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Efficient Platform Design for Screening Indications in Rare Disease

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Contents

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Background: Screening Indications in Rare Disease

Clinical Challenges

- The low prevalence of rare diseases leads to a limited patient pool
- Traditional designs struggle to recruit sufficient patients for adequate statistical power

Business Necessities

- Employ innovative trial designs to enhance study efficiency
  - Evaluate multiple treatment options in limited number of subjects
  - Accelerate development timelines to address unmet medical needs

A Promising Solution: **Platform Trials** Maximize Efficiency under Limited Sample Sizes

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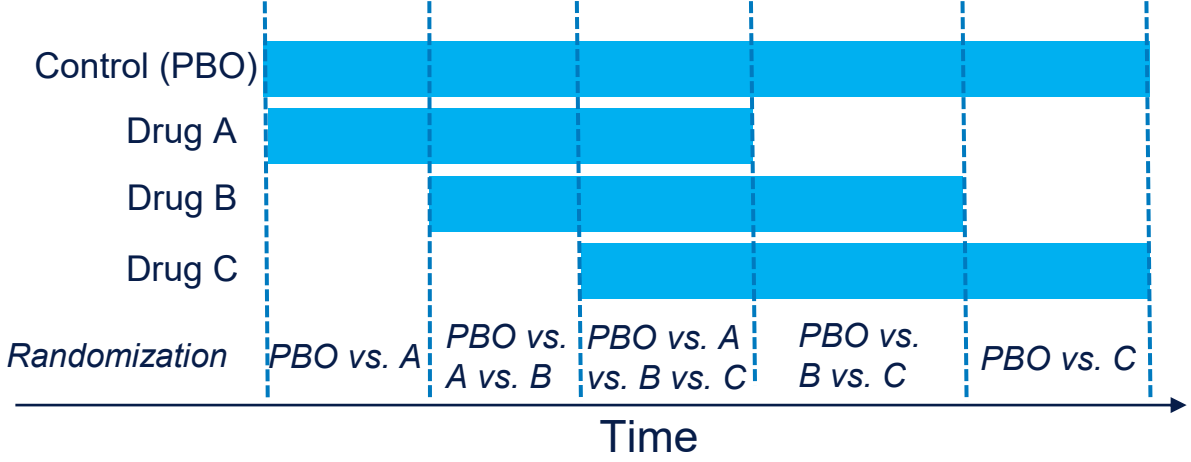
Background: Platform Trial



Accelerate Timeline & Reduce Operation Costs

- Evaluating multiple therapies simultaneously for a disease
- Enabling the dynamic addition or discontinuation of arms
- Utilizing a single master protocol and shared infrastructure

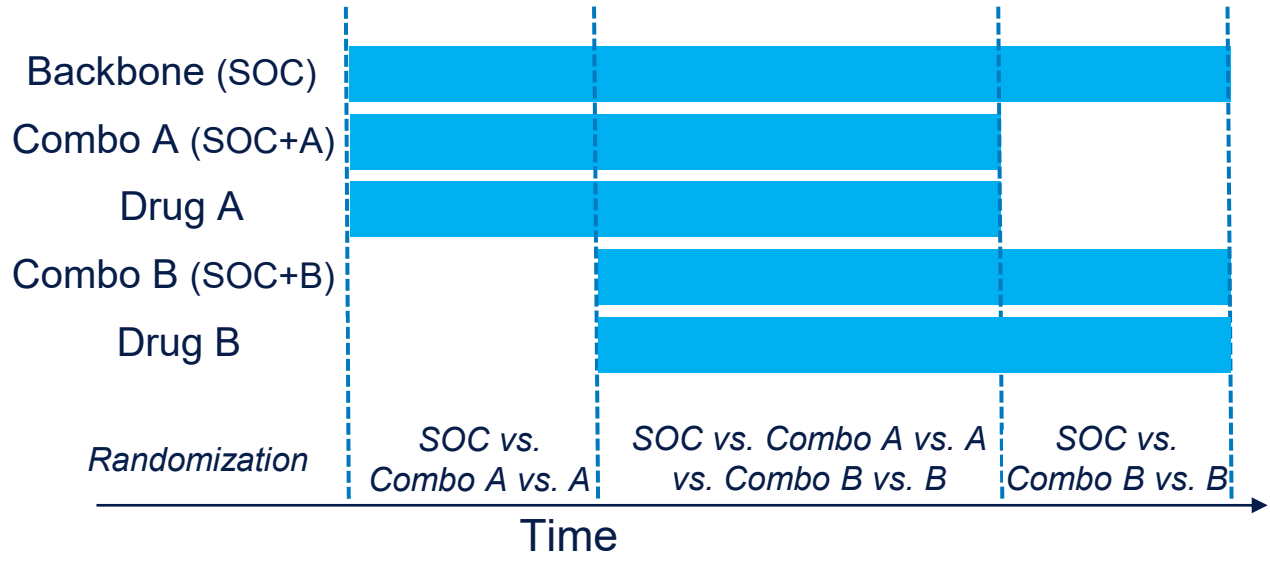
Reduce Overall Sample Size

- Using a common reference therapy arm for benchmarking all experimental therapies
- Offering an innovative design strategy for clinical trials in rare diseases to improve statistical efficiency under a limited total sample size

Dynamic Randomization

- When evaluating multiple drugs against a common control, FDA guidance suggests allocating more subjects to the shared control arm and adjusting dynamically based on the # of active treatment arms to increase overall power within a fixed total sample size

Motivation: Combination Therapy Evaluation in Platform Trial



Combination Therapy

- May offer superior efficacy, addressing the unmet medical need
- FDA requires demonstrating the contribution of each therapy component

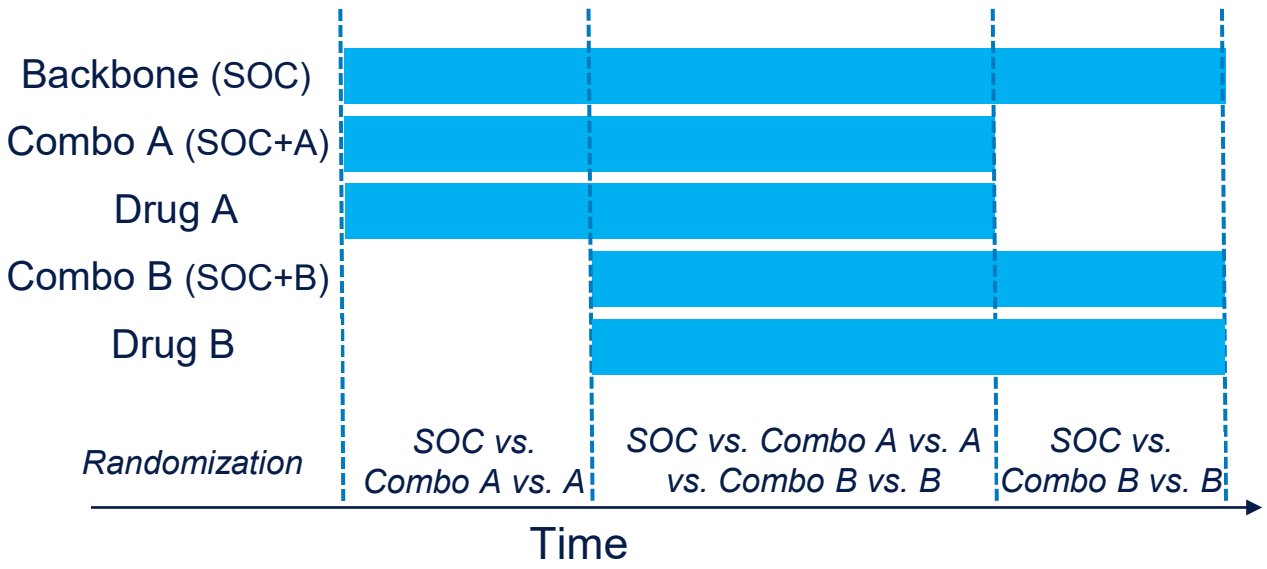
Statistical Challenges in Randomization Ratio

- Both backbone and combo will be compared multiple times – *is it still valid to assign more subjects to the backbone arm for power maximization?*
- Timing of adding or discontinuing arms – *Considering the potential staggered availability of investigational drugs, how do we choose the optimal timing? how would it impact randomization over time?*

Generalizability

- Applicable to multiple head-to-head sub-studies along with a common reference arm

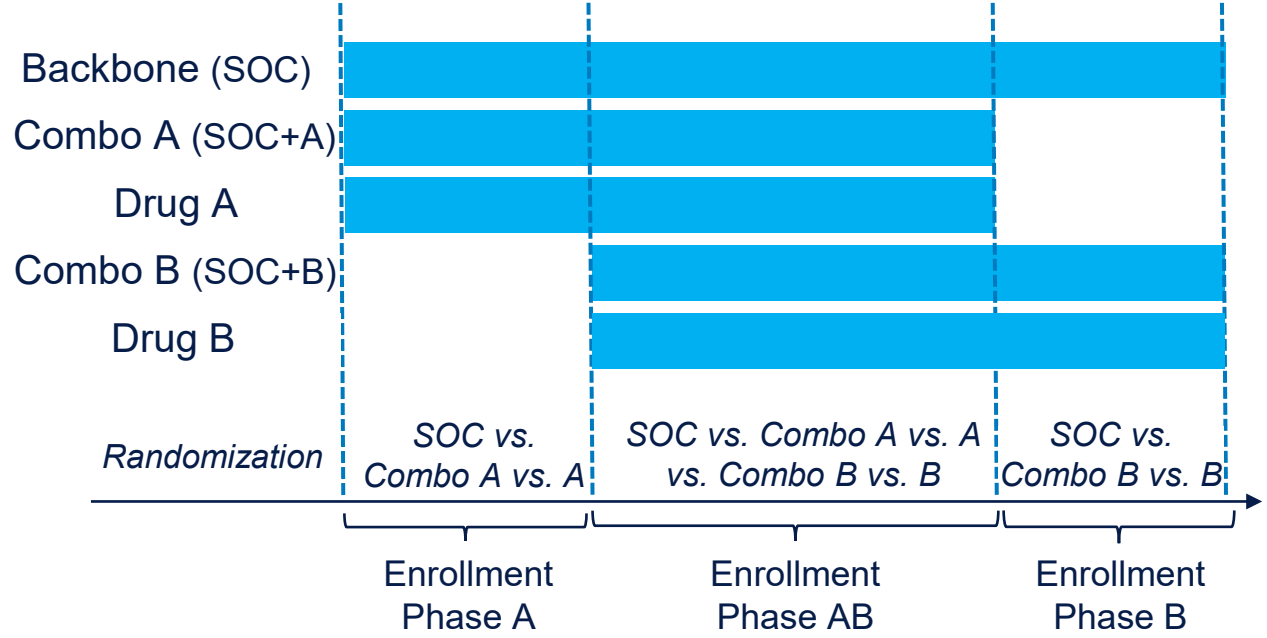
Method



Objective: optimizing allocation ratios, considering

- fix total sample size N
- pairwise comparisons
  - Combo X vs Backbone; Combo X vs Drug X (X=A,B)
  - ***concurrent*** comparison
- optimality criterion
  - to maximize the minimum power across investigational treatments
  - to ensure adequate power for the worst-performing test

Method

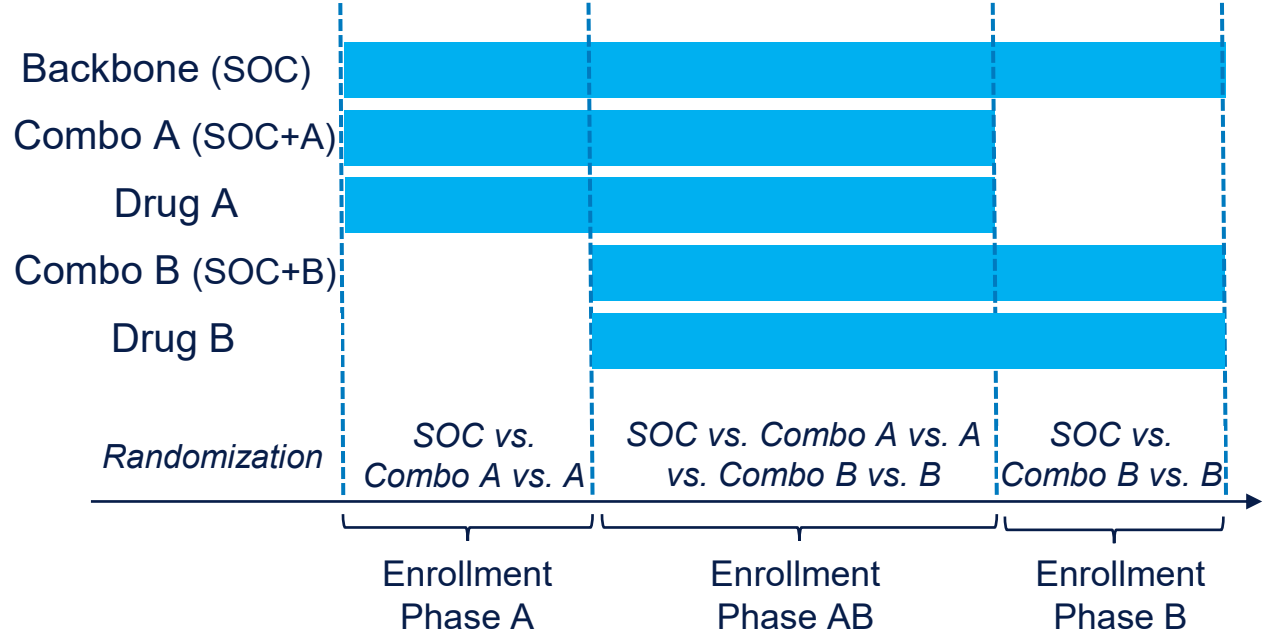


Objective: optimizing allocation ratios, considering

- the number of arms and their entry and exit time
  - stratified testing estimator, adjusting for changing ratios per enrollment phase, to formulate marginal power (in line with FDA guidance to avoid bias)

Approach: theoretical derivation & numerical optimization

Simulation Setup



- Total sample size N=200
- Endpoint follows a Normal Distribution
  - $Y_i \sim N(\mu_i, \sigma^2 = 1)$
  - $\mu_i = \begin{cases} 0, & i = \{Backbone, Drug\ A, Drug\ B\} \\ 0.5, & i = \{Combo\ A, Combo\ B\} \end{cases}$
- Allocation ratios under evaluation:
  - derived optimal allocation
  - equal allocation
- Simulated 5000 trials to obtain empirical power for each test

Design Scenarios

Flexible Launch & Exit

- All investigational drugs are ready for evaluation at the same time
- No restrictions on development timelines/when arms are added or dropped

Staggered Launch & Flexible Exit

- Investigational drugs become ready for evaluation in a staggered manner
- No restrictions on when arms must be dropped

Staggered Launch & Fixed Exit

- Investigational drugs become ready for evaluation in a staggered manner
- Business needs expect some specific development timelines

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Design Scenarios

Flexible Launch & Exit

- No restrictions on the timing of adding or dropping arms, i.e., both combo sets are ready to launch and free to drop at anytime
- *Fixed design factors*: total sample size
- *Design factors to be determined*: timing of adding/dropping combo sets, corresponding randomization ratio by enrollment phase

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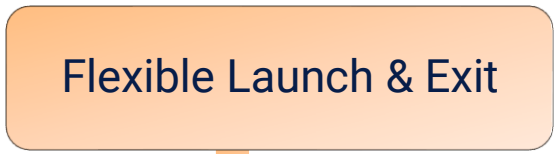

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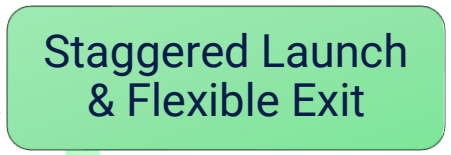

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Staggered Launch & Flexible Exit

Restriction 1 added: Combo Set B is scheduled to be launched later than Combo Set A

- *Fixed design factors*: total sample size, timing of adding Combo Sets A/B
- *Design factors to be determined*: timing of dropping Combo Sets A/B, corresponding randomization ratio by enrollment phase

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Staggered Launch & Fixed Exit

- Restriction 2 added: Combo Set A is scheduled to be dropped at certain time point
- *Fixed design factors*: total sample size, timing of adding/dropping Combo Sets A/B
- *Design factors to be determined*: corresponding randomization ratio by enrollment phase

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Design Scenario 1: Flexible Launch & Exit

- No restrictions on the timing of adding or dropping arms i.e., both combo sets are ready to launch and free to drop at anytime
- *Fixed design factors*: total sample size
- *Design factors to be determined*: timing of adding/dropping combo sets, corresponding randomization ratio by enrollment phase

✓**Optimal Timing:**

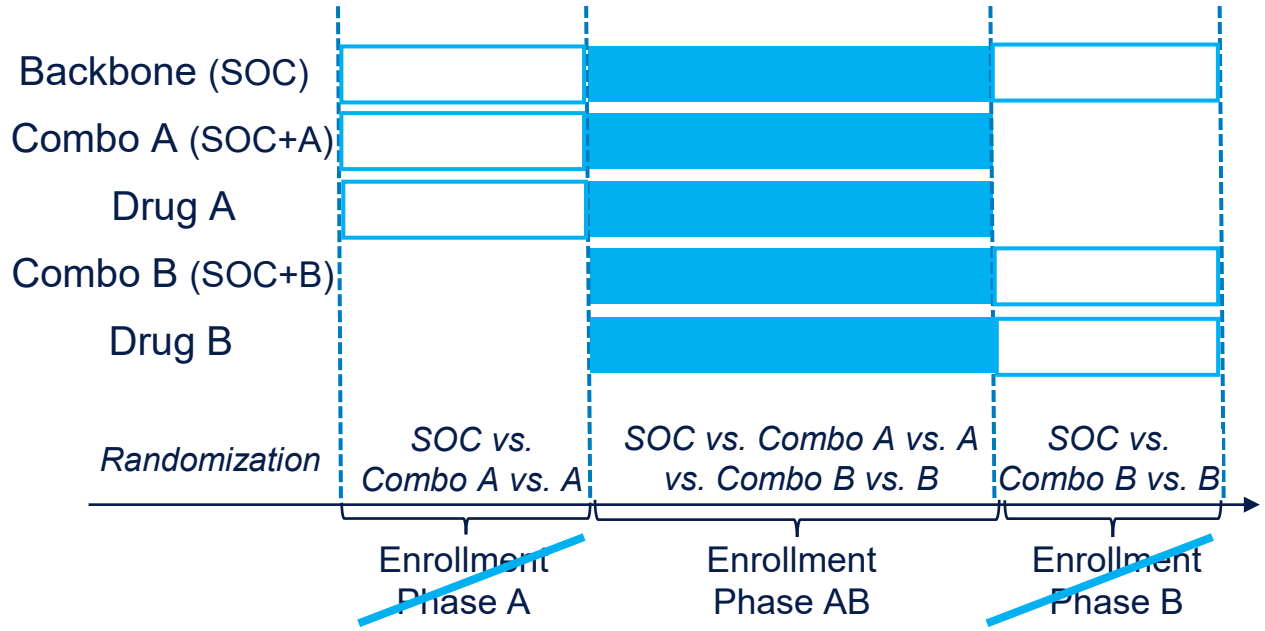
- launch and exit all arms concurrently

✓**Optimal Randomization:**

- assign more subjects to combo arms
- $\sqrt{2}$ SOC vs. $\sqrt{3}$ Combo A vs. $\sqrt{2}$ A vs. $\sqrt{3}$ Combo B vs. $\sqrt{2}$ B

✓**Power Gain:**

	Optimal	Equal
Empirical Power	**0.604**	0.597



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Design Scenario 2: Staggered Launch & Flexible Exit

- Restriction 1 added: Combo Set B is scheduled to be launched later than Combo Set A
- *Fixed design factors*: total sample size, timing of adding Combo Sets A/B
- *Design factors to be determined*: timing of dropping Combo Sets A/B, corresponding randomization ratio by enrollment phase

Sub-scenario 2.1 if, by the time Combo Set B is added, the accumulated sample size has reached half of the total sample size

✓**Optimal Timing:**

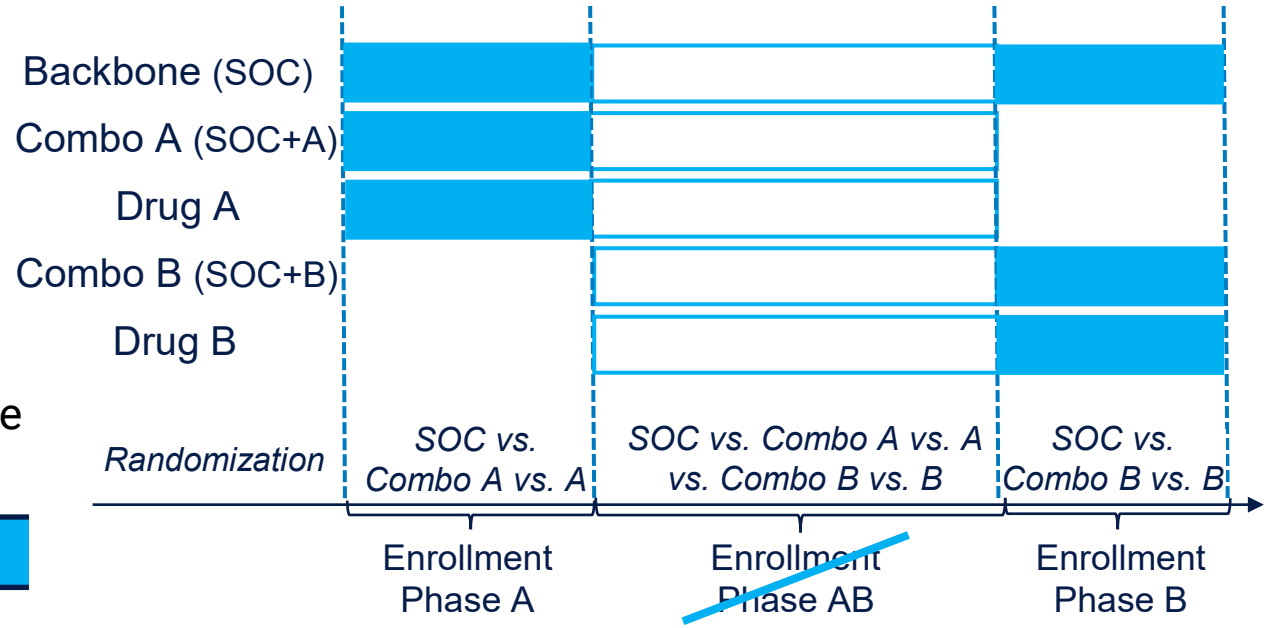
- evaluate two combo sets separately

✓**Optimal Randomization:**

- assign more subjects to combo arms
- 1 SOC vs. $\sqrt{2}$ Combo A/B vs. 1 A/B

✓**Power Gain** (a function of the proportion of sample size allocated to Combo Set A evaluation):

	0.55	0.6	0.65	0.7
Optimal	**0.492**	**0.458**	**0.402**	**0.363**
Equal	0.489	0.444	0.398	0.346



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Design Scenario 2: Staggered Launch & Flexible Exit

- Restriction 1 added: Combo Set B is scheduled to be launched later than Combo Set A
- *Fixed design factors*: total sample size, timing of adding Combo Sets A/B
- *Design factors to be determined*: timing of dropping Combo Sets A/B, corresponding randomization ratio by enrollment phase

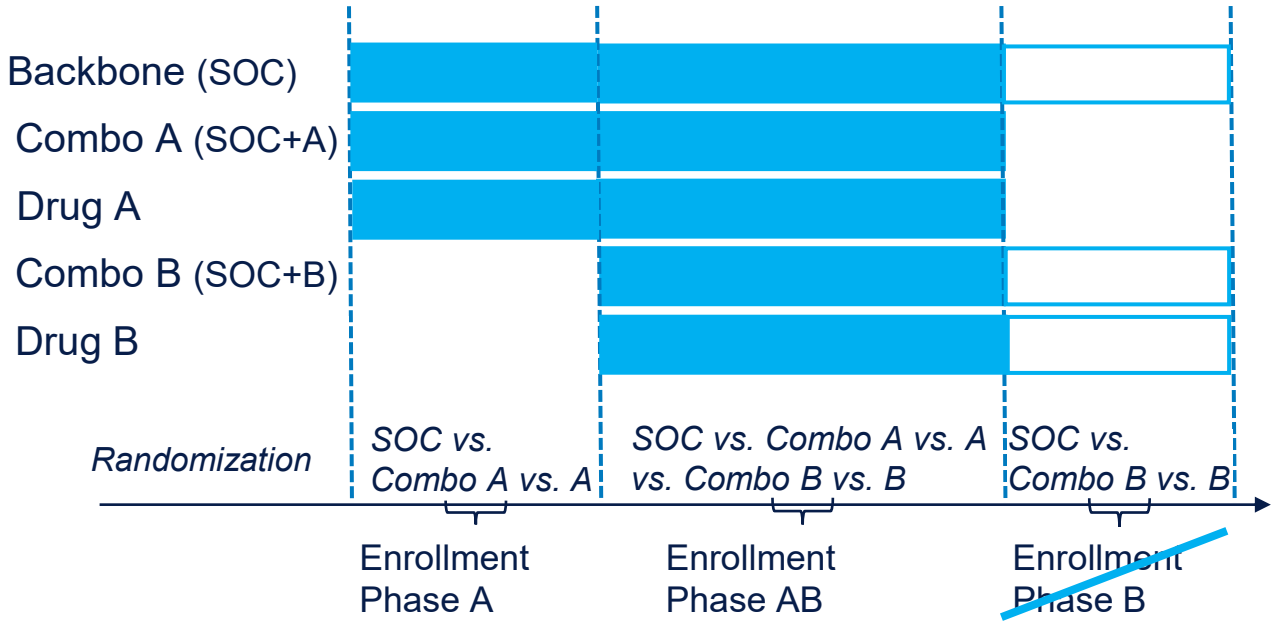
Sub-scenario 2.2 if, by the time Combo Set B is added, the accumulated sample size has NOT reached half of the total sample size

✓**Optimal Timing:**

- end two combo sets at the same time

✓**Optimal Randomization & Power Gain:**

- dependent on the proportion of sample size allocated to Combo Set A evaluation before adding Combo Set B (i.e., Enrollment Phase A)



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Design Scenario 2: Staggered Launch & Flexible Exit

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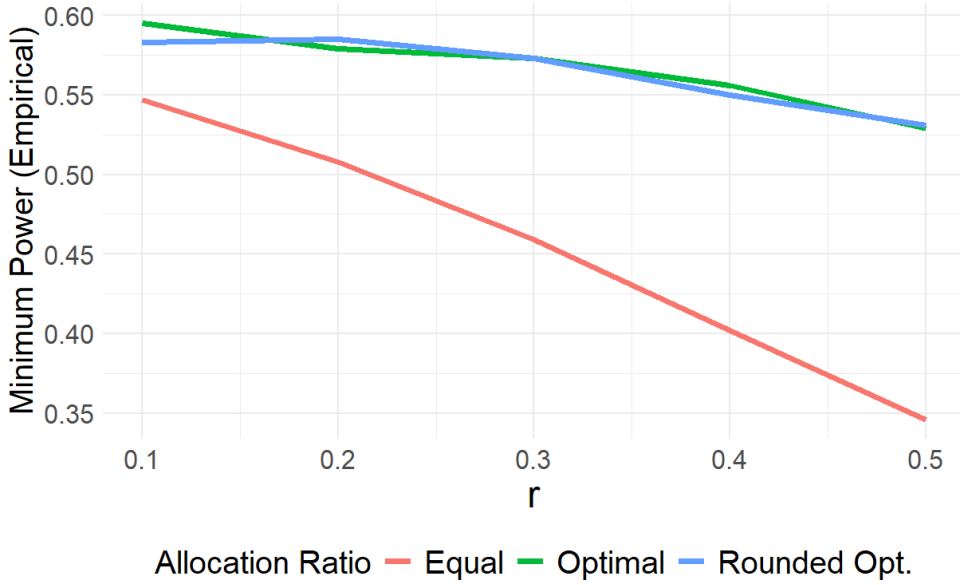
- *Fixed design factors*: total sample size, timing of adding Combo Sets A/B
- *Design factors to be determined*: timing of dropping Combo Sets A/B, corresponding randomization ratio by enrollment phase

Sub-scenario 2.2 if, by the time Combo Set B is added, the accumulated sample size has NOT reached half of the total sample size

✓**Power Gain** (a function of the r : proportion of sample size allocated to Combo Set A evaluation before adding Combo Set B)

Allocation Ratio	r				
	0.1	0.2	0.3	0.4	0.5
Equal	0.547	0.508	0.459	0.402	0.346
Optimal	**0.595**	**0.579**	**0.573**	**0.556**	**0.529**
Rounded Opt.	**0.583**	**0.585**	**0.573**	**0.550**	**0.531**

Allocation Ratio	p_1^{SOC}	$p_1^{Combo\ A}$	$p_1^{Drug\ A}$	p_2^{SOC}	$p_2^{Combo\ A}$	$p_2^{Drug\ A}$	$p_2^{Combo\ B}$	$p_2^{Drug\ B}$
Equal	1	1	1	1	1	1	1	1
Optimal	**1**	**2.8**	**2.6**	**1.8**	**1.4**	**1**	**2.3**	**1.8**
Rounded Opt.	**2**	**6**	**5**	**4**	**3**	**2**	**5**	**4**



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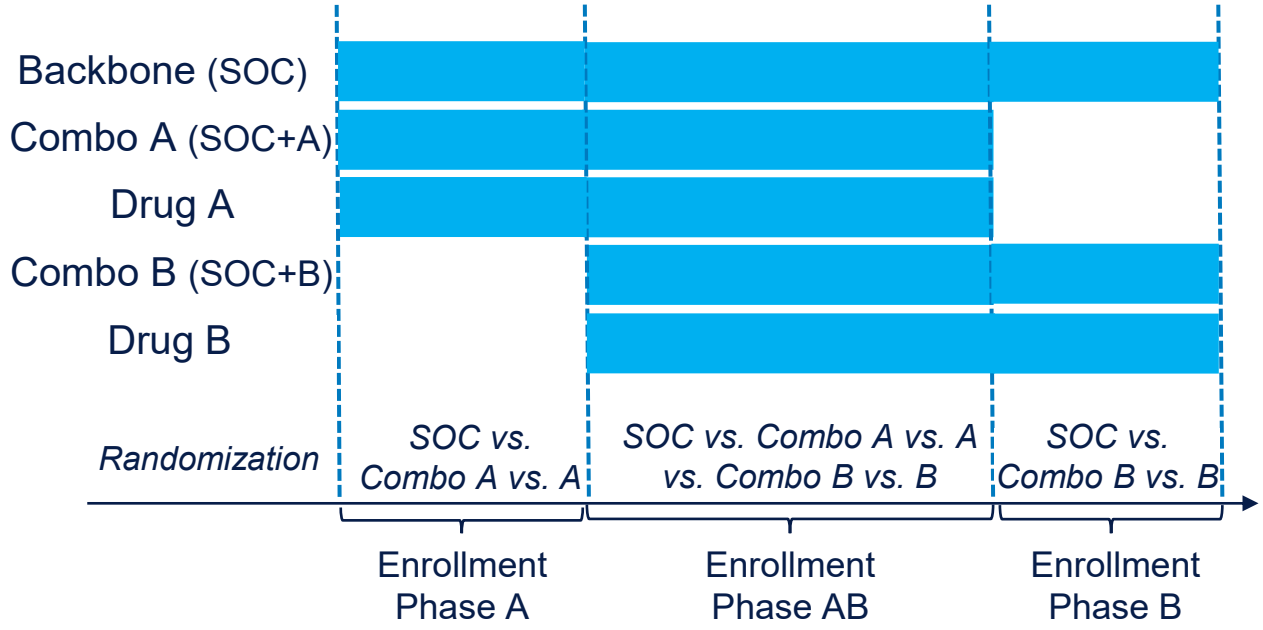
Design Scenario 3: Staggered Launch & Fix Exit

- Restriction 1 added: Combo Set B is scheduled to be launched later than Combo Set A
- Restriction 2 added: Combo Set A is scheduled to be dropped at certain time point
- *Fixed design factors*: total sample size, timing of adding/dropping Combo Sets A/B
- *Design factors to be determined*: corresponding randomization ratio by enrollment phase

✓**Optimal Randomization & Power Gain:**

- dependent on the proportion of sample size allocated to each Enrollment Phase A, AB, B



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Conclusion

Low prevalence of rare diseases poses challenges in recruiting sufficient patients for adequate statistical power

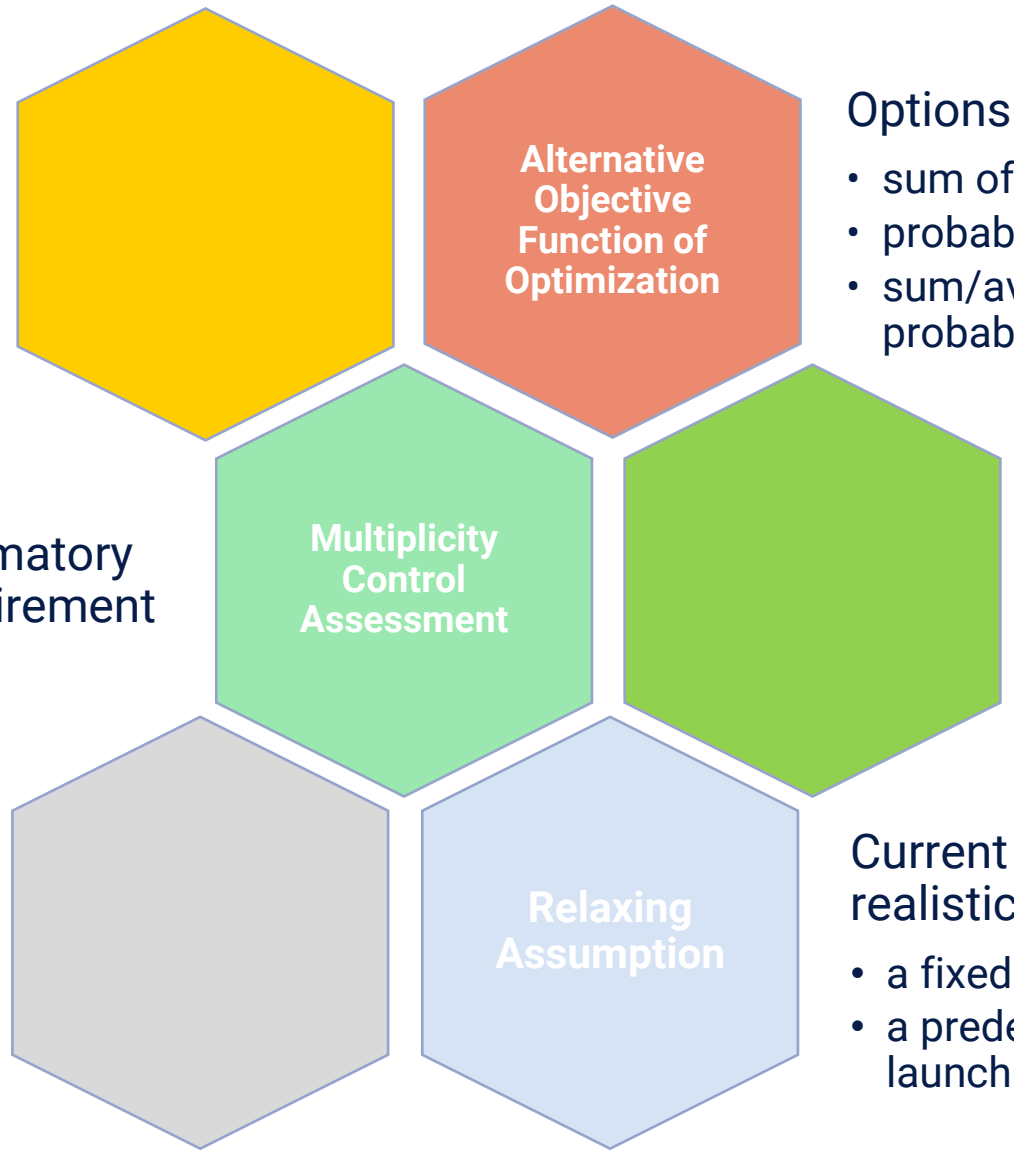
Maximize power efficiency for treatment comparisons – determining *optimal allocation ratios* across arms over time

Deliver **optimal design strategies** for *combination therapy evaluation* in a *platform trial* with *a fixed total sample size* – achieving resource savings compared to traditional designs

Platform trials evaluate multiple investigational drugs in a staggered manner against a shared reference arm – reducing overall sample size required

Ensure **operational feasibility** – adjusting theoretically derived randomization ratios

Future Work



To fulfill confirmatory trial design requirement

Options include

- sum of variances of treatment effect estimates
- probability to reject at least one null hypothesis
- sum/average of the individual rejection probabilities

Current assumptions may not be realistic in broader trial scenarios

- a fixed total sample size
- a predefined timeline for treatment arm launching and exiting

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Reference

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