Optimizing trial designs for targeted therapies - A decision theoretic approach comparing sponsor and public health perspectives[†]

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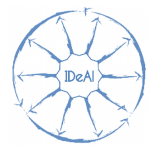

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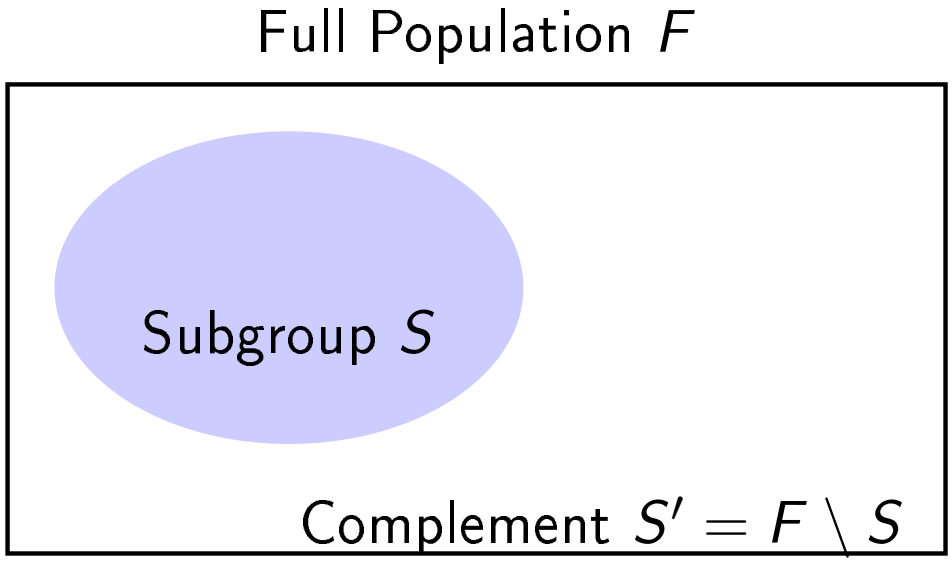
Framework



- Overall treatment effect

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

  where λ is the prevalence of subgroup S.
- We assume $\delta_{S'} \leq \delta_S$.
- Allows for investigating the hypotheses $H_F : \delta_F \leq 0$ and $H_S : \delta_S \leq 0$.

Classical, Stratification and Enrichment Design

Classical Design: Recruit from the full population F. No Biomarker is determined.

Stratification Design: Include patients of subgroup S (say Biomarker +) and patients from S' (Biomarker –). Stratify randomization by biomarker status.

Enrichment Design: Randomize only patients of subgroup S. Patients of the complement S' are excluded from the trial.

- With the classical design one can test H_F.
- With the stratification design one can test H_S and H_F.
- With the enrichment design one can test H_S, i.e., for a treatment effect in the subpopulation.

The Testing Procedures

Parallel group comparison of the means of normal distributions.

Classical Design: Test H_F with a z-test.

Stratification Design: Test H_S and H_F with closed Spiessens-Debois test at levels α_S, α_F (see Spiessens and Debois (2010)).

- If one hypothesis is rejected the other is tested at full level α.
- To reject H_F in addition to the multiple test we require for fixed **consistency parameters** $\tau_S, \tau_{S'}$ that $p_S \leq \tau_S$ and $p_{S'} \leq \tau_{S'}$.

Enrichment Design: Test H_S with a z-test.

Clinical trial designs

- When is it beneficial to include the biomarker into the clinical trial, i.e. which type of design (Classical Design/Stratified Design/Enrichment Design) to choose?
- 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, see e.g. Graf et al. (2015); Beckman et al. (2011), to model the expected utilities of a particular trial design from a sponsor's and a public health view.

The utility function

The choice of the trial design is determined by a utility function:

$$U(d) = -C(d) + \begin{cases} \varphi_{F,d} & \text{if } \psi_{F,d} = 1 \\ \varphi_{S,d} & \text{if } \psi_{F,d} = 0 \text{ and } \psi_{S,d} = 1 \\ 0 & \text{if } \psi_{F,d} = 0 \text{ and } \psi_{S,d} = 0 \end{cases}.$$

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- $C(d)$ cost for the trial.
- $\varphi_{F,d}$ reward if drug is licensed in F.
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  - For Classical designs $\psi_{S,d} = 0$.

The rewards

Sponsor view

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

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- $\hat{\delta}_{F,d}$ and $\hat{\delta}_{S,d}$ are the observed efficacy estimates.

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

- δ_S, δ_F denote true effect sizes.

The costs of a trial

- Classical Trial

$$C(d) = c_{\text{setup}} + 2nc_{\text{per-patient}}.$$

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$$C(d) = c_{\text{setup}} + c_{\text{Biomarker development}} + 2n(c_{\text{per-patient}} + c_{\text{screening}}).$$

- Enrichment Trial

$$C(d) = c_{\text{setup}} + c_{\text{Biomarker development}} + 2n(c_{\text{per-patient}} + \frac{c_{\text{screening}}}{\lambda}).$$

Optimizing the expected utility

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

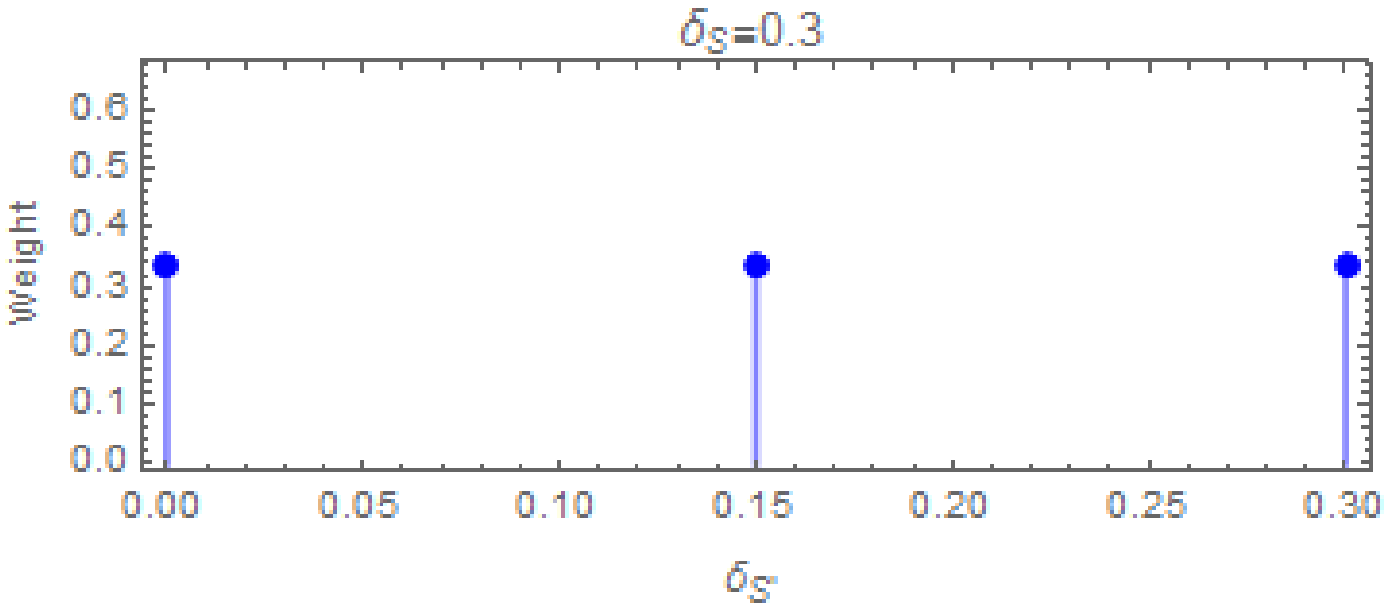
The optimal design is given by

$$d^* \in \text{argmax}_{d \in D} E_\pi \left[E_\Delta [U(d)] \right]$$

A numerical example

Prior:

- Point prior on δ_S: $P_\pi(\delta_S = 0.3) = 1$
- Discrete prior on $\delta_{S'}$



Parameter values

We choose the following parameter configuration:

$$c_{\text{setup}} = 1\text{MUSD}, c_{\text{per-patient}} = 0.05\text{MUSD}, \mu_F = \mu_S = 0.1$$

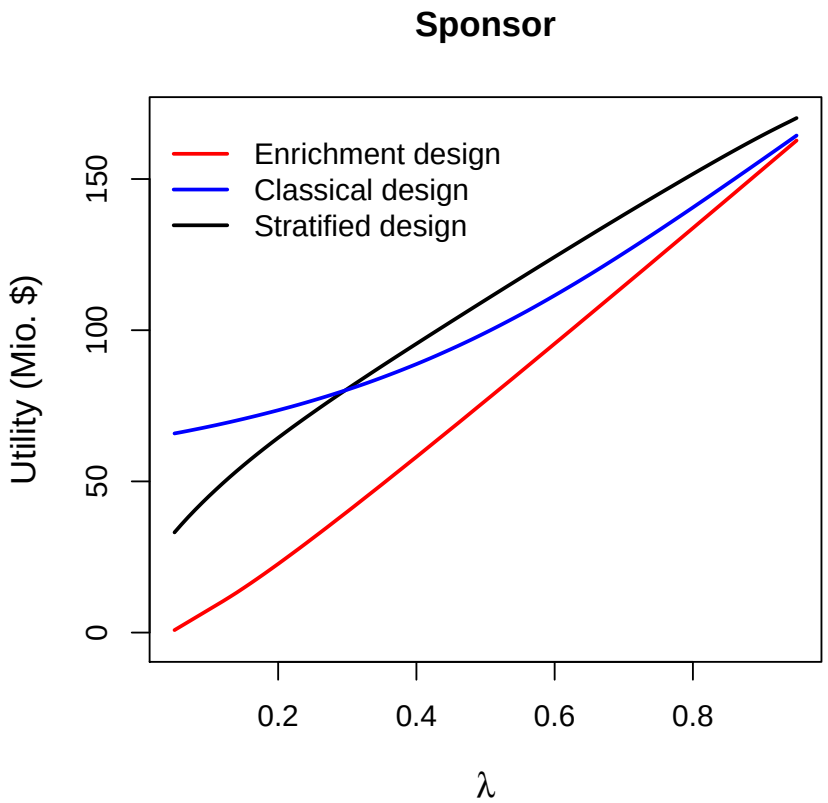
$$Nr_F = Nr_S = 1000\text{MUSD}, c_{\text{Biomarker development}} = c_{\text{screening}} = 0.$$

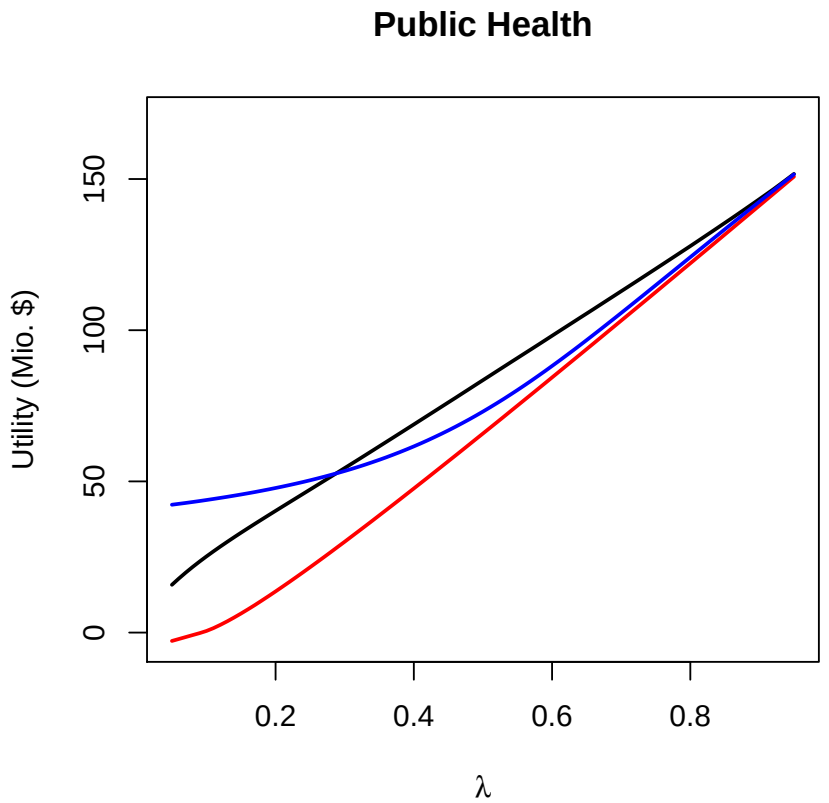
For the public health view we use the same reward and cost parameters.

Consistency parameters

- We set $\tau_S = \tau_{S'} = 0.3$ in the sponsor view.
- We set $\tau_S = 0.3$ and optimize $\tau_{S'}$ in the public health view.

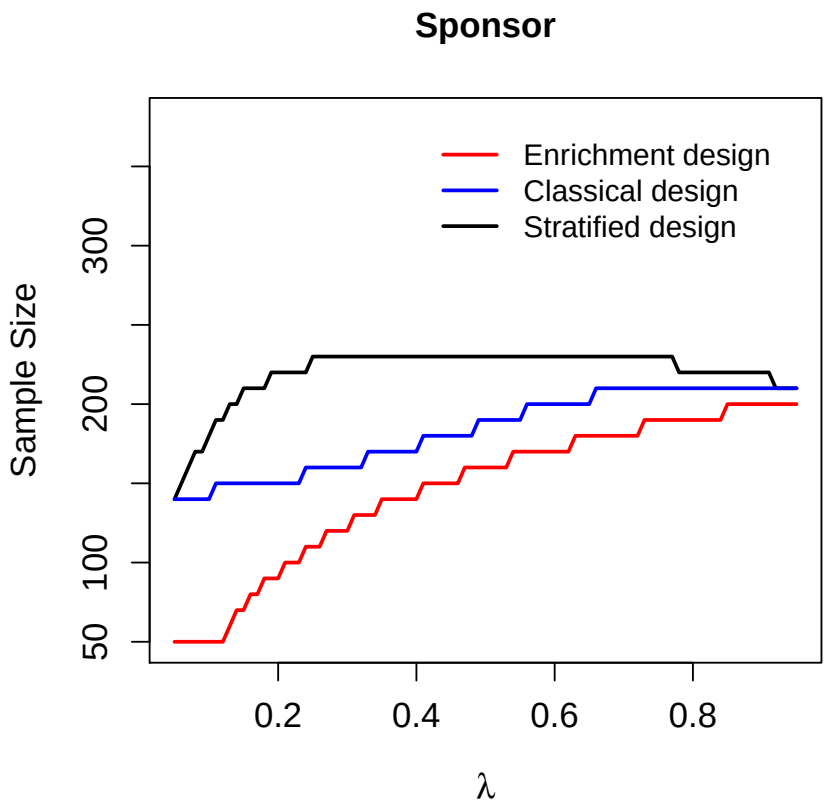
Utility

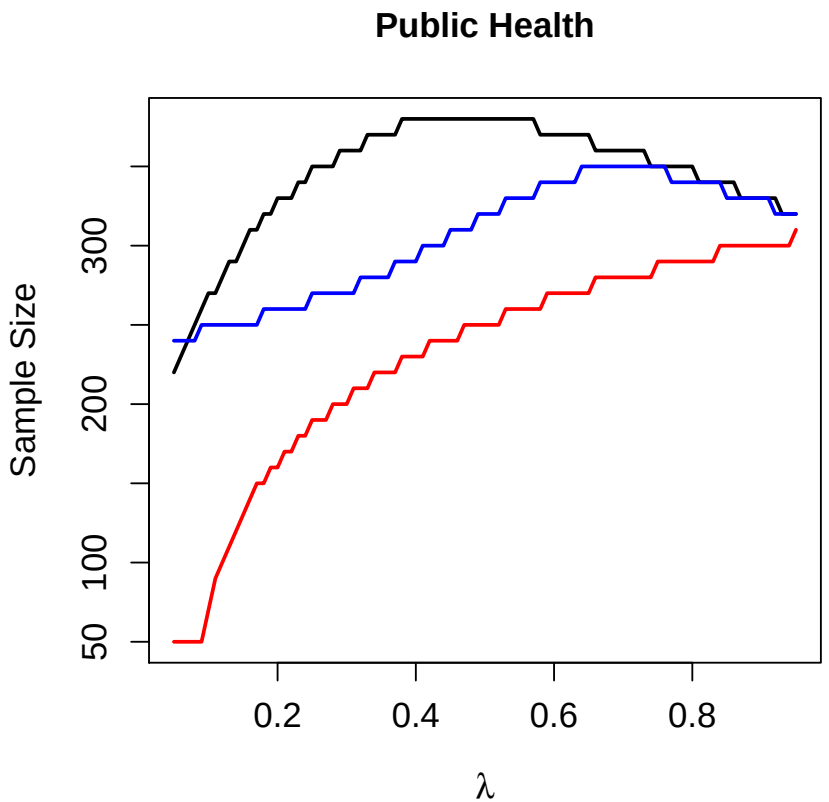




- For both views the classical design is optimal for low prevalences and the stratified design is optimal for large prevalences.
- The enrichment design is never optimal.

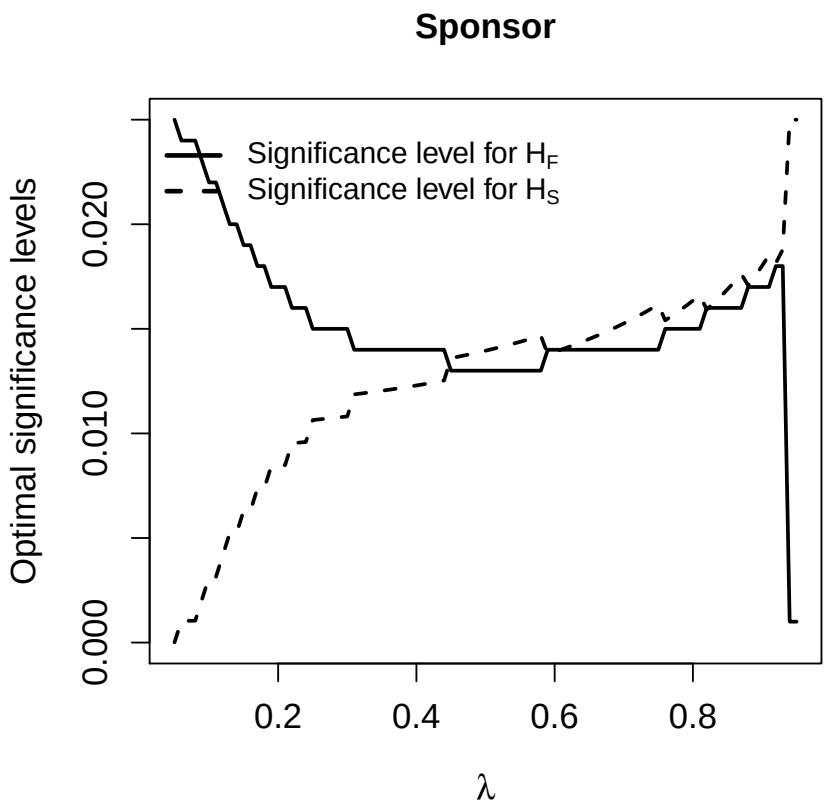
Per group sample size

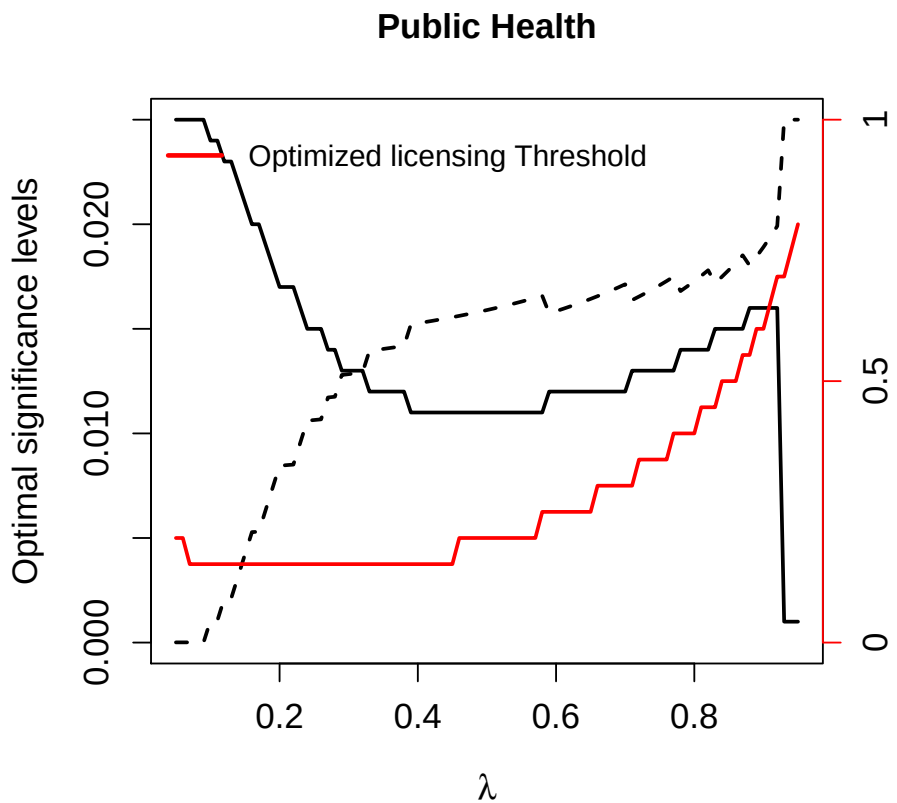




- In the public health view it is optimal to conduct larger trials.

Weights





- For low prevalences more weight is put on H_F, for large prevalences H_S is more important.
- As the subgroup gets larger, the optimal consistency parameter $\tau_{S'}$ gets larger.

What happens if we add biomarker costs?

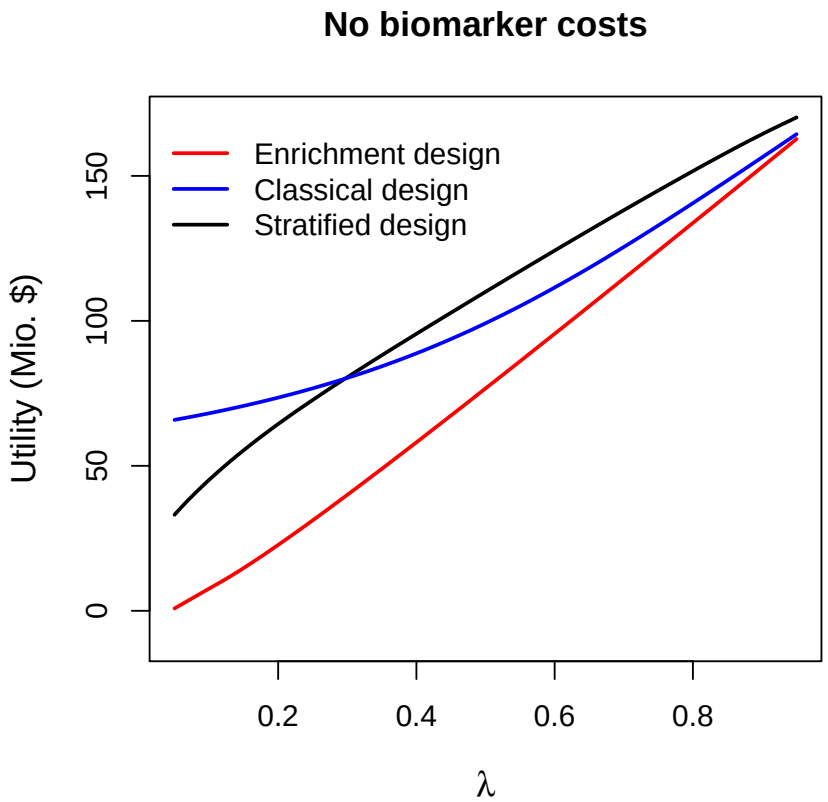
We change the biomarker related costs from

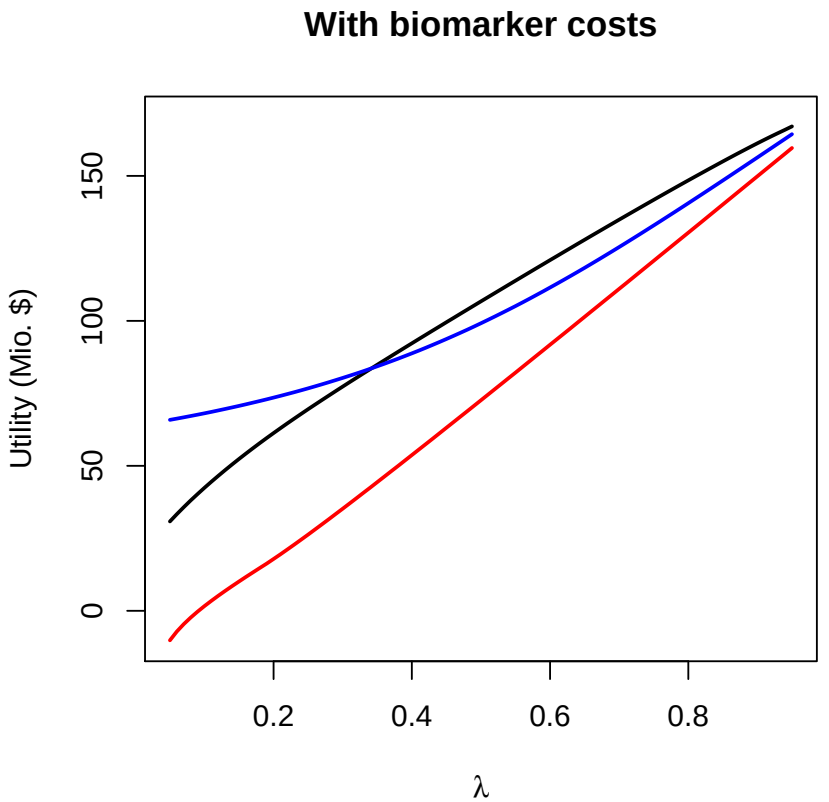
$$c_{\text{Biomarker development}} = c_{\text{screening}} = 0$$

to

$$c_{\text{Biomarker development}} = 1\text{MUSD}, c_{\text{screening}} = 5000\text{USD}$$

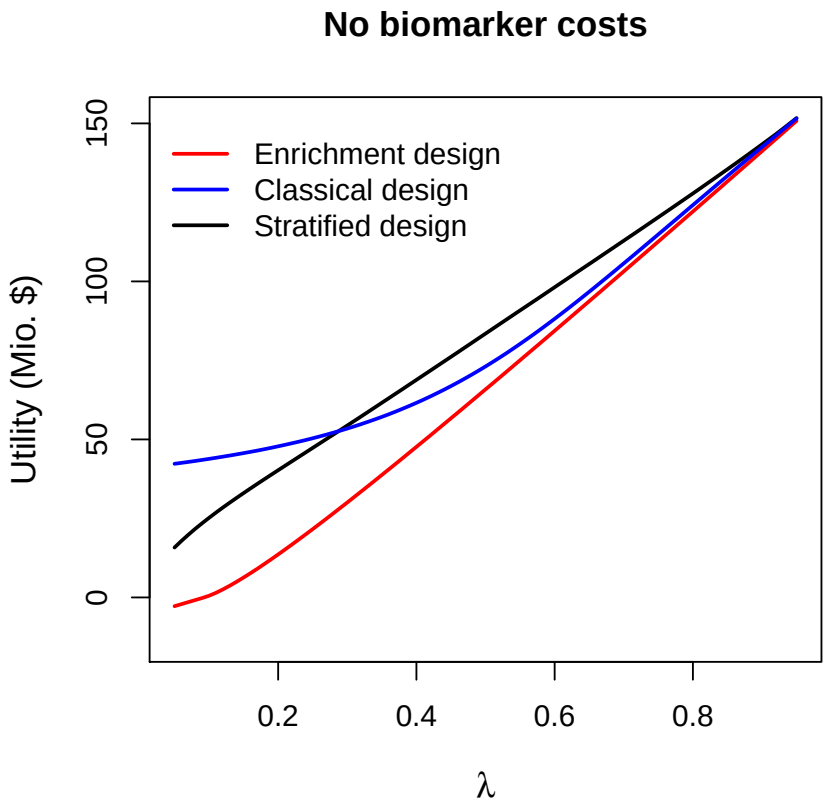
Changes in the sponsor view

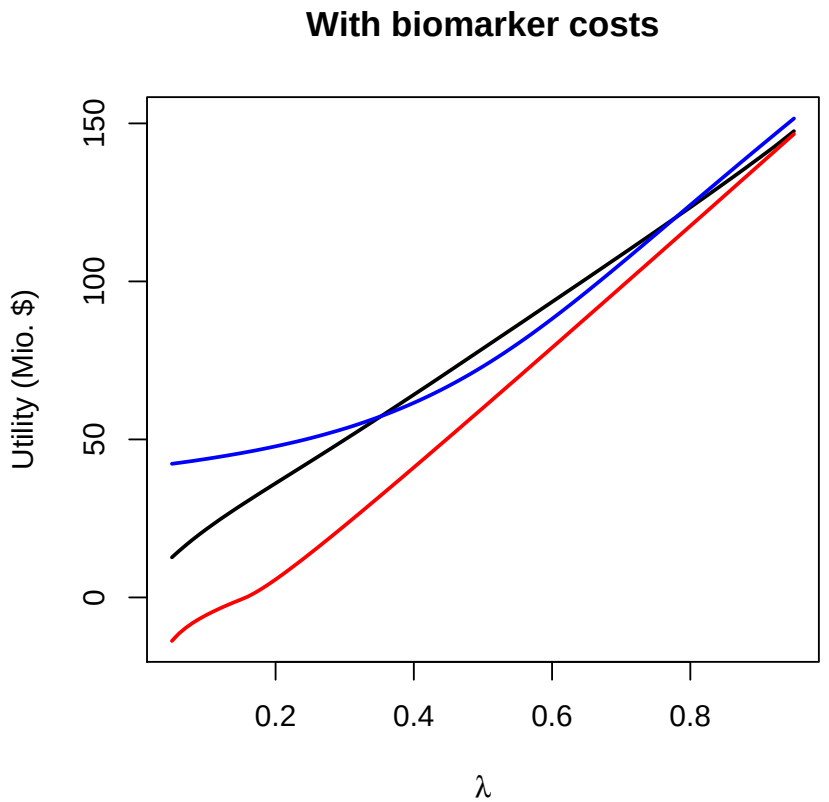




- Cutpoint is shifted to the right.
- Classical designs is not affected.

Changes in the public health view





- Cutpoint is shifted to the right
- In addition, the classical designs is also optimal for very large prevalences.

Conclusions

- In general, the decision theoretic approach gives guidance regarding the choice of the trial design (including the type of the trial, the choice of the sample size and the weights in the multiple test)
- The analysis of the example shows that the optimal sponsor decision depends strongly on the particulars of the situation. Subgroup prevalence, trial costs and initial beliefs are all important to consider when making the design choice.
- Allows for comparing optimal designs from sponsor's and public health perspective.
- The model can be extended in several directions.
  - Allow for partial enrichment.
  - Include adaptive enrichment designs.

References

Beckman, R. A., J. Clark, and C. Chen (2011). Integrating predictive biomarkers and classifiers into oncology clinical development programmes. *Nature Reviews Drug Discovery 10*(10), 735–748.

Graf, A. C., M. Posch, and F. Koenig (2015, January). Adaptive designs for subpopulation analysis optimizing utility functions. *Biometrical Journal 57*, 76–89.

Song, Y. and G. Y. H. Chi (2007, August). A method for testing a prespecified subgroup in clinical trials. *Statistics in Medicine 26*(19), 3535–3549.

Spiessens, B. and M. Debois (2010, November). Adjusted significance levels for subgroup analyses in clinical trials. *Contemporary Clinical Trials 31*(6), 647–656.