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 study of rare diseases

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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.

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Conflicts of Interest

None

Clinical Trial Design Principles

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

*Small Clinical Trials: Issues and Challenges
http://www.nap.edu/catalog/10078.html

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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.
- Some designs are better than others for rare diseases

*Small Clinical Trials: Issues and Challenges
http://www.nap.edu/catalog/10078.html

Alternative Designs

- 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

The Standard Design

- 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

Study Design Enhancements

- 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.

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

Trial	Model Based†		Observed		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					--	--

*$\log[X_{Cpep} + 1]$)

†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.

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

Trial	Model Based†		Observed		Design Parameters	
			Standard Deviation	Control Group Mean	Standard Deviation	Control Group Mean
Rituximab (TN05)			0.2578	0.3405	0.179	0.248
GAD (TN08)			0.2111	0.3491	0.179	0.248
Abatacept (TN09)			0. 2557	0.3251	0.179	0.248
Canakinamab (TN14)			0.2592	0.3155	0.179	0.248
Studies Combined			0.2409	0.3235	--	--

*$\log[X_{Cpep} + 1]$)

†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.

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

Trial	Model Based†		Observed		Design Parameters	
	SRMSE*	Control Group Mean	Standard Deviation	Control Group Mean	Standard Deviation	Control Group Mean
Rituximab (TN05)	0.1489	0.3562	0.2578	0.3405	0.179	0.248
GAD (TN08)	0.1522	0.3467	0.2111	0.3491	0.179	0.248
Abatacept (TN09)	0.1462	0.3338	0. 2557	0.3251	0.179	0.248
Canakinamab (TN14)	0.1548	0.3306	0.2592	0.3155	0.179	0.248
Studies Combined	0.1513	0.3446	0.2409	0.3235	--	--

*$\log[X_{Cpep} + 1]$)

†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

The Enhanced Design

1 Participant = 1 Treatment

1 Participant = 1 Outcome

The Enhanced Design

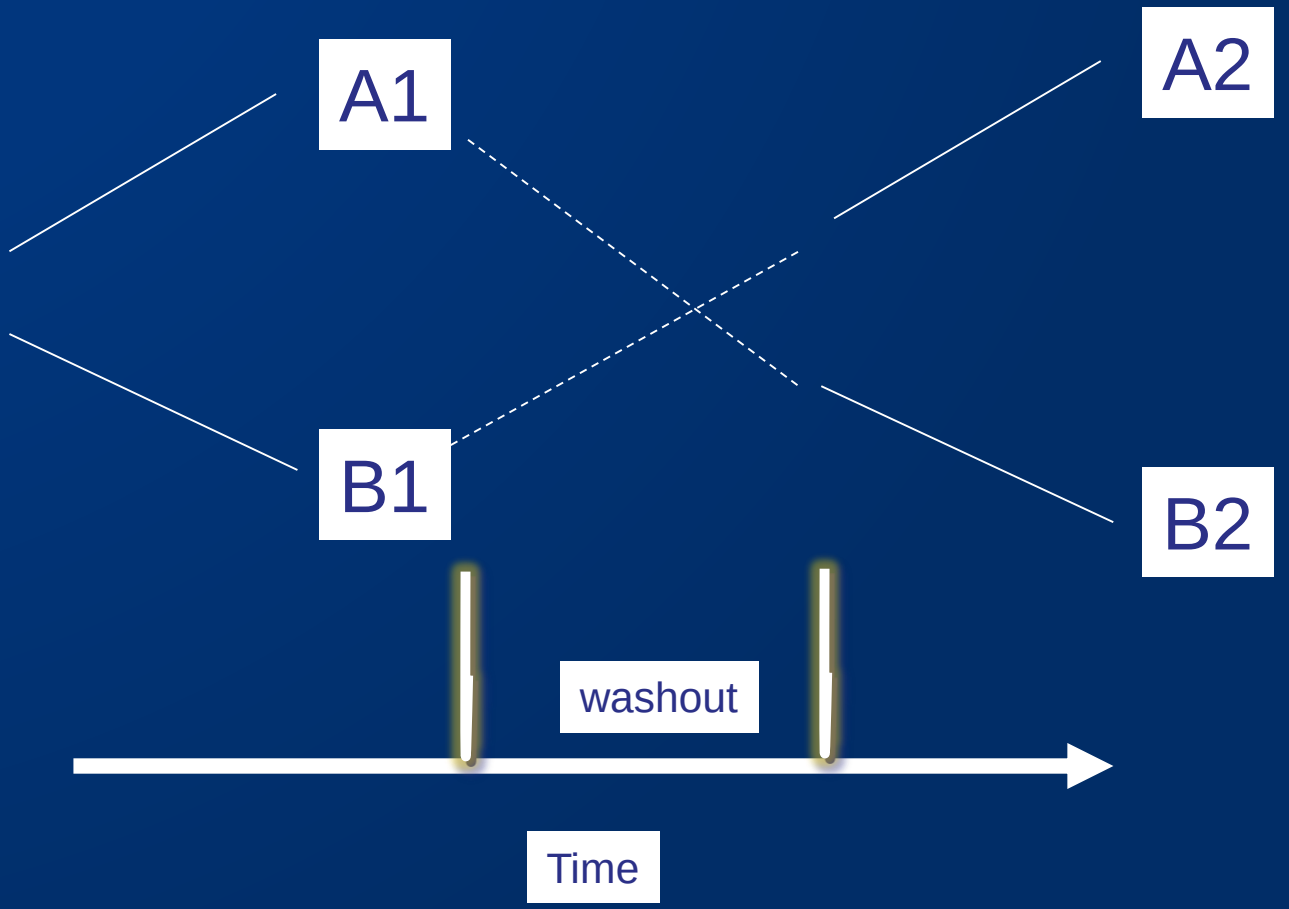
1 Participant > 1 Treatment

1 Participant > 1 Outcome

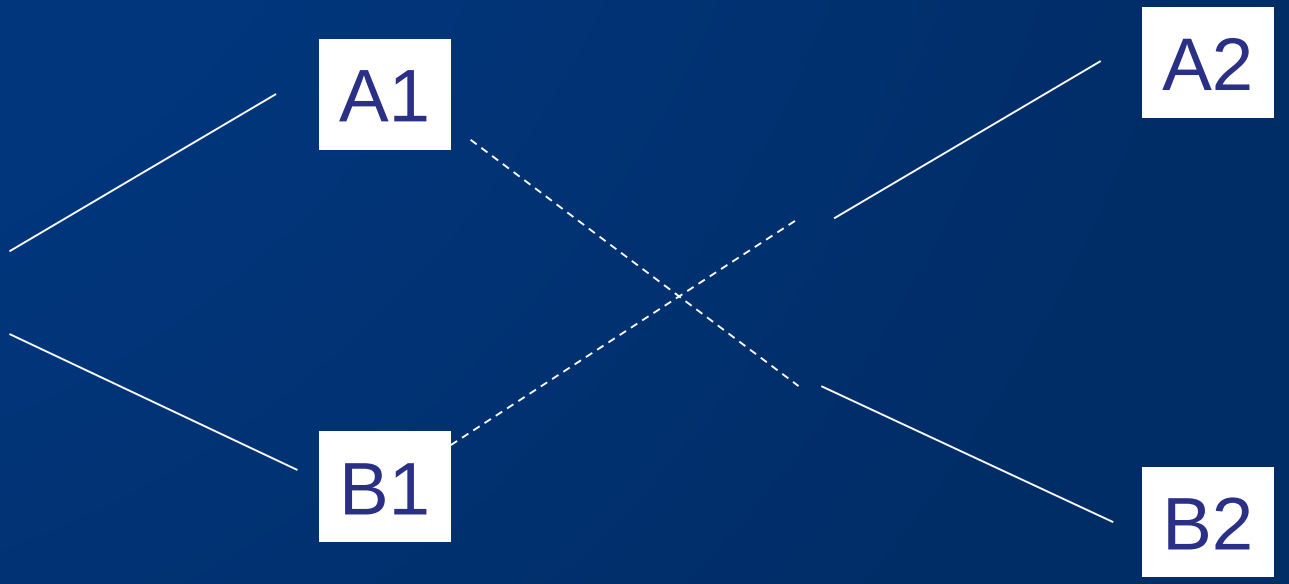
The Enhanced Design

- 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

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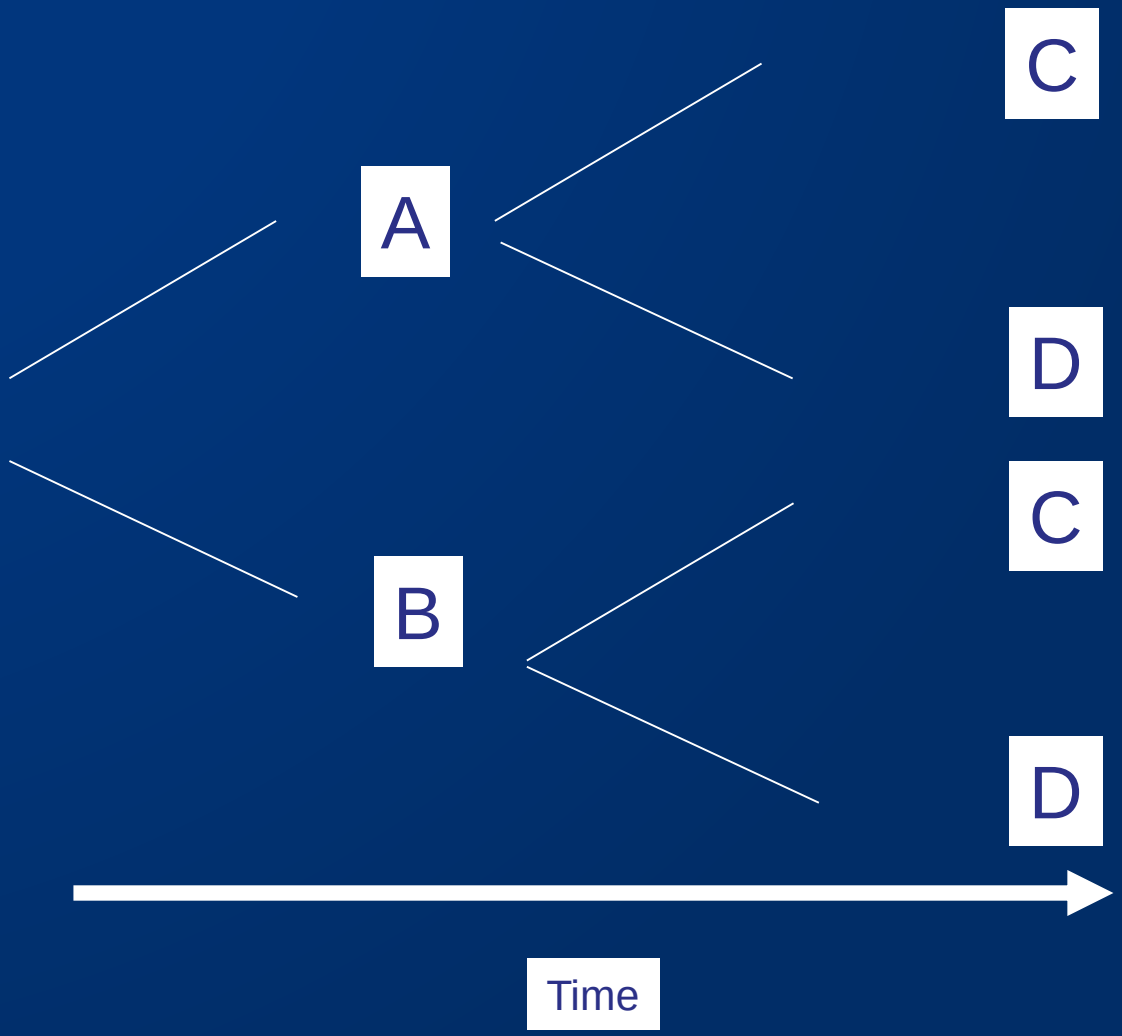
Factorial Designs



Factorial Design Analysis

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

and

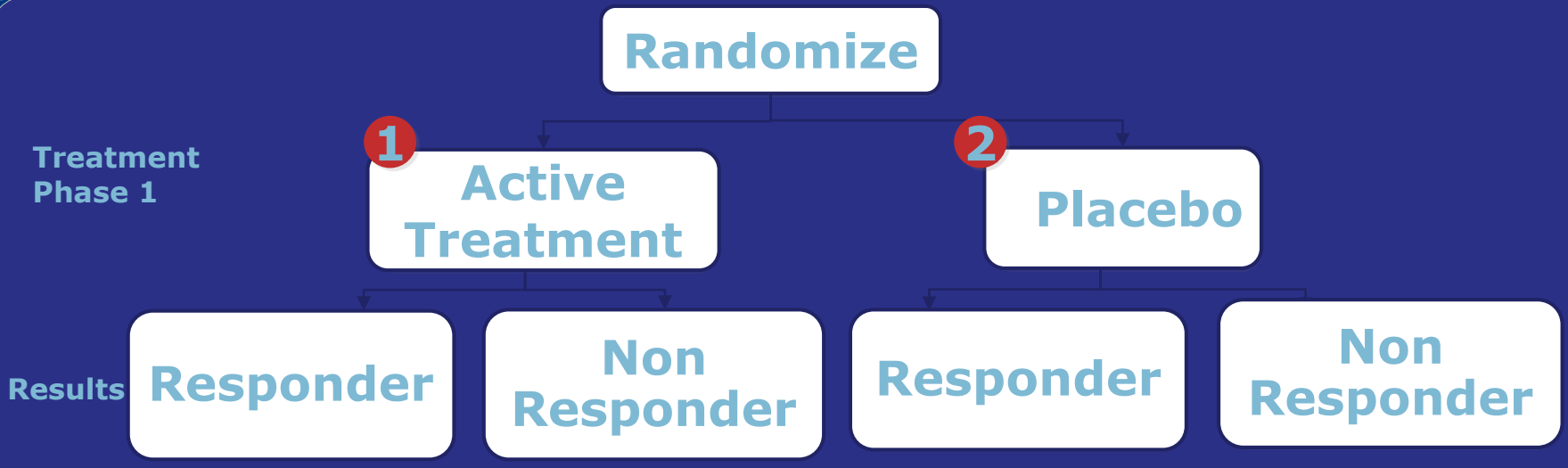
C+A + C+B vs. D+A + D+B

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

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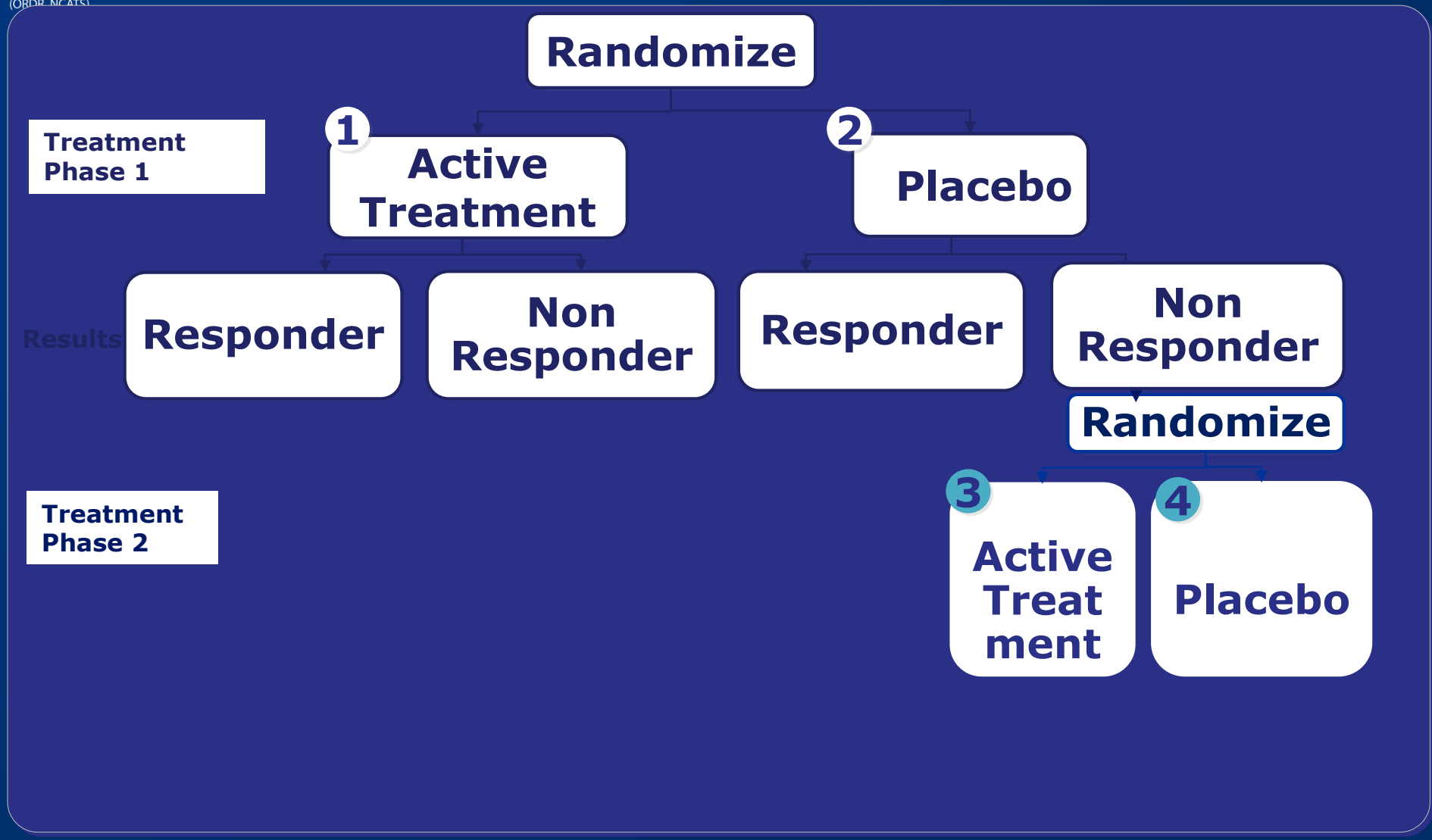
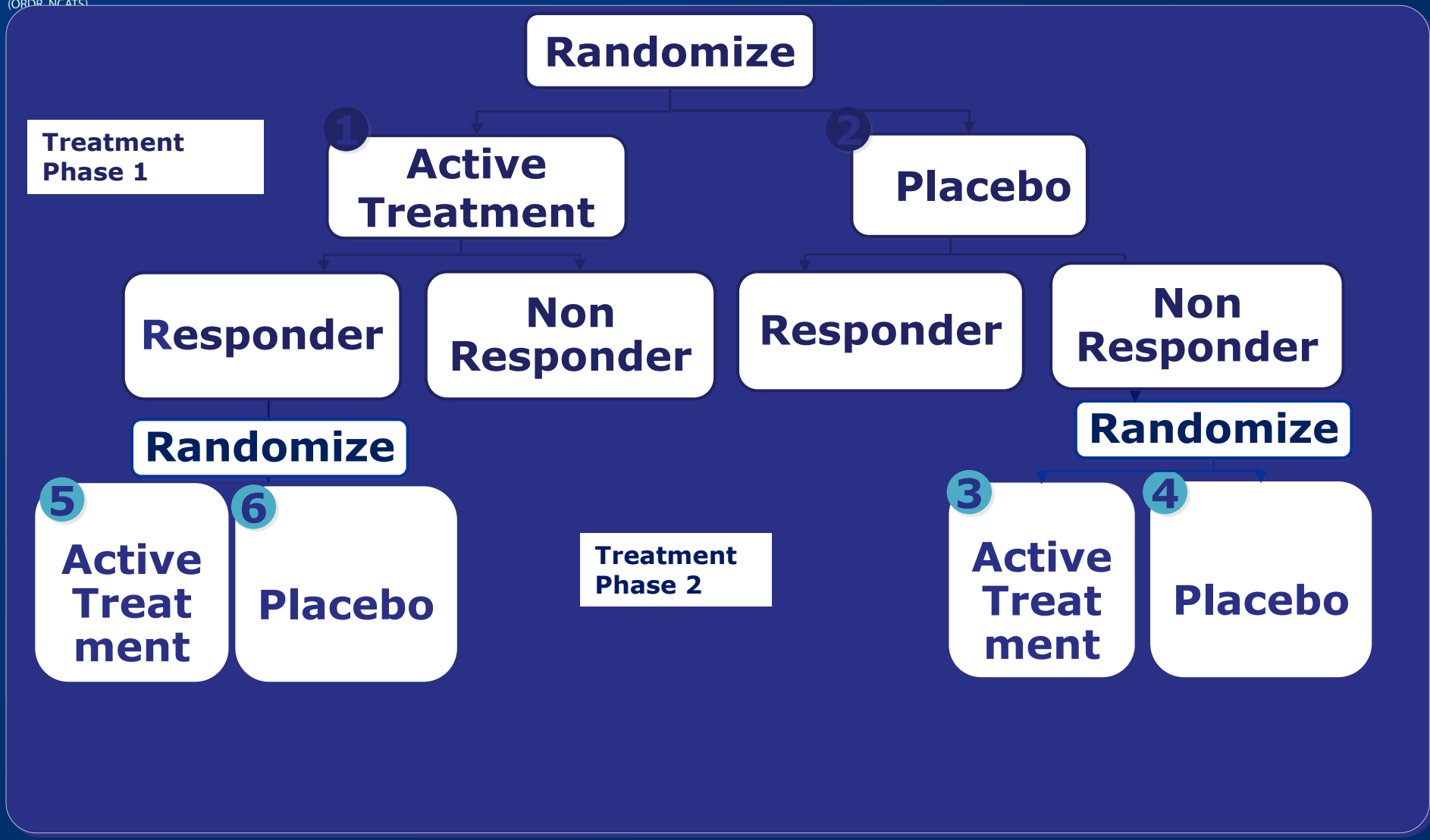
Single Enhanced Design



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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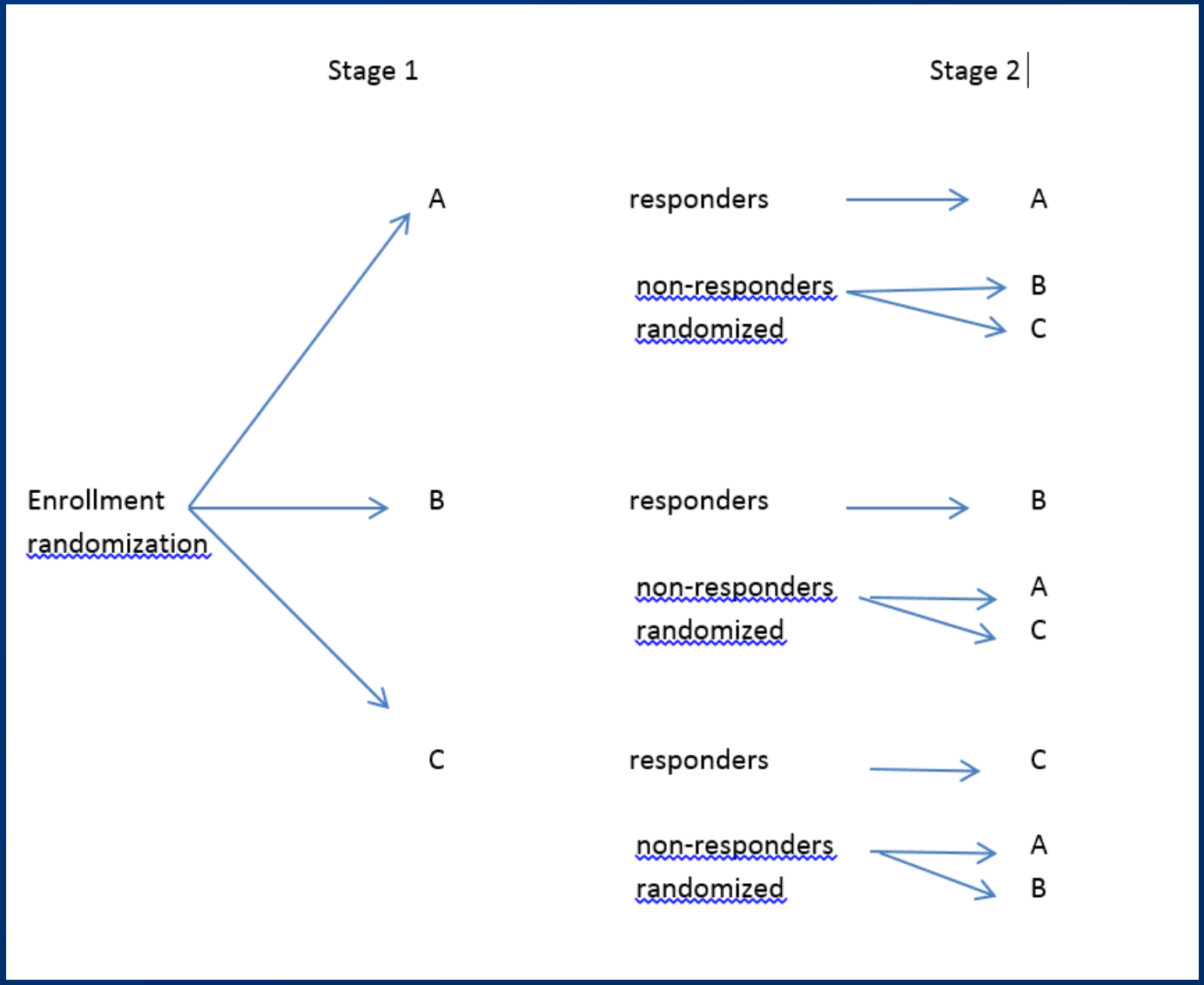
Issues

- 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



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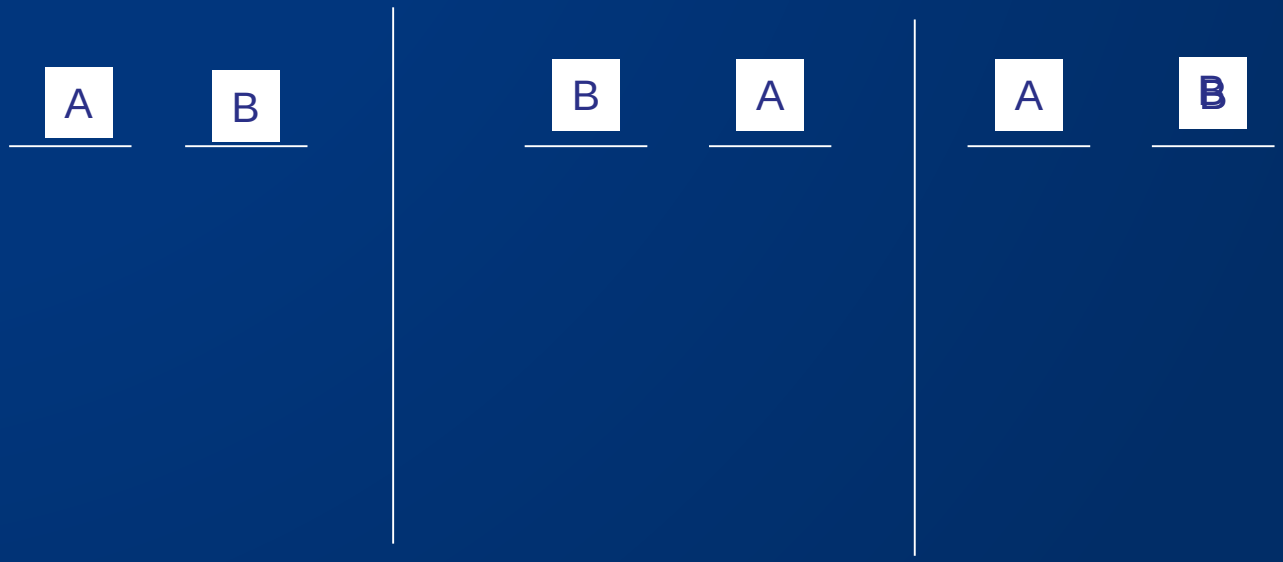
N=1 Randomized Trial Design



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).

Summary

Pros

- Each individual receives all treatments, so the best treatment for that individual is known.
- Multiple treatments in the same individuals give rise to more outcomes, so a smaller N is required.

Cons

- Study takes longer.
- Issues regarding changes in disease status (or patient's health status) over time.
- Possible carry-over effects.
- Autocorrelation limits amount gained.
- Limited numbers of patients may raise concerns re generalizability.

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.

Thank you

Reference: Small Populations Clinical Trials Task Force Workshop Report and Recommendation, July 2106
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM (IRDiRC)