Response-Adaptive Trial Designs

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Paris NASH Meeting

International Think Tank

Conflict of interest disclosure

- I have no actual or potential conflict of interest in relation to this presentation.

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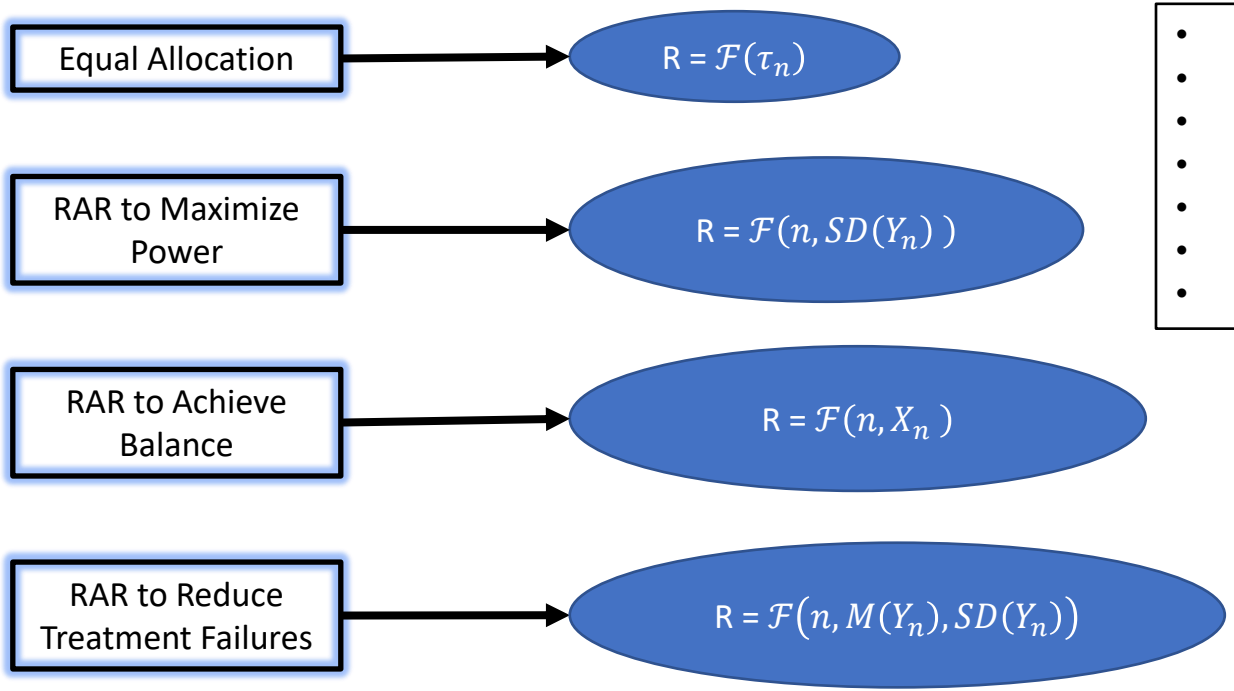
Introduction

- Randomization in Clinical Trials
  - Supports internal validity → Reduces investigator bias
  - Ensures differences between groups due to chance
  - Supports (most) statistical assumptions

- Traditional Approach Randomization
  - Fixed &/or balanced allocation ratio
  - Methods: Simple Randomization, Blocked Randomization, Stratification
  - Lead to “under treatment” if benefit exists

Response Adaptive Randomization (RAR)



- R = Allocation Ratio
- τ_n = Allocation Sequence
- X_n = Covariates / Demographics
- Y_n = Observed Outcomes
- SD() = Standard Deviation
- M() = Mean
- n = Observed / Current Sample Size

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Response Adaptive Randomization (RAR)

RAR for Binary Outcomes

$$R_A = \frac{\sqrt{\hat{p}_A}}{\sqrt{\hat{p}_A} + \sqrt{\hat{p}_B}}$$
$$R_B = 1 - R_A$$

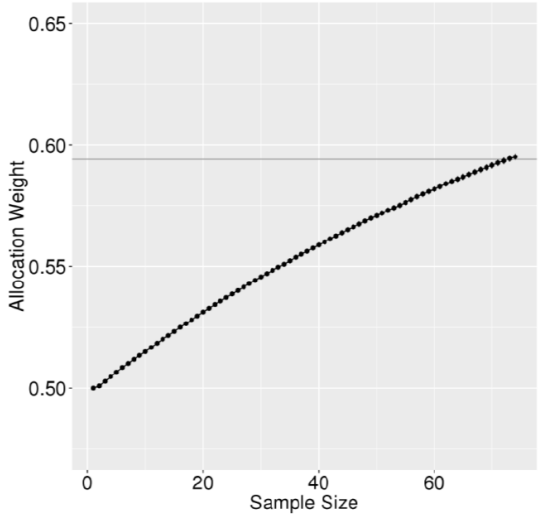
RAR for Continuous Outcomes

$$R_A = \frac{s_A\sqrt{\bar{x}_A}}{s_A\sqrt{\bar{x}_A} + s_B\sqrt{\bar{x}_B}}$$
$$R_B = 1 - R_A$$

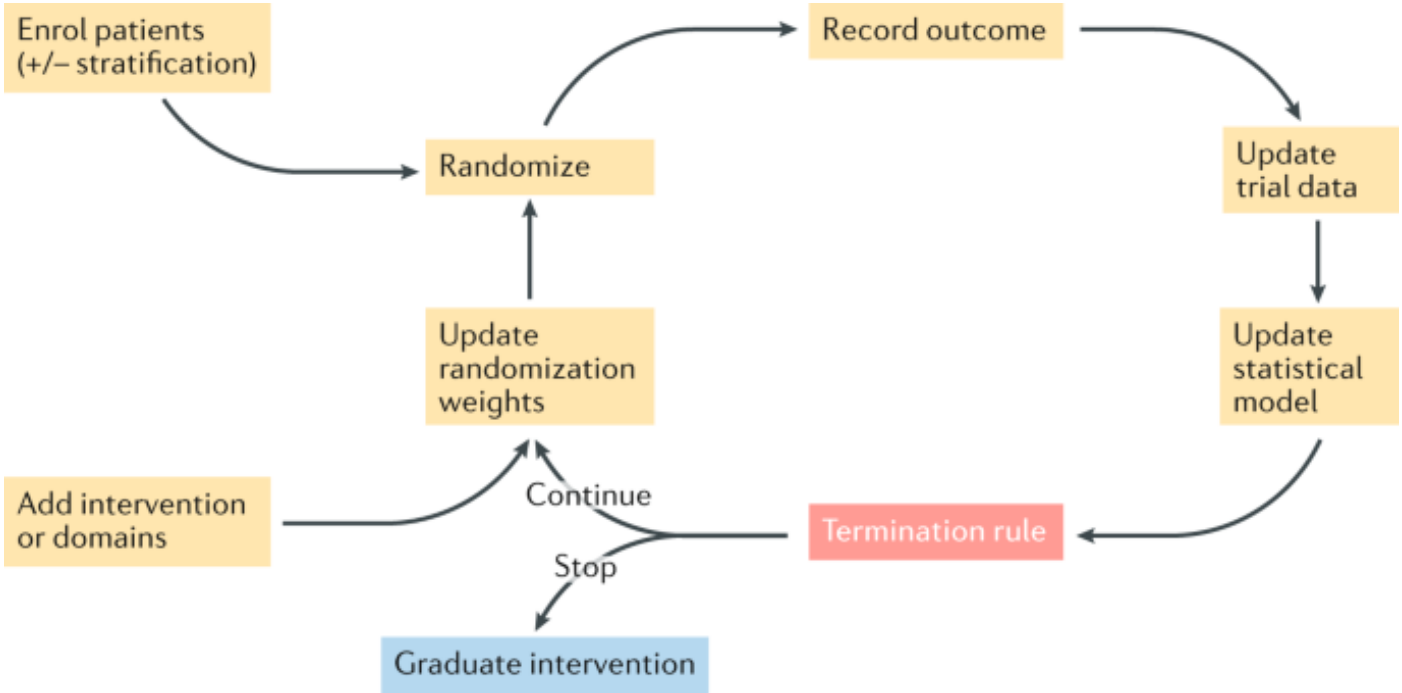
RAR for Survival Outcomes

$$R_A = \frac{\sqrt{\hat{\theta}_A^3\hat{\varepsilon}_B}}{\sqrt{\hat{\theta}_A^3\hat{\varepsilon}_B} + \sqrt{\hat{\theta}_B^3\hat{\varepsilon}_A}}$$
$$R_B = 1 - R_A$$

- $R_{A/B}$ = Allocation Ratio for Group A/B
- $\hat{p}_{A/B}$ = Response Rate in Group A/B
- $\bar{x}_{A/B}$ = Outcome Mean of Group A/B
- $s_{A/B}$ = Outcome SD of Group A/B
- $\hat{\theta}_{A/B}$ = Mean Survival Time per Event in Group A/B
- $\hat{\varepsilon}_{A/B}$ = Censoring Proportion in Group A/B



Response-Adaptive Randomization (RAR)



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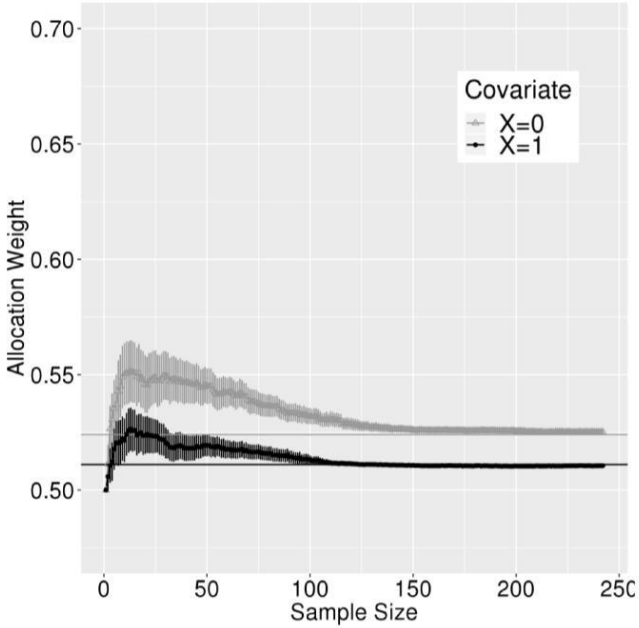
Response Adaptive Randomization (RAR)

RAR Methods Can Be *Quirky*

- At Start of Trial (Low Sample Size)
  - Undefined Estimators
  - Spurious outcomes
  - Extra Variability
  - *Inaccurate Allocation Ratio*
- Possible Solutions
  - Hard Lead-In
  - Start-Up Design

} Wait until sample size large enough to adapt



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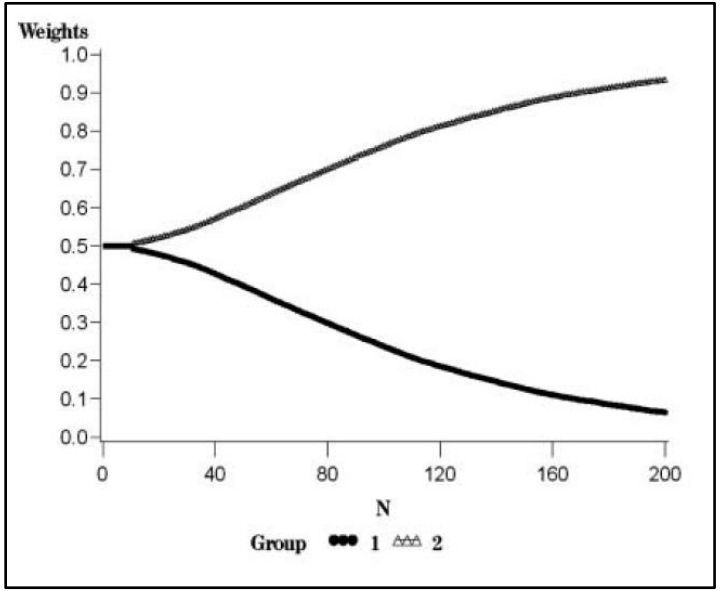
Response Adaptive Randomization (RAR)

Bayesian RAR

- Natural Lead-In
  - Restrict adaption early
  - Gradually allow more as trial progresses
- Stronger Adaptation
  - *Directly e*stimate probability of effectiveness
  - $R_A = P(\theta_A > \theta_B | Y_n, X_n, \theta_0)$
- Combine with Early Termination



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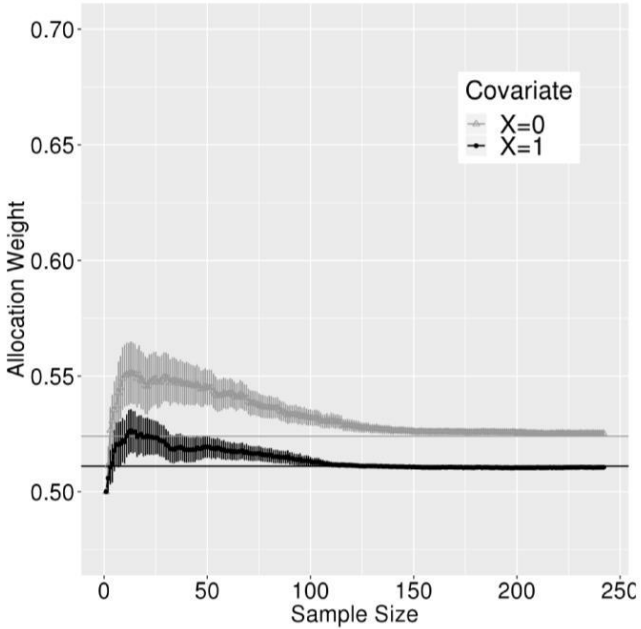
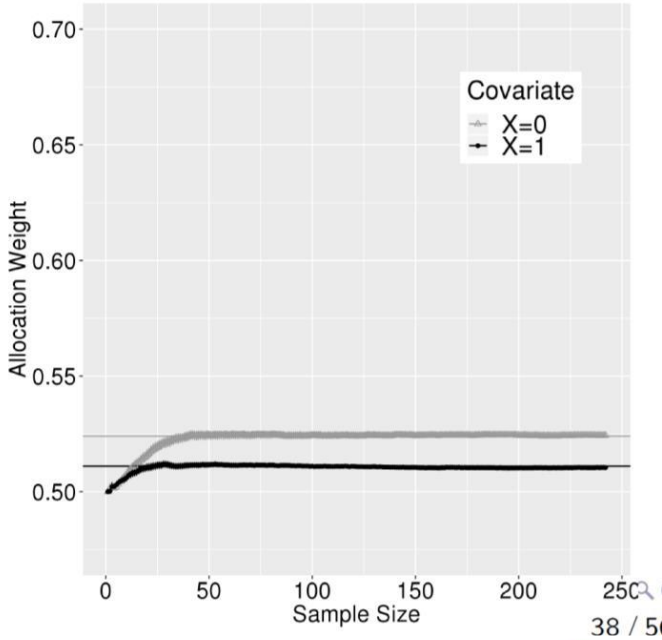
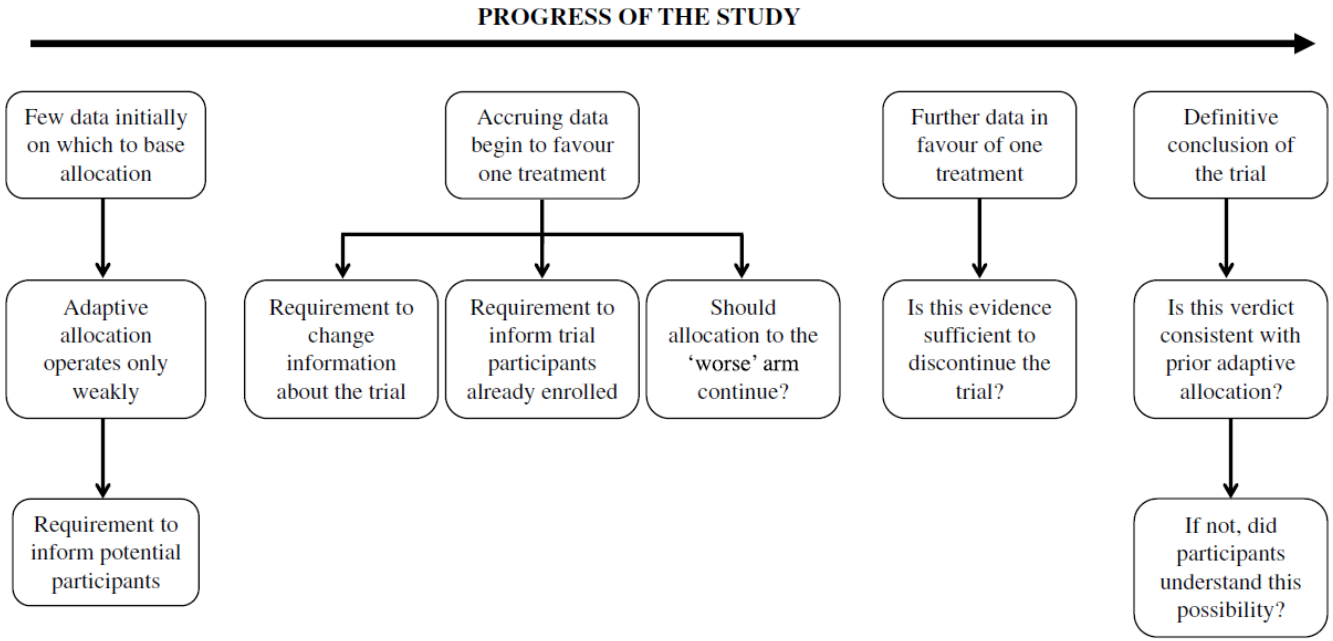
Response Adaptive Randomization (RAR)





Ethical Considerations



- Summary of Concerns:
  - Weak/Irregular Effect
  - Loss of Equipoise
  - Injustice / Unfairness
  - Consent

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Conclusions

- RAR *can* be considered in the following situations:
  - Outcomes quickly measurable &/or enrollment is slow
  - Single location &/or sufficient logistic support
  - Population / treatments stable over time
  - Treatment effect expected to be large
  - Disease / condition not life-threatening
  - (Bayesian) Methods to mitigate small-sample irregularities

References and Resources

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Thank you for your time

As always…speak with a biostatistician while planning your trial

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