Probability of Study Success for Overall Survival in Clinical Trials with Treatment Crossover

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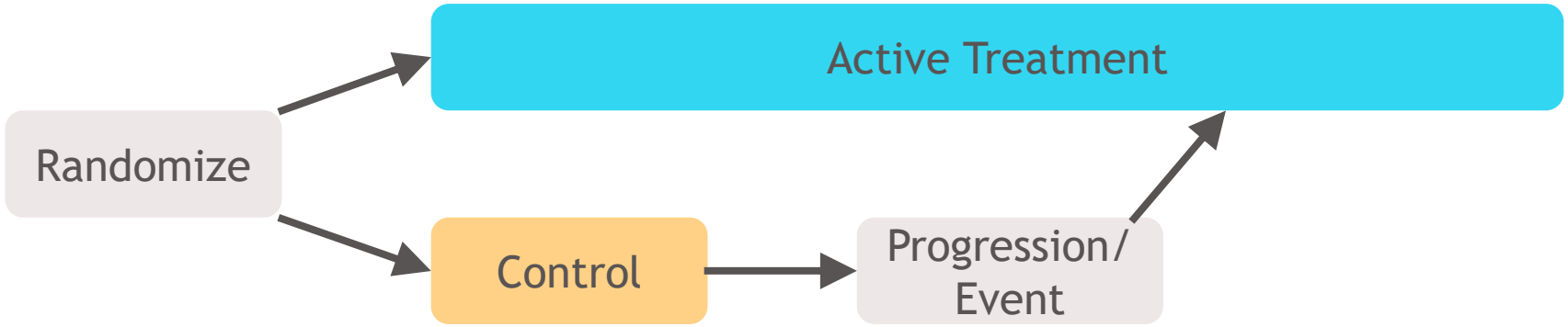
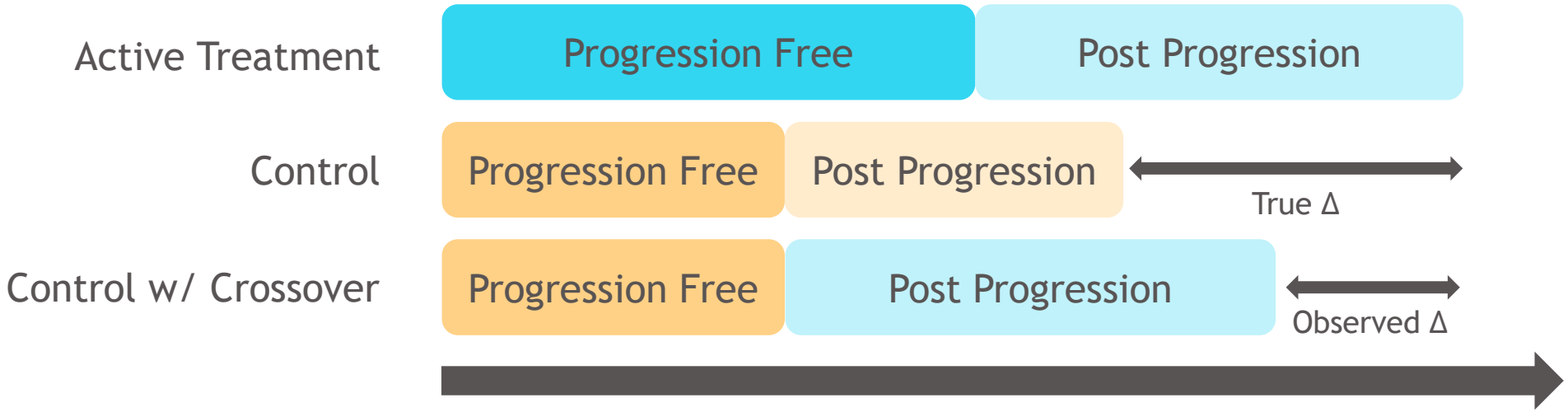
Clinical Trials with Treatment Crossover

- Randomized controlled clinical trial
  - Primary endpoint: composite survival endpoint, e.g.
    - Progression-free survival (PFS)
    - Event-free survival (EFS)
  - Key secondary endpoint: overall survival (OS)
- Crossover from control to active arm
  - Allowed once primary endpoint met
  - Crossover likelihood highly variable depending on study



Crossover Impacts Observed OS Difference



- Accounting for treatment crossover
  - Intention-to-treat analysis
  - Per-protocol analysis
  - On-treatment analysis
  - Time varying treatment variable

Δ is the difference in median overall survival

Intention-to-Treat (ITT) Analysis

- Ignores treatment crossover
- “Gold standard”
- Based on randomization
- Biased estimates of “true” treatment effect on OS
- Potentially large reduction in power

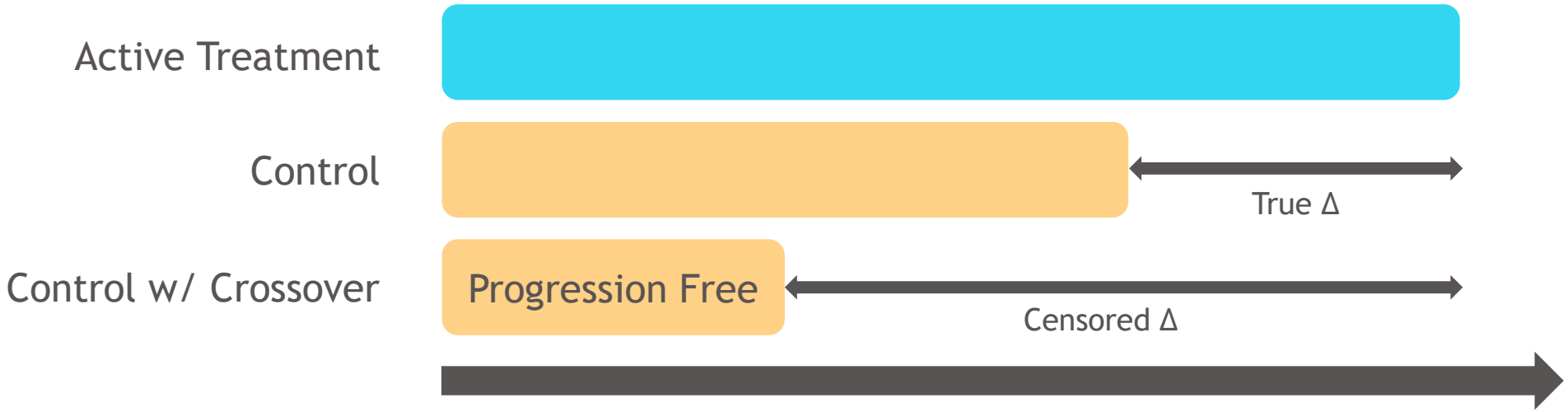
Δ is the difference in median overall survival

Per-protocol Analysis

- Exclude crossovers
- Only control group can have exclusion
- Not based on randomized groups
- Assumes prognosis of crossovers is same as non-crossovers

Δ is the difference in median overall survival

On-Treatment Analysis



- Censor at crossover
- Based on randomization
- Informative censoring
- Assumes prognosis of crossovers is same as non-crossovers

Δ is the difference in median overall survival

Time-varying Treatment Variable

- Add variable to Cox model
- Not based on randomized groups
- Assumes treatment effect same in next line of therapy

Δ is the difference in median overall survival

Advanced estimation methods for treatment crossover

Rank Preserving Structural Failure Time Models (RPSFTM)

- Reconstruct survival of patients, as if never received active treatment
- Multiplicative factor interpreted as relative decrease in survival
- Based on randomized groups
- Assumes treatment effect same in next line of therapy

Inverse Probability of Censoring Weights (IPCW)

- Censor at crossover
- Model crossover using set of predictor variables
- Weight according to probability of crossing over
  - More weight if lower probability
- Assumes no unmeasured confounders

Two-stage Weibull Estimation

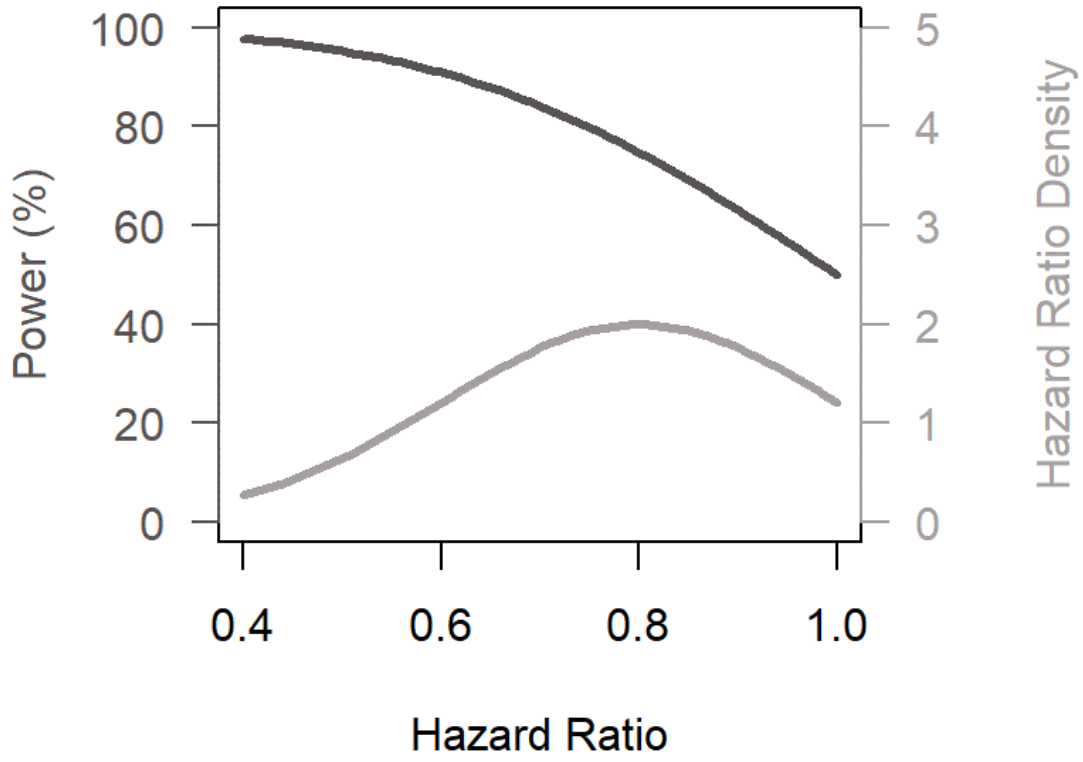
- Accelerated failure time model for crossover using a set of predictor variables
- Fit model using counterfactual survival times: survival times that would have been observed in the absence of crossover
- Assumes no unmeasured confounders

Power and Probability of Study Success (PrSS)

- Power curve
- Effect size likelihood function
- PrSS: expected power over effect size distribution

$$PrSS = \int \{\Pr(SS|\,\Delta)\Pr(\Delta|Data)\}d\Delta$$

  - SS = study success
  - Δ = effect size
- Requires prior $\Pr(\Delta|Data)$
  - Data = previous trials, etc.



Simulation program to calculate power and probability of study success for overall survival with treatment crossover

- Generate Data
  - Enrollment distribution over time
  - Randomized treatment assignment
  - Dropout time for censoring distribution
  - Progression event time for PFS distribution
  - Death event time for PFS and OS distributions
  - Adjust OS distribution after treatment crossover
    - Potentially different from OS distribution for active treatment
- Power and probability of study success (PrSS)
  - For power, use expected hazard ratios (HRs): HR_{PFS} and HR_{OS}
  - For PrSS, generate HR_{PFS} and HR_{OS} from multivariate log-normal with covariance matrix

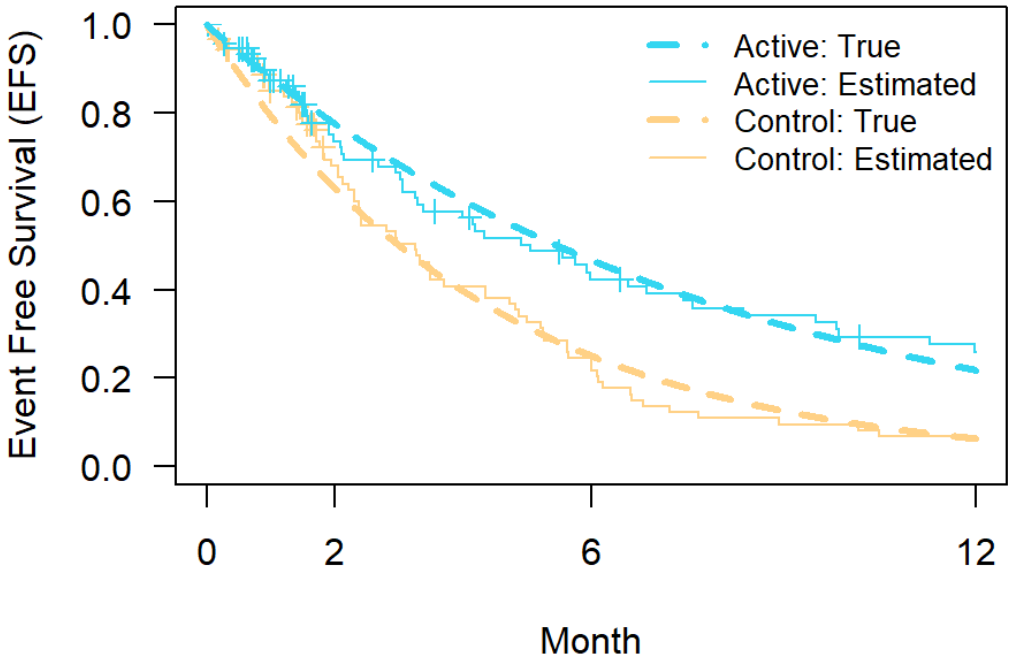
$$\begin{bmatrix} \sigma_{PFS}^2 & \rho\sigma_{PFS}\sigma_{OS} \\ \rho\sigma_{PFS}\sigma_{OS} & \sigma_{OS}^2 \end{bmatrix}$$

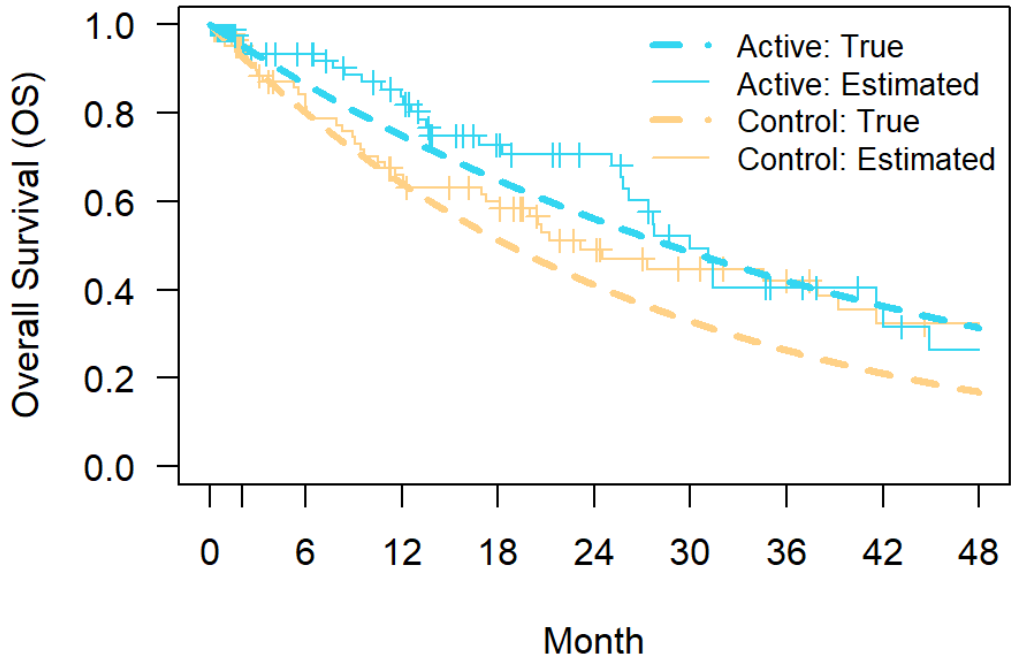
Simulations

- 1000 simulations
- Interim analysis at 60% information
- O'Brien-Fleming bound
- Recruit over 18mo
- Dropout 15% per year
- Crossover probability 0.75

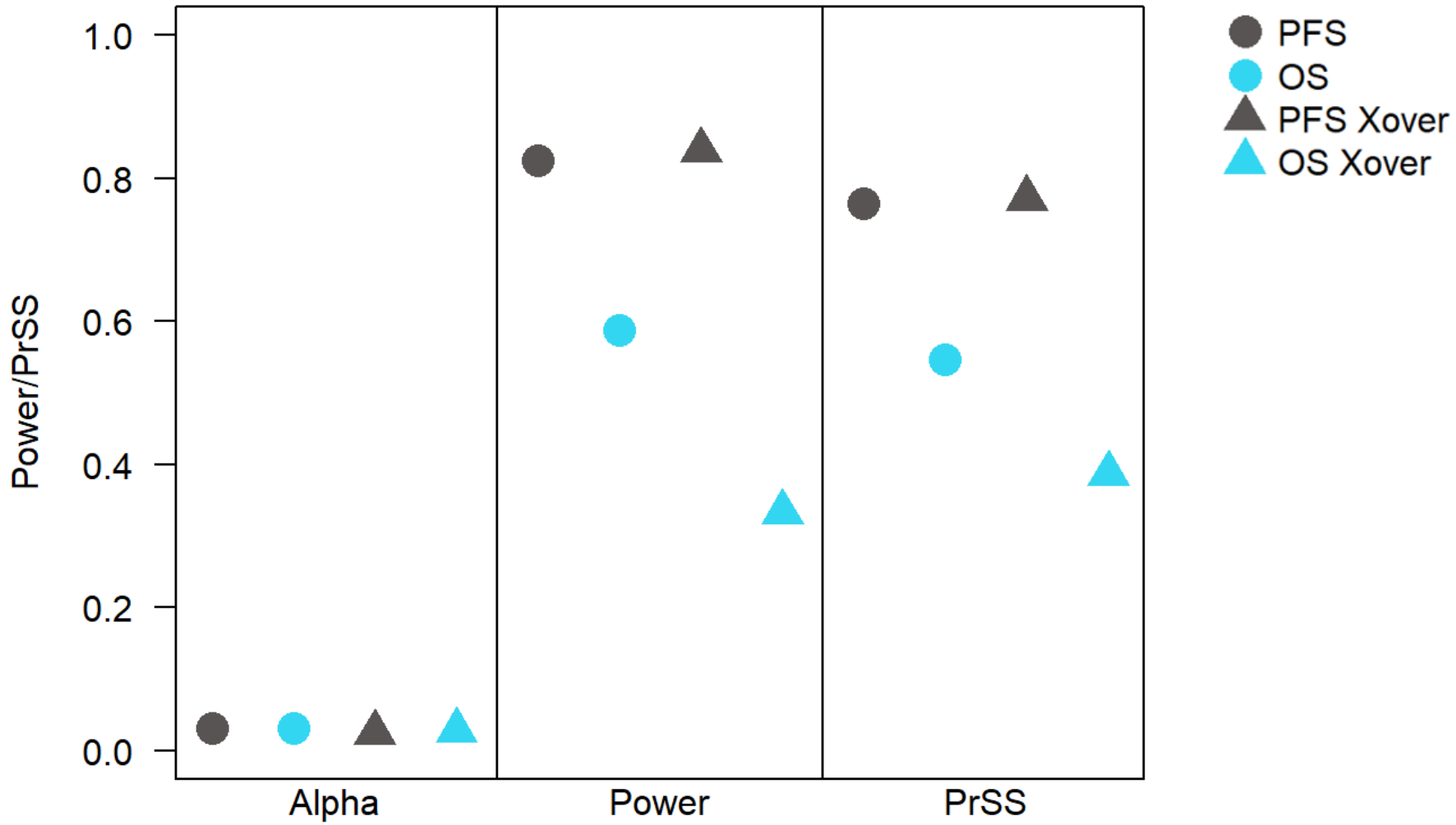
- PFS
  - Control median 12mo
  - HR = 0.55
  - PFS events 71, 119, N ~ 200
  - Prior for PrSS
    - HR = 0.55, SD_{logHR} = 0.19
- OS
  - Control median 24mo
  - HR = 0.65
  - Prior for PrSS
    - HR = 0.65, SD_{logHR} = 0.18

With treatment crossover, observed overall survival differences can be attenuated





PFS and OS Power and Probability of Study Success



Summary and Conclusions

- Developed method and simulation program
  - Randomized 2 arm trial with PFS primary endpoint and OS key secondary endpoint
  - Accounts for enrollment, dropout and interim analysis
  - Joint priors for PFS and OS hazard ratios
  - Allows treatment effect at crossover to be different
  - Uses ITT to calculates PFS and OS power and PrSS
- Simulation program was used to show impact of treatment crossover
  - No effect on PFS power or PrSS
  - Large impact on OS power and PrSS
- PFS is often a good primary endpoint for regulatory agencies
- Sometimes payers or other agencies want OS
- Treatment crossover can have large impact on OS power
- Incorporating crossover into analysis reduces bias and may have better power
- Larger sample size typically needed for OS compared to EFS/PFS

Flexible method easily generalizable

- More flexible survival times: Weibull, piecewise exponential, mixture distribution
- Incorporate other estimation methods: Per-protocol, on-treatment, time-varying covariate, RPSFTM, IPCW, two-stage
- Incorporate more endpoints: e.g. EFS, ORR, CRR
- Stratified model, covariates
- Incorporate multiple interims, plus futility
- More complex multiple comparison procedures

References

- Ishak KJ, Proskorovsky I, Korytowsky B, Sandin R, Faivre S, Valle J. Methods for adjusting for bias due to cross over in oncology trials. Pharmacoeconomics. 2014 Jun 01;32(6):533-546.
- Latimer NR, Abrams KR, Lambert PC, Morden JP, Crowther MJ. Assessing methods for dealing with treatment switching in clinical trials: A follow-up simulation study. Statistical Methods in Medical Research. 2016 Apr 25.
  - *Note: these focus on evaluation of estimation properties, e.g. treatment effect bias and confidence interval coverage*

Thank you

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Abstract

Randomized clinical trials sometimes include an option to cross over from control to active treatment to allow all subjects the possibility to experience the novel therapy under investigation. We describe a scenario where treatment crossover is allowed after the primary endpoint of progression-free survival (PFS) is met, but before a key secondary endpoint of overall survival (OS). This design allows valid evaluation of PFS; however, evaluation of OS could be impacted, especially since we are interested in estimating the treatment effect on OS in the absence of treatment crossover. We review several methods for accounting for treatment crossover to estimate the treatment effect on OS. Each of these methods has assumptions and drawbacks which are difficult to overcome, and so intention-to-treat (ITT) analysis is often considered the standard. ITT analysis simply ignores treatment crossover and therefore can underestimate the treatment effect of interest. In order to estimate this impact, we have developed a simulation program to calculate power and probability of study success incorporating treatment crossover, enrollment, dropout and interim analysis. Simulation results show that high likelihood of treatment crossover results in a large reduction in study power when conducting ITT analysis. Care needs to be taken when designing clinical trials with treatment crossover to ensure high probability of success for key secondary endpoints.