A Design for Confirmatory Studies using Response Adaptive Randomization

Tianyu Zhan, Ziqian Geng, Yihua Gu, and Ivan Chan

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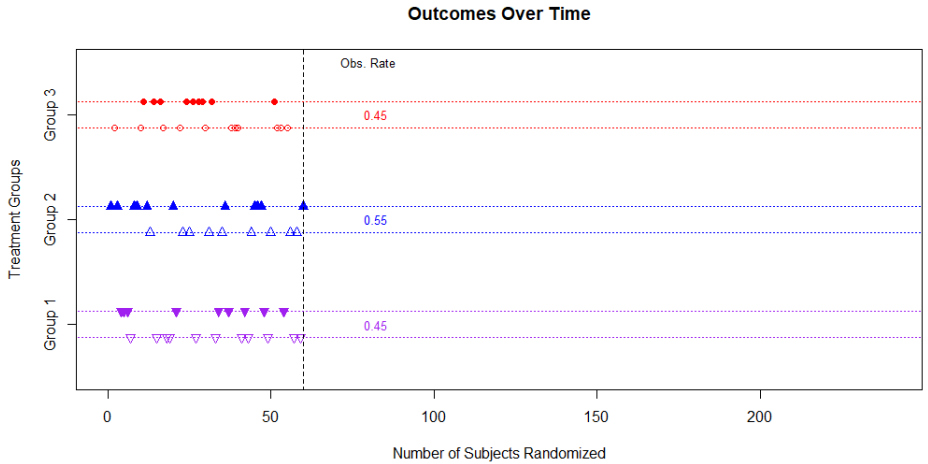
Outlines

- Background
- Design with Response-Adaptive Randomization (RAR) in Confirmatory Trials
- Case Study and Simulations
- Discussion

What is Response-Adaptive Randomization (RAR)

- FDA guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics (Nov 2019):
  - An adaptive feature in which the chance of a newly-enrolled subject being assigned to a treatment arm varies over the course of the trial based on accumulating outcome data for subjects previously enrolled.



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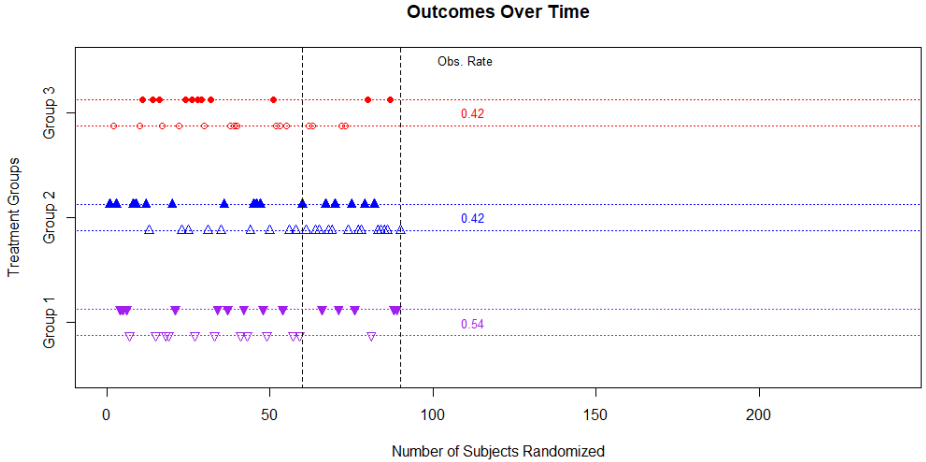

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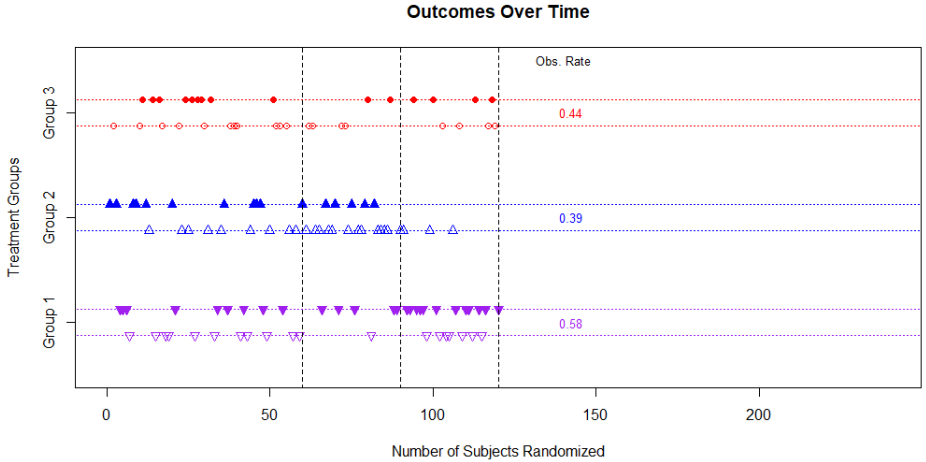

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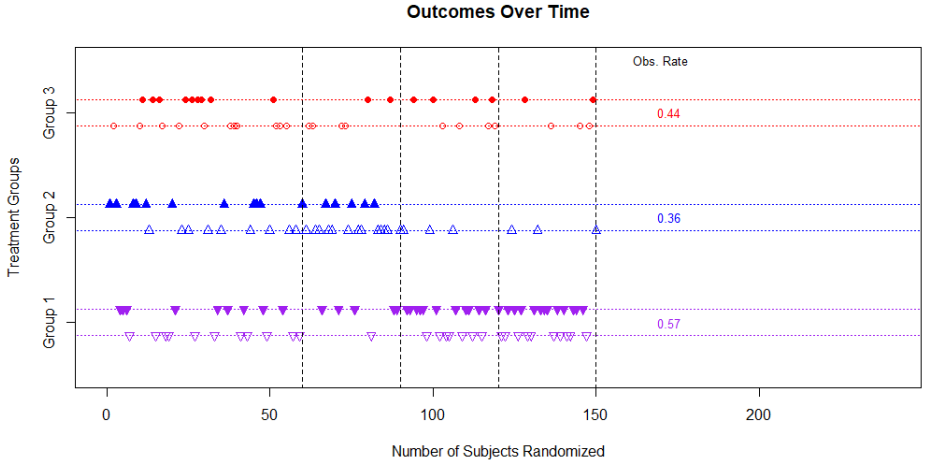

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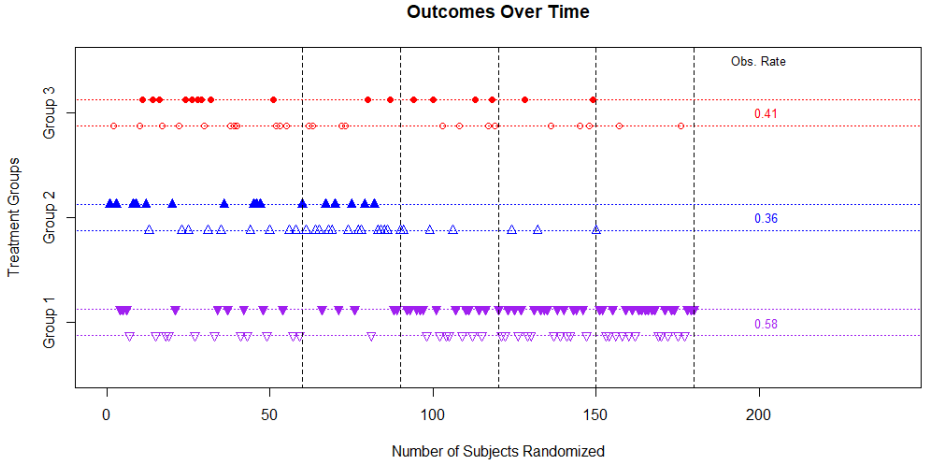

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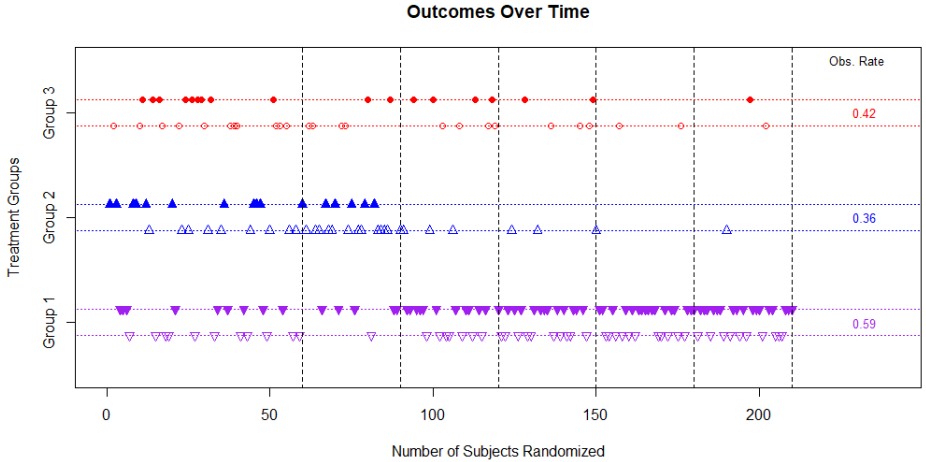


Benefits from RAR

- Ethical benefits
  - Increases the chance of newly enrolled subjects being assigned to the more promising doses, maximizes the benefit for patients participating in this study
- Pragmatic benefits
  - Increases the speed and ease of accrual
  - Shortens the overall trial timeline
- Statistical benefits (under appropriate circumstances)
  - Minimizes the variance
  - Smaller sample size and/or greater power

FDA Guidances

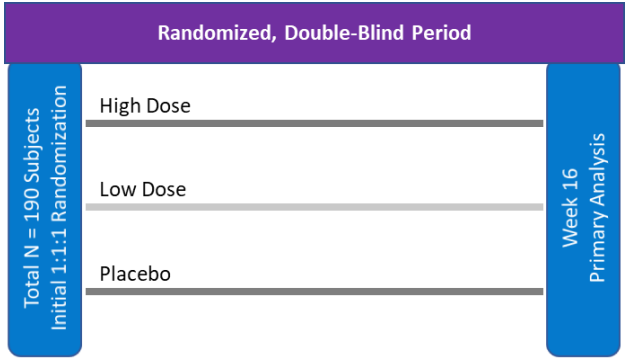
- FDA guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics (Nov 2019):
  - Response-adaptive randomization alone does NOT generally increase the Type I error probability of a trial when used with appropriate statistical analysis techniques.
  - It is important to ensure that the analysis methods appropriately take the design of the trial into account.
- FDA draft guidance on Interacting with the FDA on Complex Innovative Trial Designs (CIDs) for Drugs and Biological Products (Sep 2019)
  - Review involves challenging evaluations of design operating characteristics including extensive computer simulations
  - CID Pilot Program

From Theory to Reality

- Characteristics allowing the use of RAR
  - Relatively short-term ascertainment of outcomes (compared to accrual rate)
  - Well-defined stable endpoint guiding the adaptation
- Operational Challenges:
  - Interactive Response Technology (IRT) system must be capable of rapid adaptation
  - Traditional RAR requires IRT to adaptively changing the randomization ratio directed by magnitudes of relative efficacy from accumulative data
- Regulatory Challenges:
  - Handling of temporal trends
  - Justification of Type I error control
  - Other general concerns

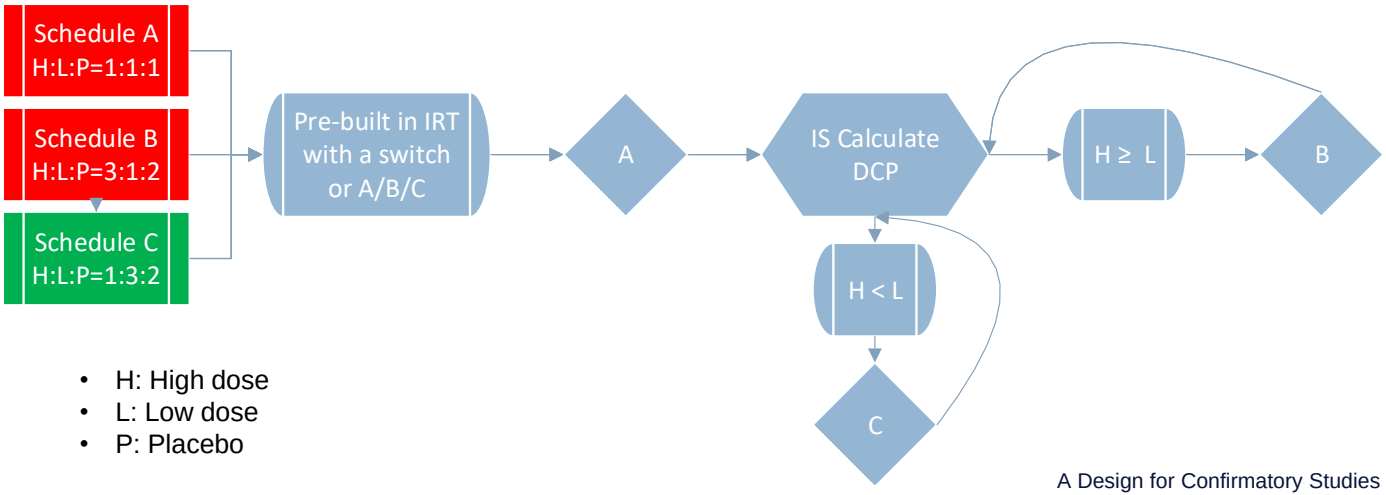
Case Study – Motivations

- Disease with high unmet medical needs
  - Only one approved medical treatment with overall response rate ~50%
  - Accelerated development program to fulfill the unmet needs
- Phase 2b Design with RAR, to achieve a 2-fold objective:
  - Select the dose for overall development program
  - Well powered Phase 2 controlling for FWER, to serve as part of the confirmatory evidences
- Characteristics allowing the use of RAR
  - Modest enrollment due to relatively low disease prevalence
  - Well defined clinical endpoints
  - Candidate doses within the range from existing programs with no safety signal
  - External DMC in place for routine safety monitoring



Overcome the Operational Burden

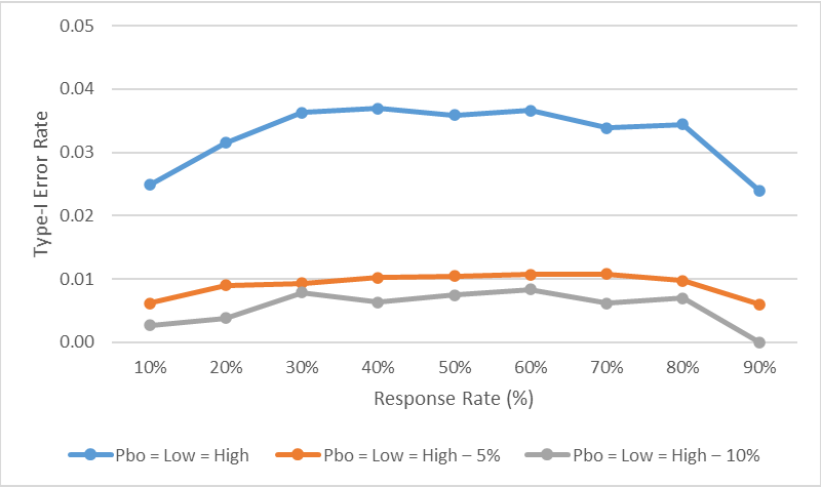
- Pre-built randomization with finite scenarios
  - Enable real-time randomization adaptation
  - Fixed allocation to placebo for stable benchmark
- *Note: Requires evaluations through simulation to determine burn-in period and frequency of adaptation, relative to accrual rate.*



- H: High dose
- L: Low dose
- P: Placebo

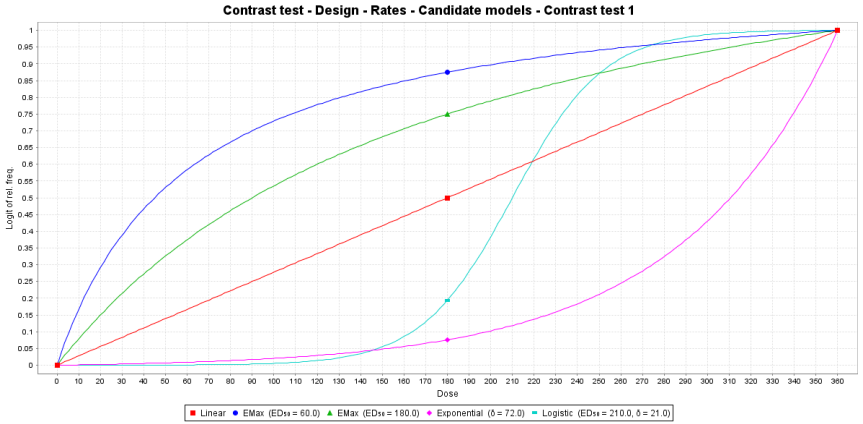
Type I Error Well Controlled

- Familywise type-I error well controlled under the level of 0.05, as demonstrated by extensive simulation
  - Under global null (select and reject the null for either dose)
  - Under single null (select and reject the null for the non-effective dose)



Evaluating the Operating Characteristics

- Conducted simulations to compare the following design options (with N=190):
  - Response Adaptive Randomization (RAR; Burn-in until first 60 subjects had primary outcome)
  - Seamless Phase II / III design w. inv-normal combination and Holm procedure (Arm dropping when first 60 subjects had primary outcome)
  - Benchmark: Traditional design with 1:1:1 randomization and no adaptive features
- Does Response Assumptions (with max. effect 27% vs 56%):

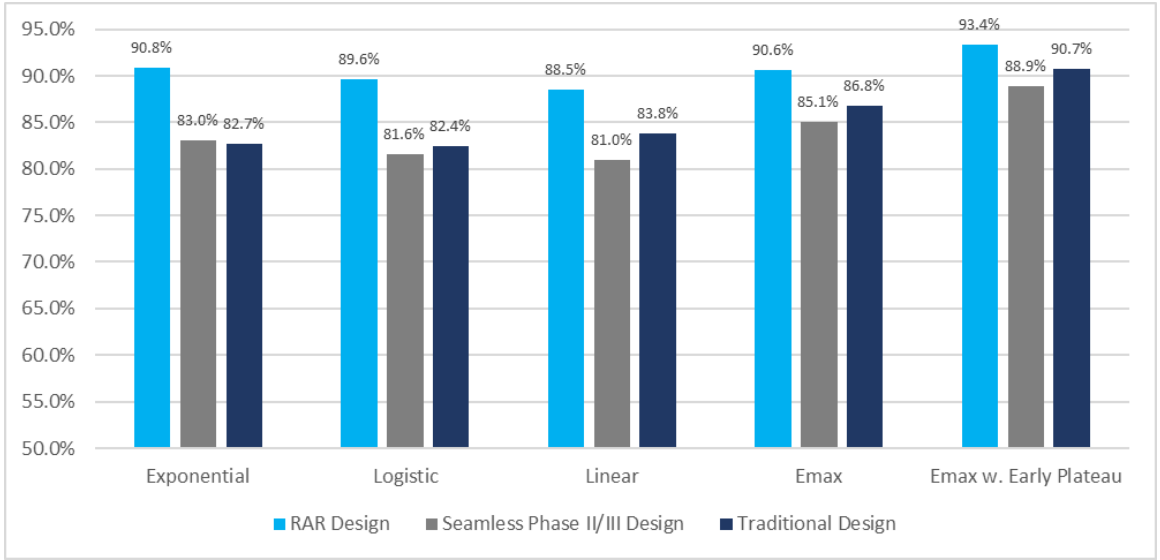


Precision in Estimation

Model	Method	MSE, Low Dose	MSE, High Dose
Exponential	RAR	0.0040	0.0034
	Seamless Ph II/III	0.0050	0.0036
	Traditional Design	0.0033	0.0039
Logistic	RAR	0.0042	0.0035
	Seamless Ph II/III	0.0053	0.0037
	Traditional Design	0.0036	0.0039
Linear	RAR	0.0043	0.0036
	Seamless Ph II/III	0.0052	0.0041
	Traditional Design	0.0039	0.0039
Emax	RAR	0.0045	0.0039
	Seamless Ph II/III	0.0051	0.0043
	Traditional Design	0.0040	0.0039
Emax with early plateau	RAR	0.0044	0.0039
	Seamless Ph II/III	0.0049	0.0046
	Traditional Design	0.0040	0.0040

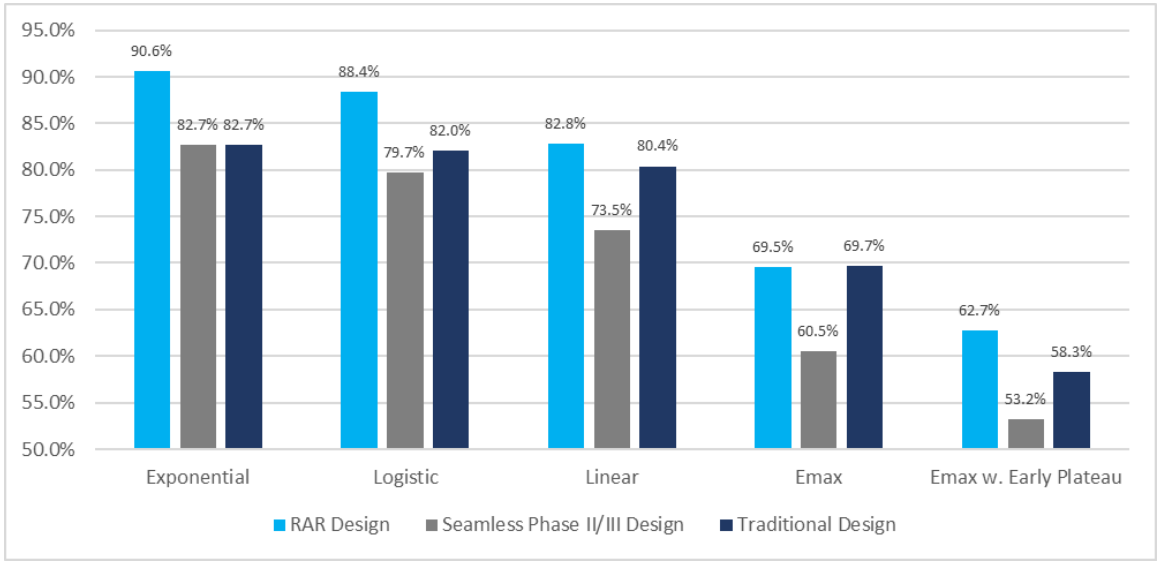
Power to Show Superiority to Placebo with At Least One Dose

- RAR shows the highest power.
- Seamless Phase II/III can accelerate the program; but may have lower power if arm dropping is made too early.



Probability to Select the Most Efficacious Dose & Demonstrating Superiority

- RAR shows the highest probability to select the most efficacious dose and demonstrate superiority.
- Seamless Phase II/III may have lower chance of selecting the best dose if arm dropping is made too early.



Points to Consider

- Take advantage from modest enrollment
  - Evaluate operating characteristics with accrual rate
  - Enabling timely adaptation
- Engage early with regulatory agencies to seek for feedbacks
  - Comprehensive evaluations including simulation results
  - Adequate review takes time
  - If planned early and appropriately, interactions may take place before RAR kick-in
- Additional consideration
  - Historical data to justify the absence of a temporal trend
  - Ensure consistency in implementing FDA guidance
  - Involvement of CID may improve the interaction between sponsors and FDA, including communications outside pilot program in the long-run

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