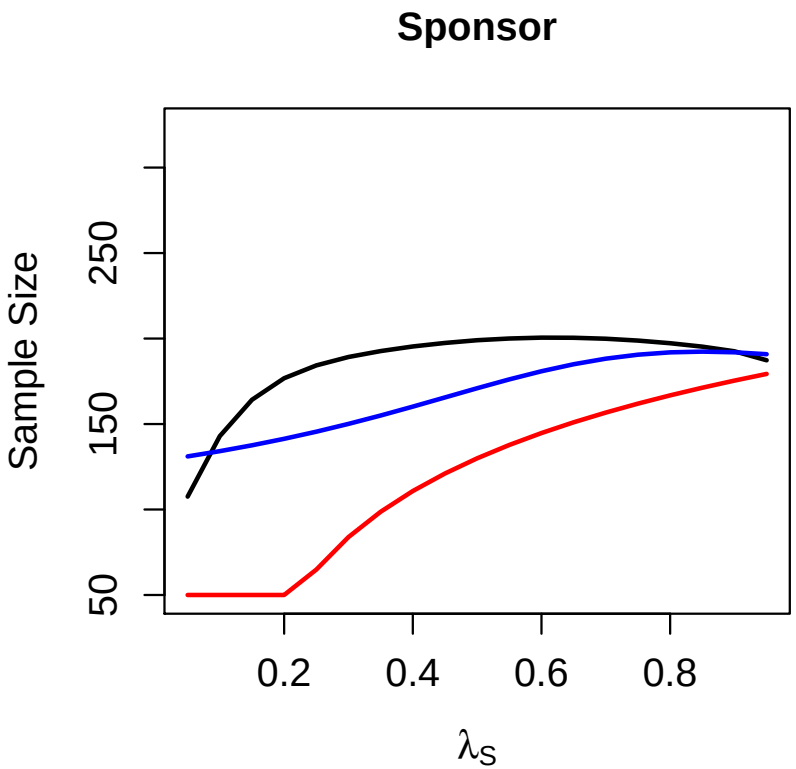
Weak Biomarker Prior

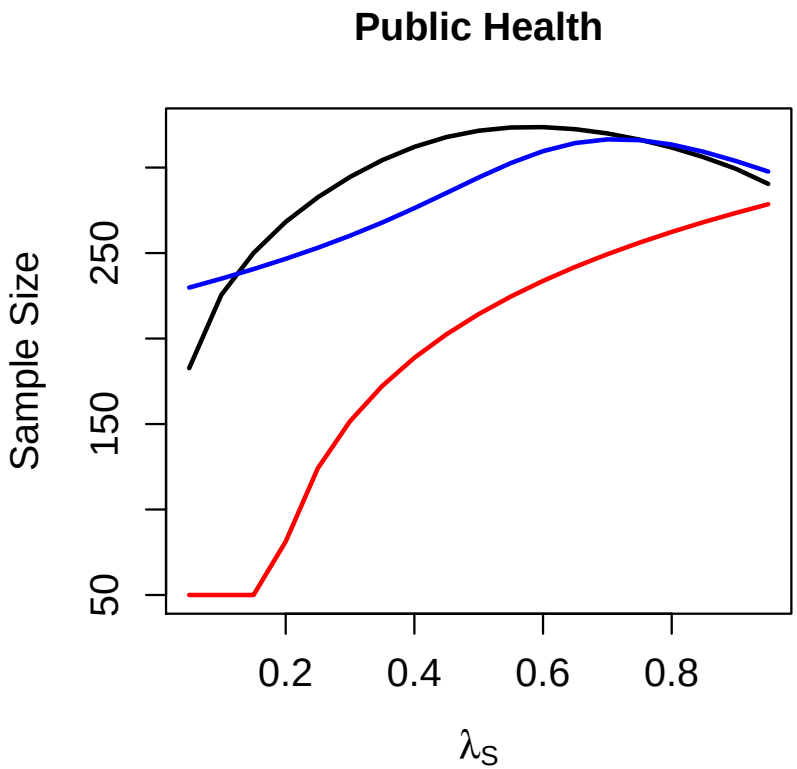




Optimized Sample Size

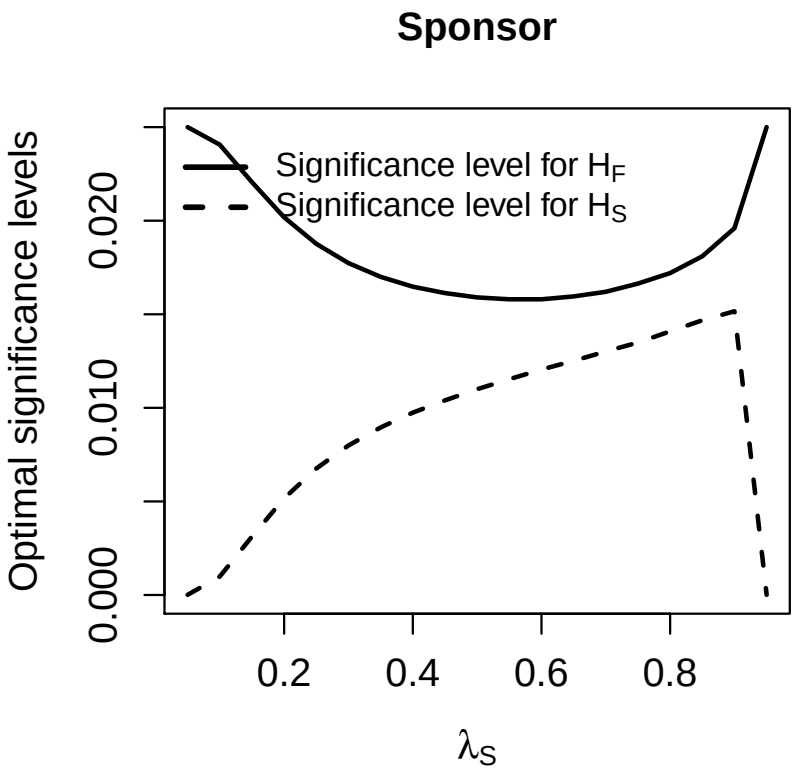
Weak Biomarker Prior

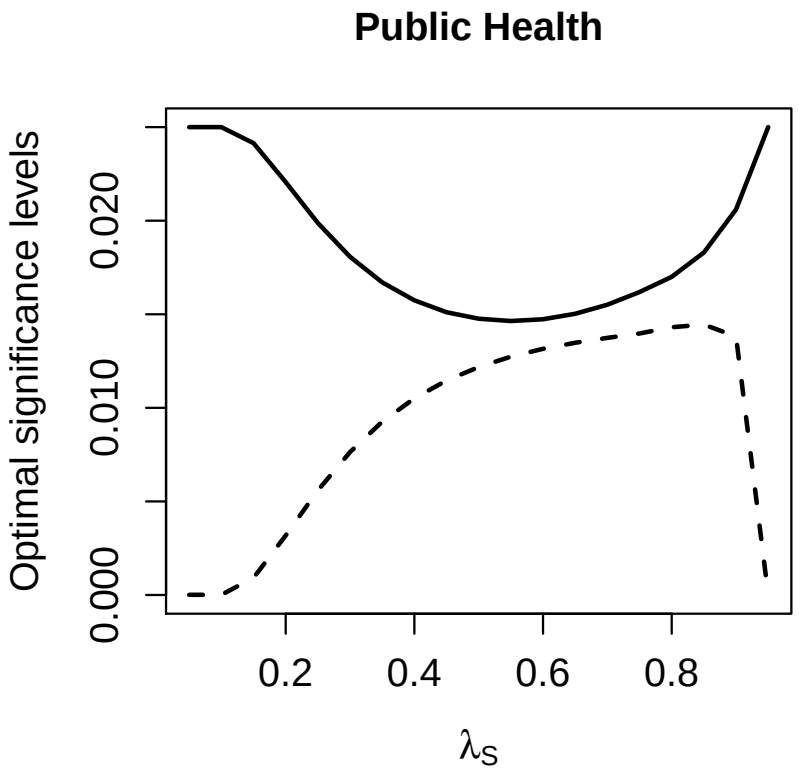




Optimized Alpha Allocation

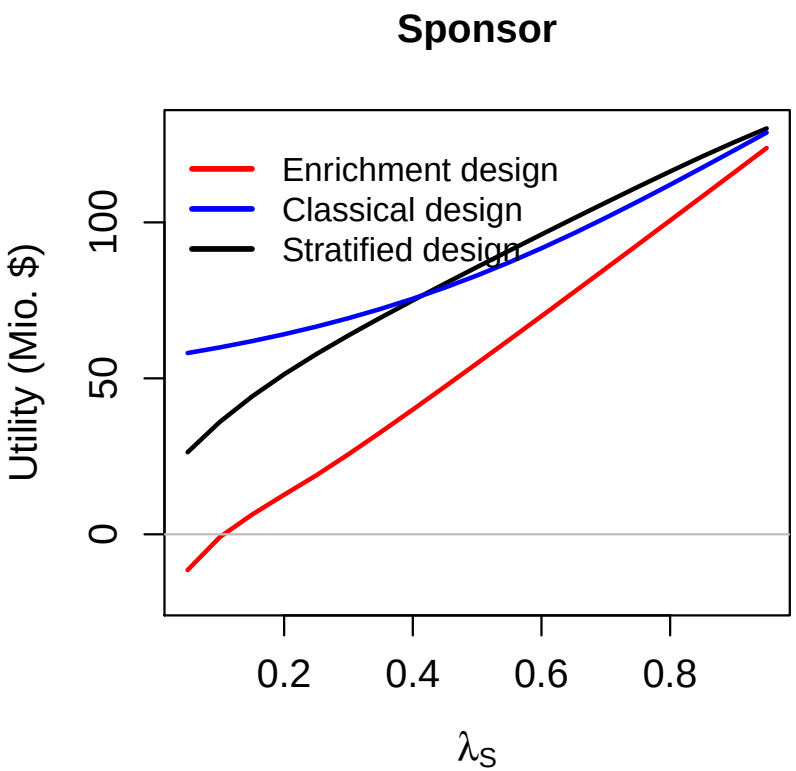
Weak Biomarker Prior

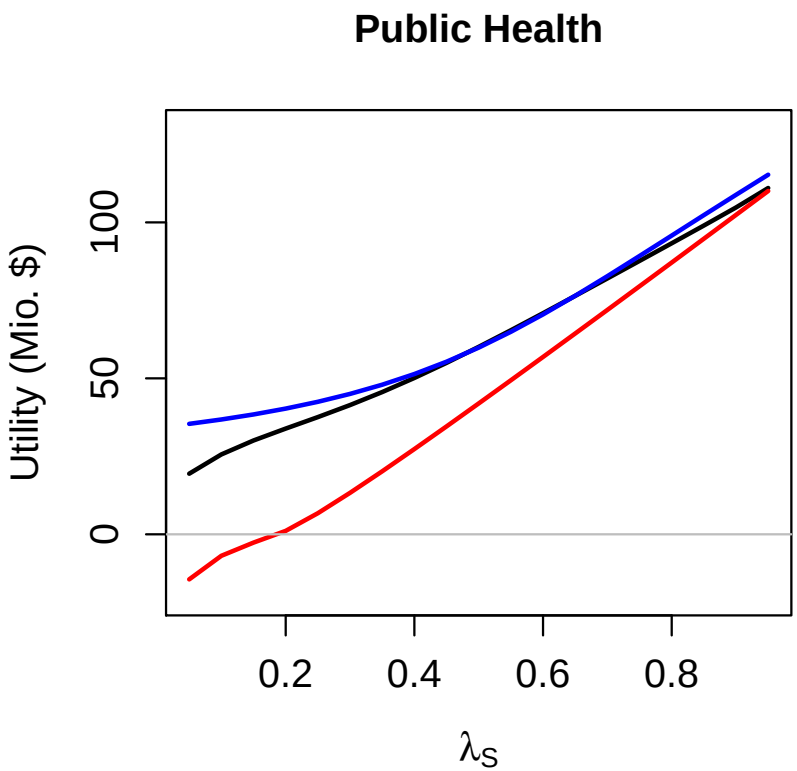




Optimized Expected Utilities – Impact of the Prior

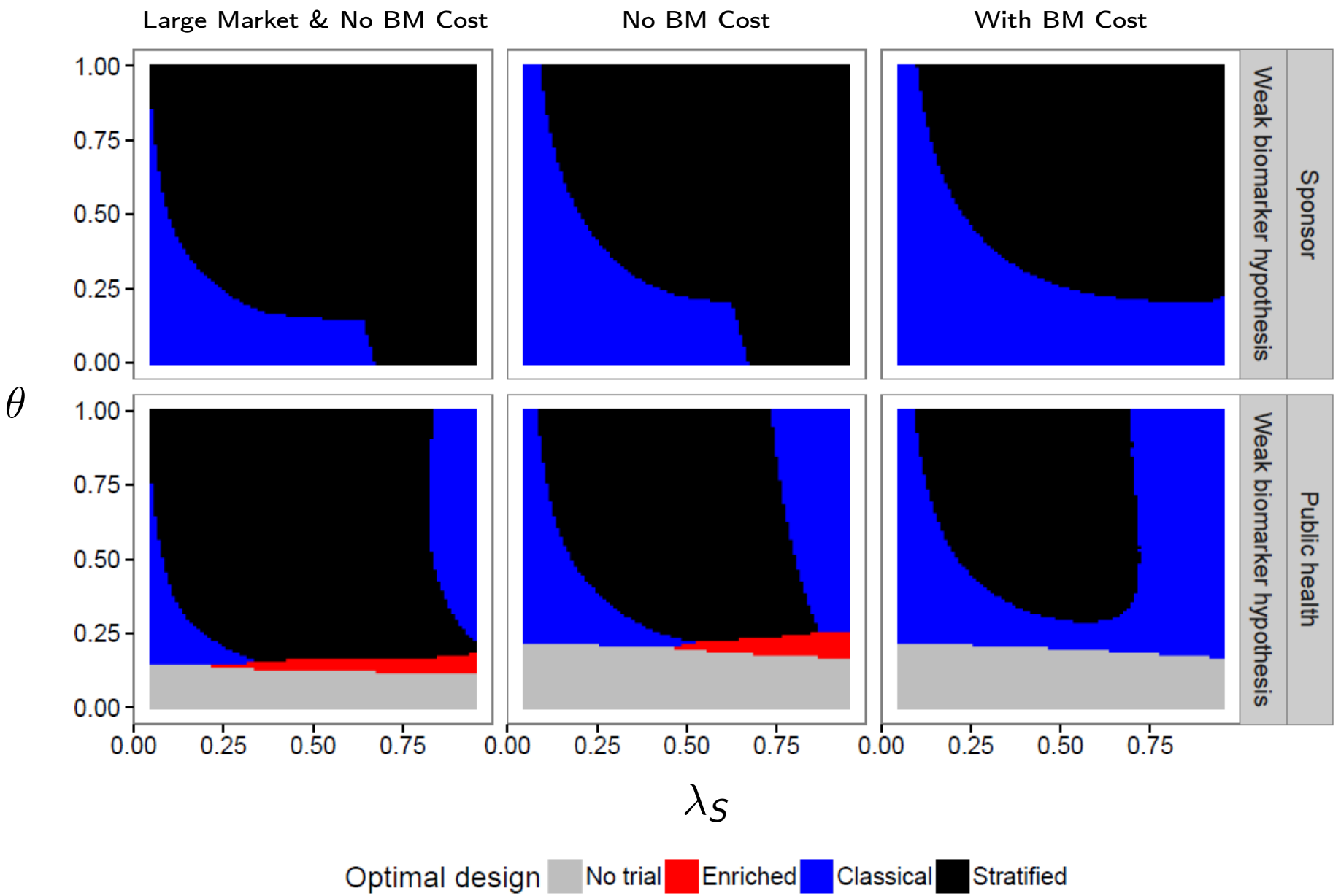
Weak Biomarker Prior Strong Biomarker Prior





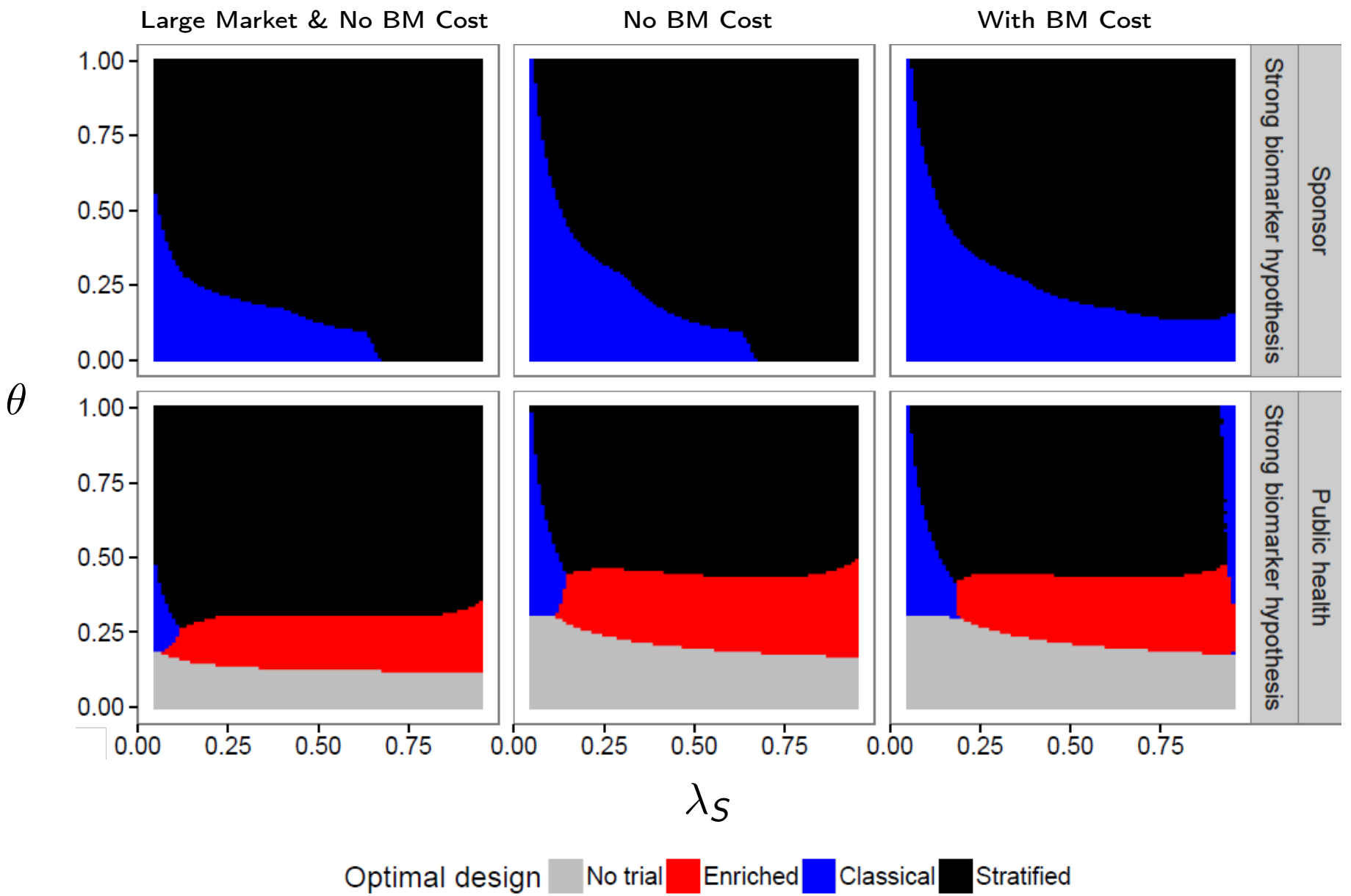
Optimal Trial Designs

Weak Biomarker Prior



Optimal Trial Designs

Strong Biomarker Prior



Some General Observations and Conclusion

- The decision theoretic model can inform the choice of
  - the type of trial design,
  - the sample size and the weights in the multiple test.
- The optimal sample size under the public health view is typically larger than in the sponsor view.
- The enrichment design is never optimal for the sponsor view
- For some scenarios the optimized designs differ, but the expected utilities of different design options are often small.
- The optimal design depends strongly on the particulars of the situation: Subgroup prevalence, trial costs and initial beliefs.

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