# Clinical Trial Design Issues and Options for the Study of Rare Diseases

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# Financial Disclosure

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## The Issue

- Few patients.
- Few patients.
- Few patients.
- Few patients.

## The Implication

- Multi-site studies.
- Difficulty getting drugs for limited indications.
- Longer studies.
- Limited design options for clinical trials.

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# The Basic Issue

- To test efficacy, need a control group.
  - Choices: literature control, historical controls, concurrent controls, patients as own controls.
- Typical design is to recruit/assign to a treatment group/observe each group and compare outcomes.
  - But what if you could design a study using the same patient more than once?

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# Possible Design Options

- Parallel group design
- Cross-over design
- Factorial design
- Historical controls design
- Randomized withdrawal design
- Early escape design
- n-of-1 design
- Group sequential design
- Case-Control design
- Prospective cohort design
- Decision analysis-based design
- Ranking and selection design
- Adaptive design
- Risk-based allocation design
- Bayesian designs
- Enhanced designs

Reduce the number of study subjects needed by using enrolled subjects more than once.

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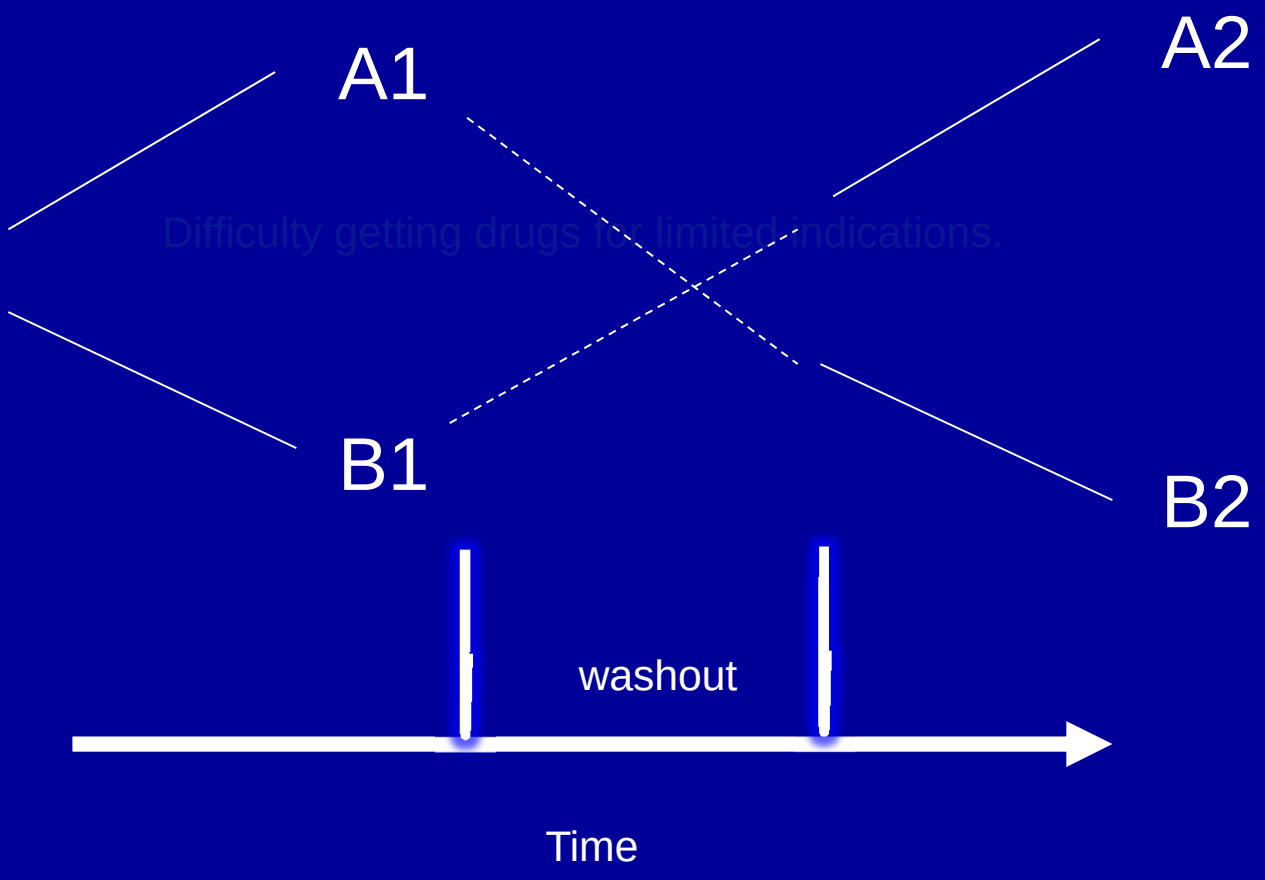
# Crossover Designs

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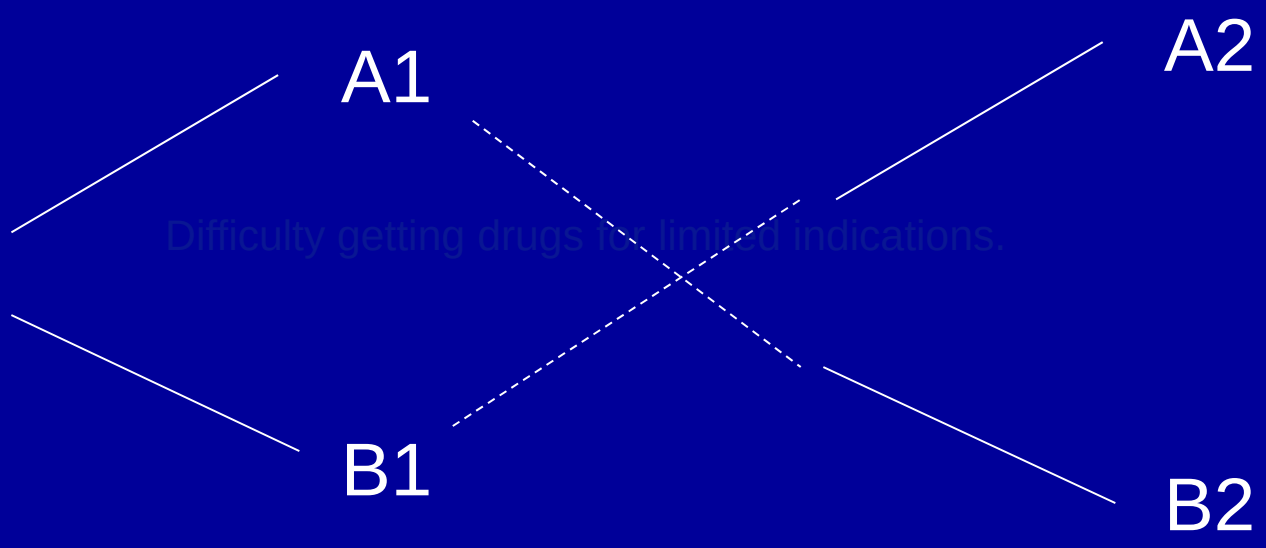
# Crossover Designs




Difficulty getting drugs for limited indications.

A1+A2 vs. B1+B2

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# Crossover Design Analysis

*Model*: $Y_{ijk} = \mu + b_{ij} + \pi_k + \phi_m + \lambda_m + \varepsilon_{ijk}$

Where i=sequence, j=patient, k=period and m=treatment

| | Period 1 | Period 2 |
|---|---|---|
| Seq. 1 | $\mu + \pi_1 + \phi_1 \ (\overline{Y}_{1.1})$ | $\mu + \pi_2 + \phi_2 + \lambda_1 \ (\overline{Y}_{2.1})$ |
| Seq. 2 | $\mu + \pi_1 + \phi_2 \ (\overline{Y}_{1.2})$ | $\mu + \pi_2 + \phi_1 + \lambda_2 \ (\overline{Y}_{2.2})$ |

Where (sequence,patient,period)

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# Treatment Effects

Estimation of Treatment Effect

$$\phi_1 - \phi_2 = \overline{Y}_{1.1} - \overline{Y}_{1.2}$$

using first period data

$$\phi_1 - \phi_2 = \{(\overline{Y}_{1.1} - \overline{Y}_{2.1}) - (\overline{Y}_{1.2} - \overline{Y}_{2.2})\}/2$$

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# Carryover Effects

Estimation of Carryover Effects

$$\lambda_1 - \lambda_2 = (\bar{Y}_{11} + \bar{Y}_{21}) - (\bar{Y}_{12} + \bar{Y}_{22})$$

Seq. AB

Seq. BA

# Using Crossover Designs

- Chronic condition.
- Relatively short study period.
- No carryover effect expected.

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# Advantages and Limitations

- **Advantages:**
  - **Doubles the effective sample size.**

- **Limitations:**
  - **Study takes twice as long.**
  - **Refusal bias.**
  - **Carryover effects make interpreting study very complex.**

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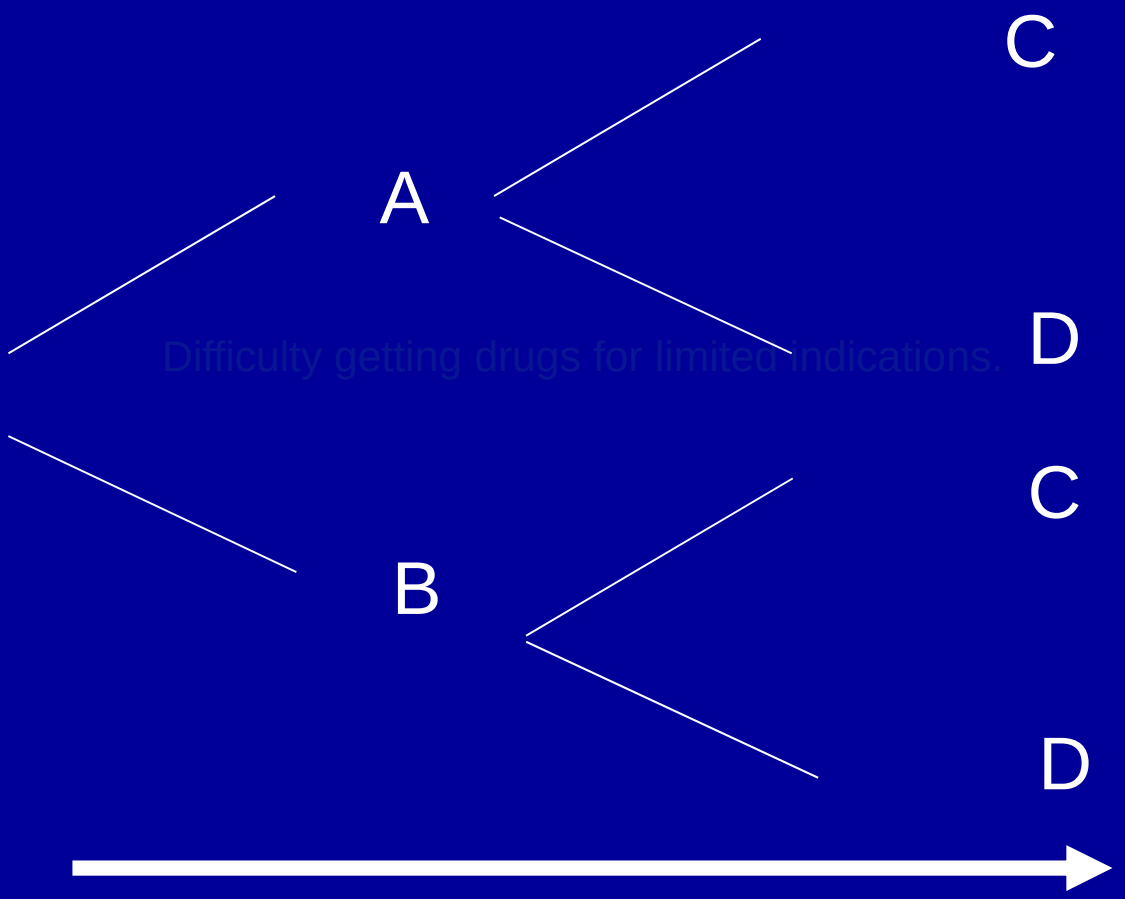
# Factorial Designs

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# Factorial Design Analysis

A+C + A+D vs. B+C + B+D

and

C+A + C+B vs. D+A + D+B

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# Factorial Design Analysis

$$y_i = \beta_0 + \beta_1 Z_{1i} + \beta_2 Z_{2i} + \beta_3 Z_{1i} Z_{2i} + e_i$$

where:

- $y_i$ = outcome score for the $i^{th}$ unit
- $\beta_0$ = coefficient for the *intercept*
- $\beta_1$ = mean difference on factor 1
- $\beta_2$ = mean difference on factor 2
- $\beta_3$ = interaction of factor 1 and factor 2
- $Z_{1i}$ = dummy variable for factor 1 (0 = 1 hr/wk, 1=4 hrs/wk)
- $Z_{2i}$ = dummy variable for factor 2 (0 = in class, 1= pull-out)
- $e_i$ = residual for the $i^{th}$ unit

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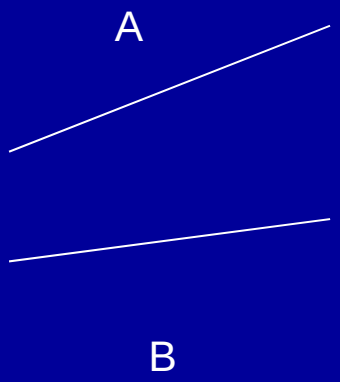
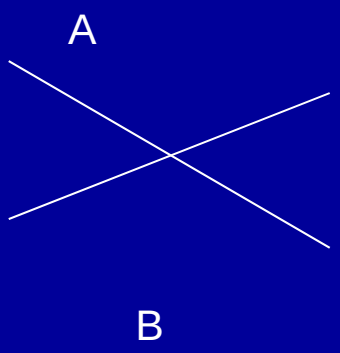
# Example of an Interaction

| | |
|---|---|
| $A_{active}$, $B_{active}$: 60% success | $A_{active}$, $B_{placebo}$: 30% success |
| $A_{placebo}$, $B_{active}$: 30% success | $A_{placebo}$, $B_{placebo}$: 30% success |

# Interactions




C




D

# Placebo Controlled Experiments (B and D are placebo)

If both questions are placebo controlled, then

A C A+C Placebo

Secondary comparison of combined effects

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# Advantages and Limitations

- Advantages:
  - Doubles the effective sample size, and it is possible for the treatments to run concurrently.

- Limitations:
  - Study could take twice as long.
  - Refusal bias.
  - Interaction effects make interpreting study very complex.

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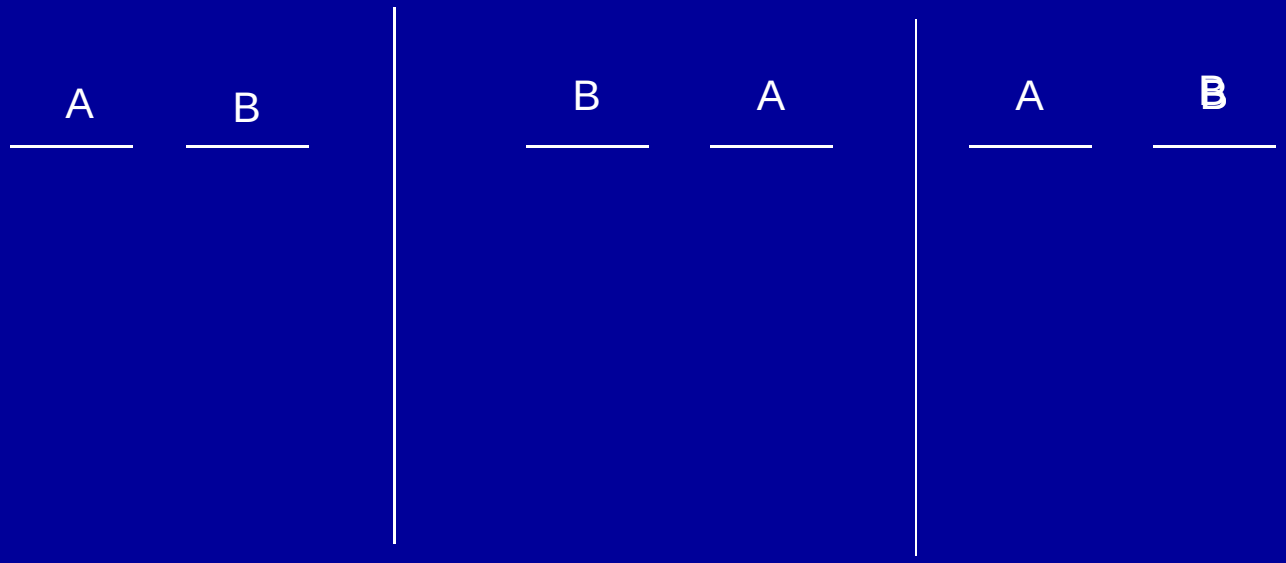
# N-of-1 Randomized Trial Design




Drug and placebo administered sequentially in a random sequence, generally 3 or more drug-placebo pairs.

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# N-of-1 Randomized Trial Design

- If patient's response was poor, that treatment stopped and the next treatment in the sequence begun immediately without breaking the randomized sequence.
- At the end of the study, the mean values for all measures and the mean differences between treatments are computed.

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# n-of-1 Randomized Trial

- **Disorder should be chronic, i.e. relatively unchanging.**
- **Treatment effect rapid.**
- **Treatment duration for optimal effect should be well known.**

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# Advantages and Limitations

- **Advantages:**
  - **Every patient receives every treatment.**
  - **Treatment is evaluated in each patient.**

- **Limitations:**
  - **Study could take very long.**
  - **Refusal bias.**
  - **Difficult to know whether design assumptions are met (duration of treatment for optimal effect ).**

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# Enhanced Trial Designs

**Using patients more than once,**

**but using the trial itself to select which group to re-use.**

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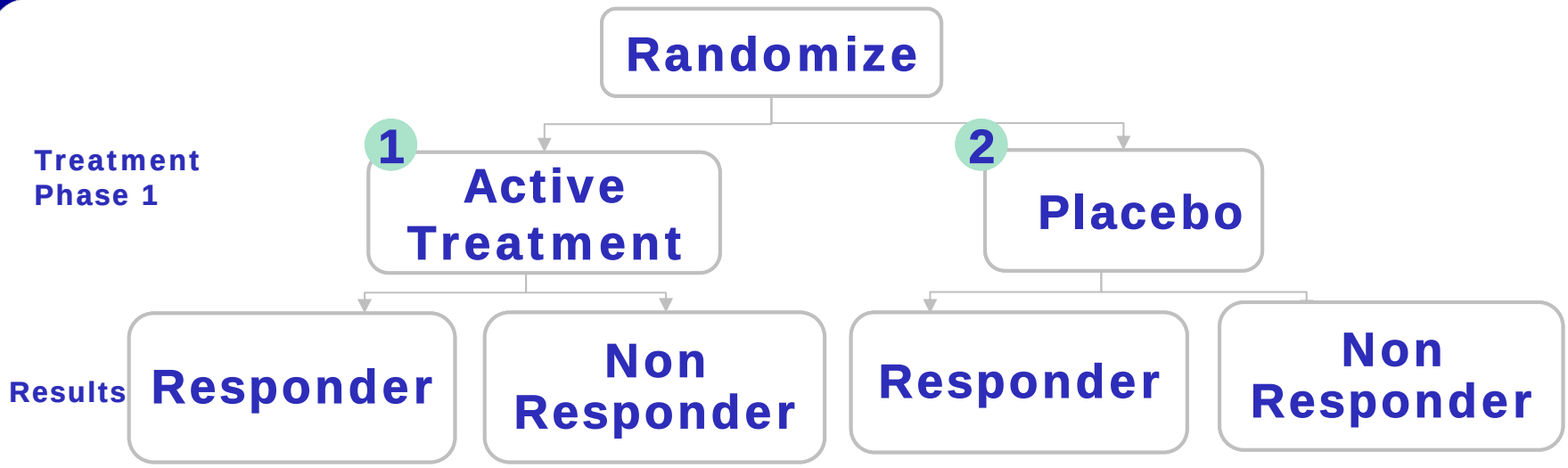
# Conventional design




**Efficacy analysis is based on comparing the results of the two treatment arms**

# Sample Size Required for a Given Power

| | Response rate | | |
|---|---|---|---|
| | Drug | Placebo | Difference |
| Single Phase Design | 60% | 45% | 15% |

| | Total *n* |
|---|---|
| Power | Single Phase Design |
| 70% | 274 |
| 80% | 346 |
| 90% | 462 |

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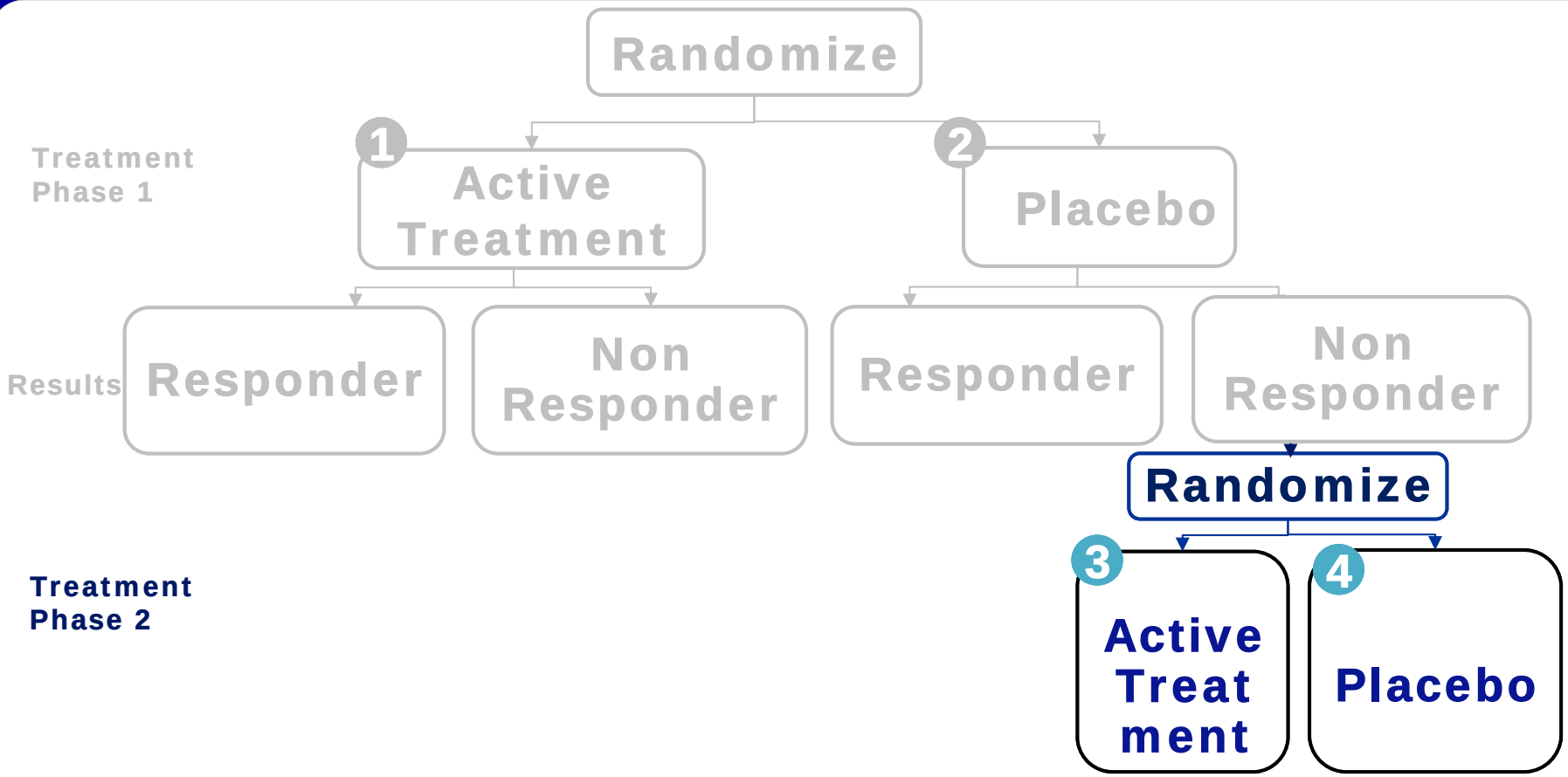
# Single Enhanced Design



# Comparison of Sample Size Required for a Given Power

| | Response rate | | |
|---|---|---|---|
| | Drug | Placebo | Difference |
| Single Phase Design or SPCD Phase 1 | 60% | 45% | 15% |
| SPCD Phase 2 | 50% | 25% | 25% |

1.6X

| | Total *n* | |
|---|---|---|
| Power | Single Phase Design | SPCD |
| 70% | 274 | **157** |
| 80% | 346 | **199** |
| 90% | 462 | **266** |

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## Comparison of Sample sizes between Parallel and SPD designs for three scenarios with low placebo response rate.

| | Stage 1 | | Stage 2 | | Parallel | SPD |
|---|---|---|---|---|---|---|
| | Drug | Pbo | Drug | Pbo | n | n |
| Scenario 1 | .40 | .20 | .30 | .10 | 164 | 101 |
| Scenario 2 | .30 | .15 | .20 | .05 | 242 | 134 |
| Scenario 3 | .25 | .10 | .20 | .05 | 200 | 116 |

All calculations are based on two-tailed alpha = 0.05, 80% power. For the SPD, the estimates are based on a 2:1 initial allocation of placebo:drug, and assumed retention of placebo patients from Stage 1 to Stage 2 = 90%.

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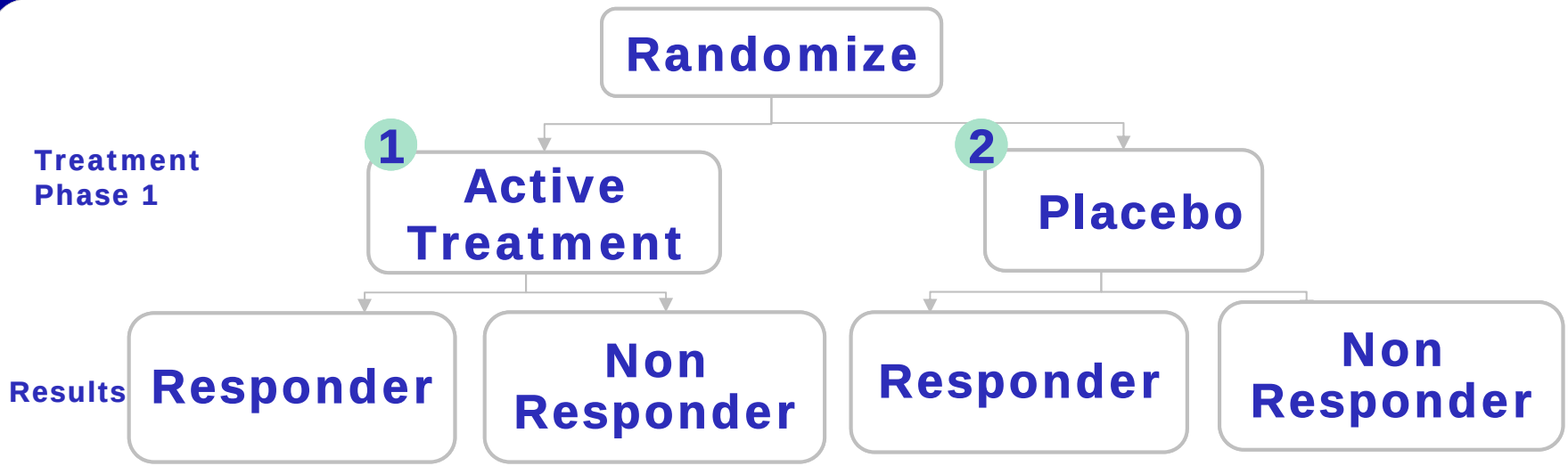
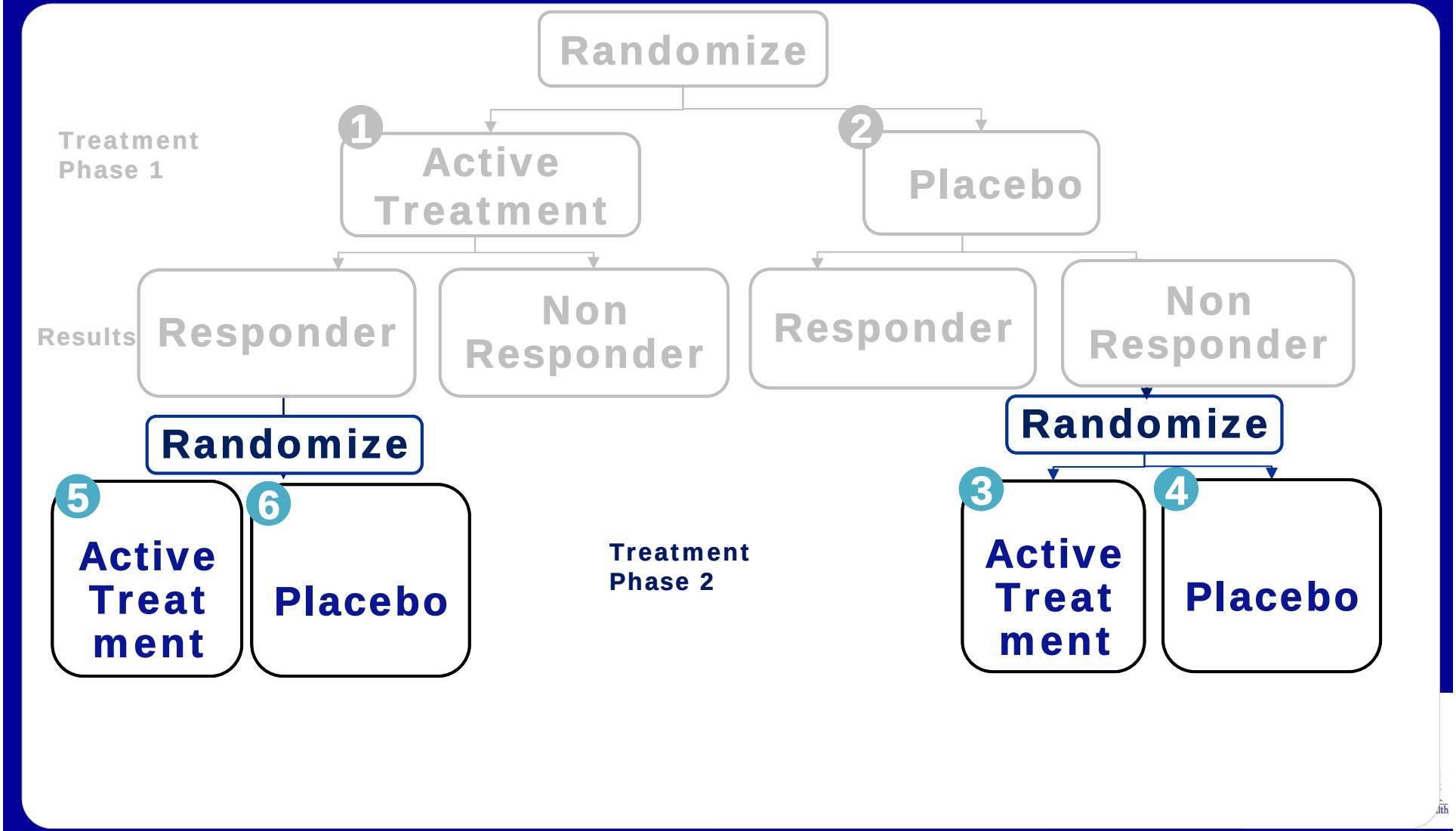
# Issues

- 2 chances to receive the active agent.
- Study takes at least twice as long.
- Efficiency depends upon response rate of those receiving placebo (placebo effect)
- Savings in sample size since all patients are used once and some are used twice.

# Conventional design



# Double Enhanced Design



# Summary

- When the number of study subjects is limited, it is possible to design studies that “re-use” the subjects enrolled to increase study power .
- Such designs require a number of assumptions that may or may not be verifiable.
- For some assumptions, it may be possible to test for their effect, but this is done after the study concludes and may complicate reporting and interpretation of results.
- Analyses are more complex and require good statistical advice at the time the study is be designed.

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# Thank You

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