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

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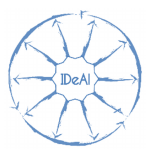
Based on work with Thomas Ondra, Sebastian Jobjörnsson, Robert Beckman, Carl-Fredrik Burman, Alexandra Graf, Franz König, Nigel Stallard



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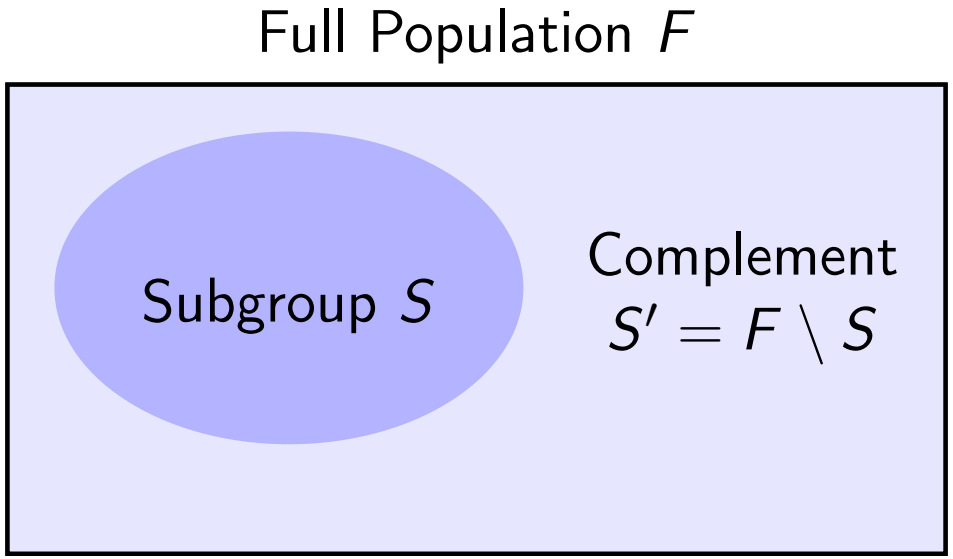
Clinical Trials for Targeted Therapies

- Knowledge on the genetic basis of many diseases enables the development of therapies that target underlying molecular mechanisms.
- Patients' responses to targeted treatments are predicted based on genetic features or other biomarkers.
- For the development of such treatments, clinical trials confirming treatment effects in sub-populations and/or in the overall populations are required.

Challenge: Identify efficient trial designs for decision making.

Patient Populations



Test for a treatment effect in the

- full population F, $H_F : \delta_F \leq 0$
- "Biomarker positive" sub-population S, $H_S : \delta_S \leq 0$.

Design and Analysis when Testing multiple Populations

Control of probability for false positive decisions

- When testing more than one hypothesis, adjustment for multiple testing is required.
- In addition, if the treatment effect in F is only driven by the subpopulation, H_F should not be rejected.

Planning of Enrichment Designs

- Power alone is not sufficient to describe the utility of trial outcomes.
- The utilities of showing an effect in F or S differ.
- Utilities are not the same for all stakeholders involved.
- The costs of the clinical trial need to be taken into account.

A Decision Theoretic Approach

Modeling Utilities from a Sponsor's and a Public Health View

Sponsor's View

Utility is given by the profit which depends on

- The size of the population for which a treatment effect is demonstrated with the multiplicity adjusted test.
- The observed effect size in that population.
- The trial costs.

Public Health View

Utility is given by the total health outcome which depends on

- The size of the population for which a treatment effect is demonstrated with the multiplicity adjusted test.
- The actual effect size in that population.
- The trial costs.

Considered Trial Designs

Clinical Trial in the full population

Testing only H_F or testing H_F and H_S.

Partially enriched design testing H_S and H_F

The subgroup prevalence in the trial may exceed the population prevalence.

Enrichment design in population S only (testing H_S only)

Recruitment in S only.

Adaptive (partially) enriched design, testing H_S and, if selected, H_F

- First stage: (partially) enriched full population
- Second stage: selection of the population and the sample sizes.

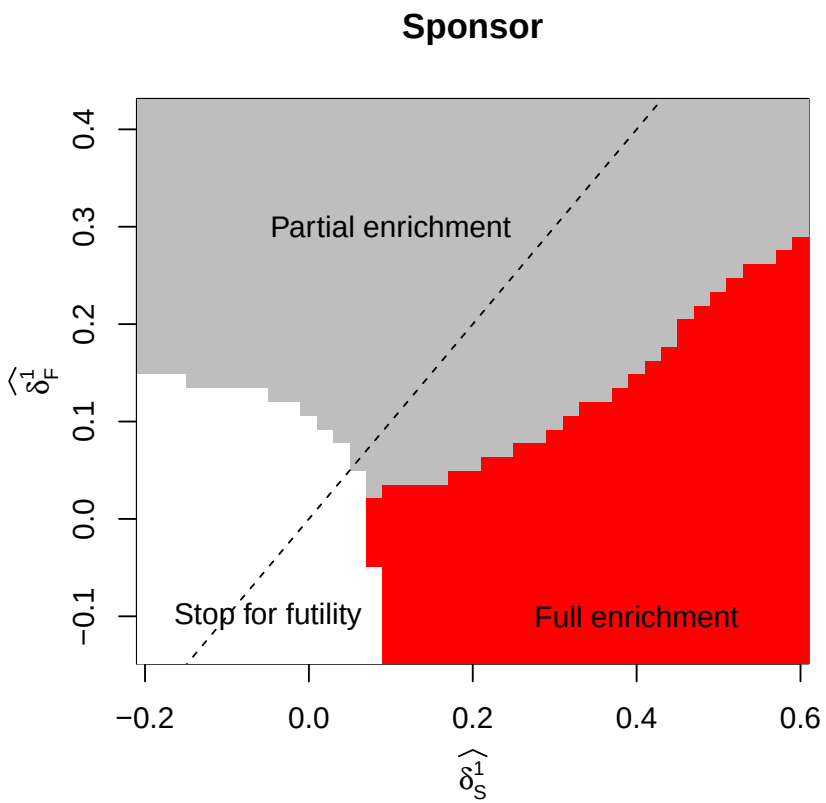
Optimizing Clinical trial designs

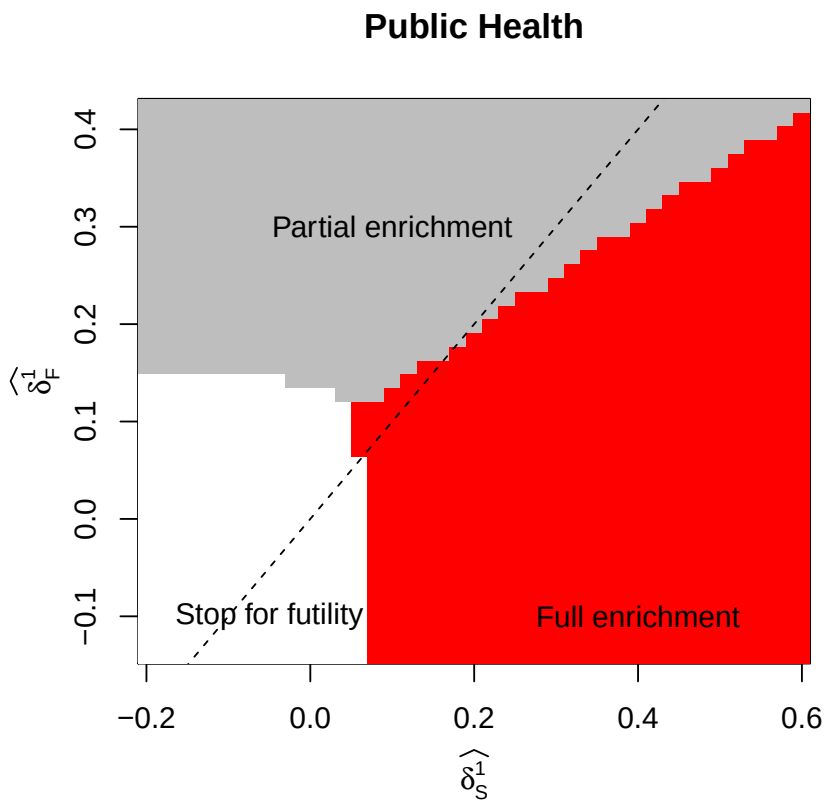
- When is a biomarker (BM) design beneficial compared to a classical design?
- When to choose an adaptive, a (partially) stratified, when an enrichment design?
- Which sample size?
- Which multiple test for the stratified design is optimal?
- What is the optimal adaptation rule in an adaptive design?

Bayesian Viewpoint to Design Optimal Frequentist Trials

- The operating characteristics of all trial designs depend on the actual effect sizes
- Expected utilities (that depend on frequentist hypothesis tests) can be defined averaging across
  - priors on the effect sizes
  - the distribution of the data, given the effect sizes
- Optimal designs that maximize the expected utilities are identified.

Example: Optimal Adaptation Rules





General Observations

- Optimal trial designs depend sensitively on the subgroup prevalence, prior and parameters in the utility function.
- Sponsor and public health view lead to different optimized trial designs:
  - Sponsor tends to use smaller sample sizes.
  - Sponsor tends to recruit in F even if there is strong prior evidence of treatment effect in S only.
- Partial Enrichment Designs can increase the utility (mainly for the sponsor).
- Adaptive Enrichment Designs
  - Lead to higher expected utilities
  - Are more robust with regard to the planning assumptions.

Conclusions and Outlook

The utility based approach

- allows one to account for the size of the patient population in the trial design.
- makes the impact of differences in incentives transparent.
- maximizes "total health benefit" to get the best outcome for the population in the public health view. This, however, can imply that small patient groups are neglected in order to allocate resources for a larger populations.
- can be extended to define optimal decision rules (instead of the frequentist multiple hypothesis tests).

Project Publications on Enrichment Designs

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

Ondra, T., A. Dmitrienko, T. Friede, A. Graf, F. Miller, N. Stallard, and M. Posch (2016). Methods for identification and confirmation of targeted subgroups in clinical trials: a systematic review. *Journal of Biopharmaceutical Statistics 26*(1), 99–119.

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

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