Robust Designs for Response-Adaptive Randomization

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What is a Response Adaptive Randomization (RAR) Design?

- RAR designs utilize accumulating information on outcomes as the trial progresses in order to alter the treatment assignment probabilities and assign more patients to the better-performing treatment arm.
- Previous outcomes are used to tilt the randomization probabilities in favor of the treatment currently observed to have superior results.

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- The trial needs to be short to be able to obtain the outcome of the trial for future randomization

What is the issue with RAR?

Peto (1985):
" . . . patients entering a trial are often not uniform in prognosis. For example, both in the European Coronary Bypass Trial and in the Medical Research Council's 8th Acute Myeloid Leukaemia Trial there was a statistically significant trend towards better prognosis as time went by. If, therefore, there had also been a trend in allocation proportions towards the apparently better treatment, an appreciable bias might have been engendered."

Time- Trends in Clinical Trials!

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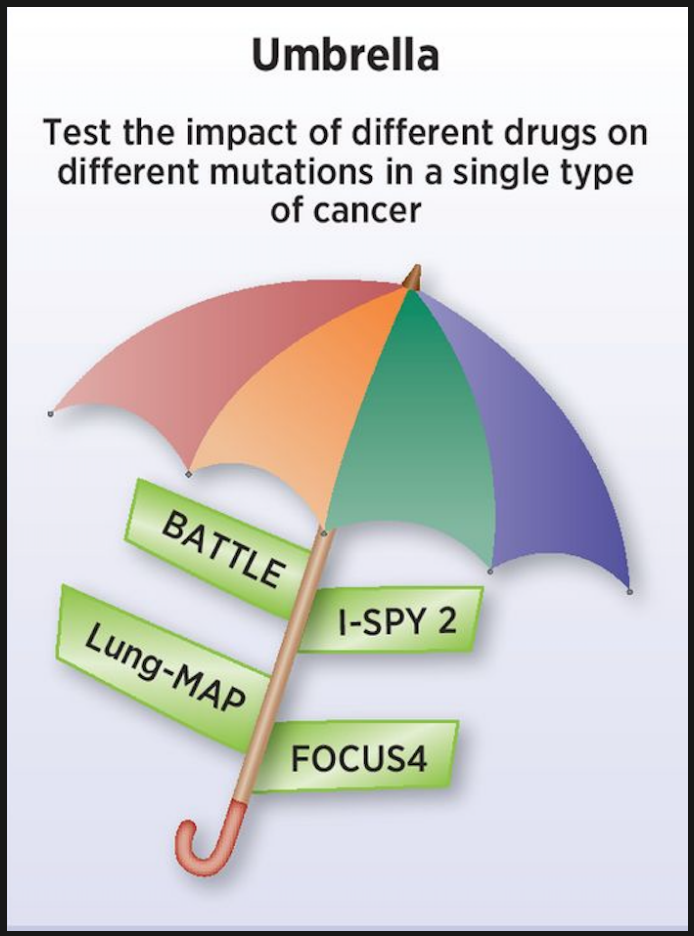
- Inclusion criteria can change, either formally (in which case we can stratify analysis on before vs. after the change) or informally due to “recruiting zeal” or other issues (in which case we can’t).

Time-trends in RAR

- Thall et al. (2015) investigated type-I error under a linear time-trend induced in the traditional response-adaptive randomization design and showed that the type-I error is significantly above the nominal level.

BATTLE-1 Trial

Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE - 1)



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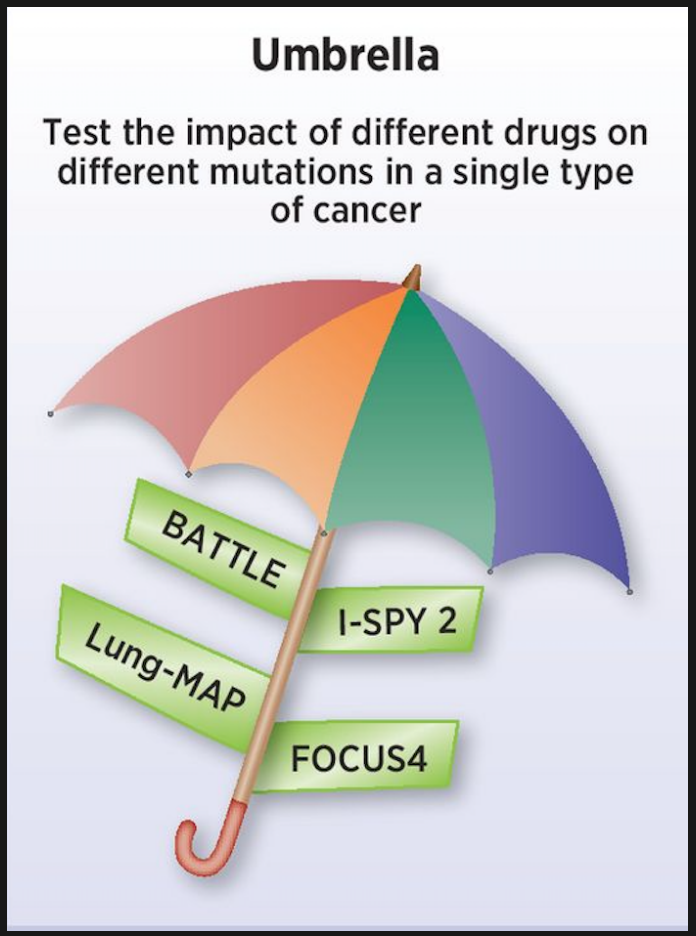

- 4 treatments, 5 biomarker;
- primary end point, 8-week disease control rate;
- treat more patients in promising groups based on biomarker profile;
- suspend ineffective groups early

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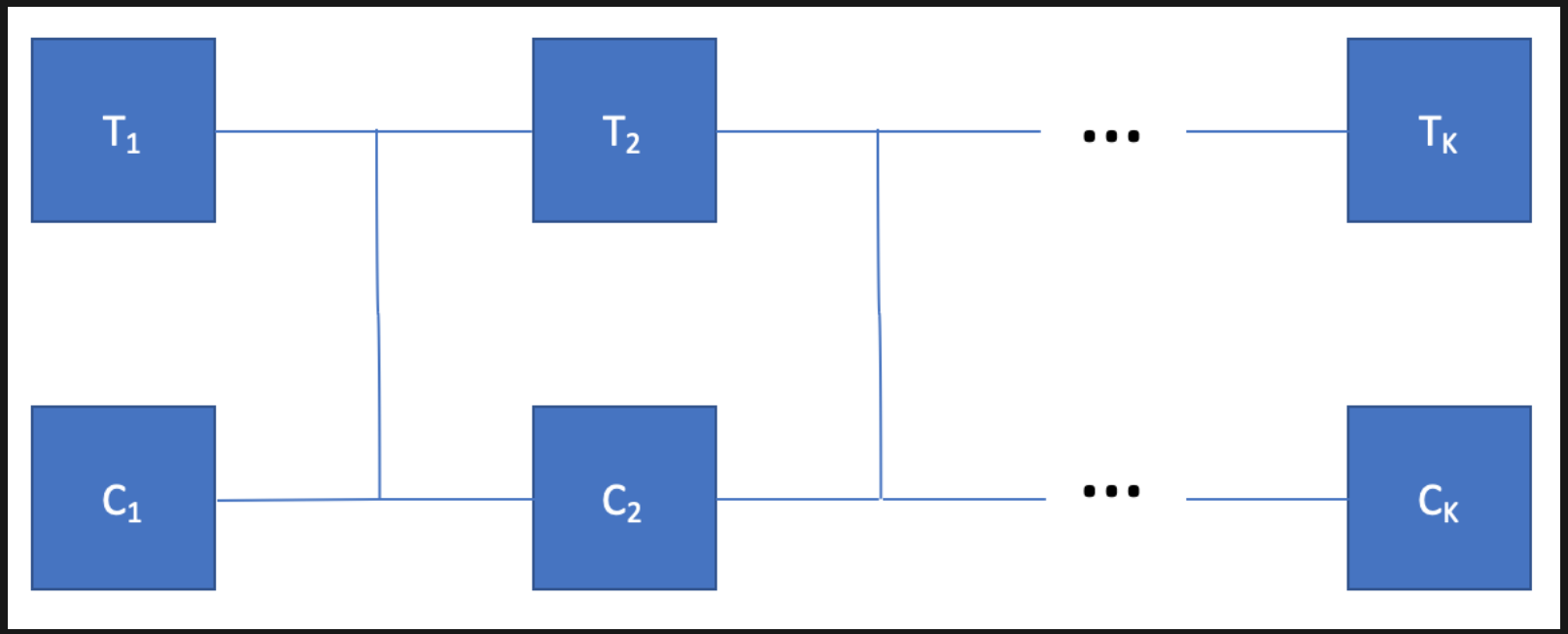
Time trends are nearly universally ignored among RAR proponents.

Blocked Design for RAR

- Group-sequential procedure.
- Update allocation ratio for groups rather than patients.



Simulation Setup

- N = 200 subjects
- K = 1, 2, 4, 5, 10, 20, 100, 200.
- 10,000 independent simulations were performed
- p_A is set to 0.25, p_B is set to 0.25 (null case), 0.45.
- Run-in period of 20 patients (fixed randomization).
- Allocation probability bounded between 0.2 and 0.8.

Simulation Setup

To examine the effects of time-trends, we increased both p_A and p_B linearly from their initial values to a final value of 0.25 larger.

- $p_A(n) = 0.25 + 0.25(n/N)$, where n is the patient that have been accrued and N is the total sample size.
- for null case, $p_B(n) = 0.25 + 0.25(n/N)$.
- for alternative case, $p_B(n) = 0.45 + 0.25(n/N)$.

Simulation Setup: Bayesian Design

- The probability of randomizing subjects to treatment A in stratum j, $\pi_{j,A}$ is defined as

$$\pi_{j,A} = \frac{(p_{A>B,j-1}(data))^{n/2N}}{(p_{A>B,j-1}(data))^{n/2N} + (p_{B>A,j-1}(data))^{n/2N}},$$

  where $p_{A>B,j-1}(data)$ is the posterior probability that treatment A has a higher success rate than treatment B, $p_{A>B,j-1}(data)) = 1 - p_{B>A,j-1}(data))$ after the $j-1^{st}$ block, n is the number of accrued patients and N is the maximum sample size. .

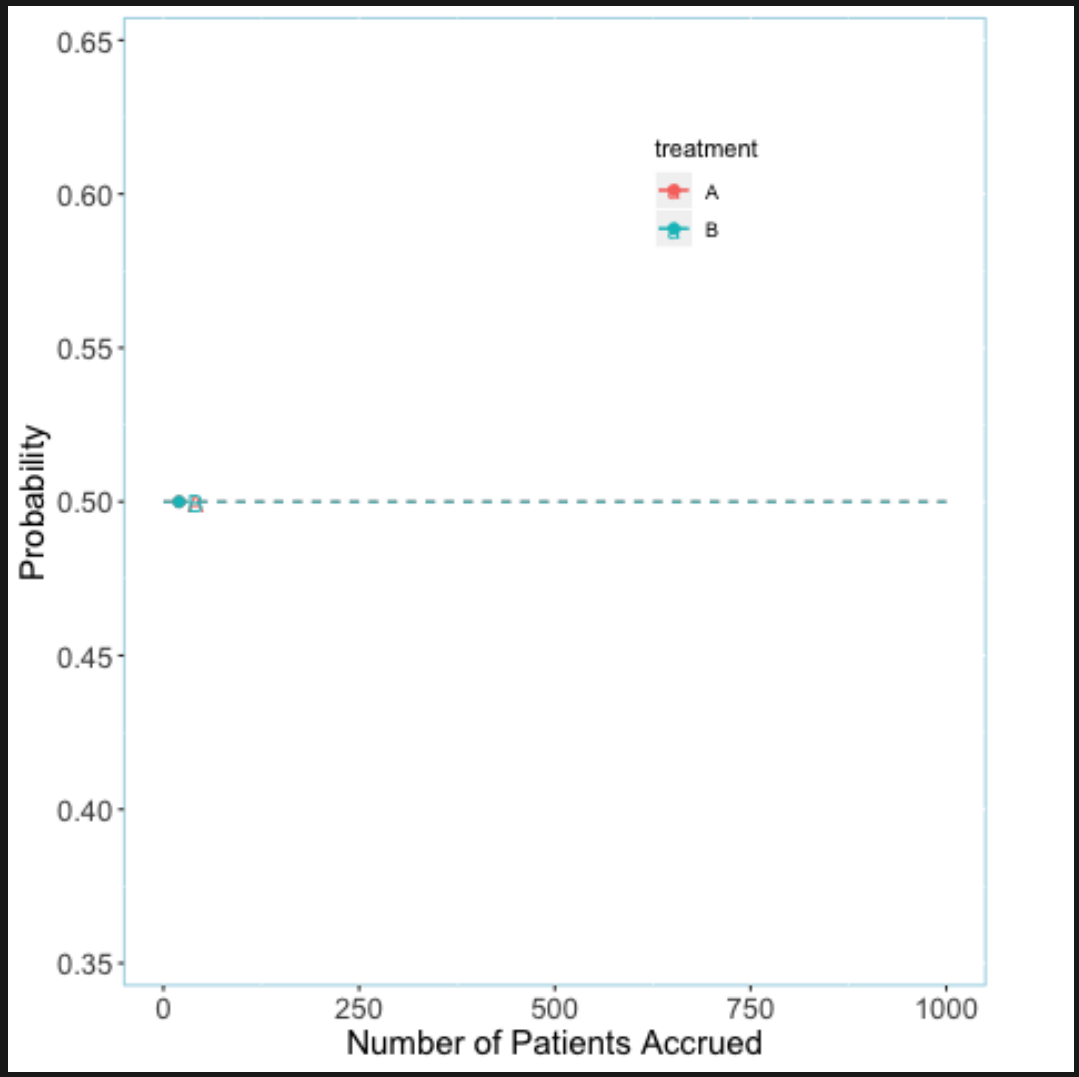
- Beta-binomial conjugate prior is used with $\mathcal{B}eta(0.5, 0.5)$ priors.

Simulation Setup: Bayesian Design

- If treatment B is selected to be better than treatment A, then if $P_{B>A}(data) > .99$, the trial is stopped early for success and if $P_{B>A}(data) < .01$, the trial is stopped early for failure.
- For non-stratified design, where K = 1, 200, if the final posterior probability $P_{B>A}(data) > .95$, then treatment B is declared superior to treatment A.
- For stratified design by block, Bayesian logistic regression was implemented to estimate the posterior probability of treatment difference and block effects.

Simulation

A single simulation for RAR with $p_A = 0.07$, $p_B = 0.05$ with N of 1000 and 50 number of blocks.



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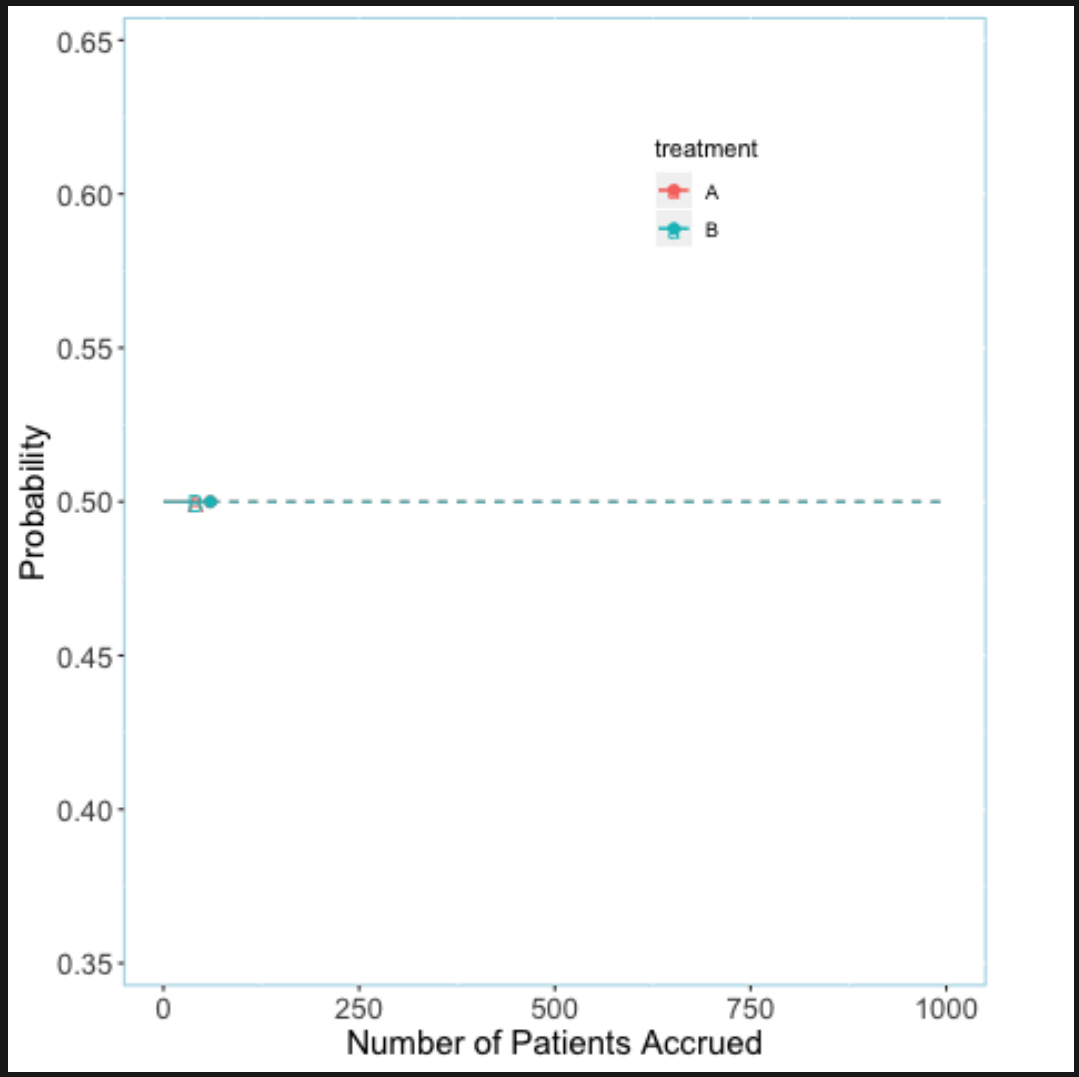

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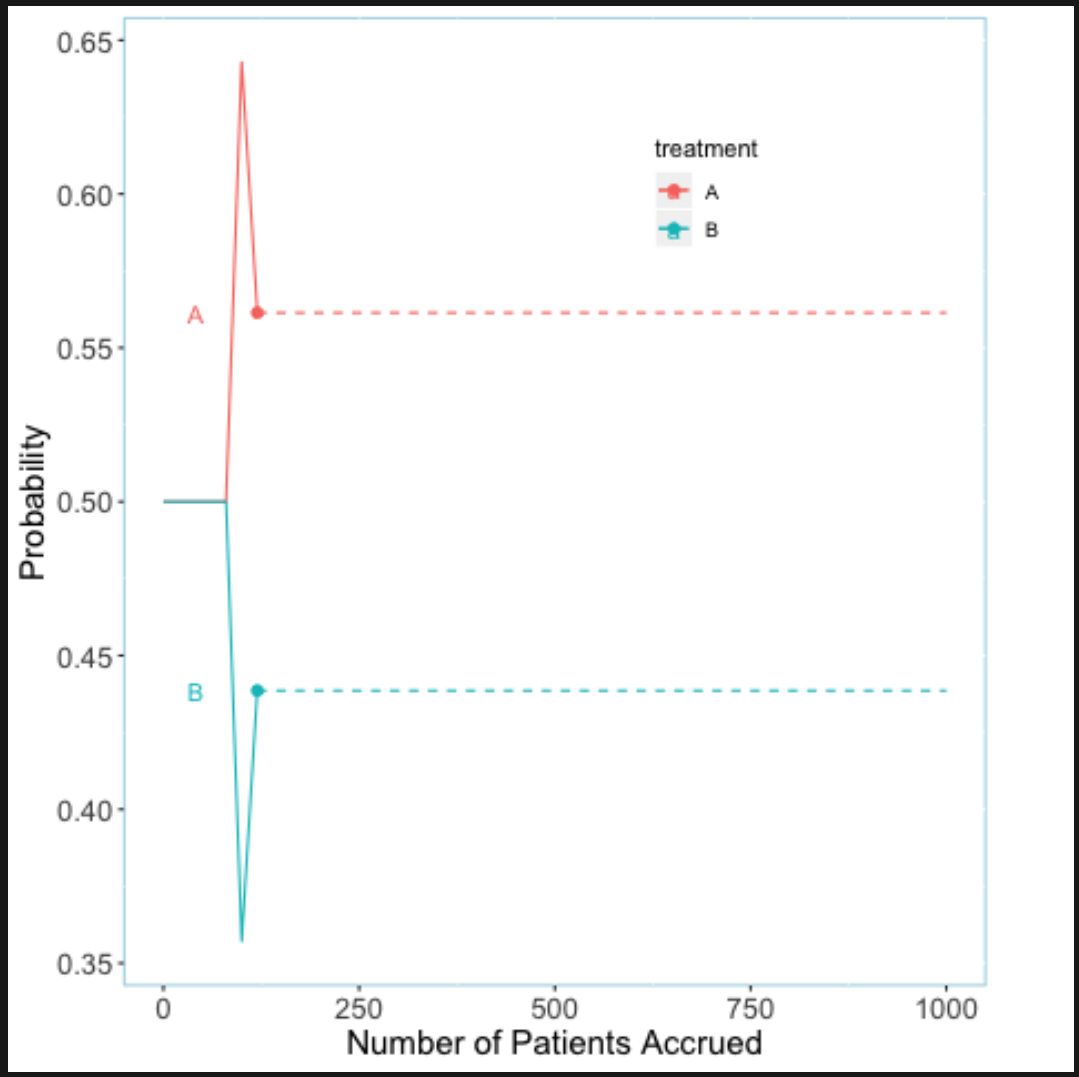

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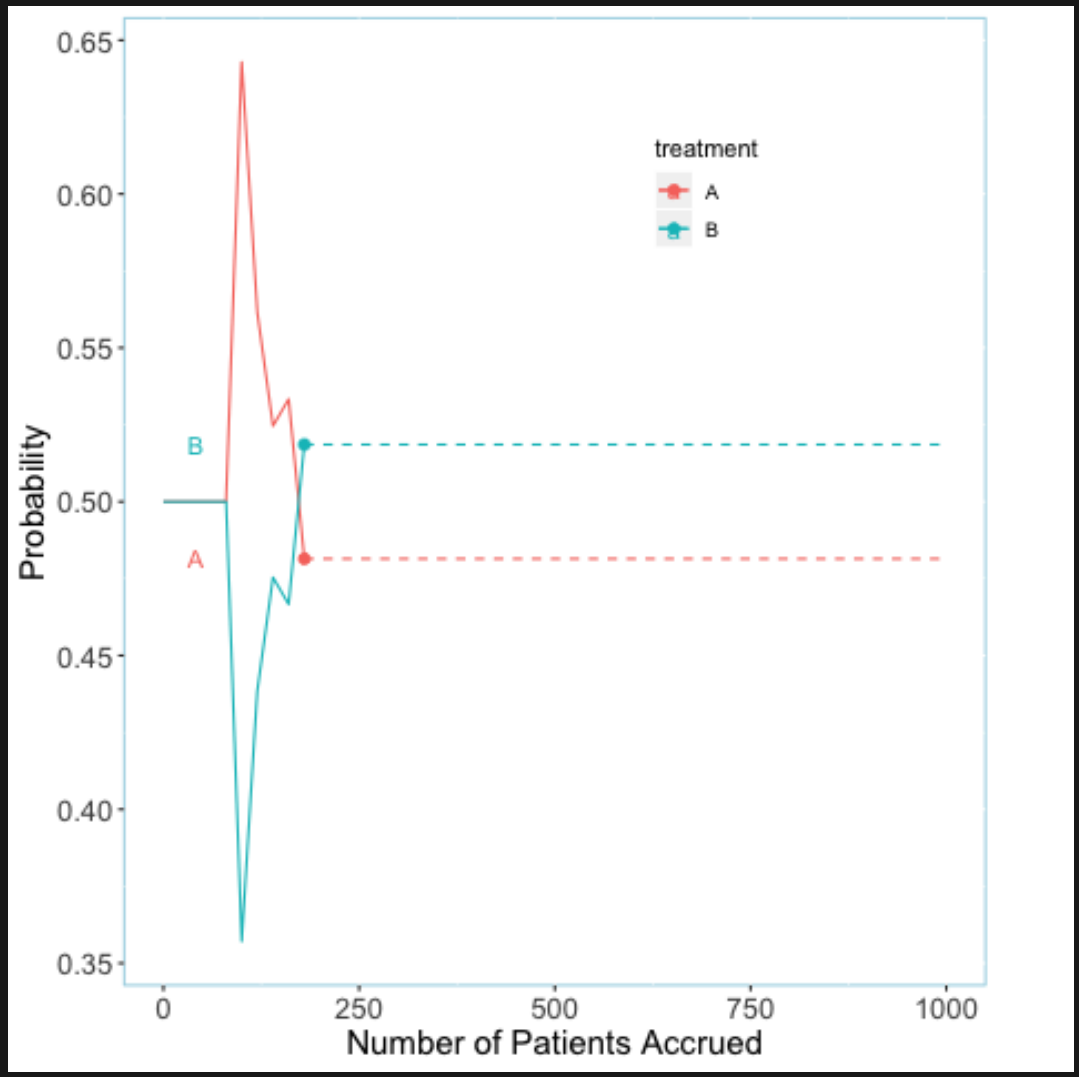

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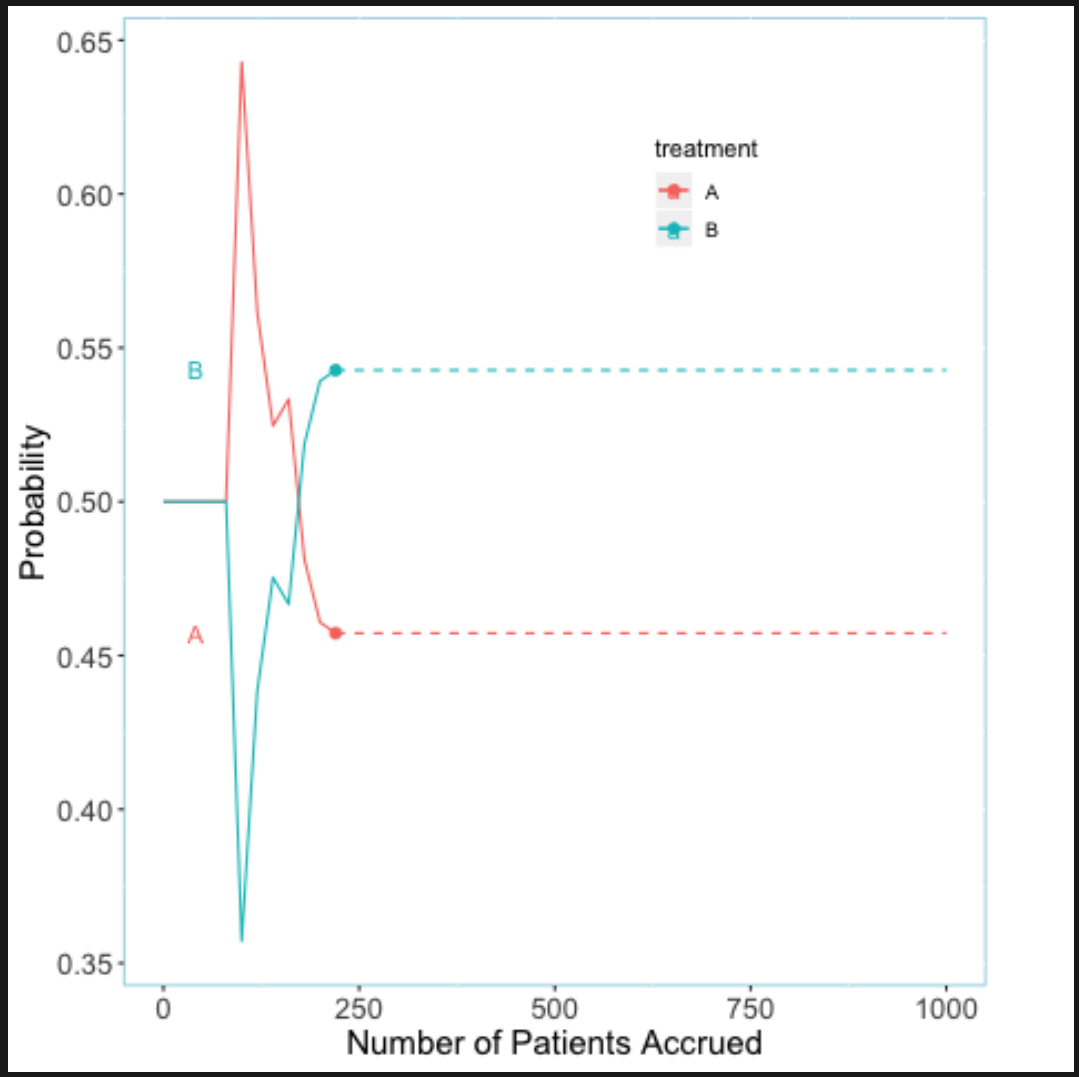

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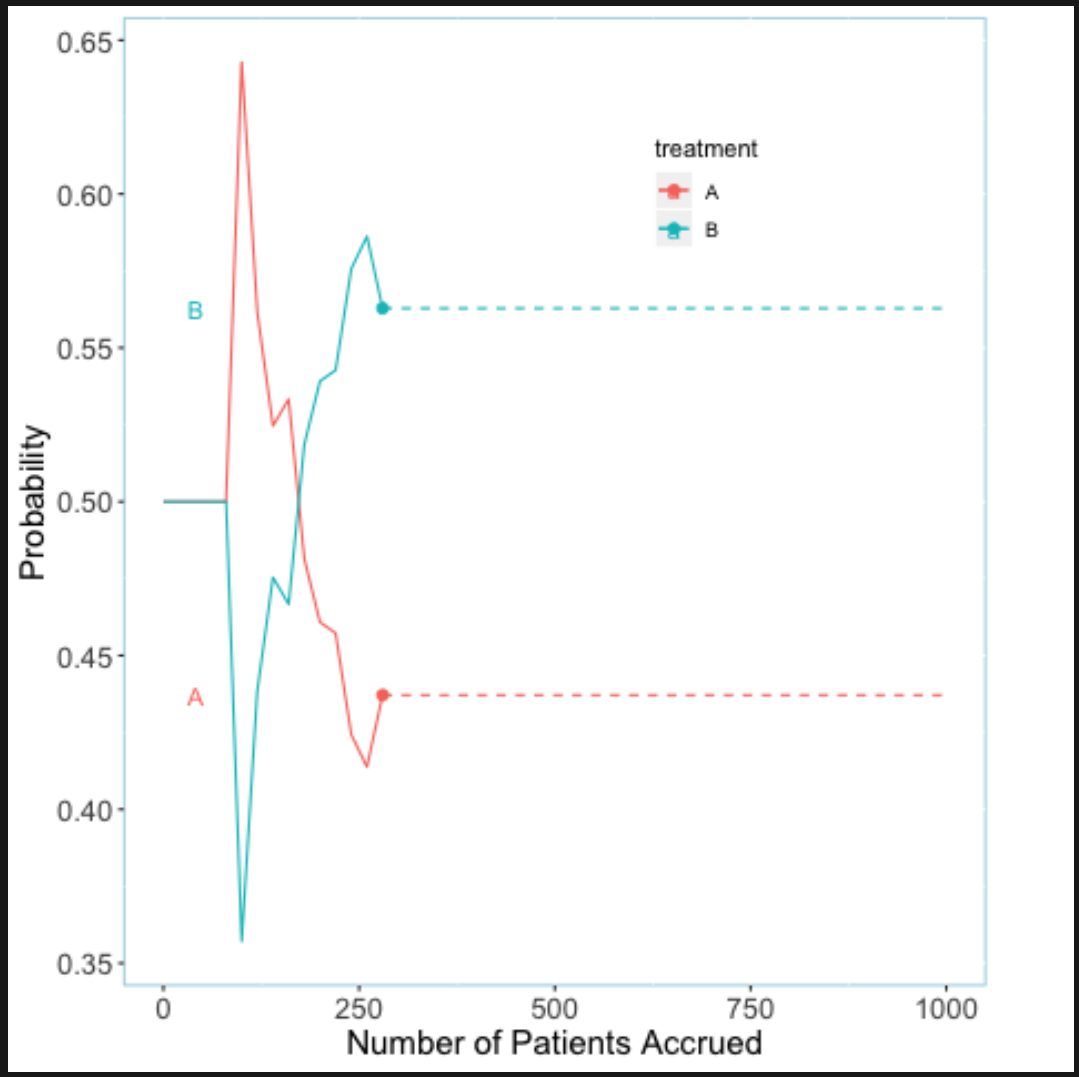

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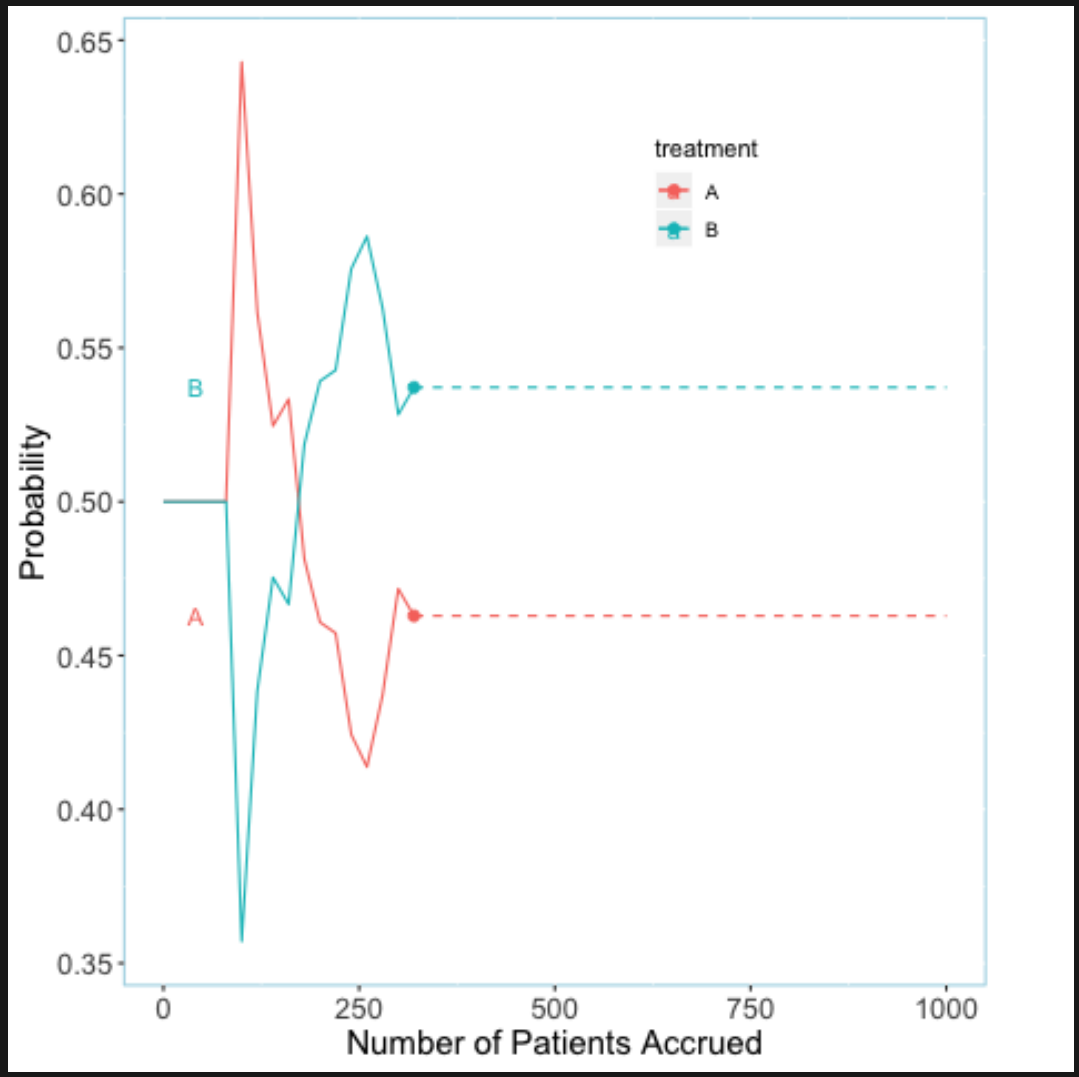

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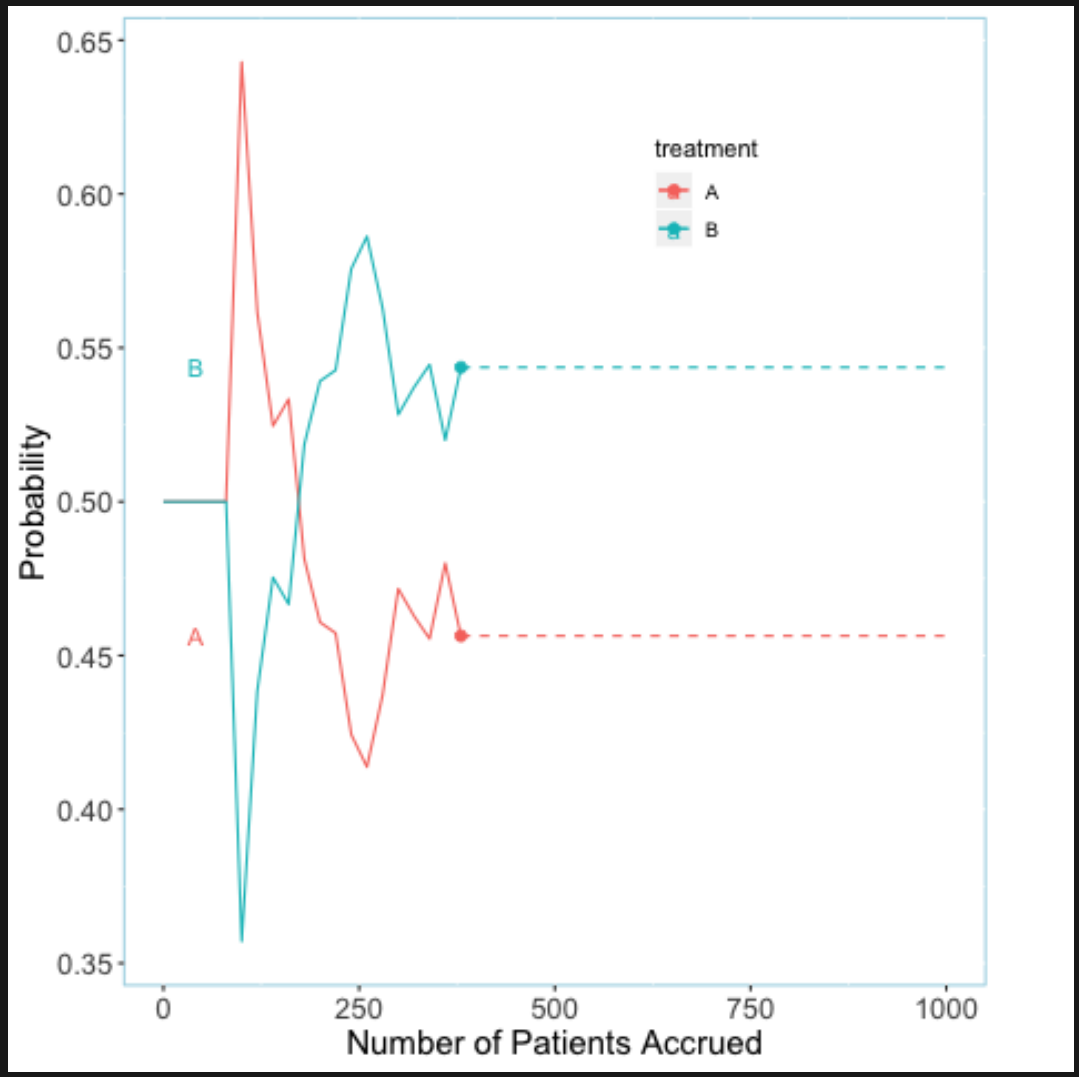

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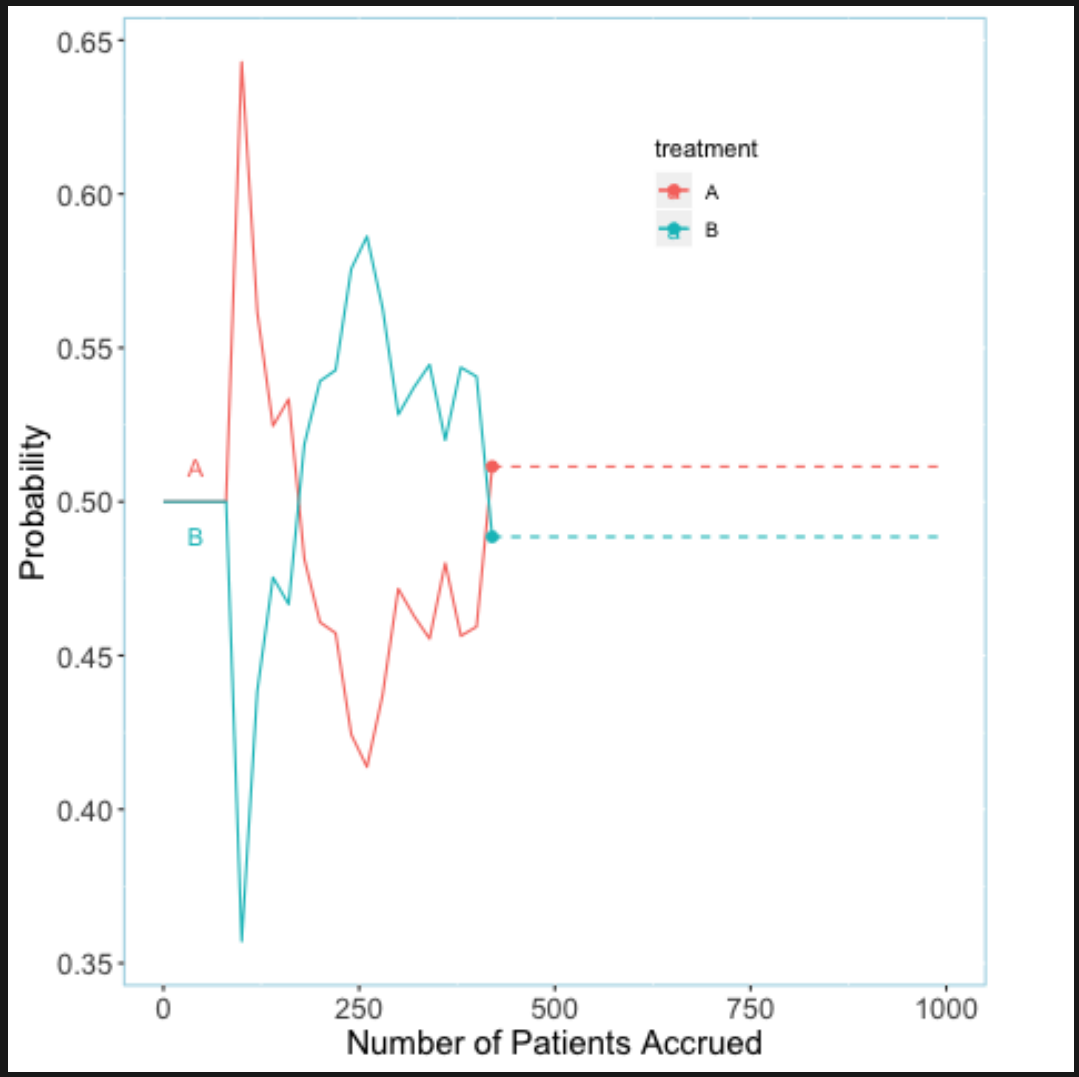

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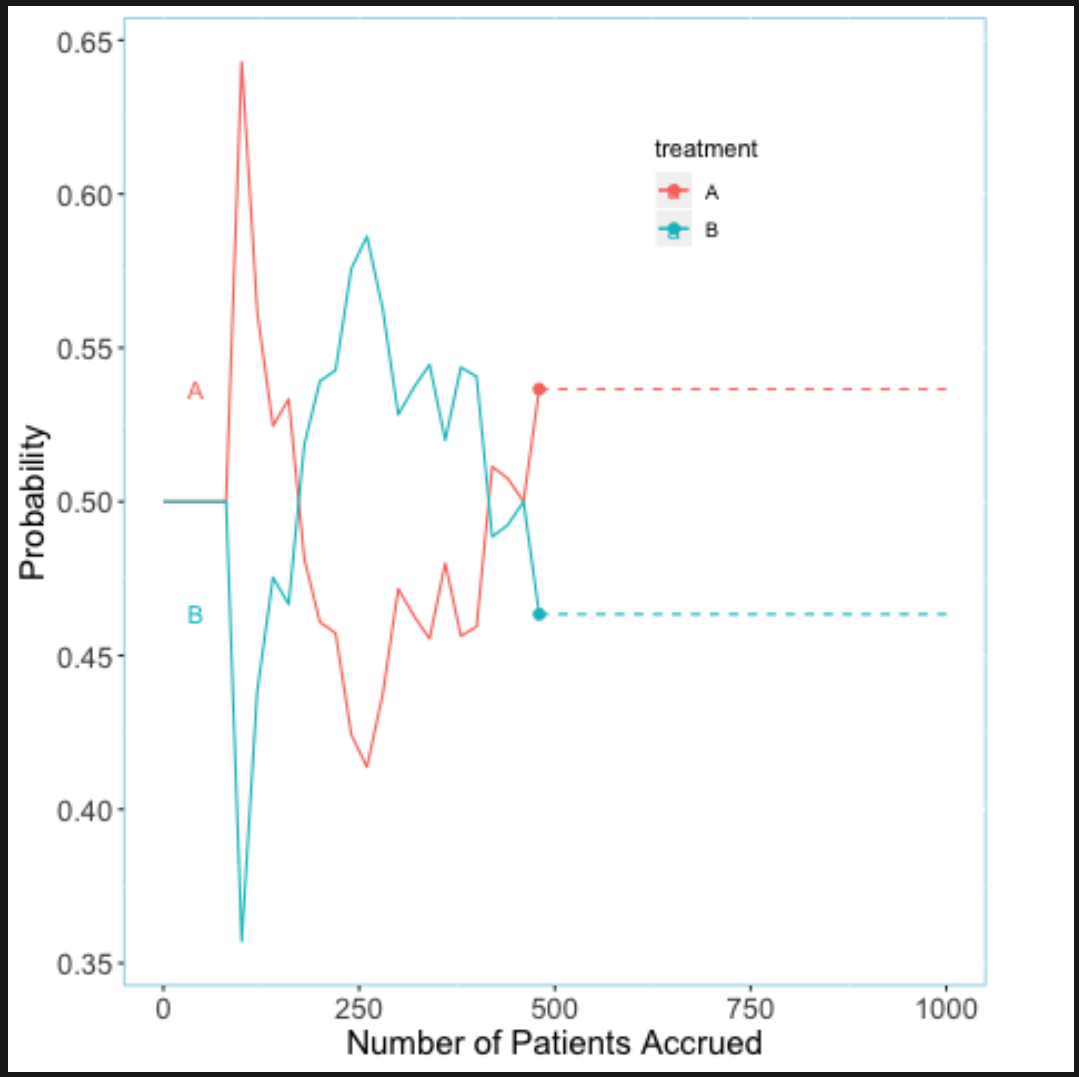

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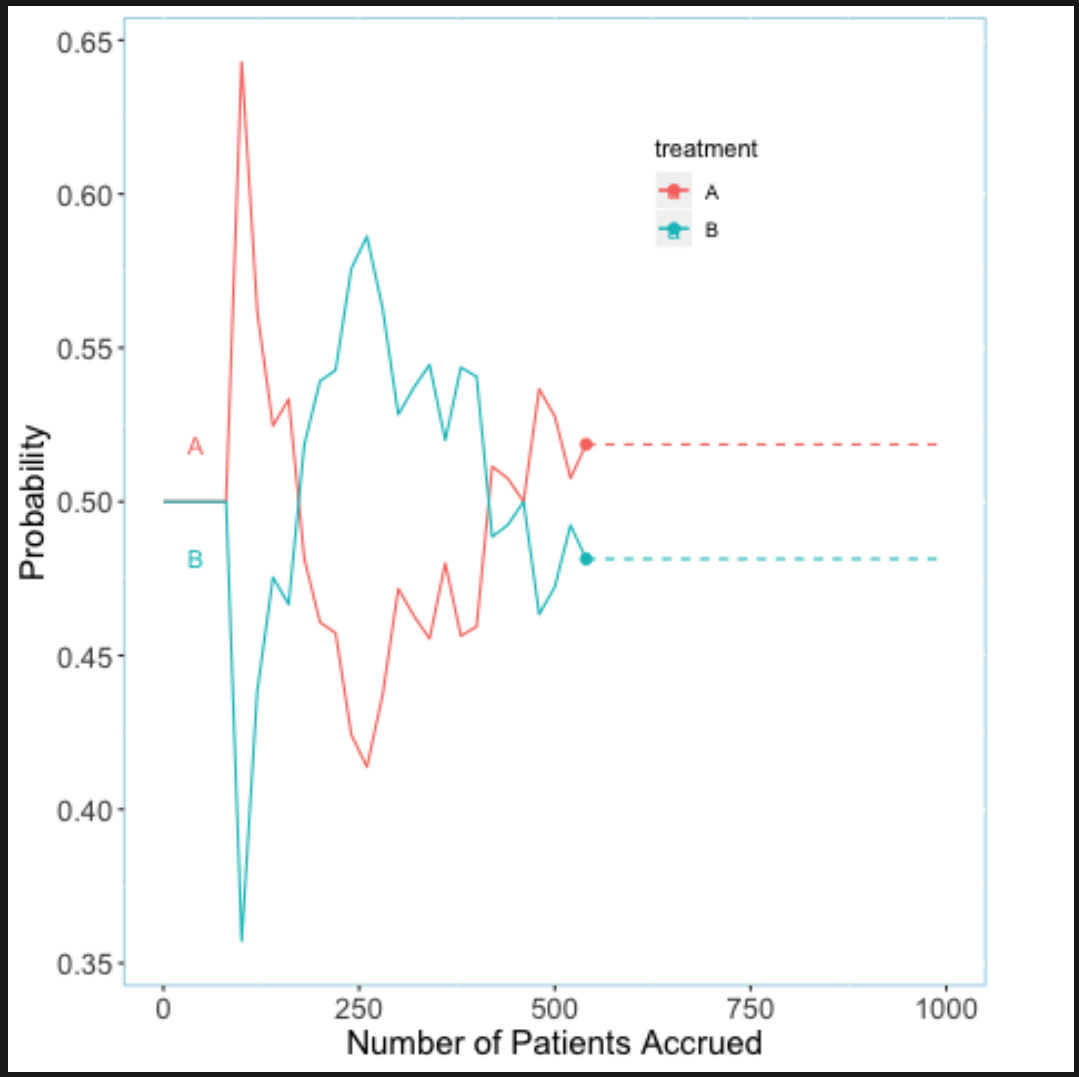

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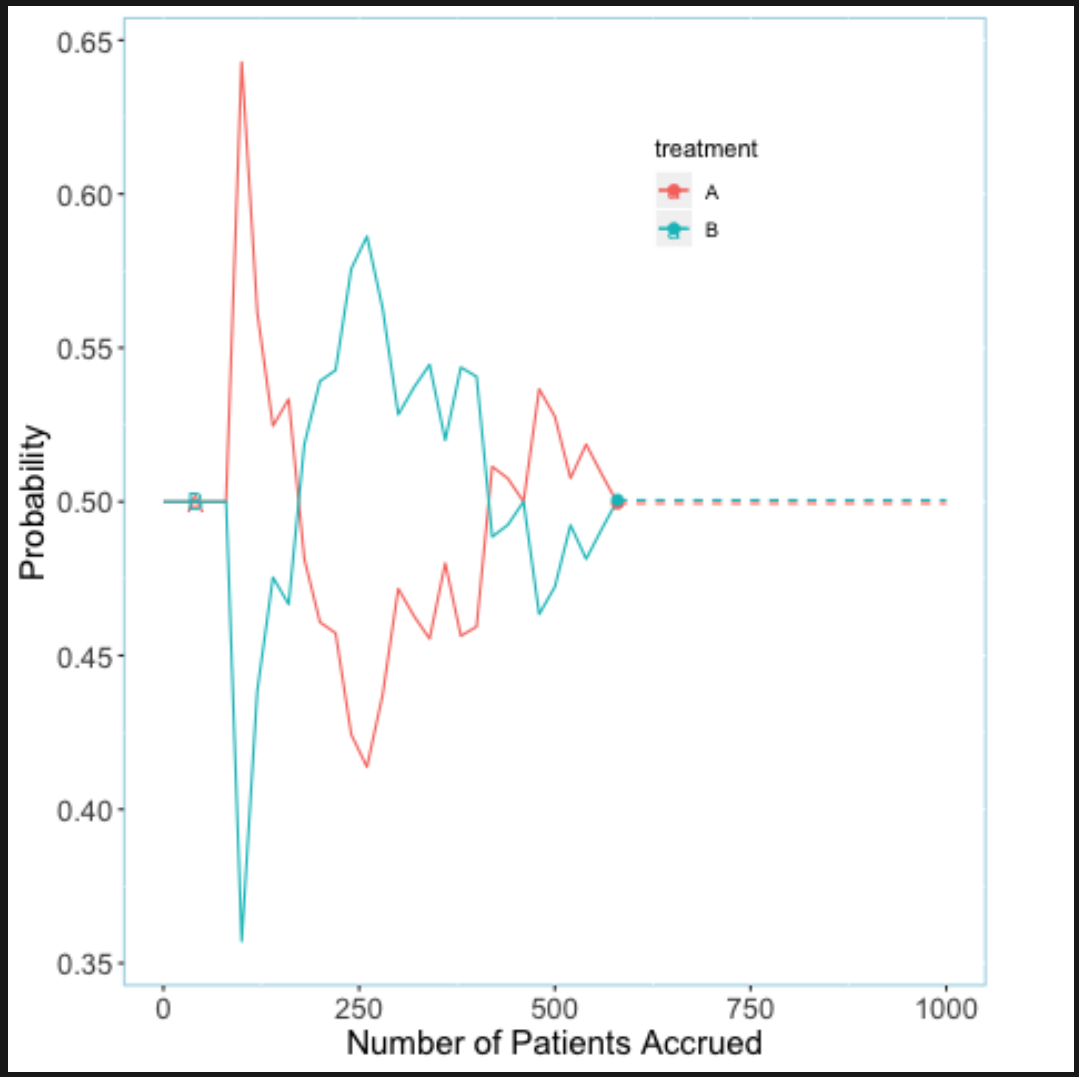

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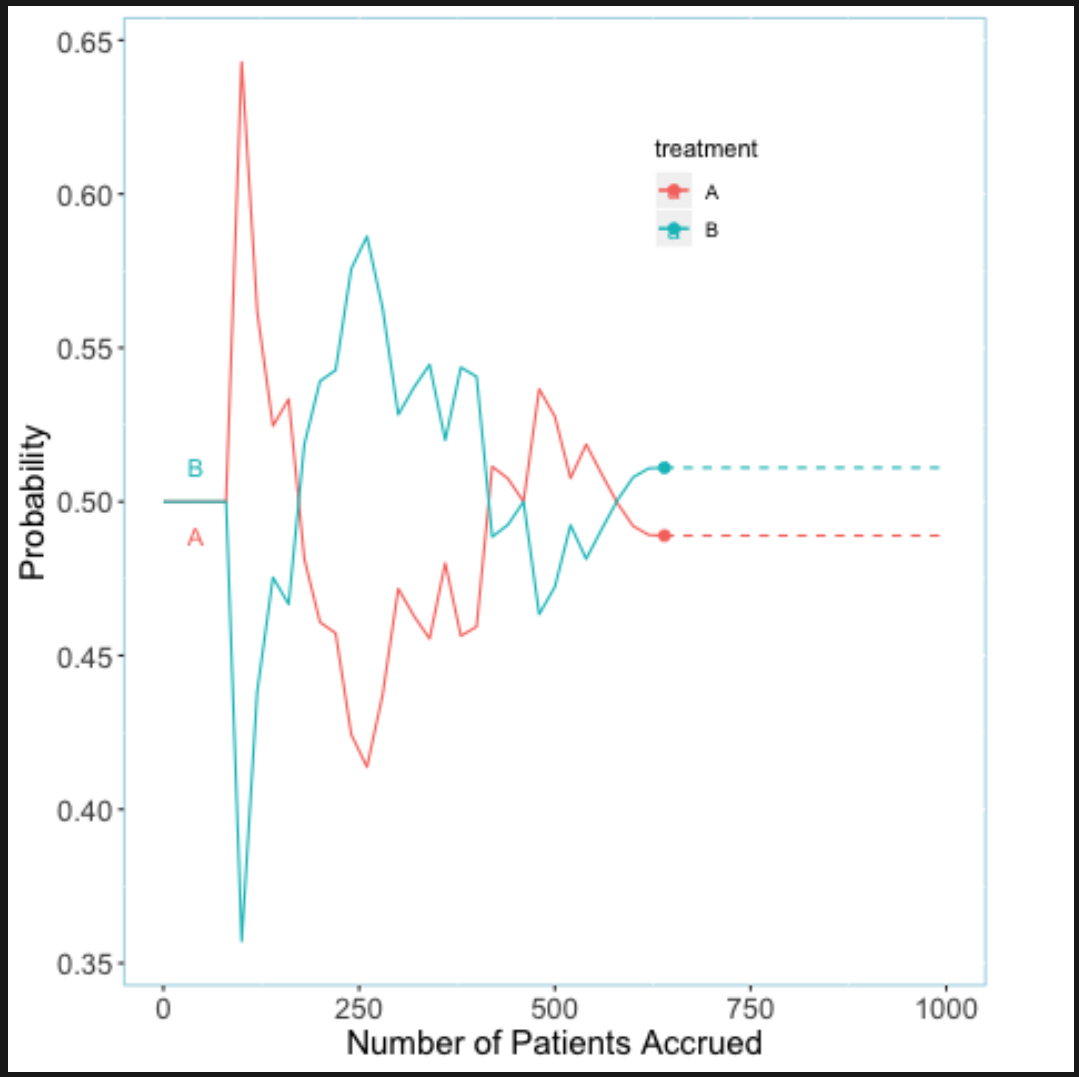

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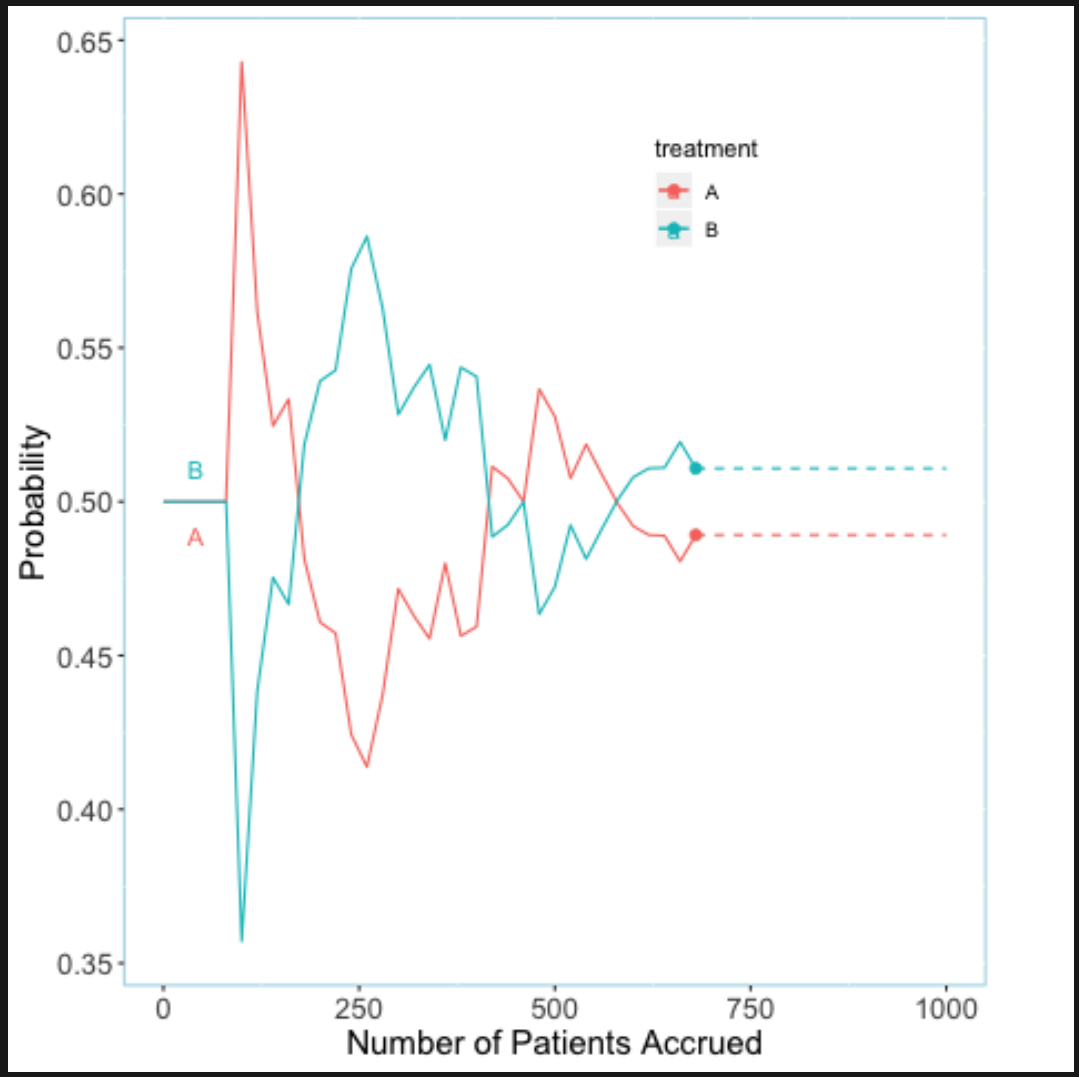

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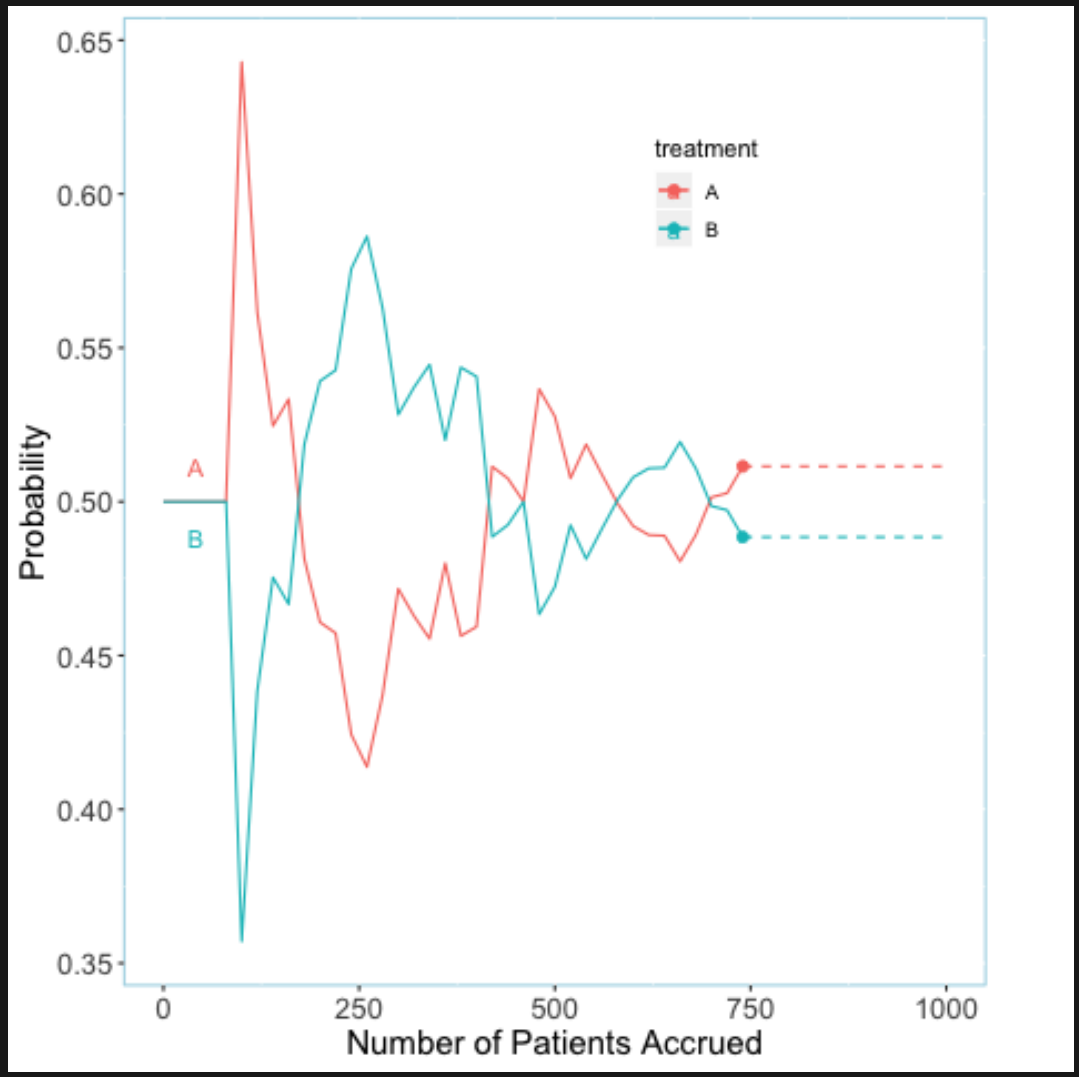

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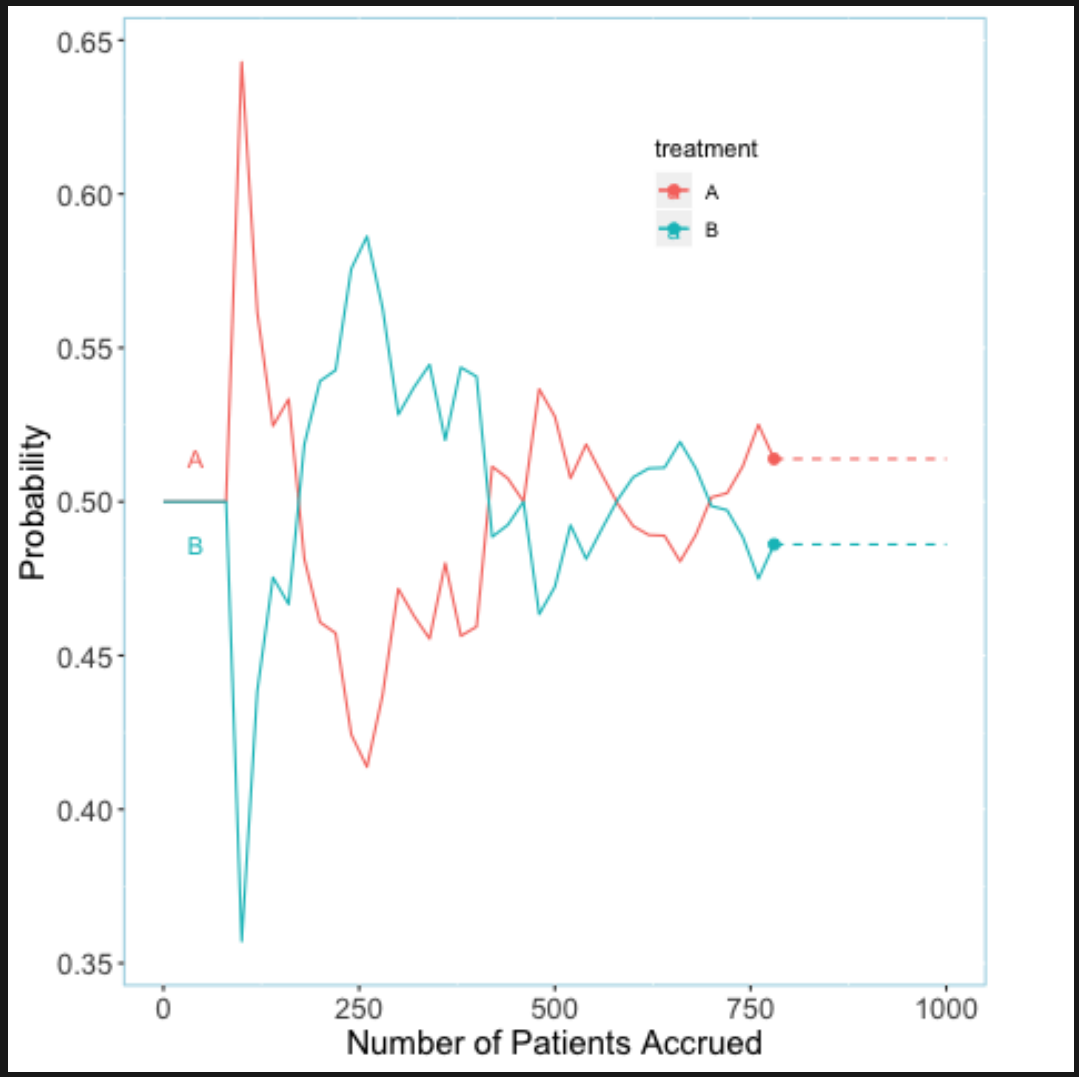

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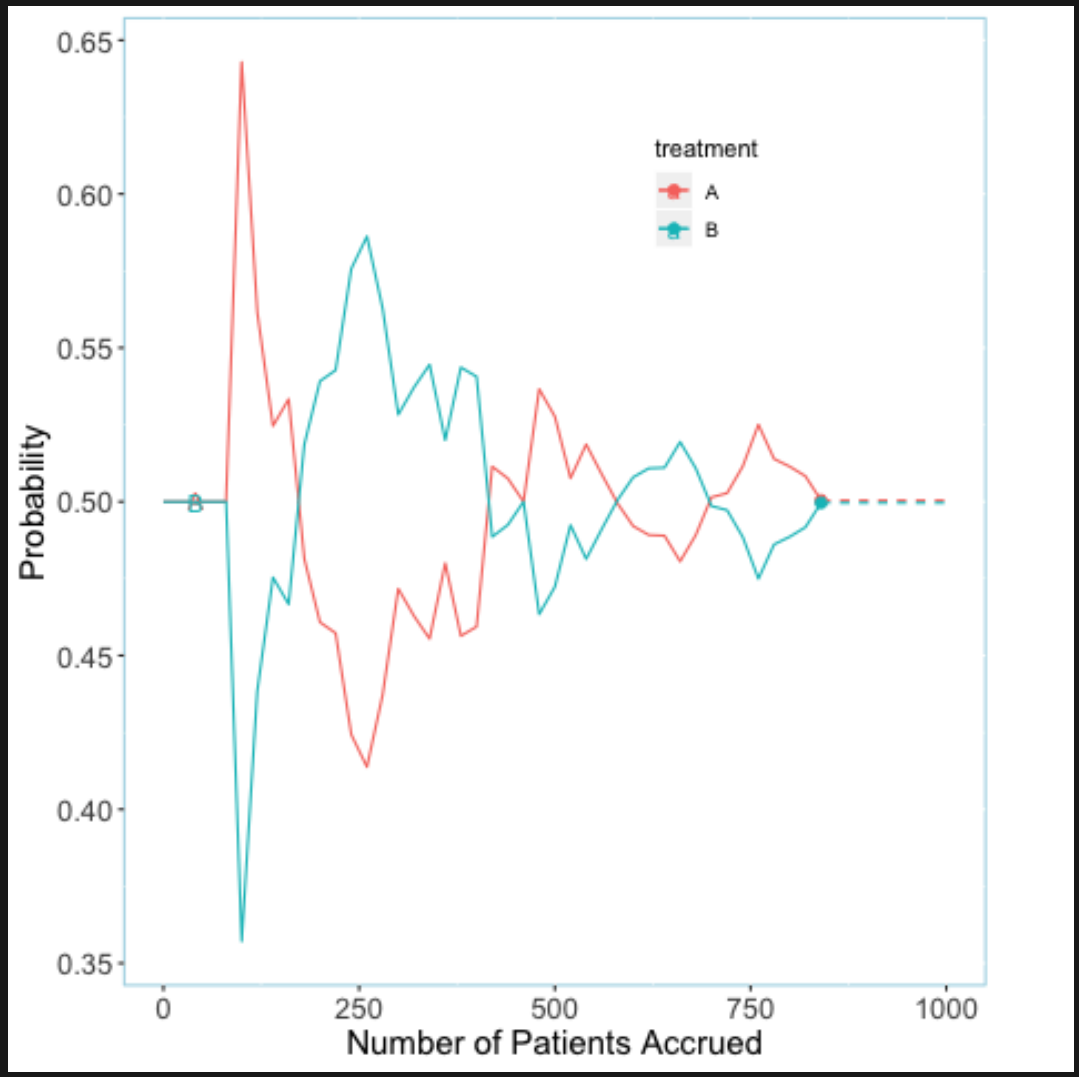

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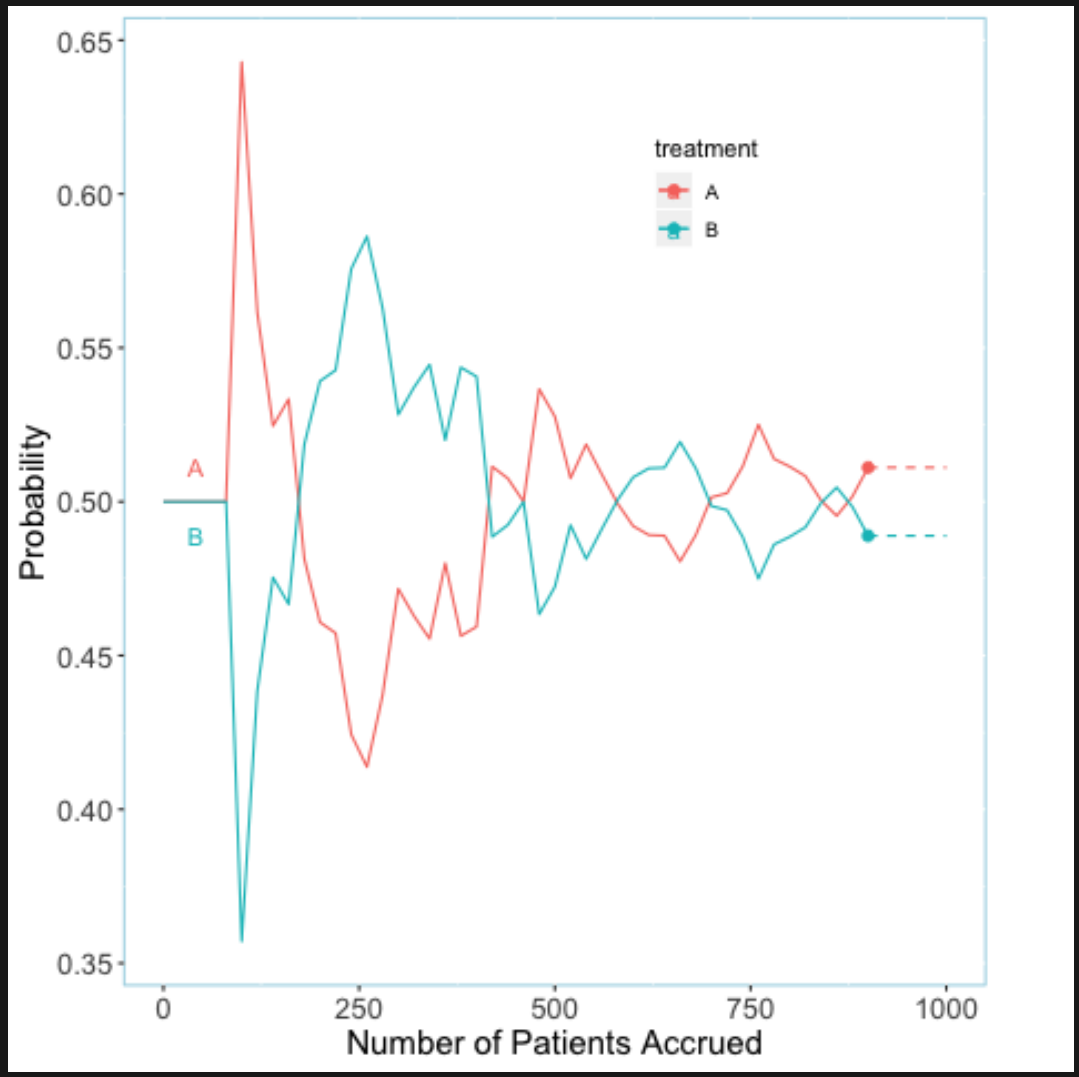

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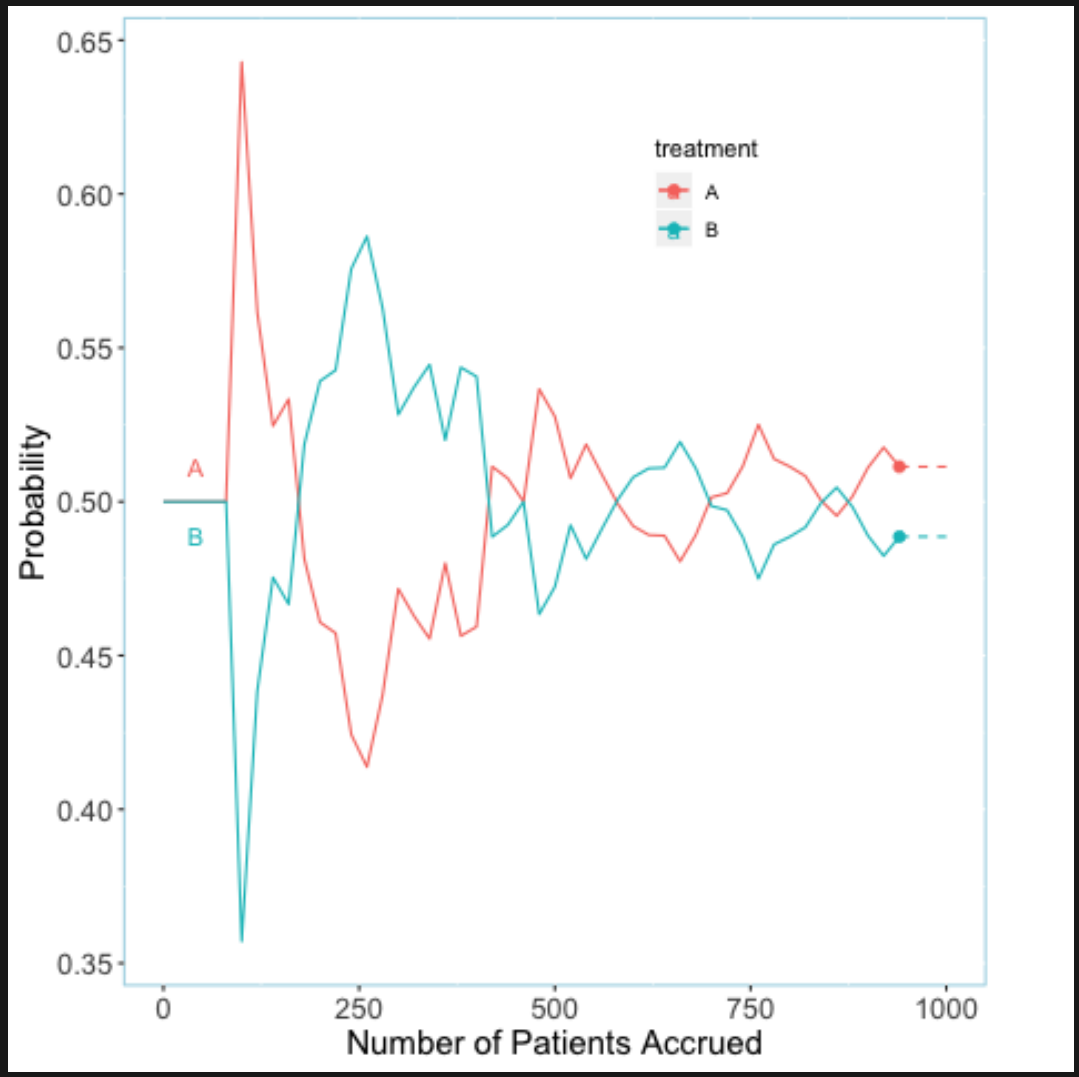

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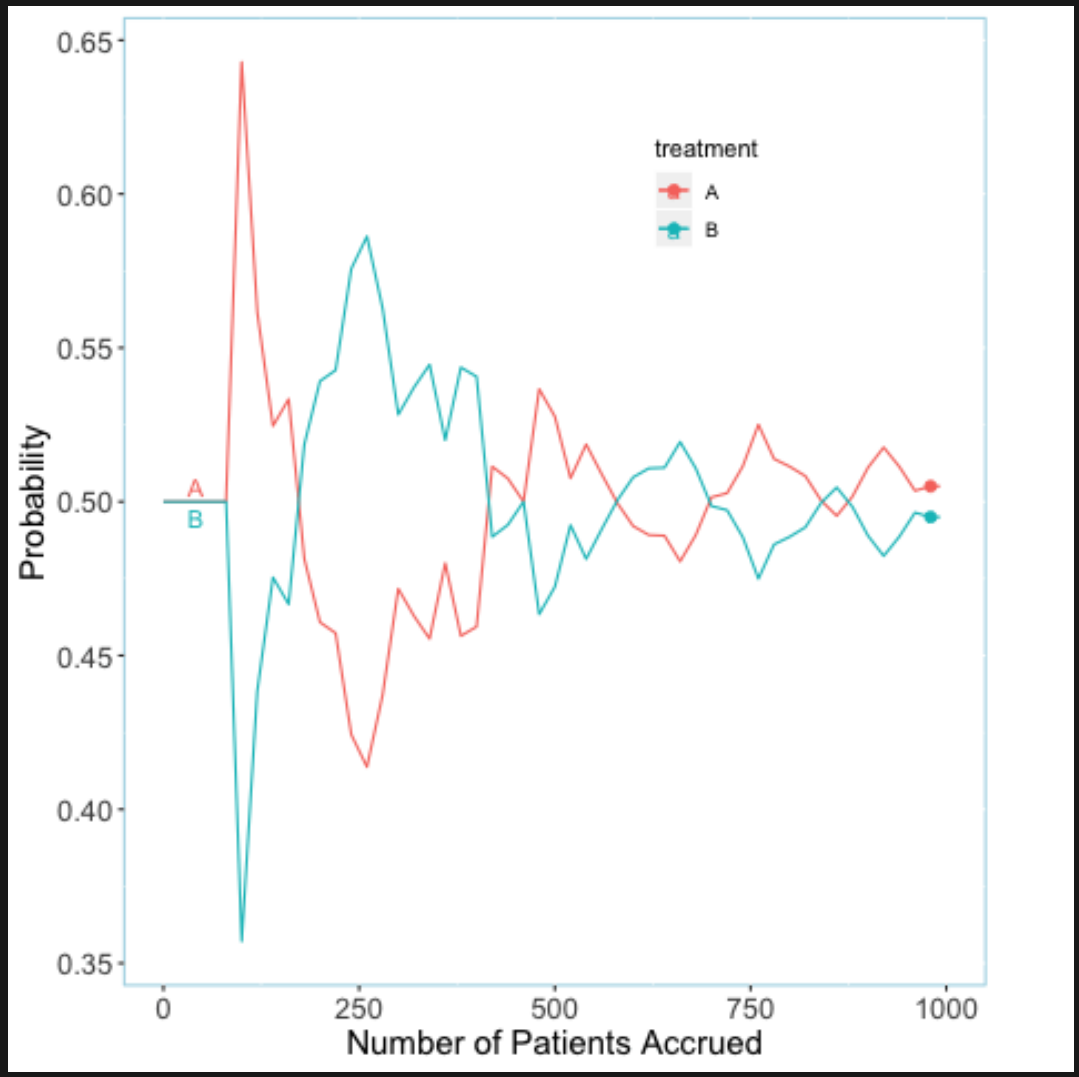

Results using Bayesian Approach: With Drift

Block	Type I error	Bias	E(N)	π_{20}	$N_B - N_A$
FR	0.05	0.00	180	0.06	0.27 (-28, 28)
2	0.05	0.00	178	0.20	-0.14 (-48, 48)
4	0.07	0.00	178	0.24	-0.09 (-56, 58)
5	0.08	0.00	180	0.25	0.03 (-58, 58)
10	0.08	0.00	179	0.27	-0.39 (-62, 62)
20	0.08	0.02	179	0.27	0.01 (-62, 62)
100	0.03	0.01	177	0.25	0.02 (-60, 60)
trad RAR	0.16	0.00	175	0.26	-0.24 (-60, 60)

Table: RAR using Bayesian approach and with 0.25 drift. $E(N)$ represents the mean sample size. $\pi_{20} = P(N_A - N_B > 20)$. N_A and N_B denotes the number of patients assigned to treatment A and B. The mean (2.5%, 97.5%) of $N_B - N_A$ is reported.

Results using Bayesian Approach: With Drift

Block	Power	Bias	E(N)	π_{20}	$N_B - N_A$
FR	0.88	0.01	98	0.07	-0.13 (-28, 28)
2	0.88	0.02	98	0.01	18.46 (-18, 62)
4	0.88	0.03	99	0.01	20.91 (-12, 68)
5	0.89	0.04	99	0.00	21.48 (-10, 68)
10	0.87	0.05	99	0.00	20.9 (-8, 68)
20	0.87	0.06	98	0.00	19.36 (-8, 68)
100	0.35	-0.07	97	0.00	16.5 (-8, 66)
trad RAR	0.95	0.08	93	0.00	15.4 (-9, 64)

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Discussion

- Blocks with a large number of patients also help reduce the large probability of imbalance in the wrong direction, where more patients are assigned to the inferior treatment compared to traditional RAR.
- Blocks with fewer patients can reduce the power of the trial because if patients are not randomized to both treatments in a block, the block becomes uninformative.
- Small number of blocks (K = 2, 4 and 5) has a good tradeoff between efficiency and ethically treating patients to the best known superior treatment.

Discussion

- Large number of blocks should be clearly avoided for both ethical reason and poor design.
- Statisticians need to be careful with issues of time-trend and methods to alter the randomization ratio.
- Time-trend can significantly impact the type-I error rate.
- R package **blockRAR**

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- Peter Thall (MD Anderson)

References

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THANK YOU!