BASS 2024 presentation

Power Estimation for Overall Survival in Randomized Controlled Trials With Crossover at Disease Progression: A Simulation Method

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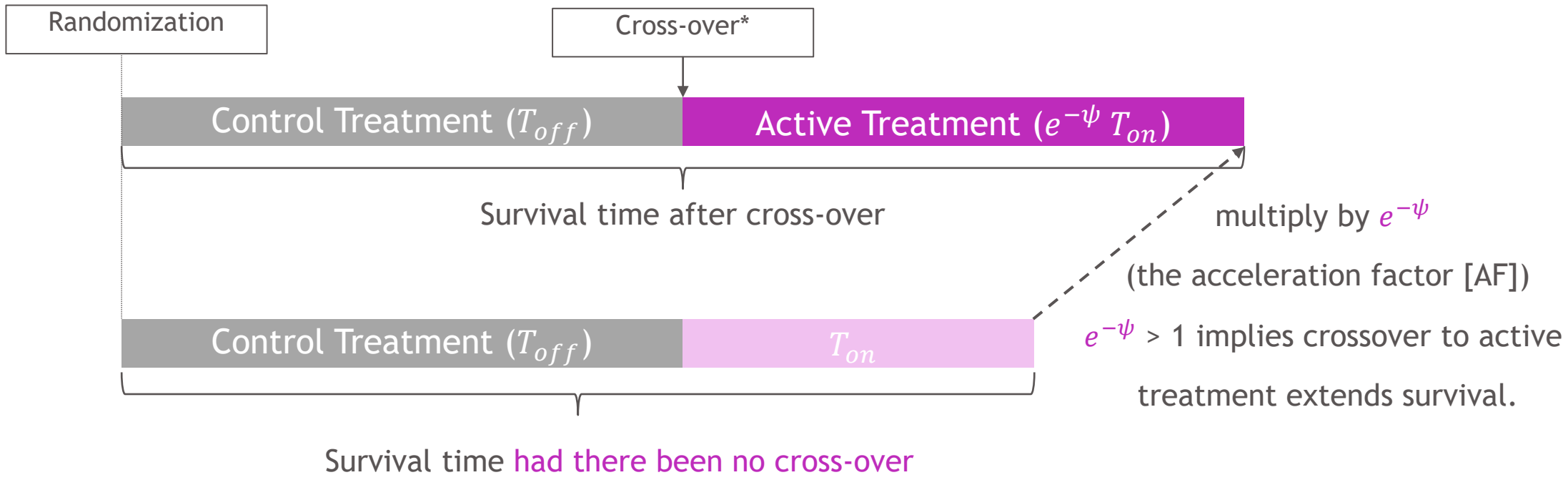
Background

- Oncology clinical trials frequently allow patients in the control arm to receive the experimental therapy after disease progression (PD) on the control arm, which is referred as “crossover”.
- crossover may make a trial more appealing to patients and may improve enrollment and retention rate. However, crossover can lead to a change in overall survival (OS) afterwards therefore introduce uncertainty of the true treatment effect and power.
- There are available statistical methods to handle treatment switching including:
  - 2-Stage Accelerated Failure Time
  - Rank Preserving Structural Failure Time Model
  - Inverse Probability of Censoring Weighting
- It is important to assess crossover impact on OS power at the trial design stage. We propose a simulation-based method to assess the impact of crossover on the power for overall survival in randomized clinical trials.

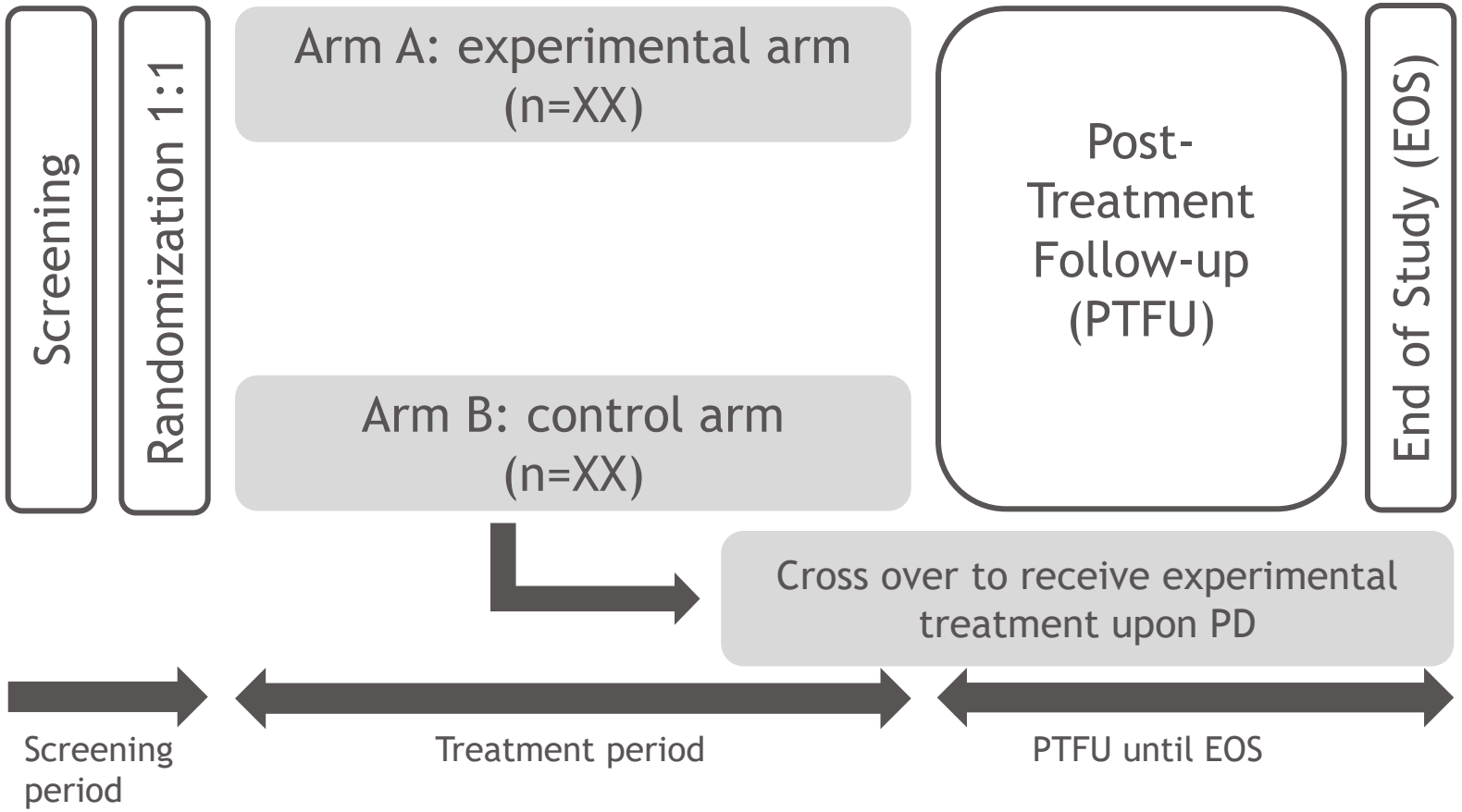
Crossover can extend survival time in control arm and dilute OS treatment effect



Study Design Example

Study Population:

- Criteria #1
- Criteria #2
- …



- Primary endpoint: PFS; key secondary endpoint: OS

Methods

- It is assumed that crossing over to the active treatment will extend survival time in the control arm and introduce uncertainty to the treatment effect.
- The previous slide #3 has displayed the two scenarios of survival time with and without crossover.
- Let T_{off} be the time from the randomization to crossover (confirmation of PD).
- Let T_{on} be the time from crossover to death had there been no crossover.
- If crossover occurs, the additional survival time after crossover is now updated to be T_{on} multiplied by $e^{-\psi}$ (the acceleration factor [AF]).
- The impact of AF on the survival time can be summarized as follows:
    - When AF = 1, it means that survival time is the same had there been no crossover.
    - When AF > 1, it implies crossover to active treatment extends survival.

Simulation Setup

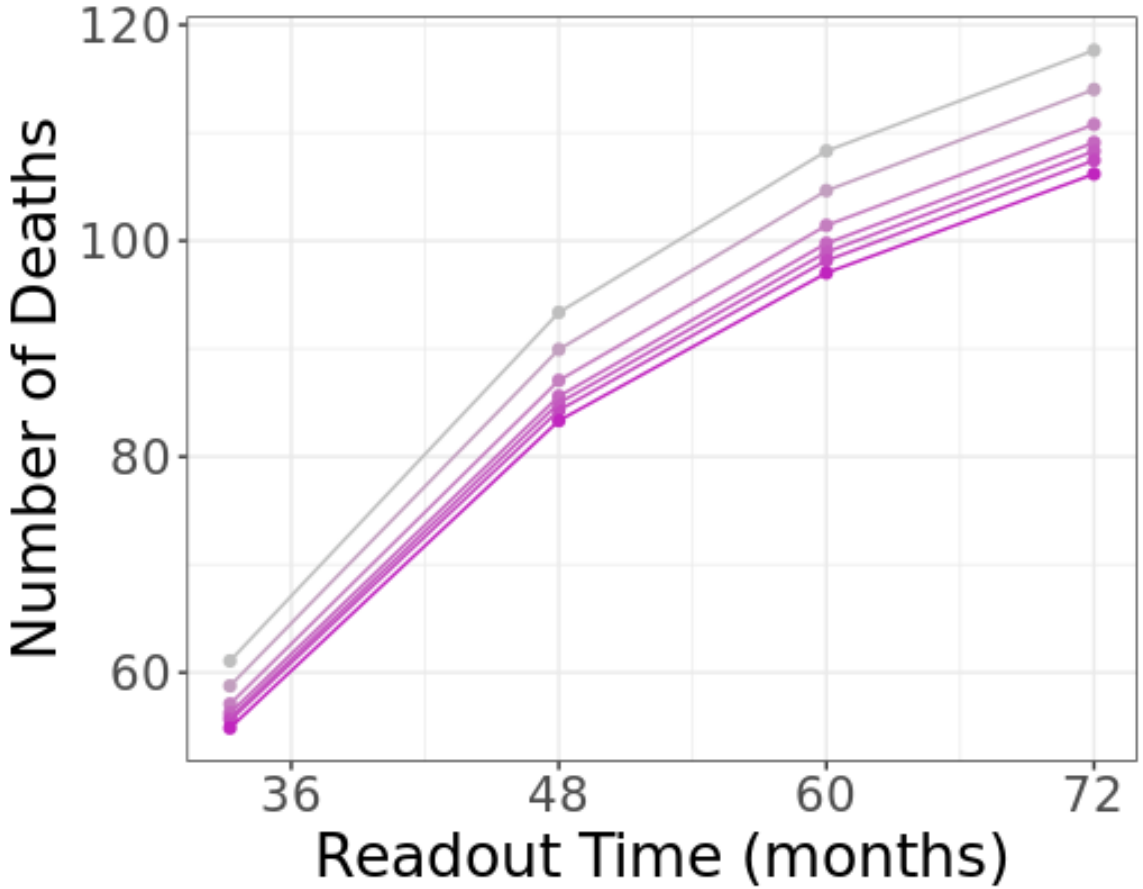
Parameters

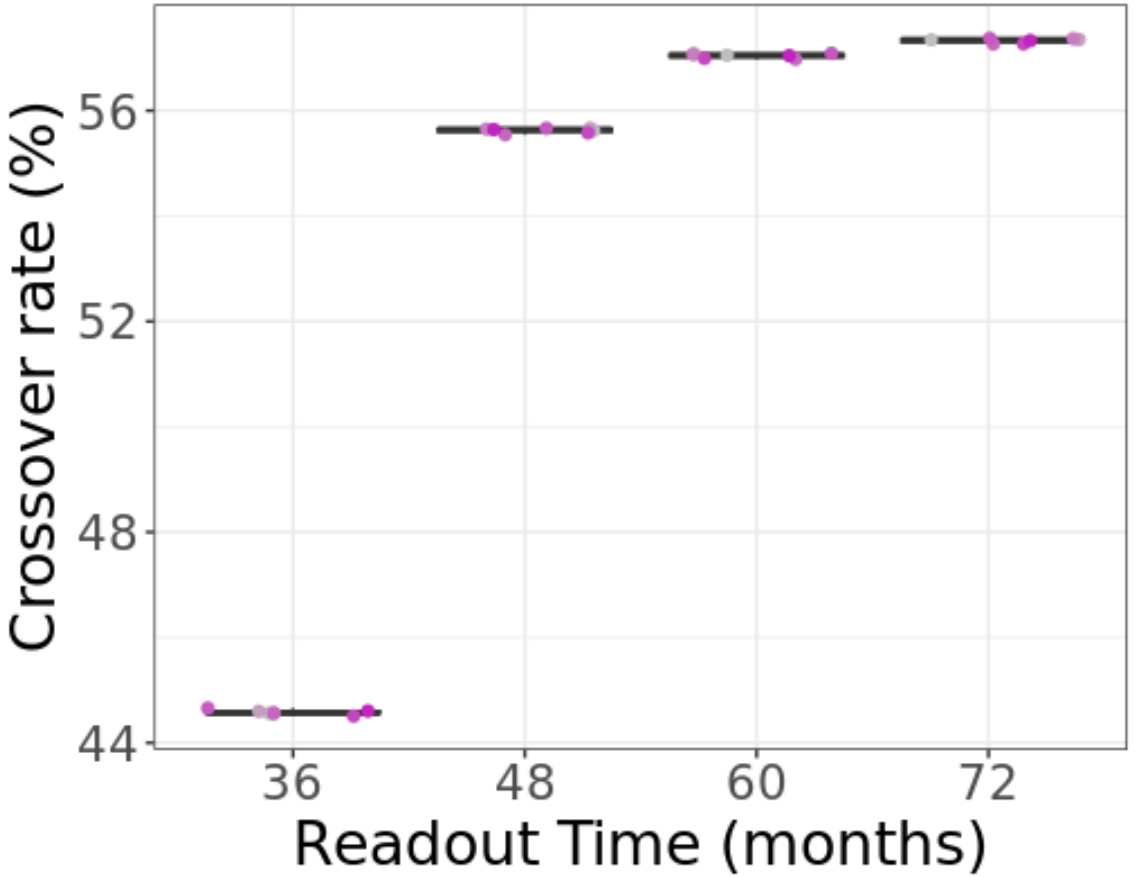
- In the control arm, T_1 (median = 9m) is the time to PD, T_2 (median = 18m) is the time to death (median OS), while mOS in the experimental arm is 36 m.
  - If PD occurs before death, there will be crossover, and set $U = T_1 + (T_2 - T_1) * \mathrm{AF}$
  - If death occurs before PD, there will be no crossover, and set $U = T_2$
- Let T_3 be dropout time, then observed OS time $T = \min(T_3, U)$, and OS event $= 1\ if\ T_3 > U$
- T_1, T_2, T_3 follow exponential distributions with corresponding hazard rates.

Scenarios

- N = 200; Dropout rates = 10% in Arm A and 20% in Arm B yearly
- Readout time for OS = 36m, 48m, 60m, 72 m
- Acceleration factors = 1, 1.25, 1.5, 1.667, 1.75, 1.85, 2

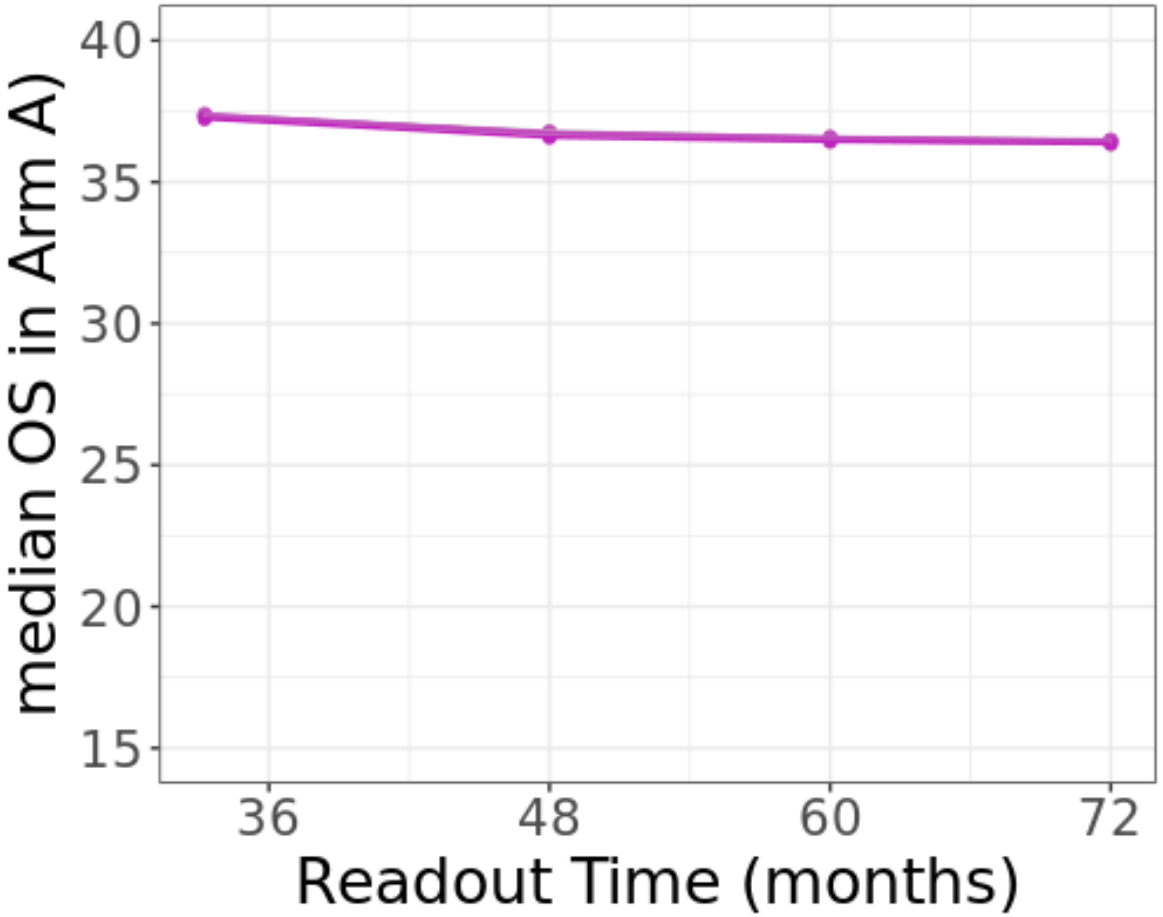
Overview of Readout Time, Number of Events and Crossover Rate

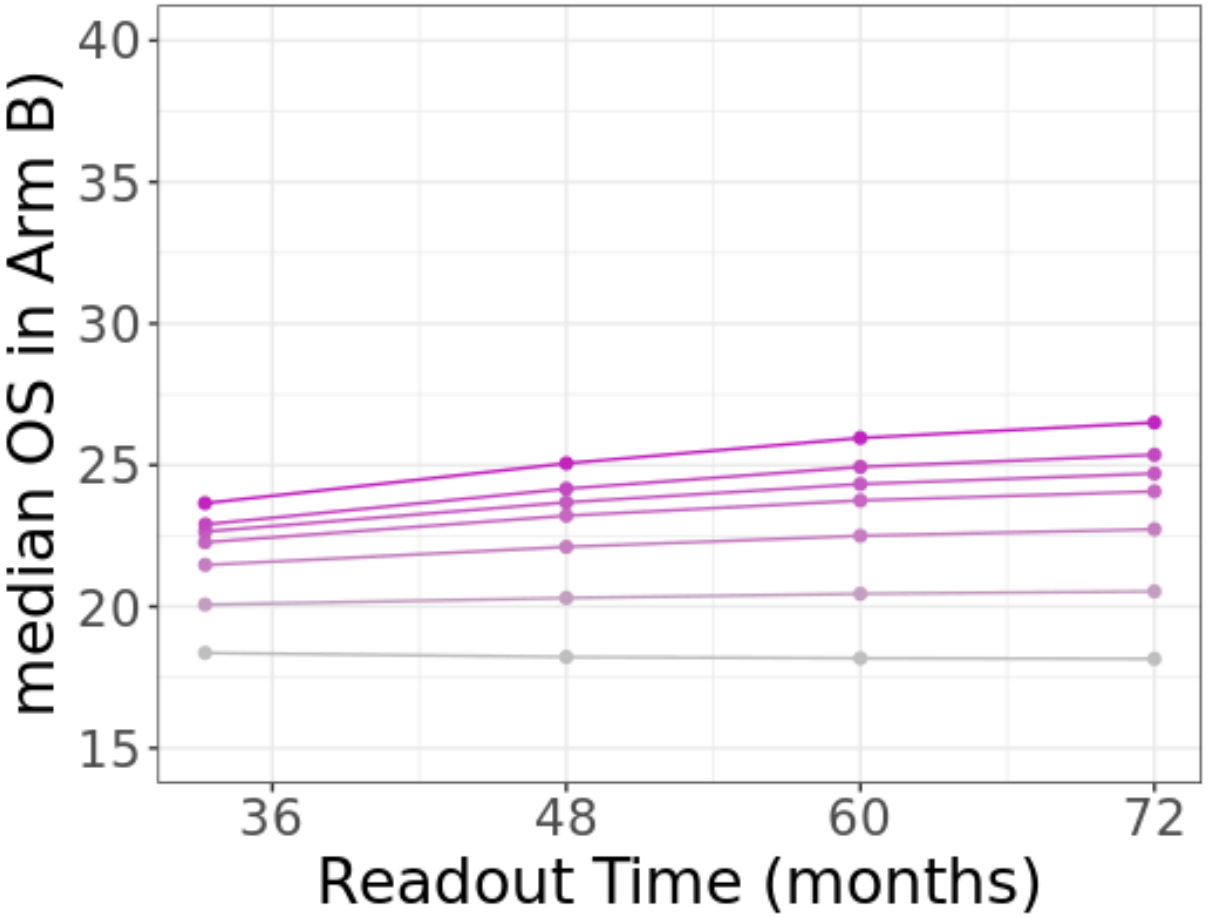




- Higher AF is associated with fewer OS events in Arm B (Control). The later the readout time is, the higher the crossover rate is. The AF doesn't impact the crossover rate because crossover occurs before AF takes effect.

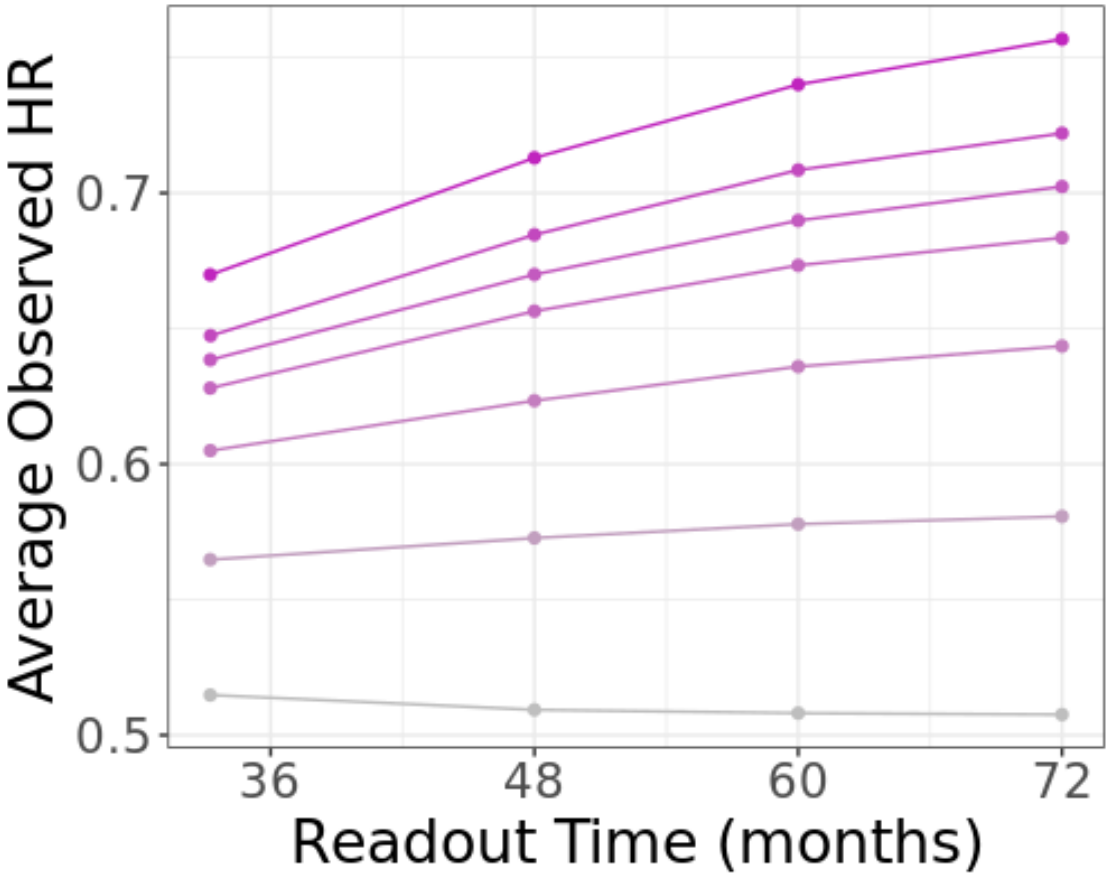
Impact of Crossover on Effect Sizes of Arm A (Experimental) & B (Control)

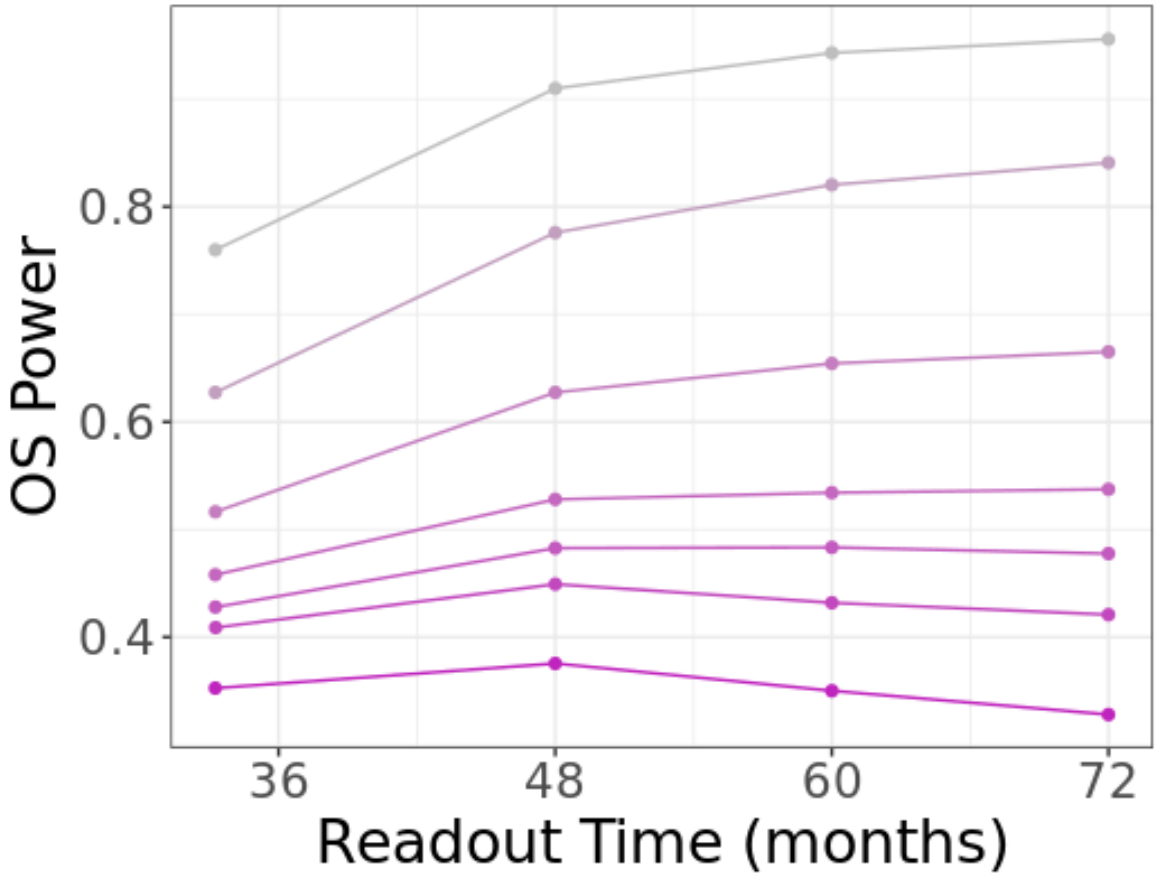




- The median OS in Arm A (Experimental) stays constant while the median OS in Arm B (Control) increases when AF increases.

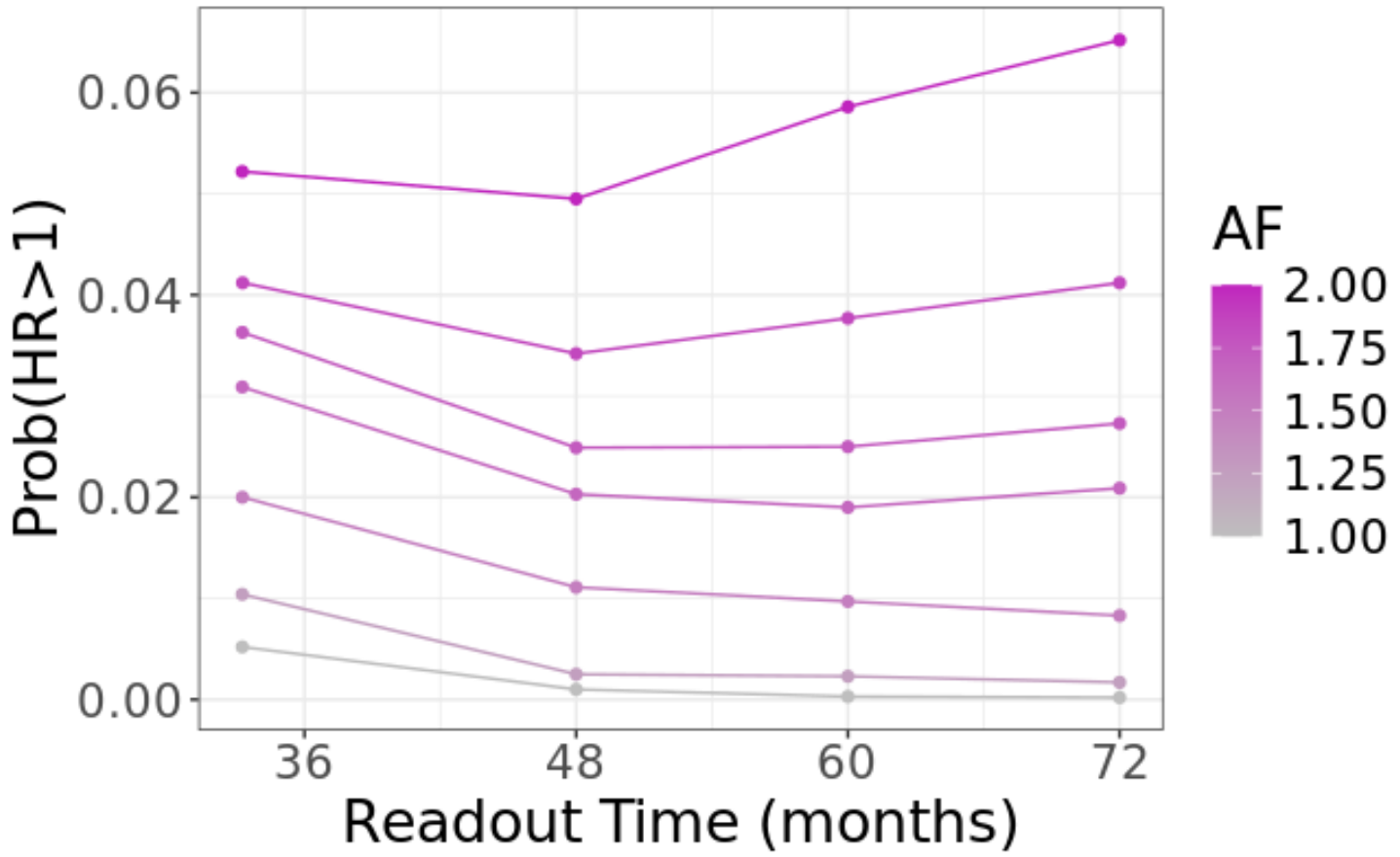
Impact of Crossover on Relative Treatment Effect (HR) and Power





- The average HR is more likely to approach 1 at a later readout time and a higher AF value if AF > 1.

Risk of Observing HR Greater Than 1



- Once AF becomes greater than 1.67, the upward trend of power over readout time starts to diminish; the probability of observing a detrimental effect (HR>1) has a sudden rise at a later readout time.

Discussion

For studies with crossover, with longer follow-up time:

- The number of OS events increases.
- As the crossover rate increases, the OS improves in the control arm and the average HR gets closer to 1.
- The trends and magnitude of the crossover impact depend on the acceleration factor (magnitude of the treatment effect).
- Higher AF attenuates the OS treatment effect and has a high impact on the OS power.

References

- Anderson K, Zhang Y (2023). simtrial: Clinical Trial Simulation. https://merck.github.io/simtrial/, https://github.com/Merck/simtrial.
- Isbary, Georg, et al. "Effect of crossover in oncology clinical trials on evidence levels in early benefit assessment in Germany." Value in Health 21.6 (2018): 698-706.
- Jönsson, Linus, et al. "Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation." Value in Health 17.6 (2014): 707-713.