RARE CLINICAL DISEASES RESEARCH NETWORK

National Institutes of Health

Office of Rare Diseases Research
National Center for Advancing Translational Sciences
(ORDR, NCATS)

Clinical trial design issues and options for the study of rare diseases

November 19, 2018

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Rare Diseases Clinical Research Network

Rare Diseases Clinical Research Network (RDCRN) is coordinated by Office of Rare Diseases Research, NCATS.
Funding and programmatic support is provided by ORDR in collaboration with participating NIH Institutes.

Conflicts of Interest

None

Clinical Trial Design Principles

- The design and conduct of any type of clinical trial requires three considerations:
  1. the study should examine valuable and important biomedical research questions;
  2. the study must be based on a rigorous methodology that can answer a specific research question being asked; and
  3. the study must be based on a set of ethical considerations, adherence to which minimizes risks to individuals.

Clinical Trial Designs for Rare Diseases

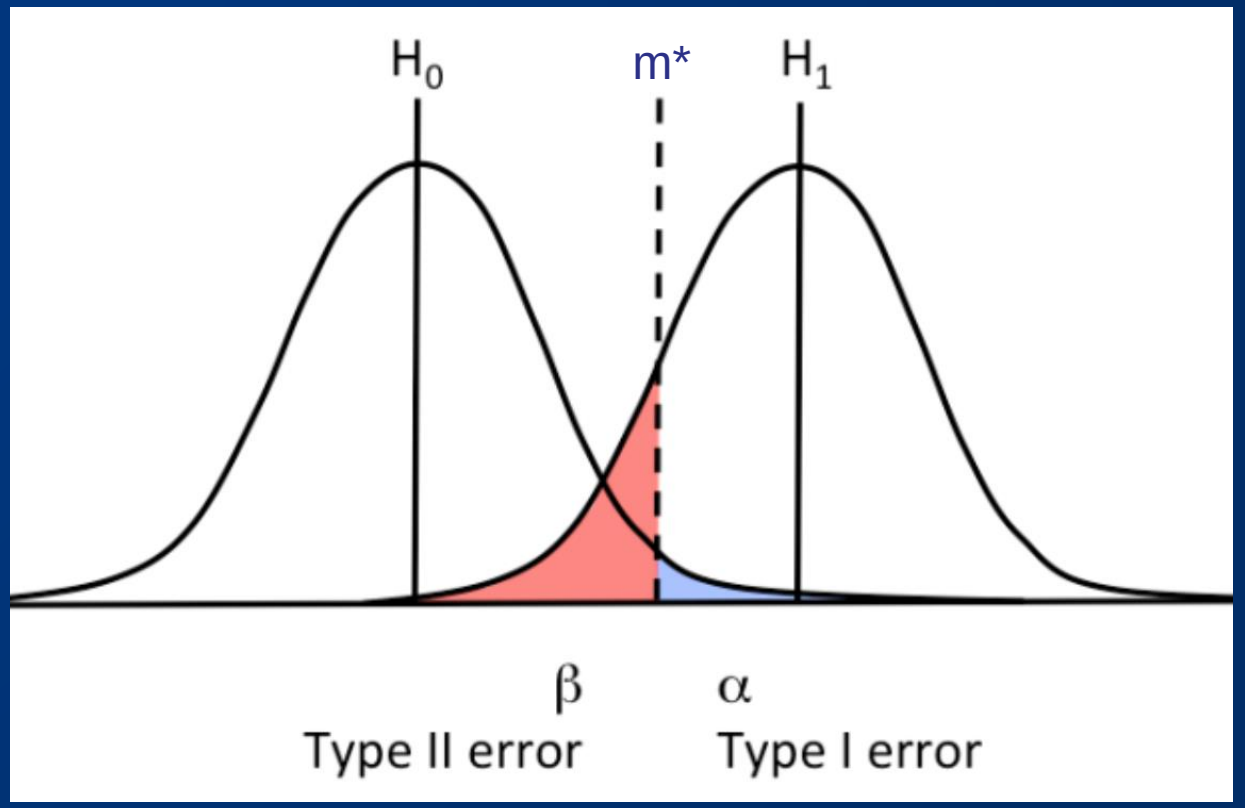
A study design that is considered appropriate should include sufficient sample size (n, statistical power, and proper control of bias) to allow meaningful interpretation of the results.

- Enrolling the planned number of subjects is often a major barrier in orphan diseases.

Sample Size Considerations

1. The type 1 error α
2. The type 2 error β
3. One sided vs. two sided hypothesis
4. The study group mean under the null hypothesis μ
5. The minimum increase in the experimentally treated group that we desire to detect $\mu_1 - \mu_2$
6. The variation in the study population (i.e., standard deviation). σ

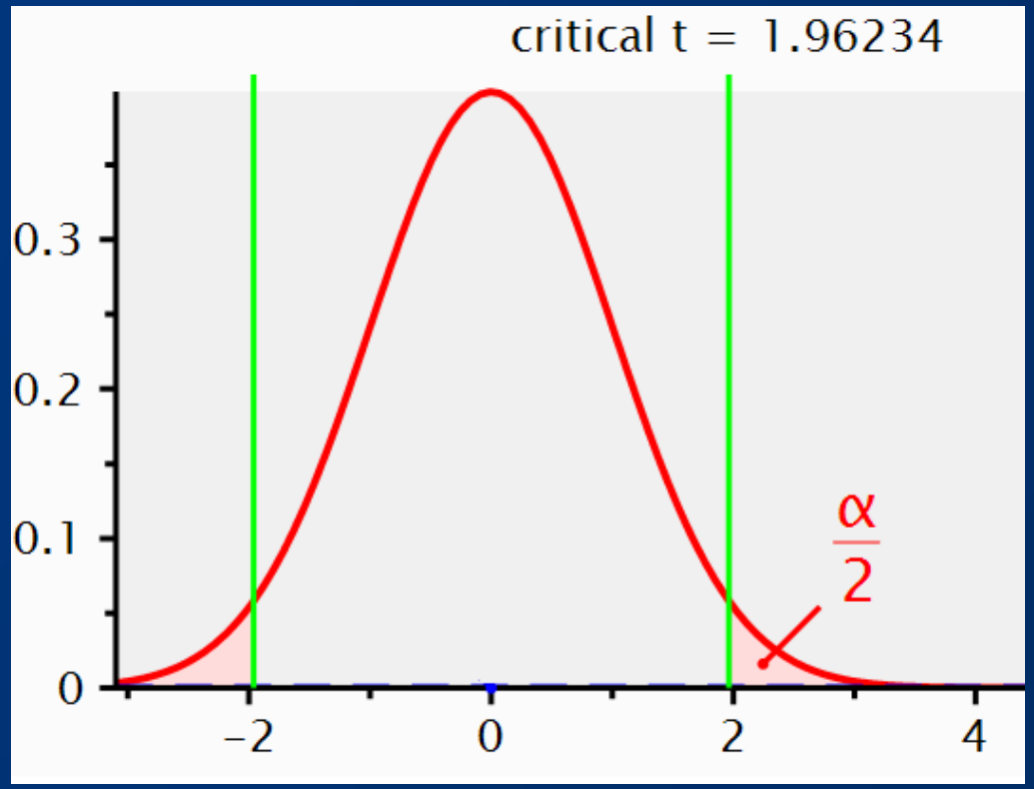
Type 1 and Type 2 errors



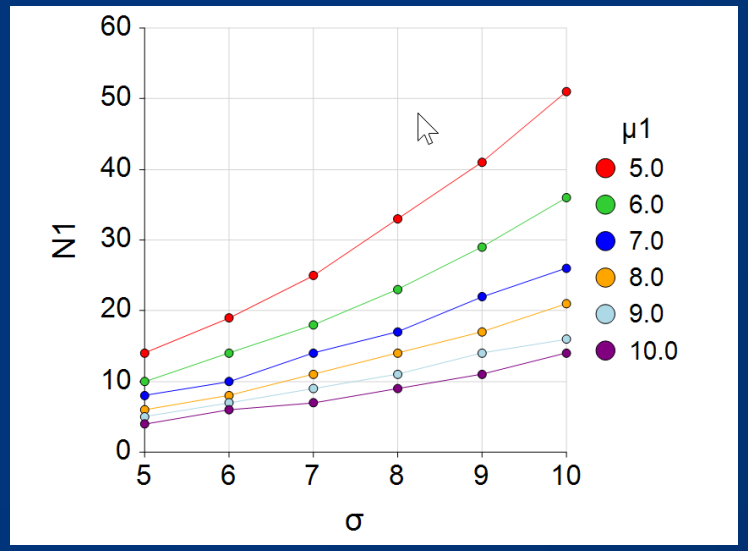
Blue = Probability of observing a result m* or larger given H_0

Orange = Probability of observing a result m* or less given H_1

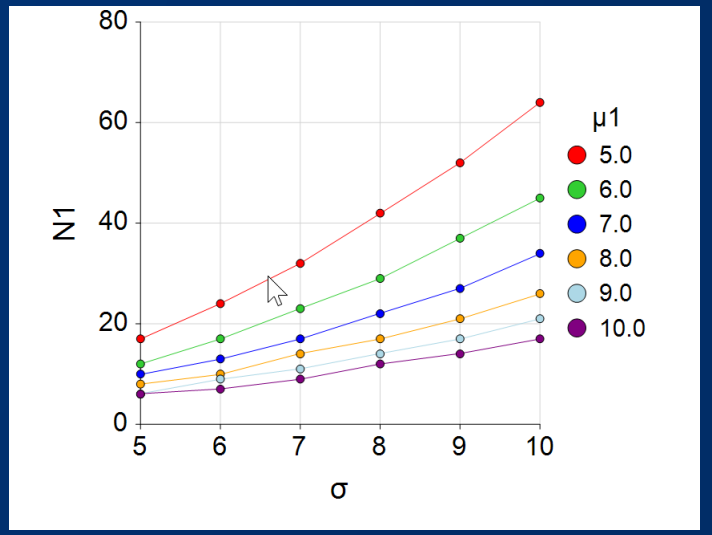
Type 1 error: 1 vs. 2-sided



1-sided vs. 2-sided



1-sided



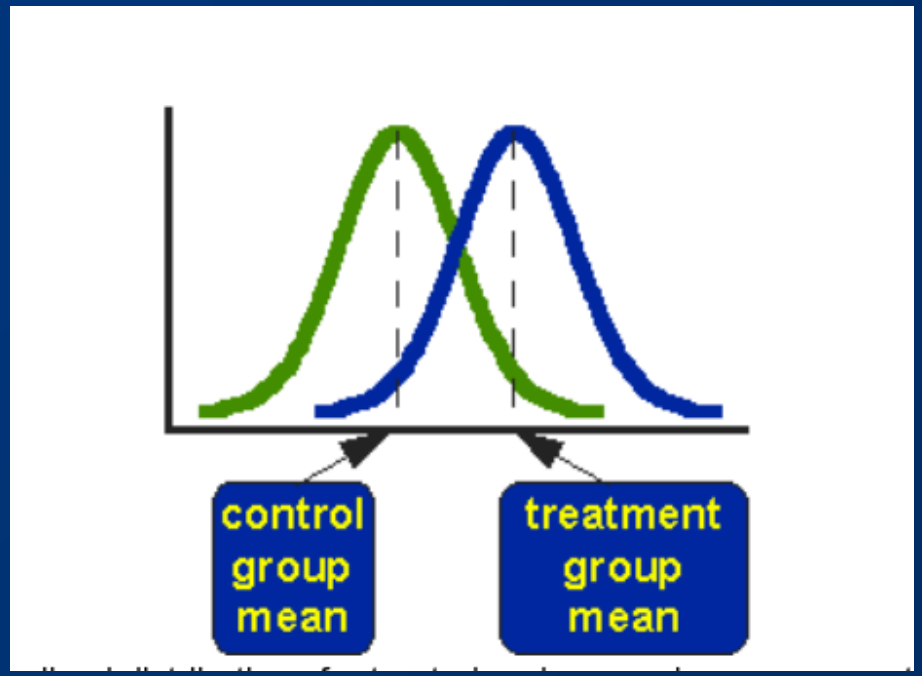
2-sided

20-30% more subjects needed for a 2-sided test as compared to a 1-sided test of significance.

Sample Size Considerations

- The type 1 error α
- The type 2 error β
- One sided vs. two sided hypothesis
- The study group mean under the null hypothesis μ
- The minimum increase in the experimentally treated group that we desire to detect $\mu_1 - \mu_2$
- The variation in the study population (i.e., standard deviation). σ

The statistics of comparing 2 means

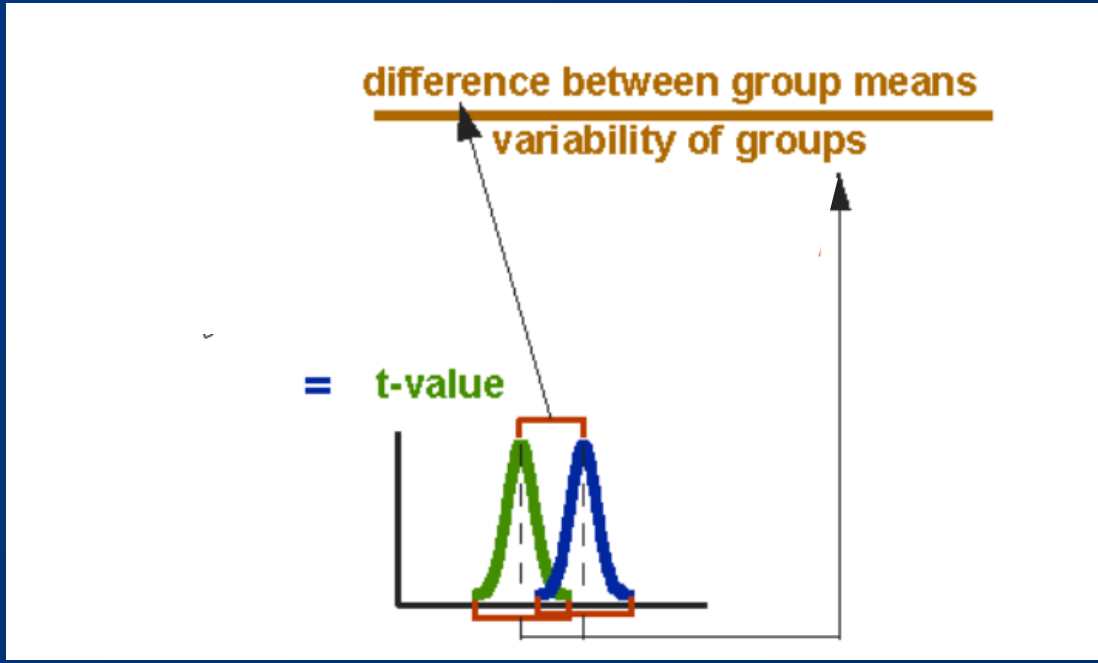


$$t = \frac{\mu_T - \mu_C}{\sqrt{\frac{var_T}{n_T} + \frac{var_C}{n_C}}}$$

T = Treatment
C= Control

$$var = \sigma^2$$

T statistic



T = Treatment
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t statistic

$$t = \frac{\mu_T - \mu_C}{\sqrt{\frac{var_T}{n_T} + \frac{var_C}{n_C}}}$$

T = Treatment
C= Control

$$var = \sigma^2$$

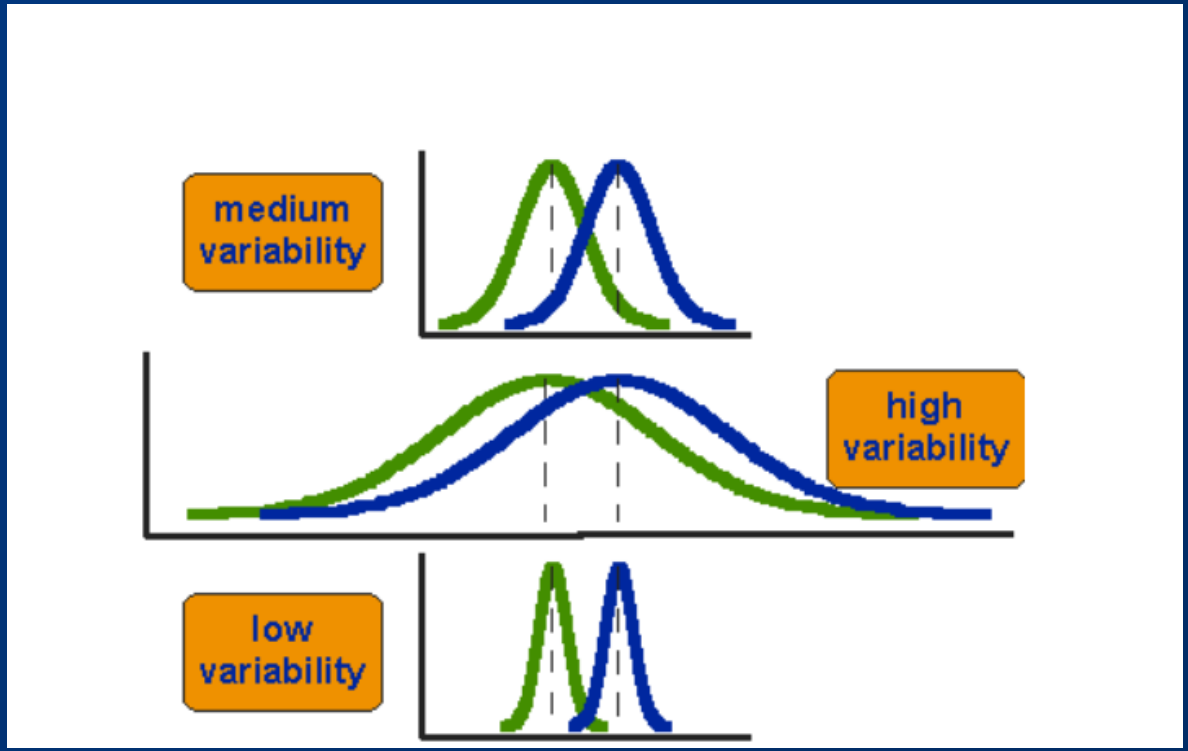
Sample Size

$$n = \sigma^2 \frac{(t_{\alpha/2} + t_{\beta})^2}{(\mu_0 - \mu_a)^2}$$

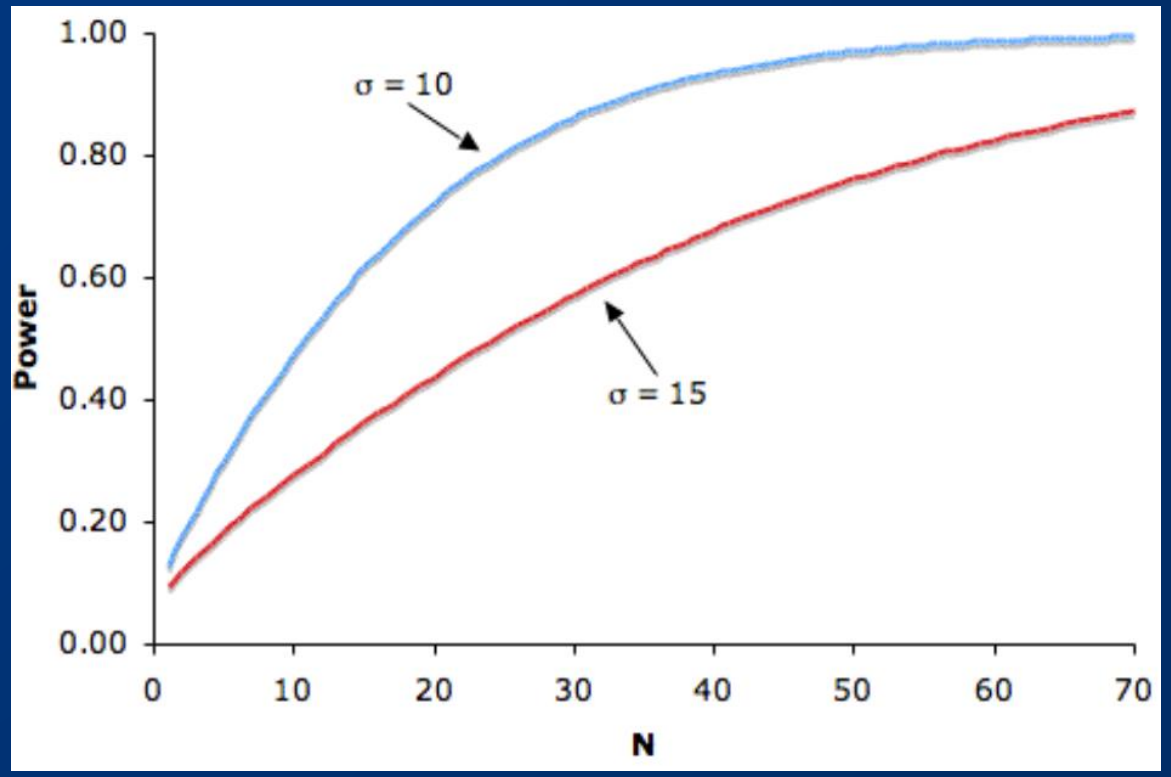
Sample size is directly proportional to the variance,

inversely proportional to the detectable difference.

Variance



Power as a function of σ



Take home message

- When designing a trial:
  - Decide whether it is a 2-sided or 1-sided question.
  - Consider the magnitude of the “minimally clinically significiant difference” the study is designed to detect.
  - Imagine ways that can reduce the variability of the treatment response.

Reducing variance example

- Modeling source of variance in endpoints
- Premise that sample size calculations should utilize the same statistical approach as will be used in the analysis.
  - Accounting for covariates at enrollment in predicting outcomes.
  - Using the modeled or “adjusted” estimates of means and variances in sample size calculations.
  - Incorporating adaptive designs with sample size re-estimation.

C-Peptide Levels at 1 Year from the TrialNet New Onset T1D Trials

Trial			Design Parameters	
			Standard Deviation	Control Group Mean
Rituximab (TN05)			0.179	0.248
GAD (TN08)			0.179	0.248
Abatacept (TN09)			0.179	0.248
Canakinamab (TN14)			0.179	0.248
Studies Combined			--	--

The Model

A linear model adjusted for baseline C-peptide, and age.

$$\log(Cp_{12}+1) = \hat{\beta}_0 + \hat{\beta}_{Cp_0} \log(Cp_0+1) + \hat{\beta}_{Age} X_{Age} + \varepsilon$$

Cp_y = c-peptide level at time "y"

X_{Age} = Age at trial entry

$\hat{\beta}_0, \hat{\beta}_{Cp_0}, \hat{\beta}_{Age}$ = coefficients to be estimated from the model fit

ε = measurement error (normally distributed)

C-Peptide Levels at 1 Year from the TrialNet New Onset T1D Trials

Trial	Model Based†		Design Parameters	
	SRMSE*	Control Group Mean	Standard Deviation	Control Group Mean
Rituximab (TN05)	0.1489	0.3562	0.179	0.248
GAD (TN08)	0.1522	0.3467	0.179	0.248
Abatacept (TN09)	0.1462	0.3338	0.179	0.248
Canakinamab (TN14)	0.1548	0.3306	0.179	0.248
Studies Combined	0.1513	0.3446	--	--

†The linear model is adjusted for baseline C-peptide, and age. The estimated mean is evaluated at the mean baseline C-peptide level, and the mean age.

Comparative Study Design

Trial	Actual Planned Sample Size including 10% inflation factor	Model Based Sample Size including 10% inflation factor
TN-05 (Rituximab)	66	34
TN-08 (GAD)	126	66
TN-09 (Abatacept)	108	55
TN-14 (Canakinumab)	66	34

Modelled design requires 52% the number of subjects

Study Designs

Study Designs

- Randomized clinical trial:
  - Assign participants as they are enrolled to an experimental treatment or a standard treatment (control).
  - Treat and assess the outcome.
  - When the outcome for the last participant enrolled has been observed, compare the experimental and control arms on their average response.

The Standard Design

1 Participant = 1 Treatment

1 Participant = 1 Outcome

The Standard Design

1 Participant = 1 Treatment

1 Participant = 1 Outcome

The Enhanced Design

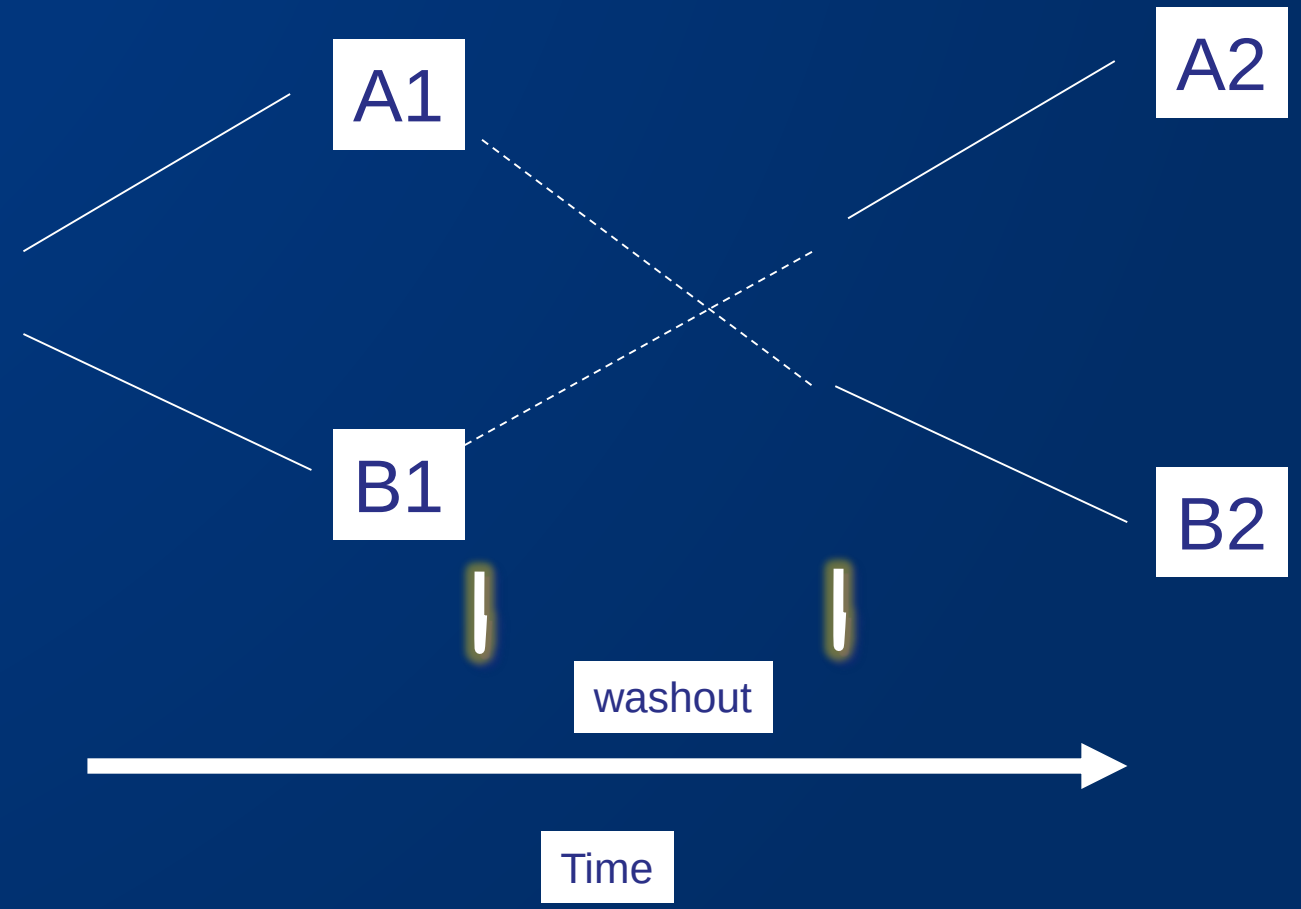
1 Participant > 1 Treatment

1 Participant > 1 Outcome

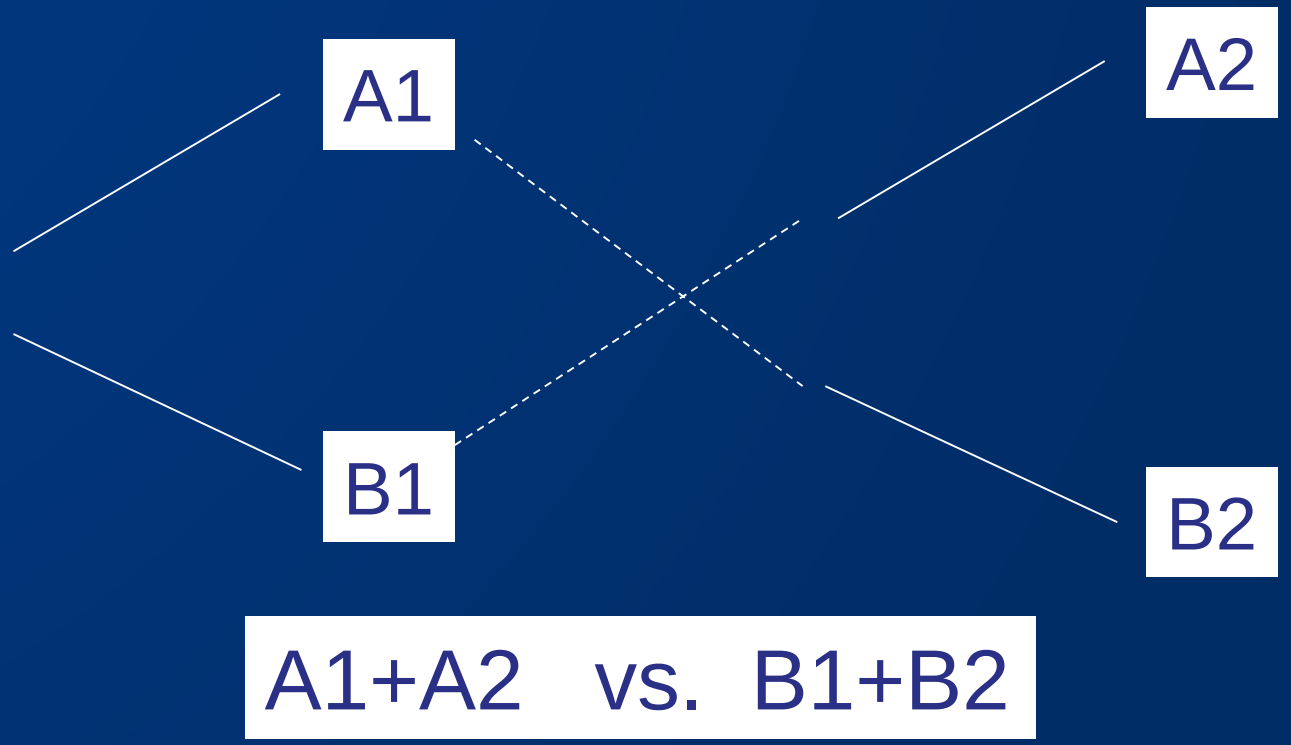
The Enhanced Design

- Cross over designs
- Factorial Designs
- Single and Dual Enhanced Designs
- Sequential Multiple Assignment Randomized Trials
- N=1 Designs

Crossover Designs

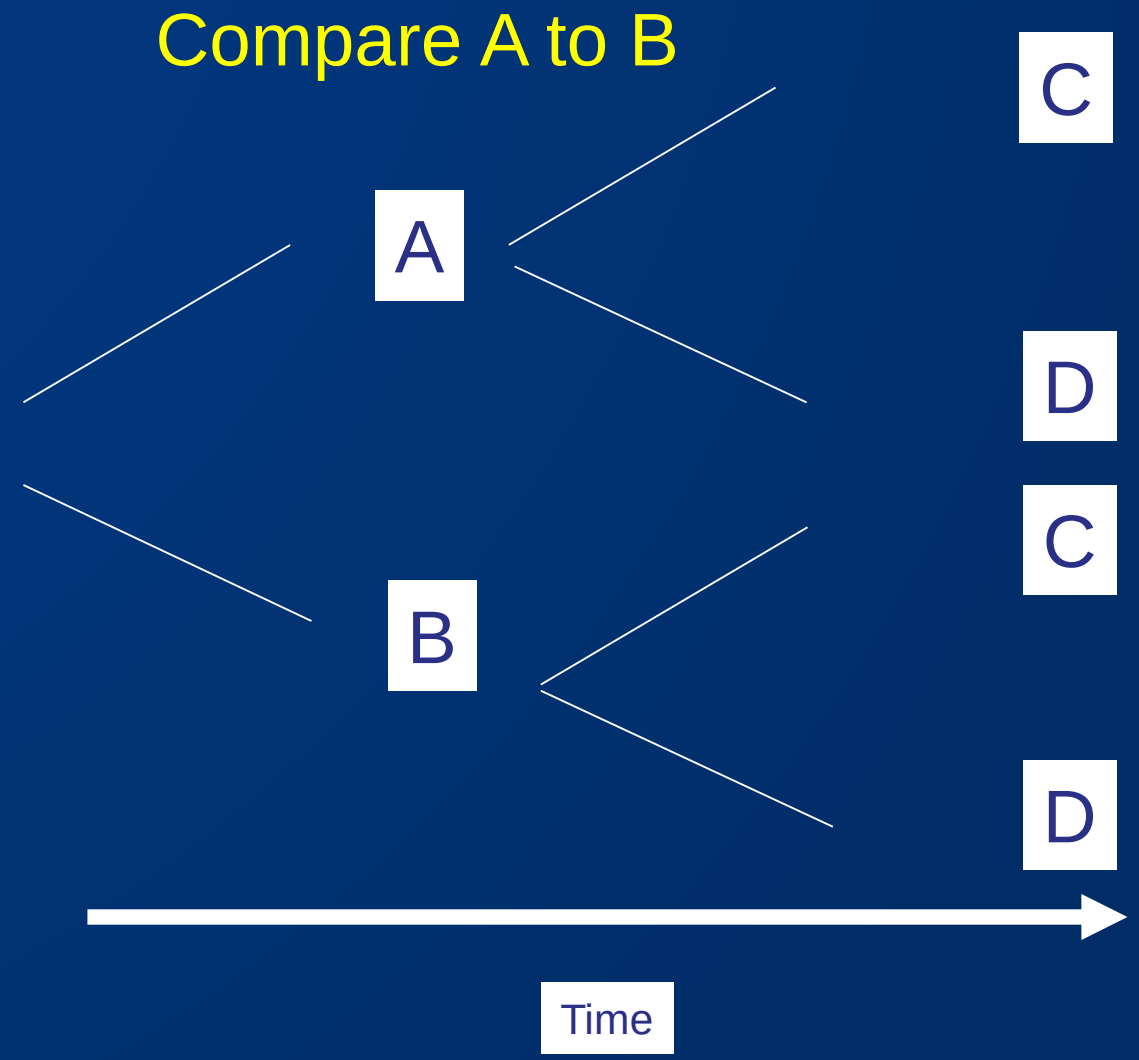


Crossover Designs



A1+A2 vs. B1+B2

Factorial Designs

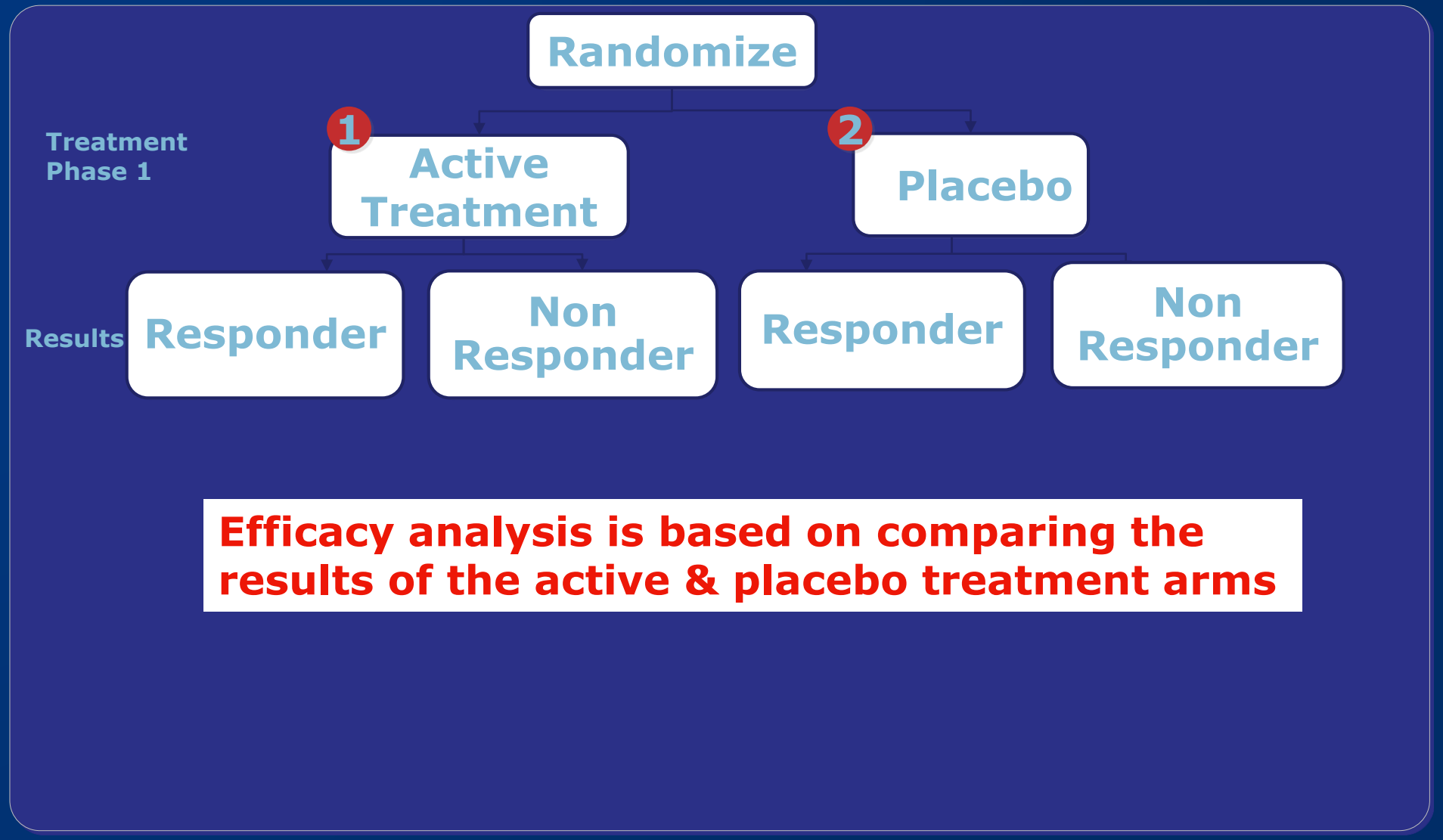


Enhanced Trial Designs

Using patients more than once,

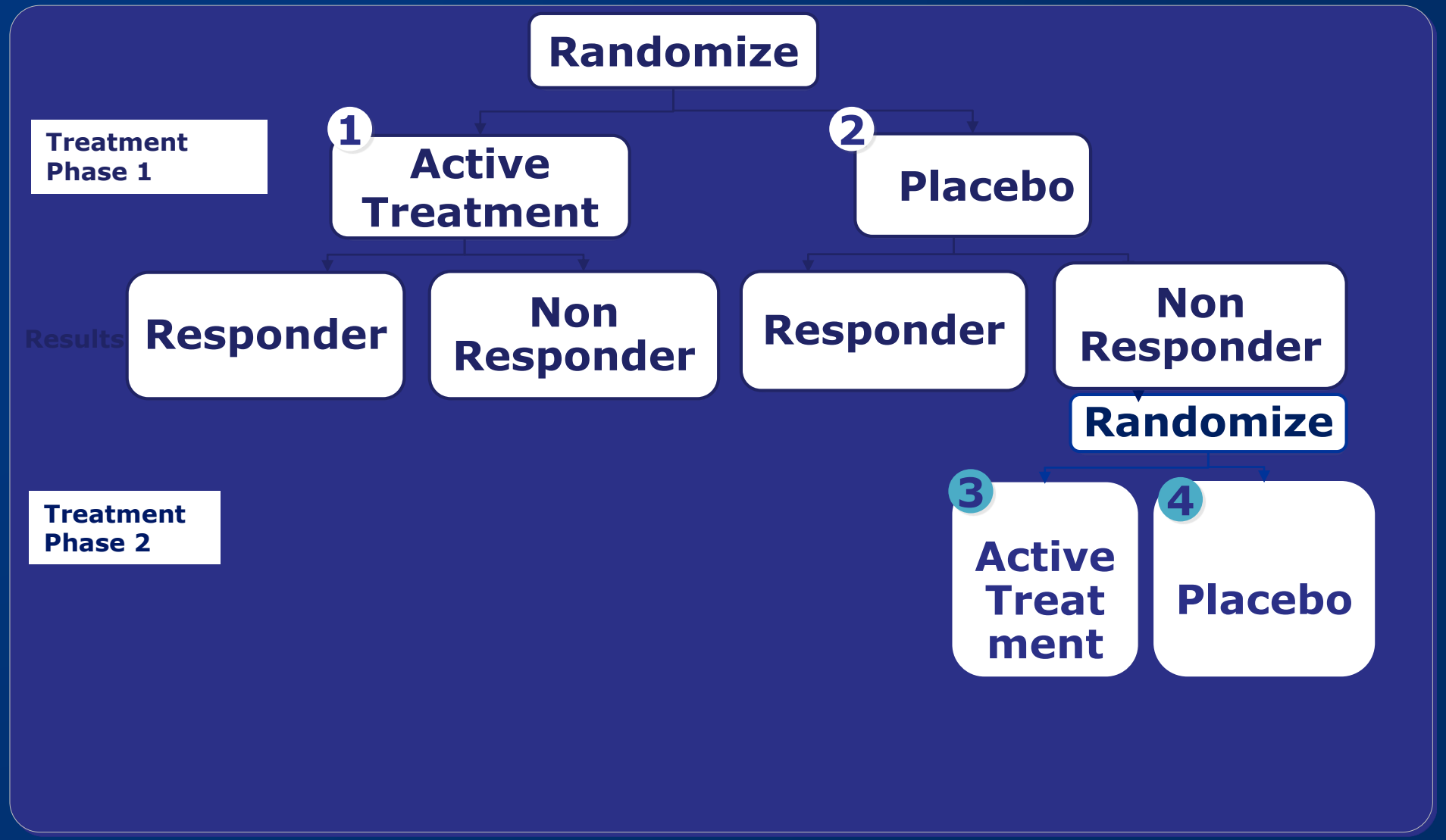
but using the trial itself to select which group to re-use.

Conventional design

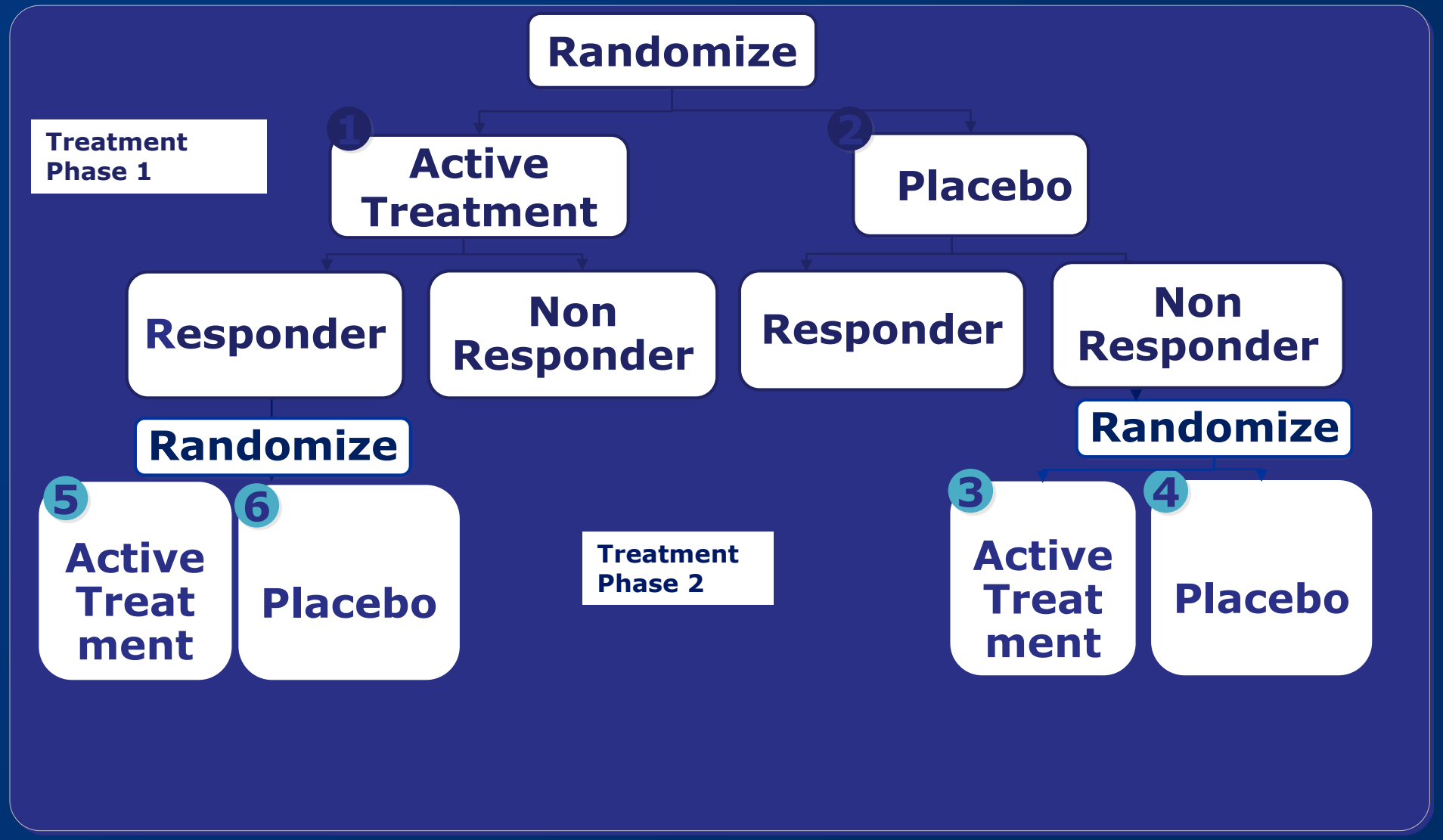


Efficacy analysis is based on comparing the results of the active & placebo treatment arms

Single Enhanced Design



Double Enhanced Design



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

	Stage 1		Stage 2		Parallel	Enhanced
	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 enhanced, 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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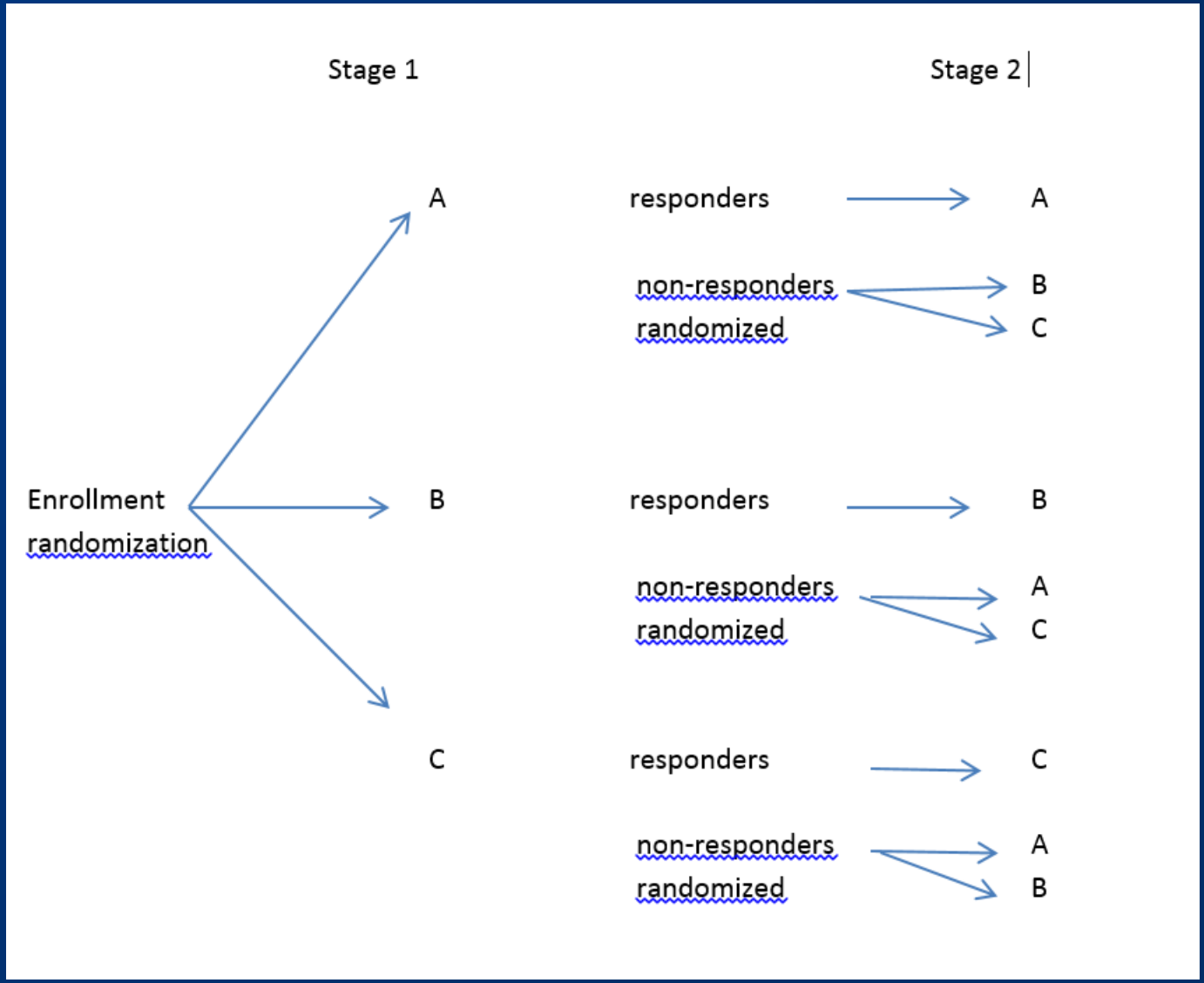
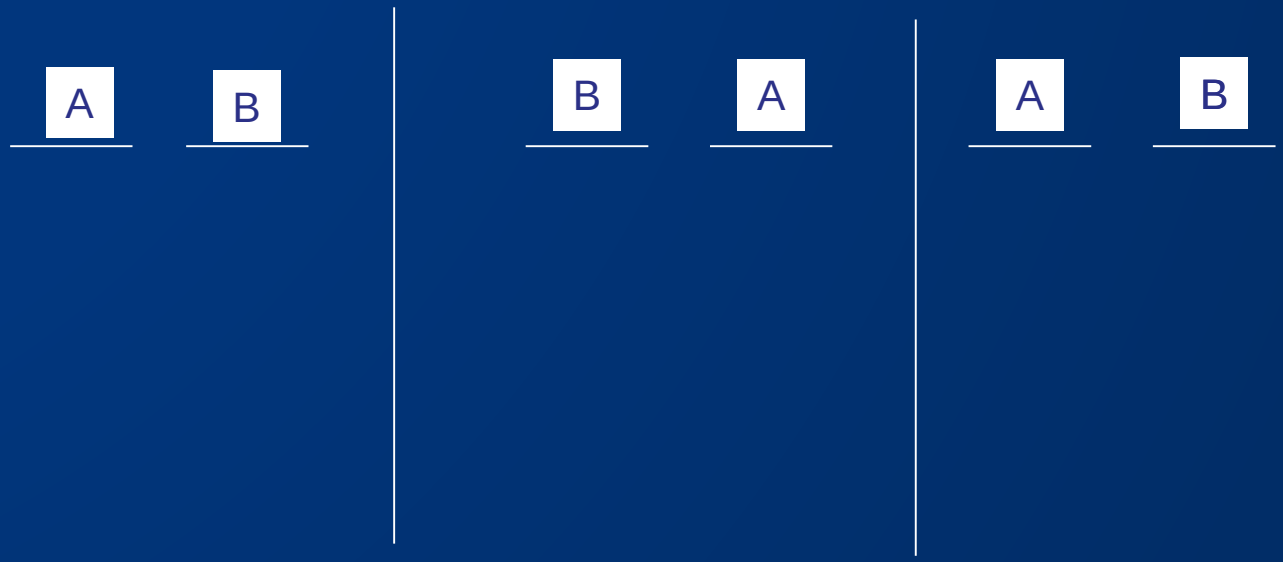
Issues

- 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.

Sequential Multiple Assignment Randomized Trials



N=1 Randomized Trial Design



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

Concept

- Can be thought of as multiple cross-over designs in the same participant.
- The successful N=1 design requires commitments on the part of the clinician and the participant.
- Suitable for chronic or slowly progressive disorders.

Concept

- When participants experience the different treatments being studied, then their outcomes can inform clinical decision making at the level of the individual (i.e., personalized medicine).
- The data across individuals can also be aggregated according to treatment groups for comparative effectiveness outcomes.

N=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.

N=1 Randomized Trial

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

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).

Conclusions

- Journal editors often prefer 2-sided testing designs.
- Looking for larger differences requires fewer study participants.
- Reducing the variance through adjusting for confounders has the same proportional effect on sample size as does looking for larger differences.

Conclusions

- 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 being designed.

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Thank you

Day *et al. Orphanet Journal of Rare Diseases* (2018) 13:195
https://doi.org/10.1186/s13023-018-0931-2

Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

Recommendations for the design of small population clinical trials

Simon Day[1*], Anneliene Hechtelt Jonker[2], Lilian Pek Lian Lau[2], Ralf-Dieter Hilgers[3], Ilan Irony[4], Kristina Larsson[5], Kit CB Roes[6] and Nigel Stallard[7]