Application of Analyses of Doubly Randomized Delayed-Start and Matched-Control Design to Demonstrate Disease Modification

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Janssen Research and Development, LLC

Disclaimer

- Current employee of Janssen Research & Development, LLC
- Stock in Johnson & Johnson

Outline

- Existing Designs
- New Study Design
- Conditional Non-inferiority Margin
- Suggested Statistical Models
  - Non-Subject Specific
  - Subject Specific
- Discussion

Existing Trial Designs and Statistical Methods

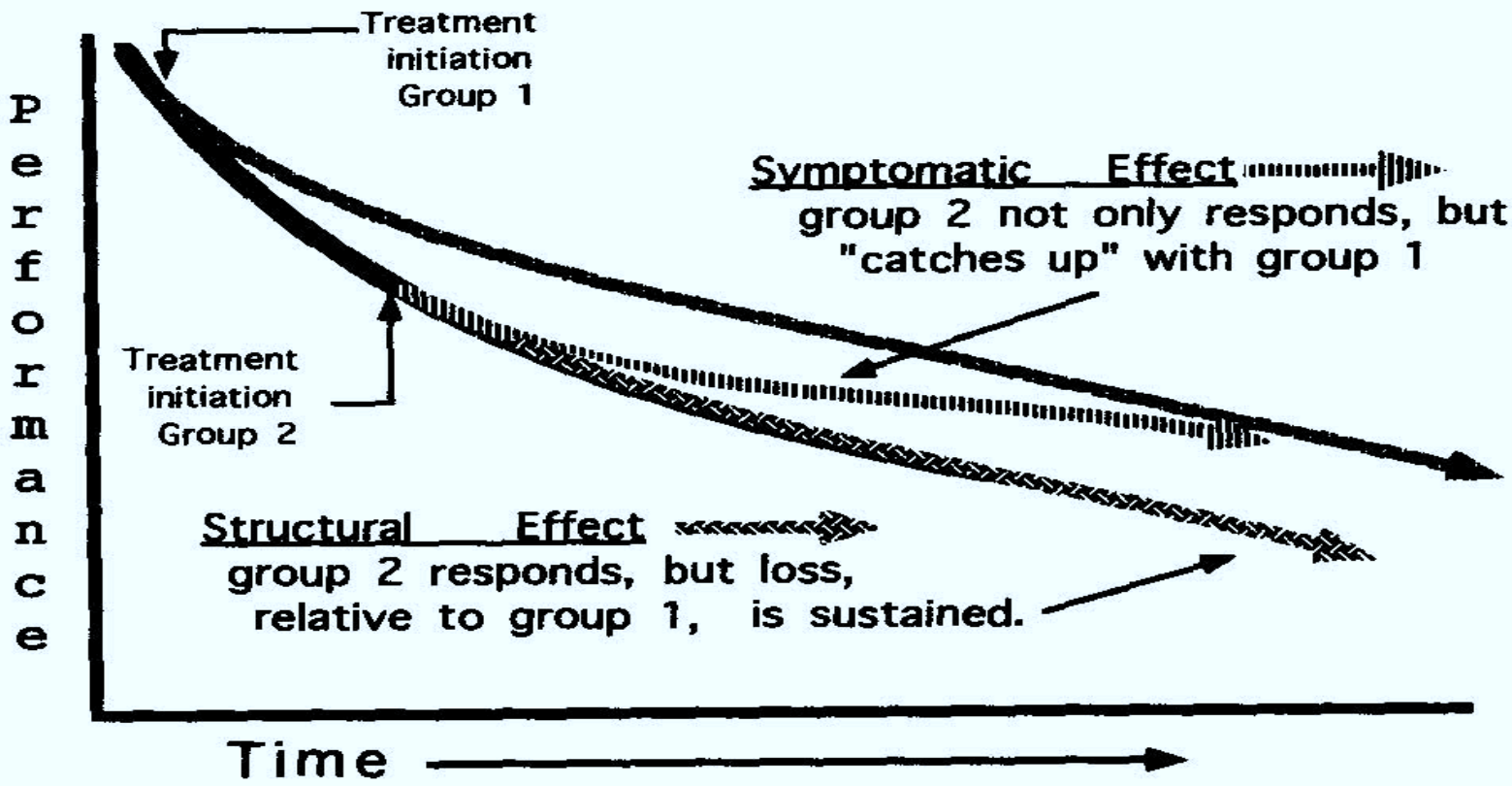

FIG. 2. Randomized start design.

Alzheimer Disease and Associated Disorders, Vol. 10, Suppl. 1, 1996

Randomized Delayed-Start Design

- Proposed by Leber (1994, 1996)
  - Two basic treatment sequences TT and PT
  - Clinical effects in period 1 between T and P, sustained effects between TT and PT after delayed-start in period 2
  - More “ethical” than randomized withdrawal?
- Fleming
  - Adequate duration required to allow meaningful interpretation
  - An order of magnitude too small for non-inferiority margin for the second period

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  - Suitable for drugs with large effect
  - Too complicated to interpret
  - Disease modifying effect to reflect physiological changes
- D’Agostino
  - Second phase observational study with differential drop-out
  - Careful to buy into this design

Period 1 Issues

- Slope Analysis
  - Disease progression generally non-linear; instruments with ceiling effects
  - Specification of duration of exclusion (Fleming) or "data-not-used zone" (D'Agostino)
  - Bias due to early differential drop outs
- Last-Visit Analysis
  - Biased "completer analysis" (consider, MMRM with treatment contrast for the last visit)
  - "Sensitivity analysis" with un-verifiable assumptions (consider, multiple imputation or pattern mixture models)
  - Lacking serious evaluations of robustness of any analytical method under a range of plausible MNAR models or assumptions

Period 2 Issues

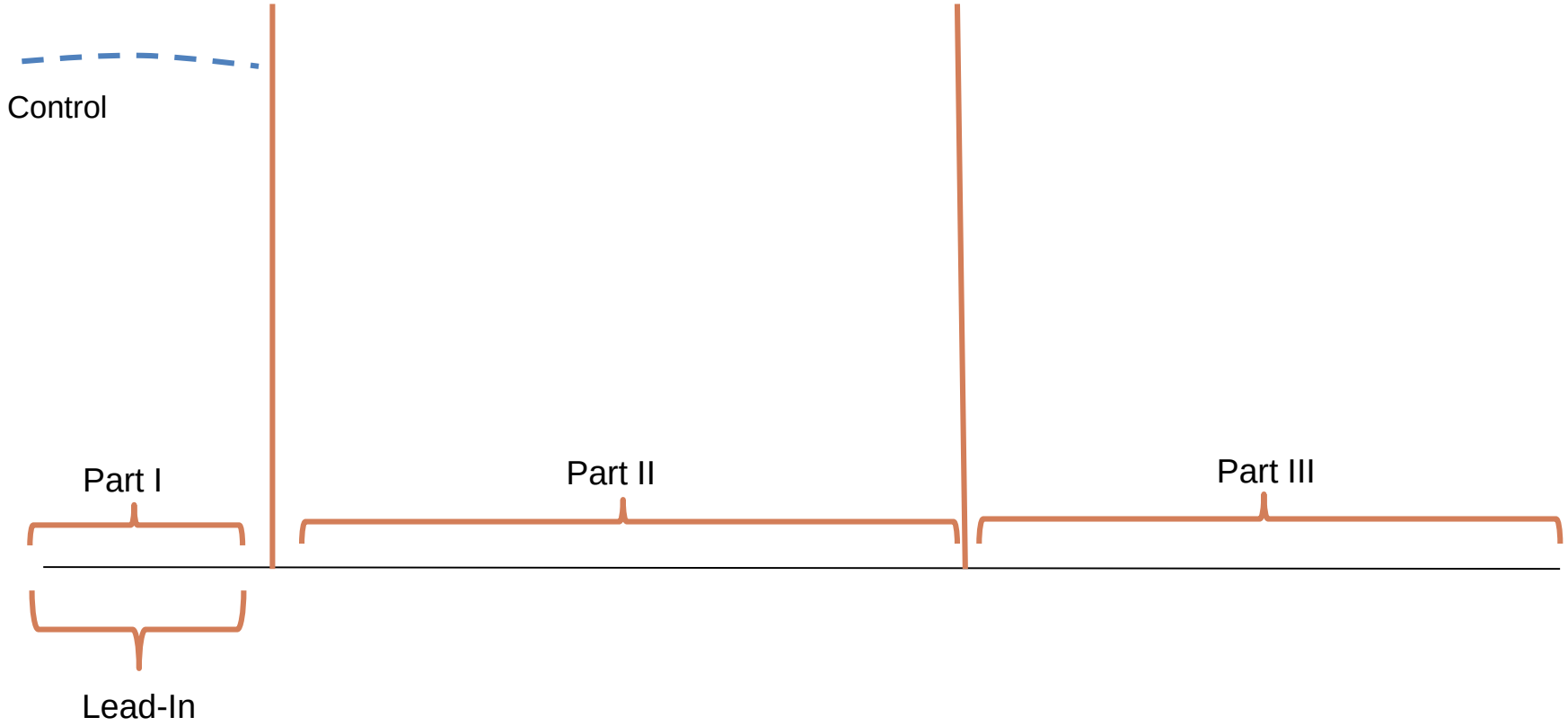
- Analysis of clinical evidence of disease modifications
  - Slope analysis difficult to interpret due to non-linear response curves
  - Bias due to excessive missing data (in period 1) and lack of blinding with controls
- Clinical trial design
  - Presumption of delayed-start effects
  - Lacking mechanisms for the verification and quantification of the delayed-start effects

Adaptations with Potential Mediation Biomarkers

- Early futility, modification of enrollment criteria, or sample size adjustment
- Bias mediation analysis
- Validity of design established mathematically

Research Initiatives

Case 1: Disease Modification Effects



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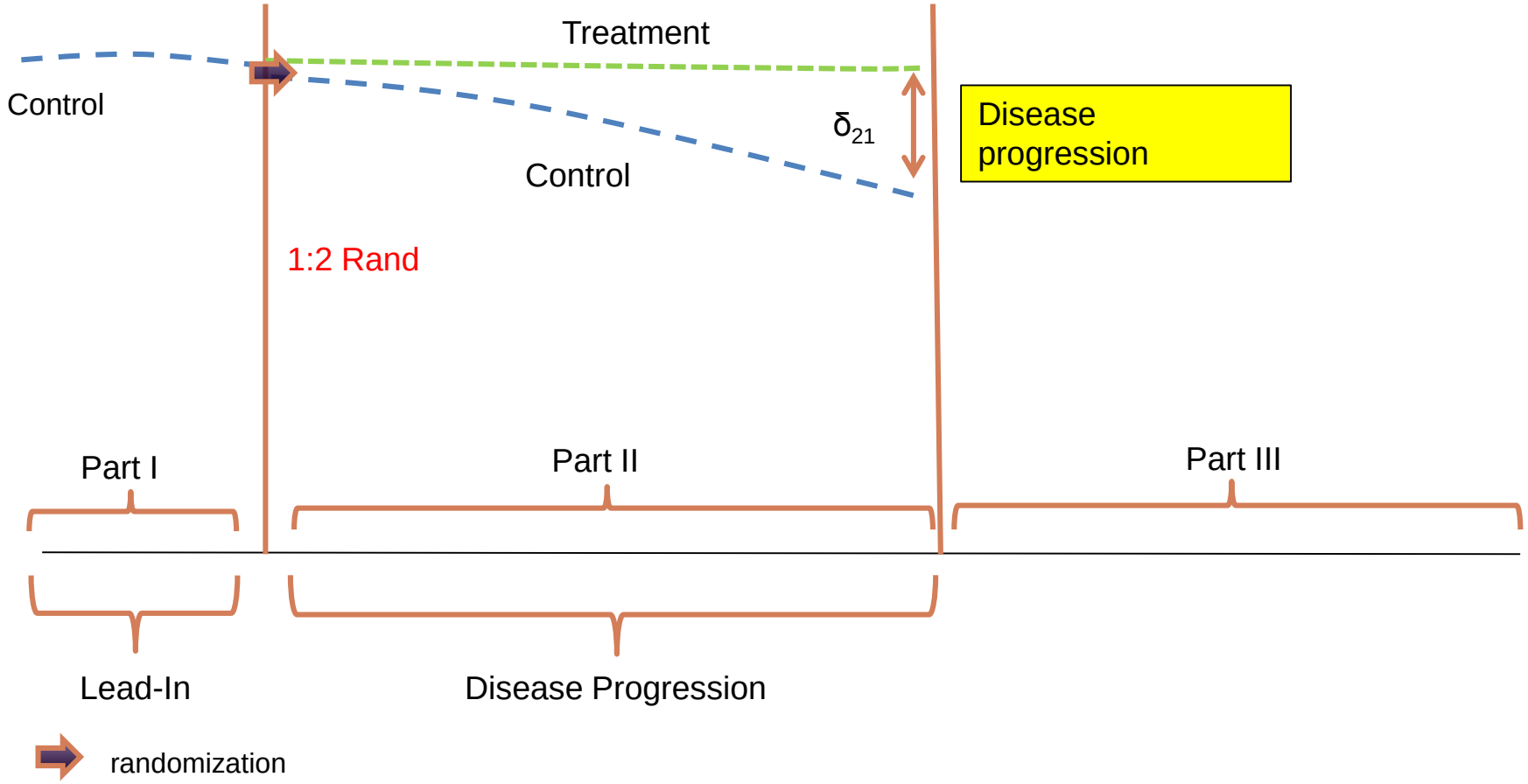

δ_{21}:Treatment effect on disease progression;

Research Initiatives

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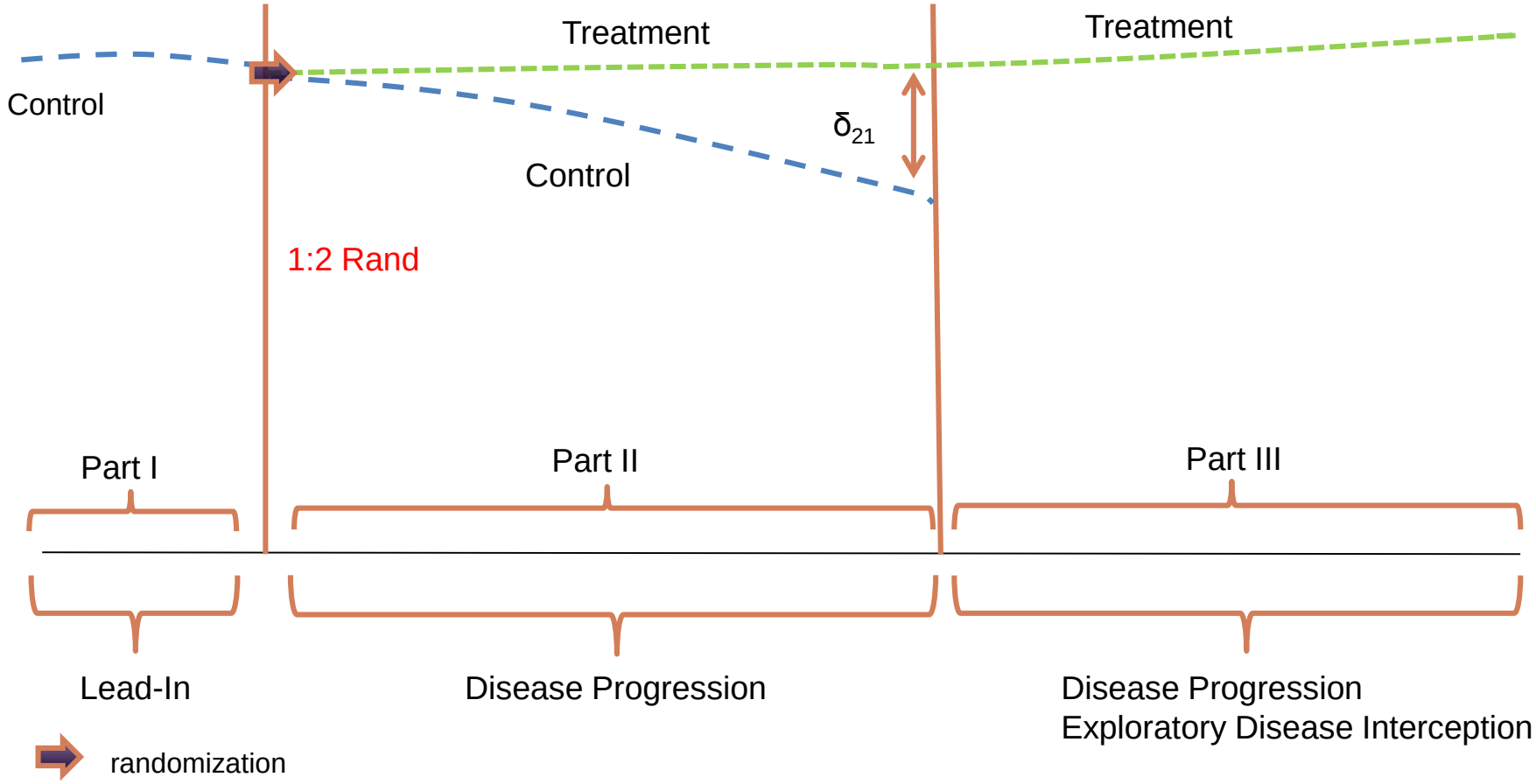

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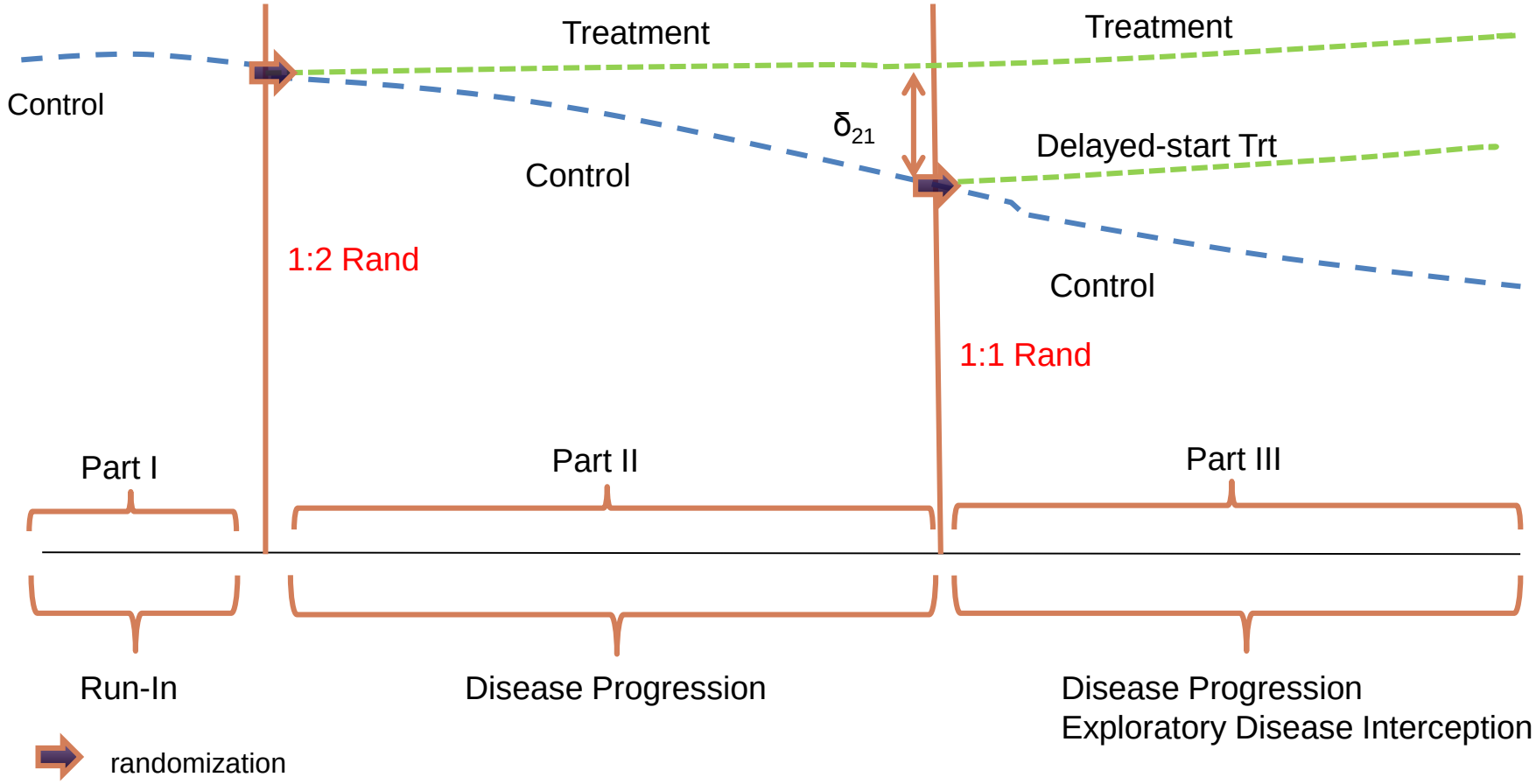

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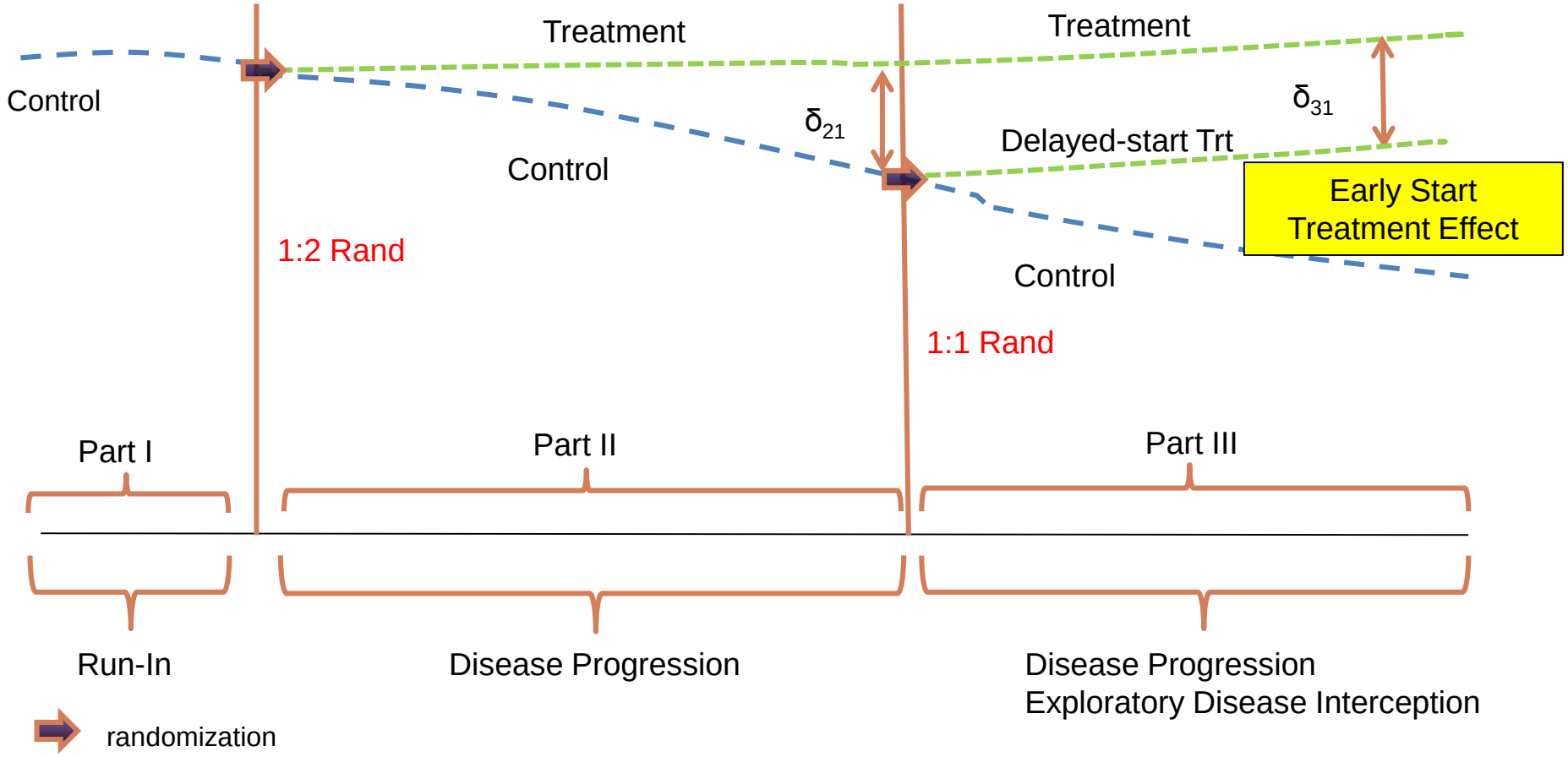

δ_{21}:Treatment effect on disease progression; δ_{31}:Early start treatment effect;

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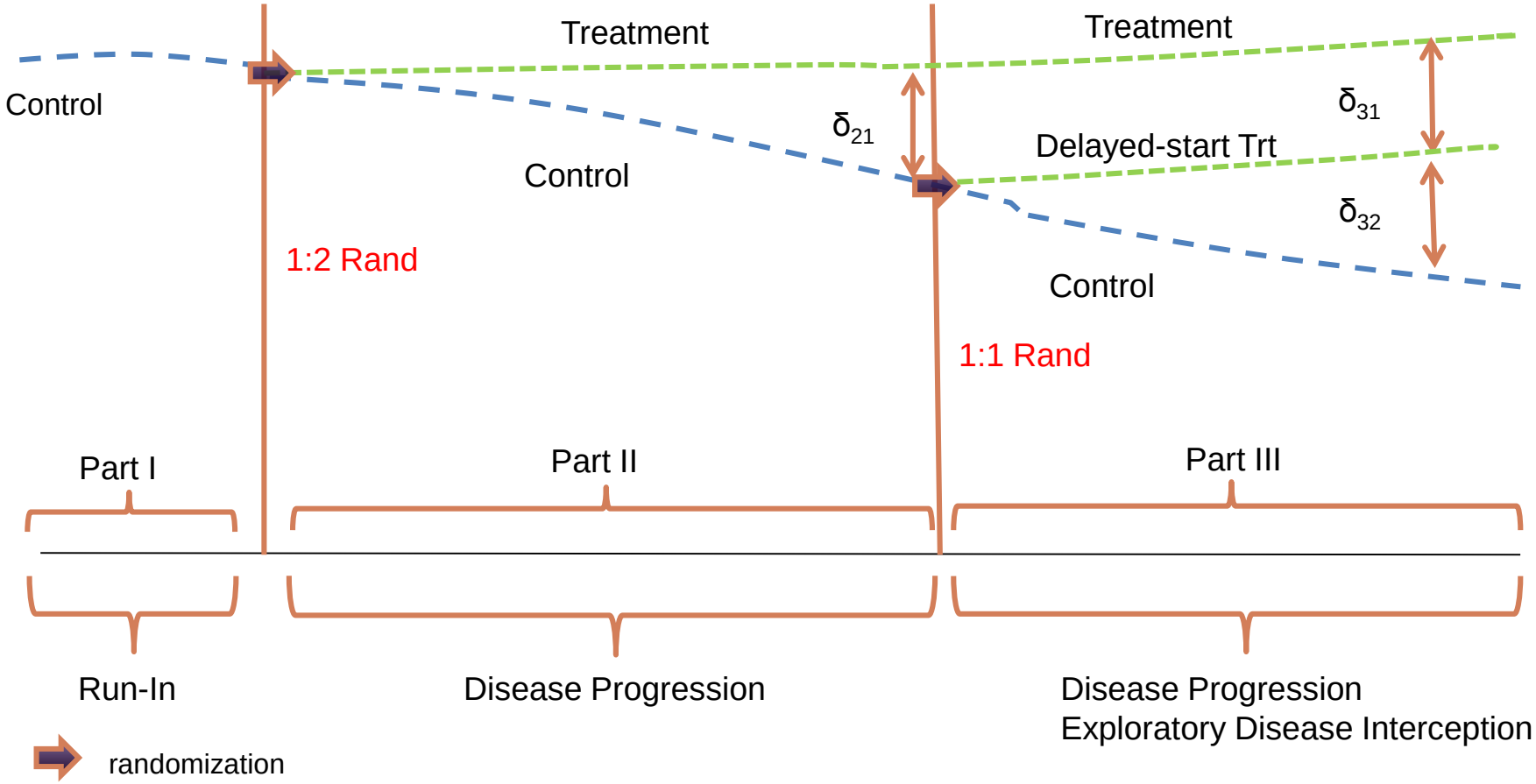

δ_{21}:Treatment effect on disease progression; δ_{31}:Early start treatment effect; δ_{32}:Delayed-start treatment effect on disease progression;

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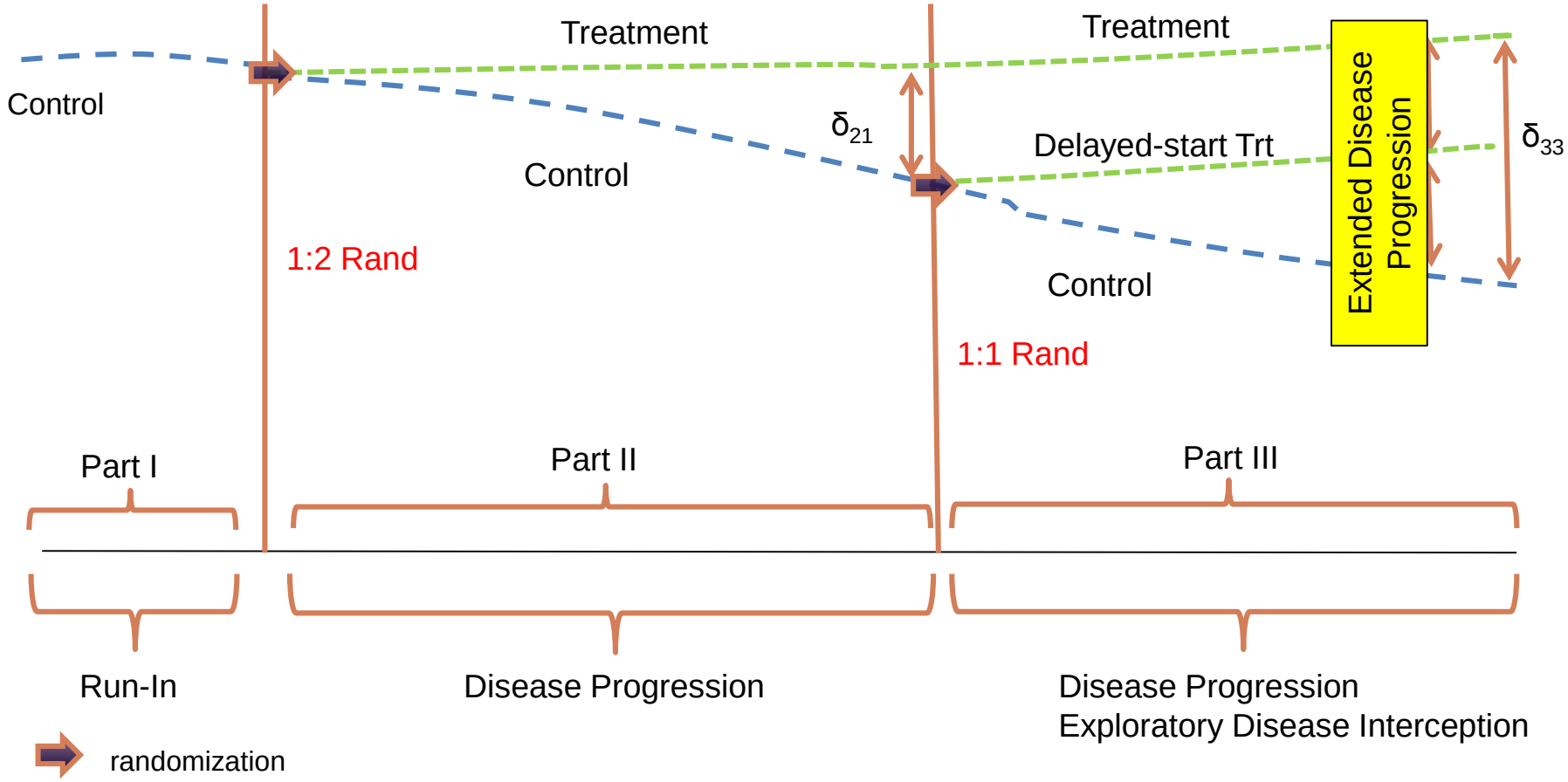

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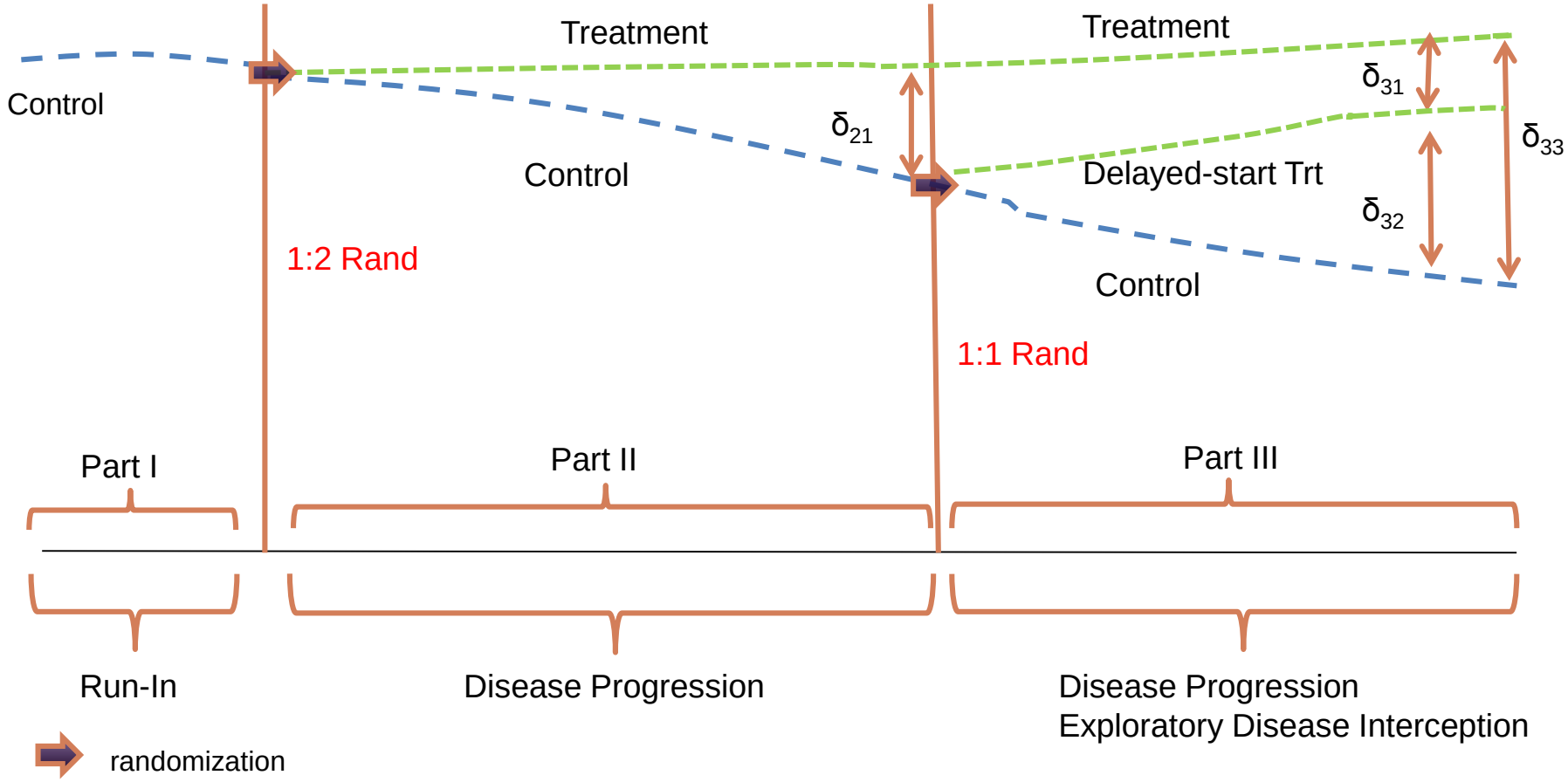
Case 2: Delayed-Start Effects



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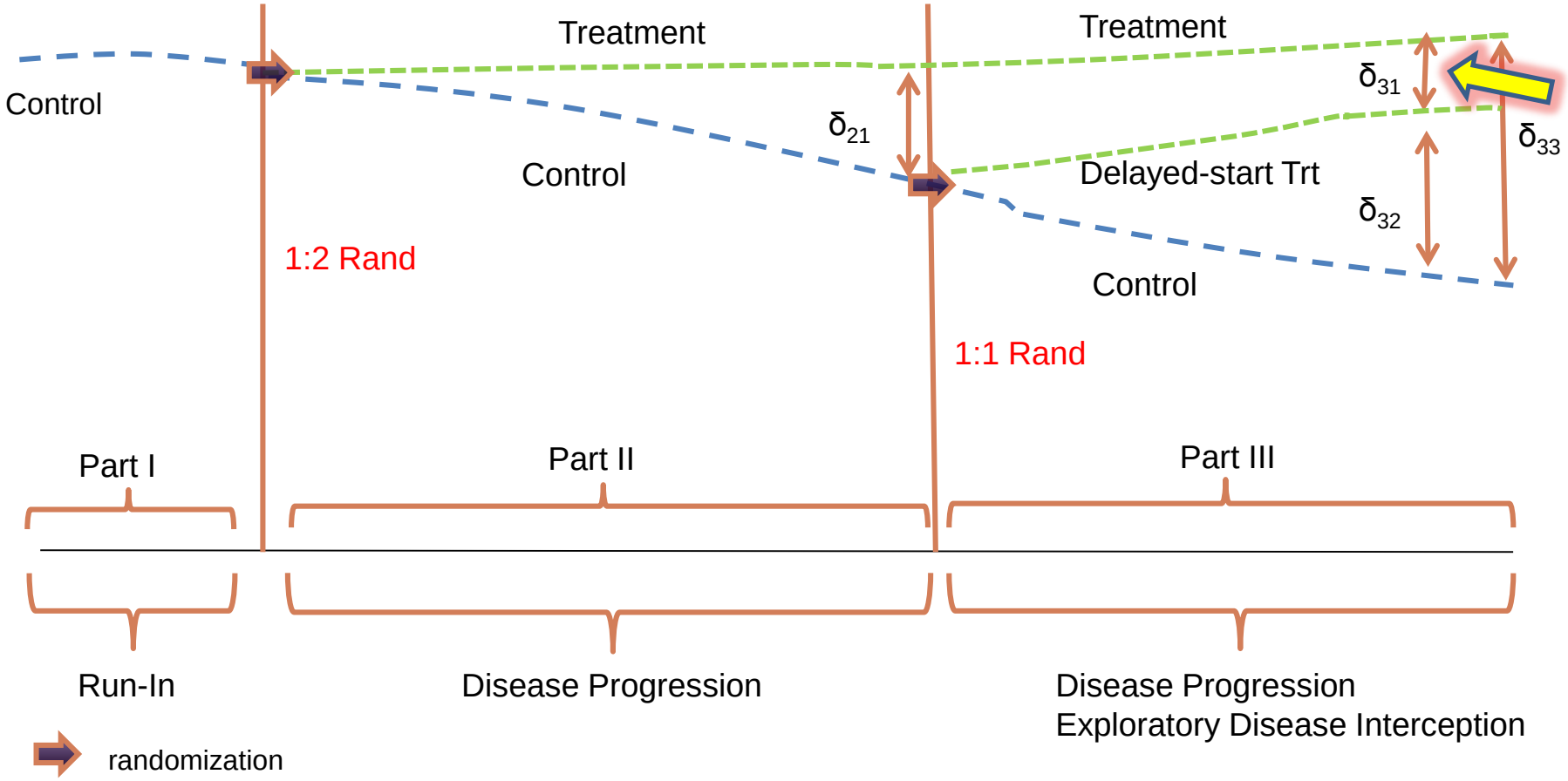
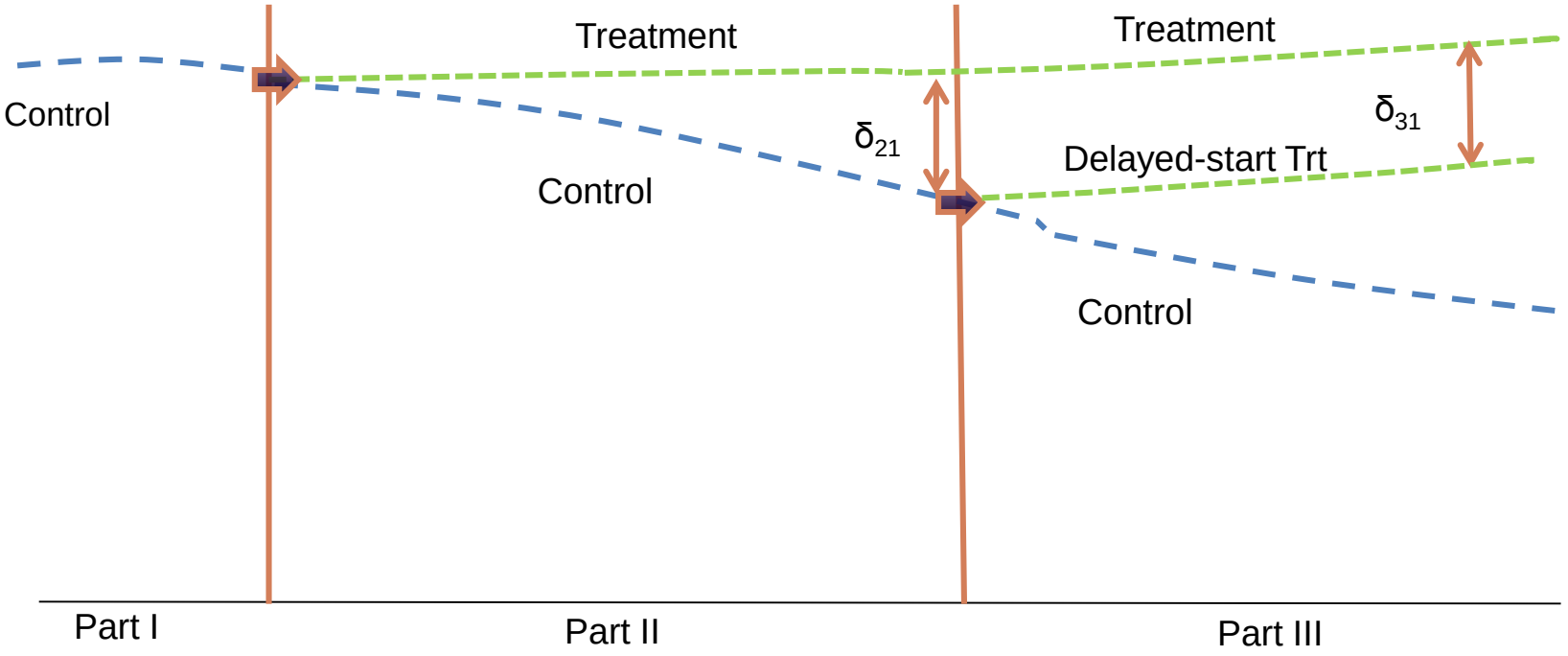


δ_{21}:Treatment effect on disease progression; δ_{31}:Early start treatment effect; δ_{32}:Delayed-start treatment effect on disease progression; δ_{33}:Extended disease progression.

Objective

- Examine whether the delayed start treatment progression catches-up with early-start treatment effect. If it does treatment effect does not represent disease modification.



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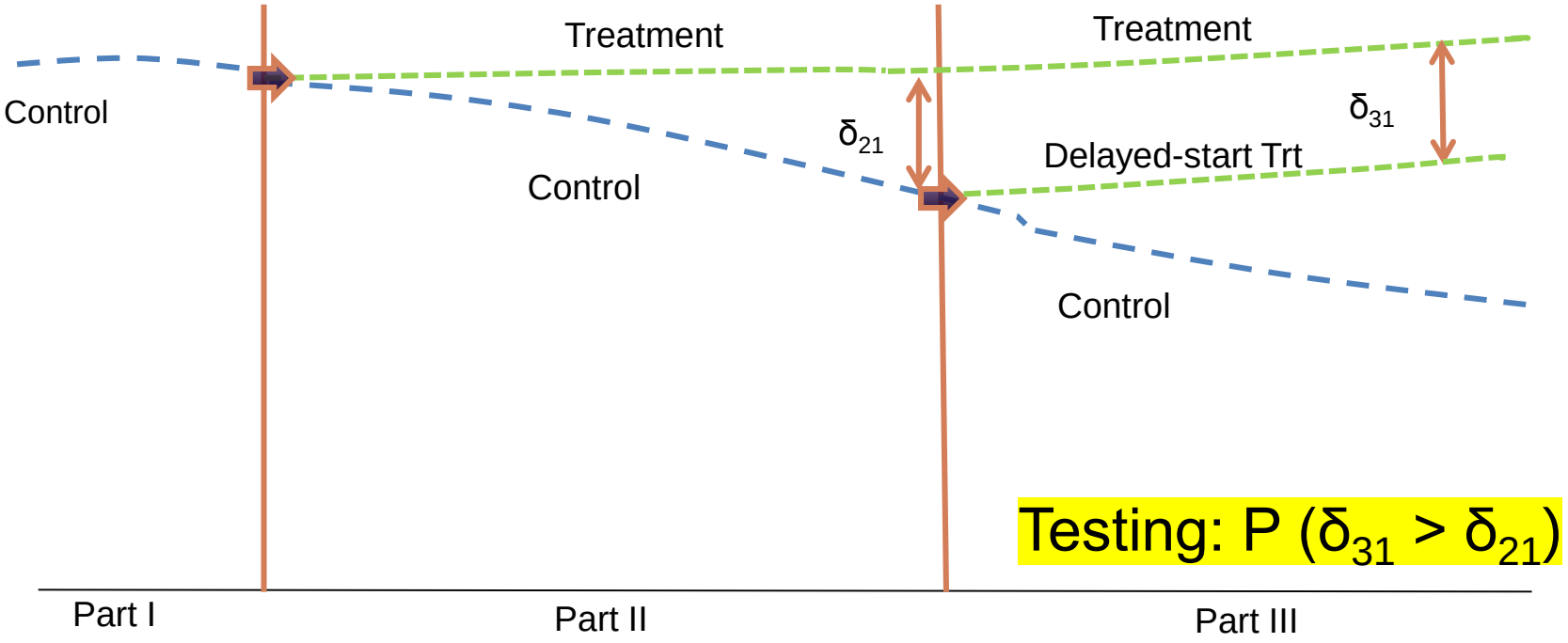

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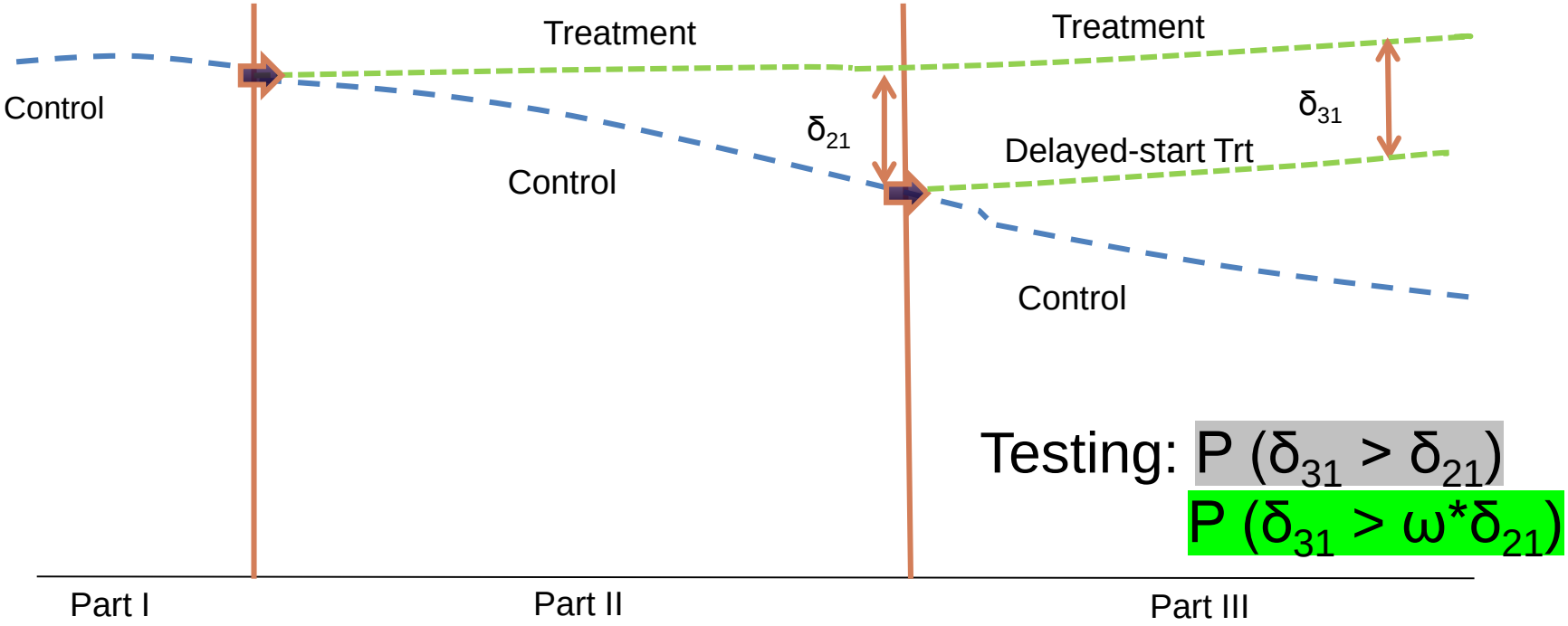
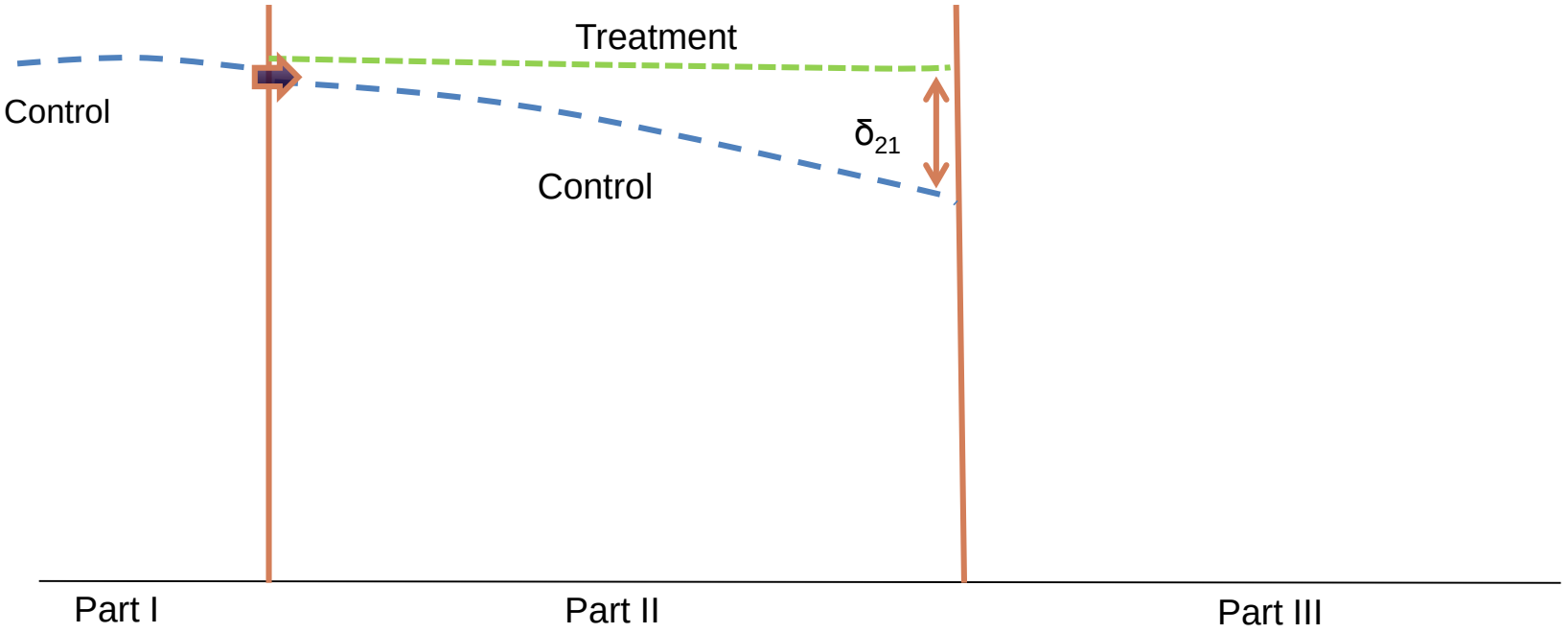


δ_{21}:Treatment effect on disease progression; δ_{31}: Early start treatment effect

Objective

To evaluate for disease modification – first, demonstration of disease progression at the end of Part II (δ_{21}) is required.

- Is it statistically significant? Is it clinically meaningful at the population level?



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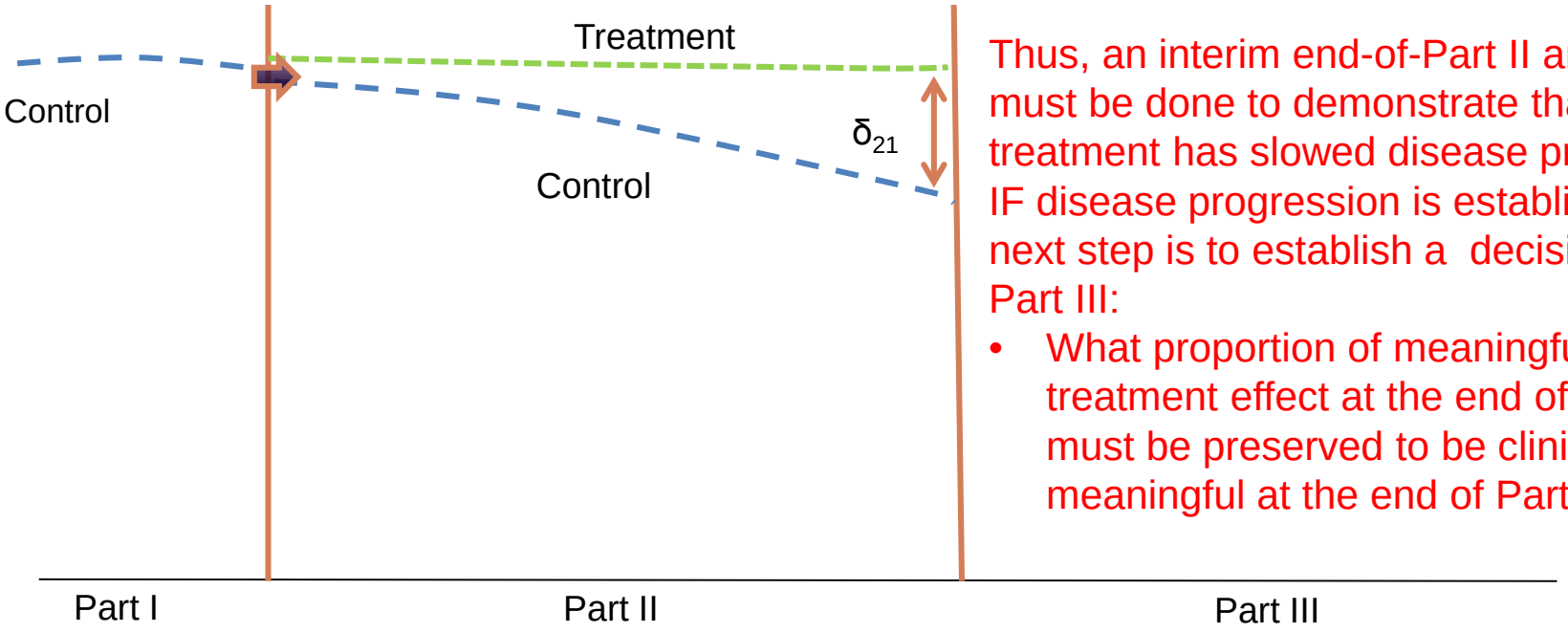

Thus, an interim end-of-Part II analysis must be done to demonstrate that the treatment has slowed disease progression. IF disease progression is established the next step is to establish a decision rule for Part III:

- What proportion of meaningful treatment effect at the end of Part II must be preserved to be clinically meaningful at the end of Part III?

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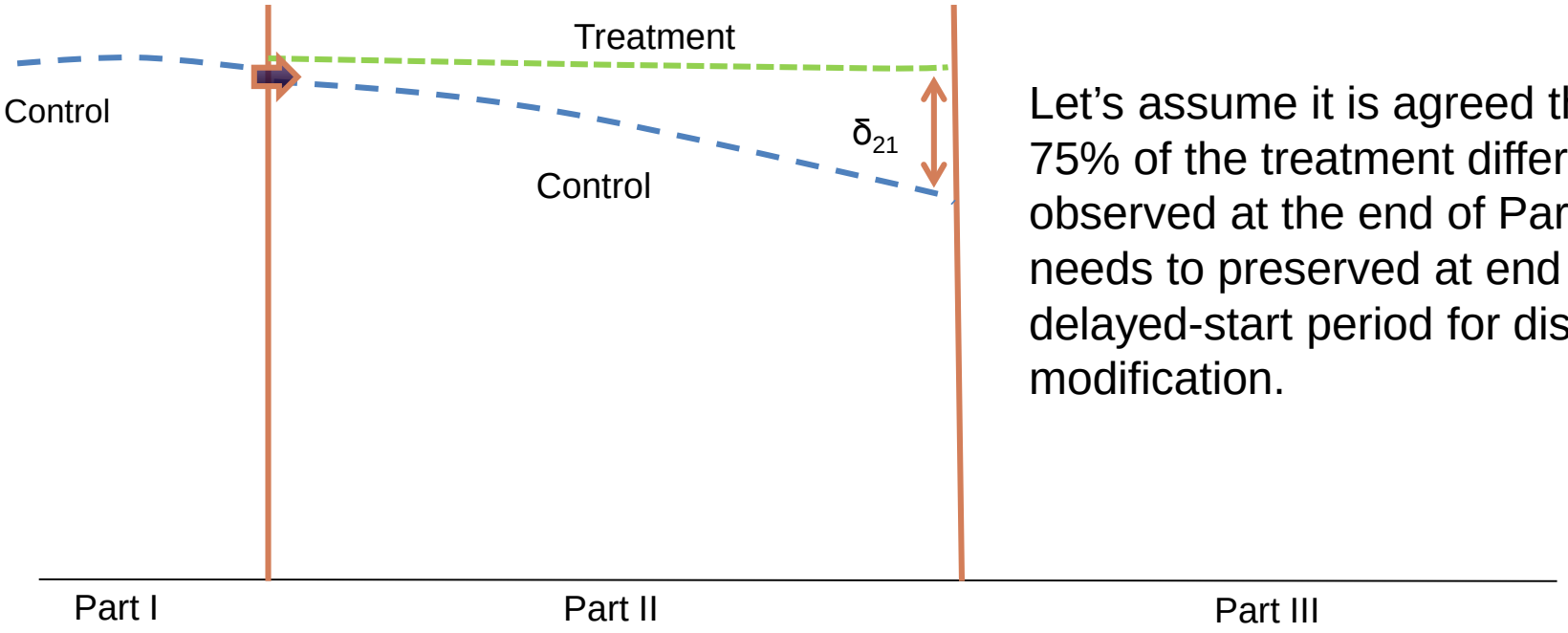

Let's assume it is agreed that 75% of the treatment difference observed at the end of Part II needs to preserved at end of the delayed-start period for disease modification.

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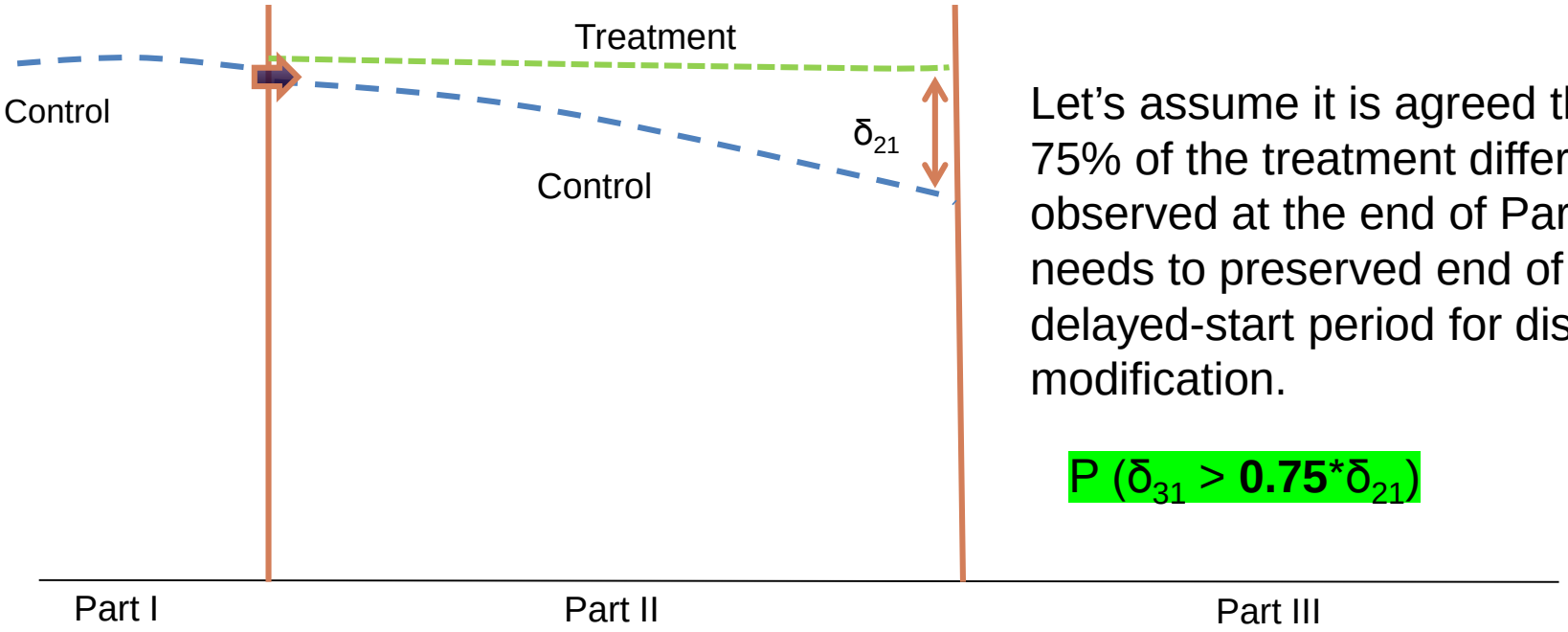

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$P(\delta_{31} > \mathbf{0.75}^{*}\delta_{21})$

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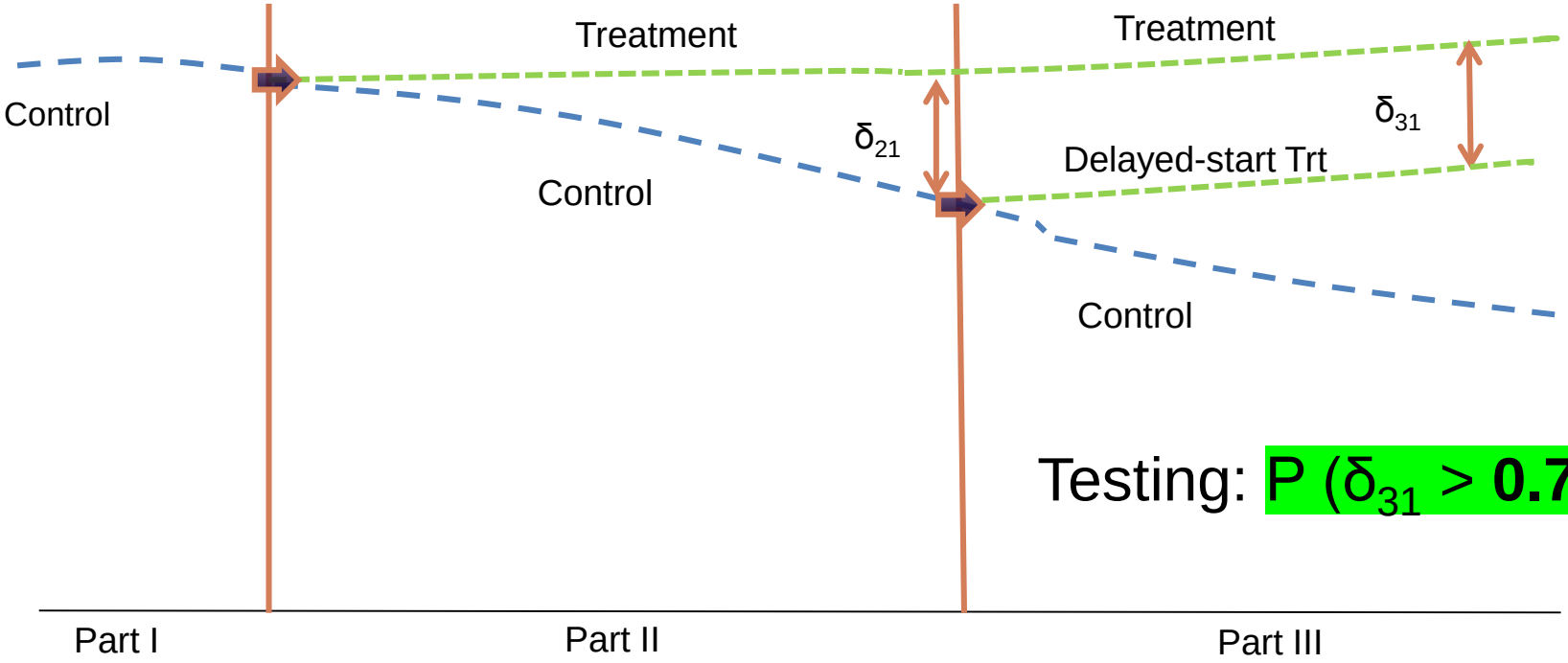
Objective

- Example: 75% of the treatment difference observed at the end of Part II needs to preserved end of the delayed-start period for disease modification



Testing: $P(\delta_{31} > \mathbf{0.75}^{*}\delta_{21})$

$$H_0: \delta_{31} \leq 0.75\ ^{*}\delta_{21}$$
$$H_1: \delta_{31} > 0.75^{*}\delta_{21}$$

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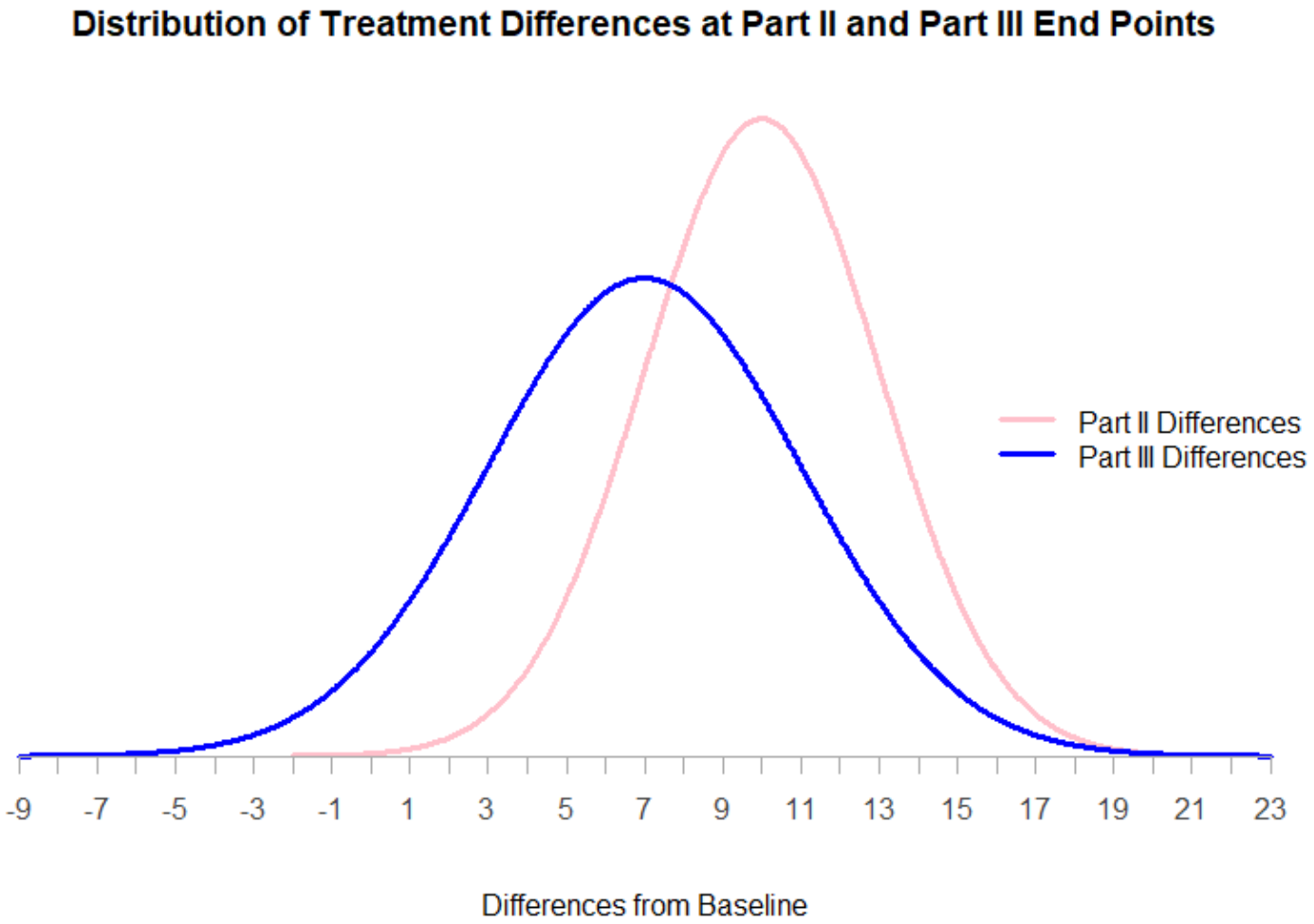
Why Bayesian Analysis



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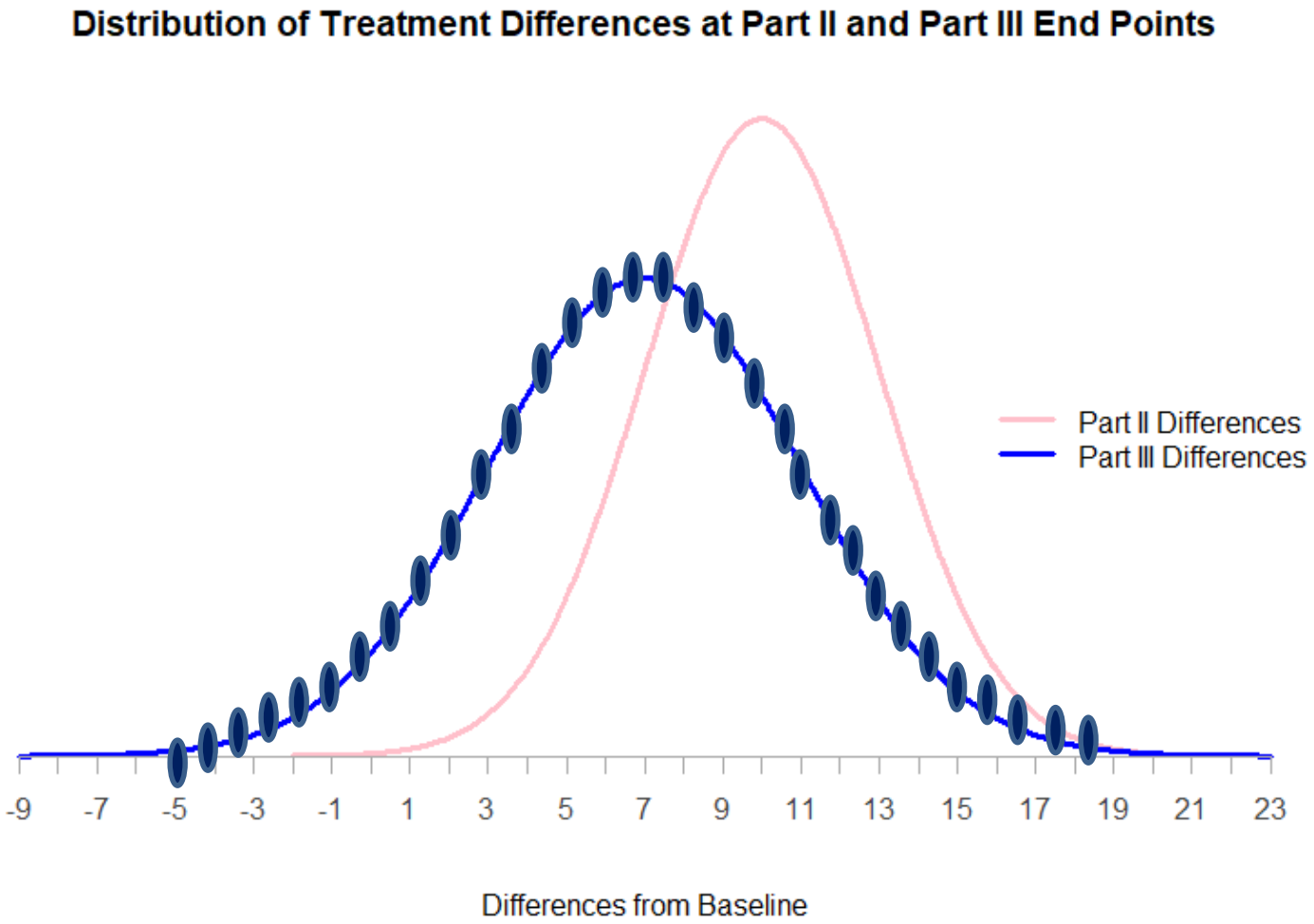

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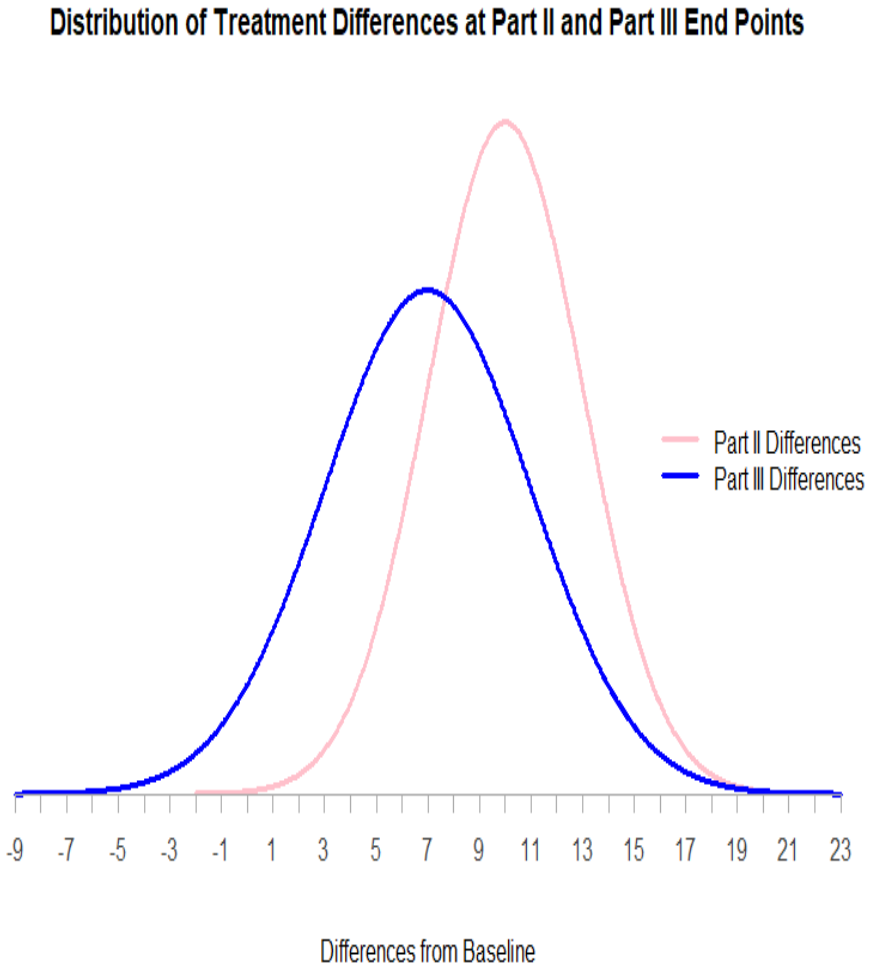
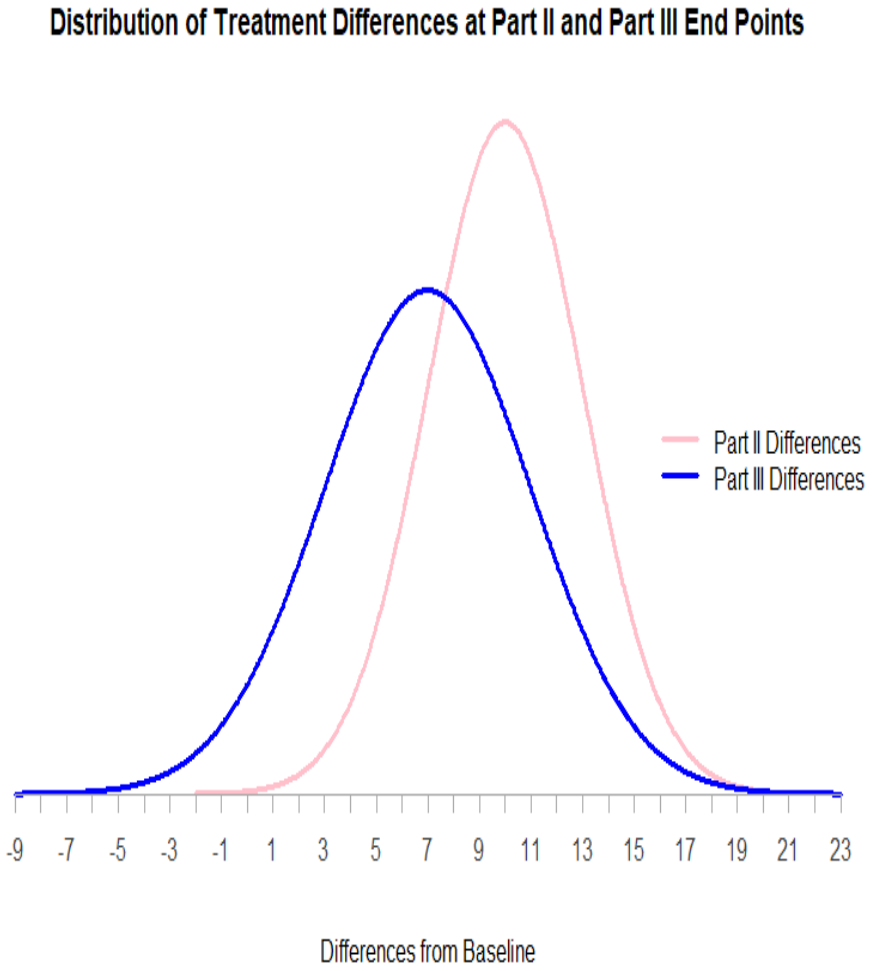


Iter. Num	Part II Diff	Part III Diff	Decision PIII -0.75*PII
1	9.8	7.2	-0.15
2	8.1	5.4	-0.675
3	8.7	8.9	**2.375**
4	10.7	8.7	**0.675**
5	10.9	7.1	-1.075
6	10.5	7.2	-0.675
…			
…			
…			
…			
1000	10.0	7.0	-0.5

Why Bayesian Analysis



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…			
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$$P(\delta_{31} > 0.75*\delta_{21})$$

Selection of Statistical Method

- Simple Linear
- Random Intercept
- Random Intercept and Random Slope
- Autoregressive

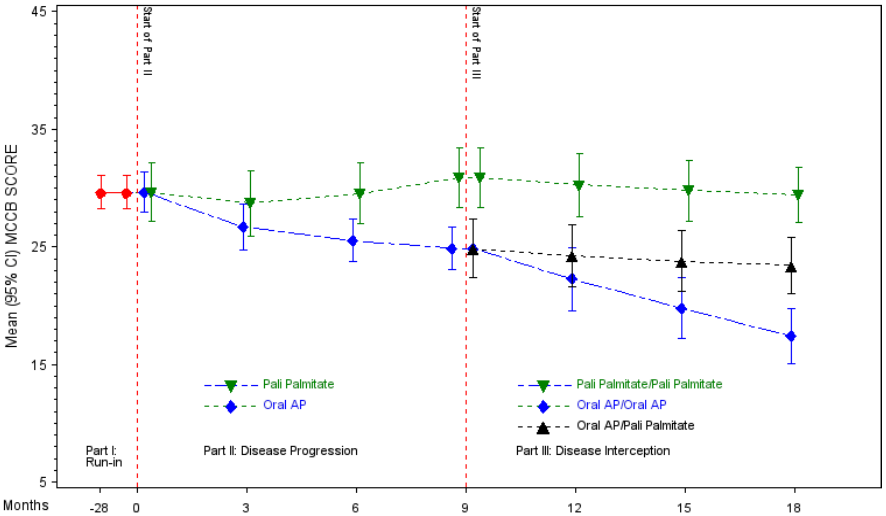
Nonlinear Models

Spline models with random intercept

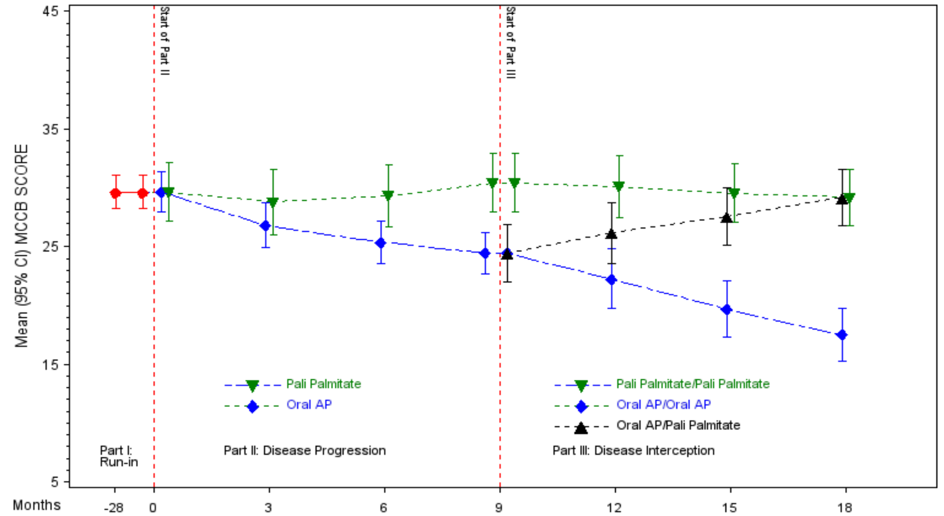
Spline models with random intercept and random slope

Model Averaging with Spline Models

Scenarios



Start of Part II
Start of Part III
Mean (95% CI) MCCB SCORE
Pali Palmitate
Oral AP
Pali Palmitate/Pali Palmitate
Oral AP/Oral AP
Oral AP/Pali Palmitate
Part I: Run-in
Part II: Disease Progression
Part III: Disease Interception
Months
-28 0 3 6 9 12 15 18
5 15 25 35 45



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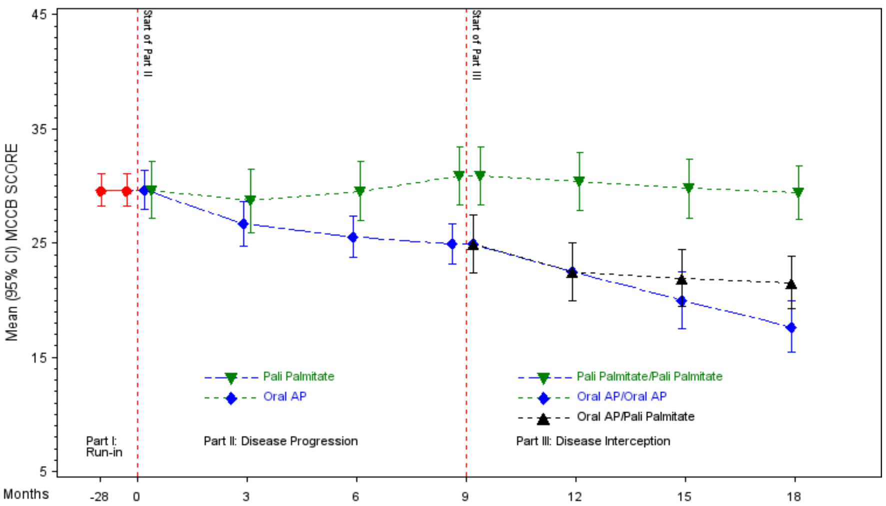

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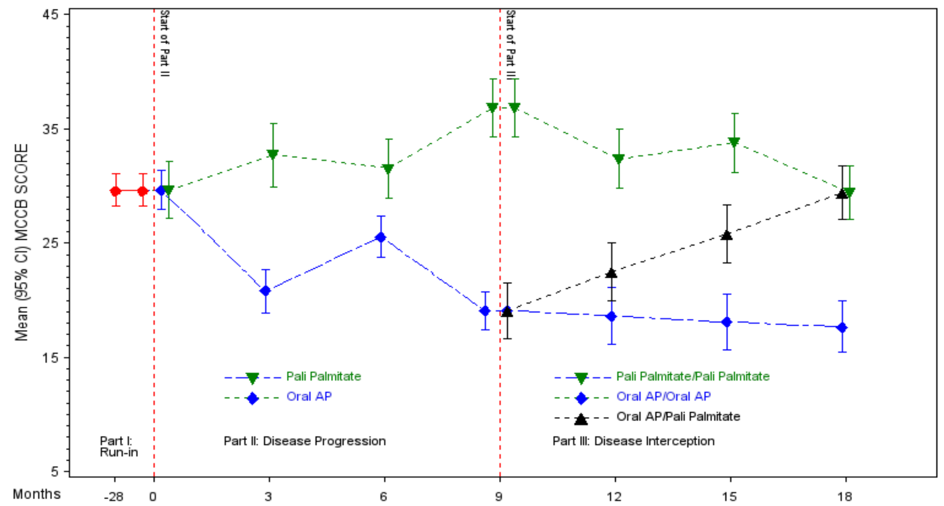

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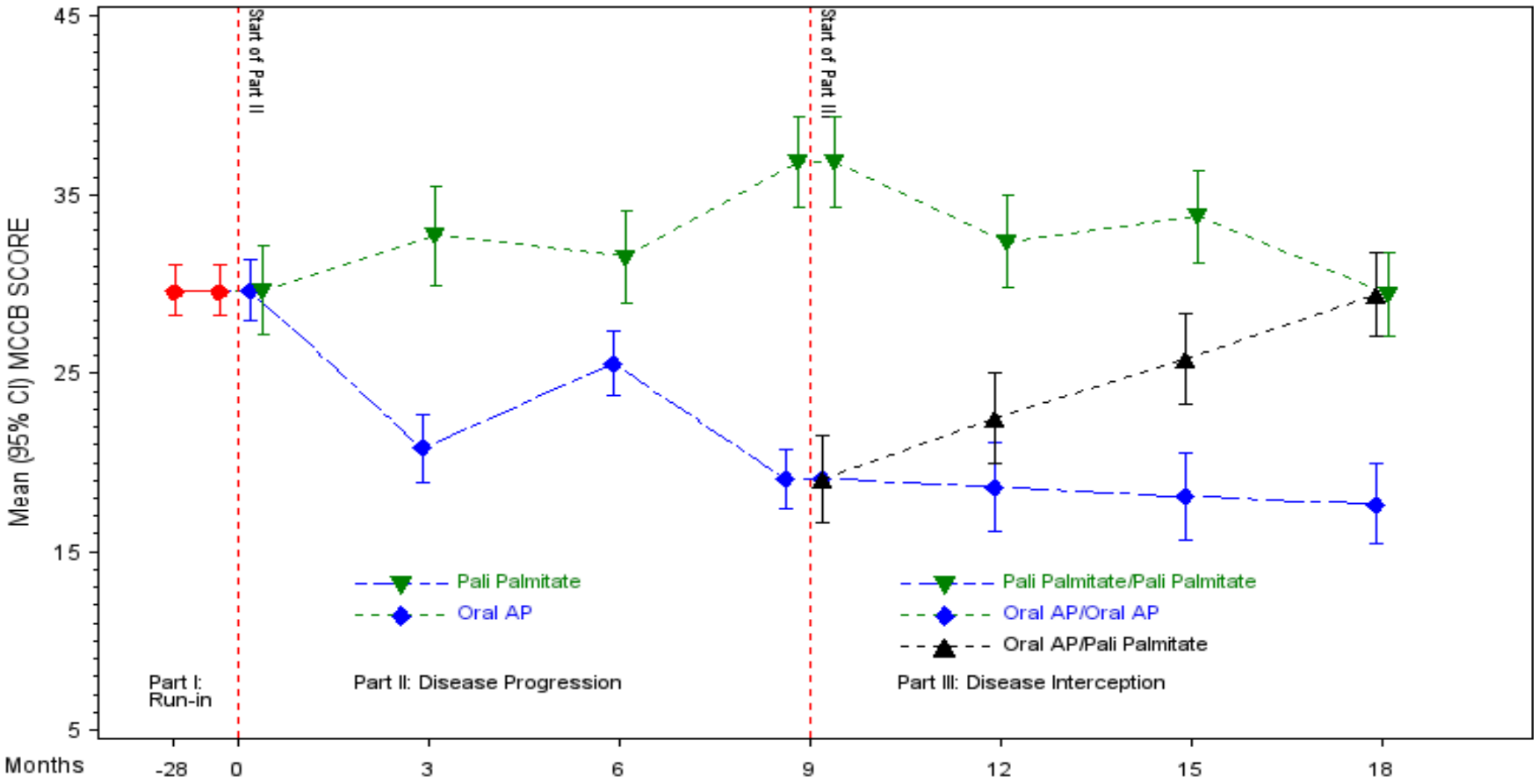
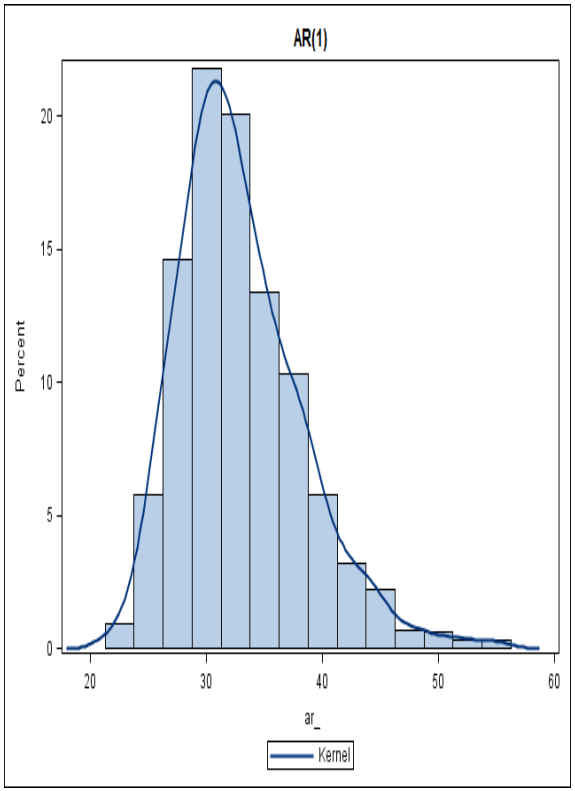
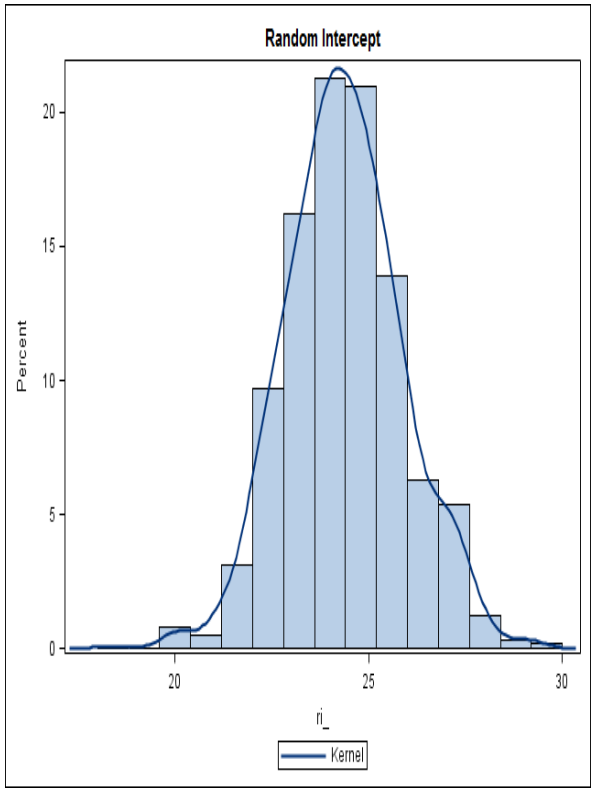
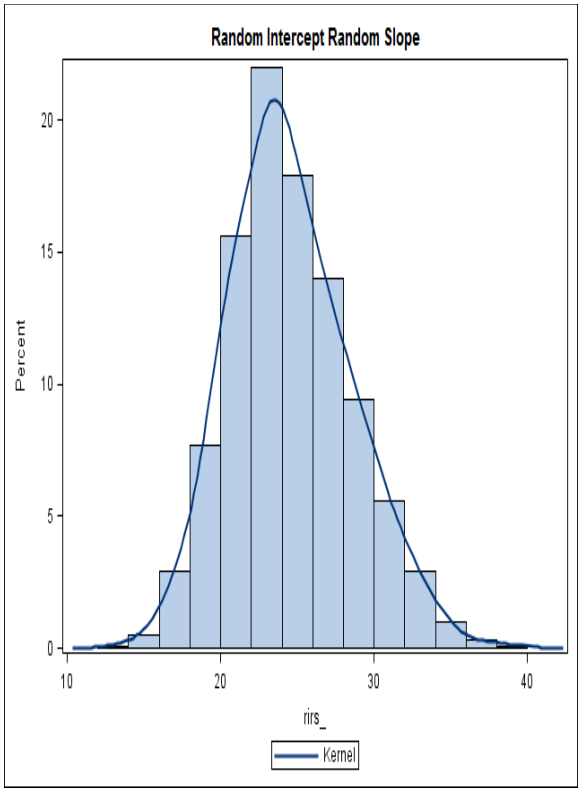
Scenario – No Disease Modification and Nonlinear Response



Scenario – No Disease Modification, DIC Scores





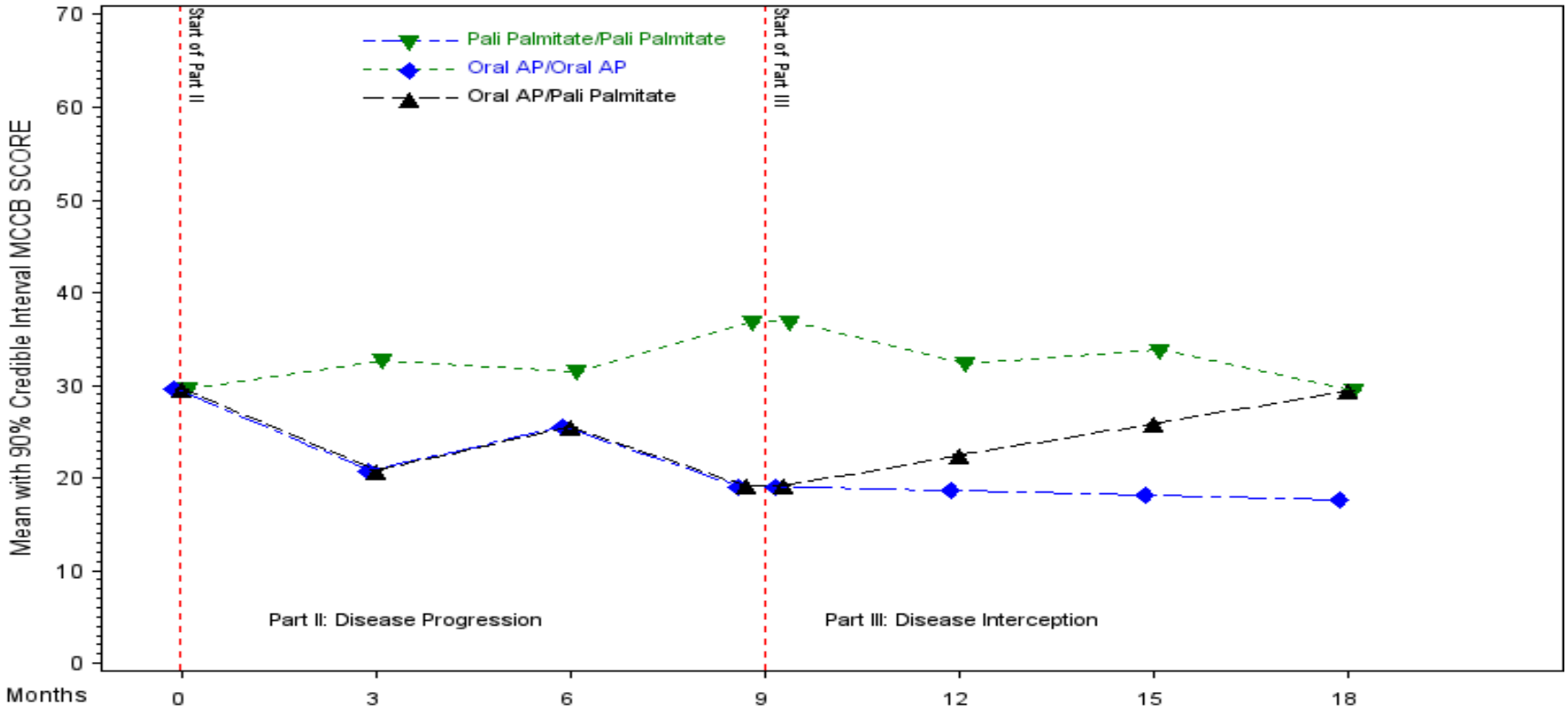


Means: 32.89 24.07 23.53

Model Averaging, Posterior Means and 90% Credible Intervals

Bayesian Methods for Nonlinear Classification and Regression

By Denison, Holmes, Mallick, and Smith.



Results using Nonlinear Models: Posterior Treatment Means of MCCB Scores and 90% Credible Intervals for Scenarios A and D

	Scenario 2A						Scenario 2D					
	Spline Polynomials			Model Averaging			Spline Polynomials			Model Averaging		
	APAP	PPPP	APPP	APAP	PPPP	APPP	APAP	PPPP	APPP	APAP	PPPP	APPP
BASELINE (PARTII)	29.7 (27.8-31.7)	29.6 (27.6-31.5)	29.7 (27.7-31.8)	29.7 (27.8-31.7)	29.6 (27.6-31.5)	29.7 (27.7-31.8)	29.7 (29.3-30.0)	29.5 (29.2-29.9)	28.0 (27.6-28.4)	29.7 (29.7-29.7)	29.6 (29.6-29.7)	29.6 (29.6-29.6)
MONTH 3 (PARTII)	26.8 (25.0-28.7)	28.7 (26.9-30.5)	26.8 (25.0-28.5)	26.8 (25.0-28.7)	28.7 (26.9-30.5)	26.8 (25.0-28.5)	20.7 (20.6-20.9)	32.2 (32.1-32.4)	23.2 (23.0-23.3)	20.8 (20.8-20.8)	32.7 (32.7-32.7)	20.8 (20.8-20.8)
MONTH 6 (PARTII)	25.5 (23.5-27.3)	29.6 (27.7-31.6)	25.6 (23.5-27.6)	25.5 (23.5-27.3)	29.6 (27.7-31.6)	25.6 (23.5-27.6)	25.8 (25.7-25.8)	32.9 (32.9-33.0)	26.1 (26.1-26.2)	25.5 (25.5-25.6)	31.6 (31.5-31.6)	25.5 (25.5-25.6)
MONTH 9 (PARTII)	24.8 (23.0-26.7)	30.8 (28.8-32.8)	24.9 (23.1-26.6)	24.8 (23.0-26.7)	30.8 (28.8-32.8)	24.9 (23.1-26.6)	18.8 (18.7-18.8)	35.0 (35.0-35.0)	22.9 (22.9-22.9)	19.1 (19.1-19.1)	36.9 (36.8-36.9)	19.1 (19.1-19.1)
MONTH 12 (PARTIII)	22.5 (20.7-24.4)	30.4 (28.5-32.2)	24.5 (22.6-26.4)	22.5 (20.7-24.4)	30.4 (28.5-32.2)	24.5 (22.6-26.4)	18.7 (18.8-18.7)	32.8 (32.8-32.8)	24.1 (24.1-24.1)	18.6 (18.6-18.6)	32.4 (32.4-32.4)	22.5 (22.5-22.5)
MONTH 15 (PARTIII)	20.1 (18.2-22.0)	29.8 (27.7-31.7)	23.9 (22.1-25.8)	20.1 (18.2-22.0)	29.8 (27.7-31.7)	23.9 (22.1-25.8)	18.1 (18.1-18.2)	33.9 (33.8-34.0)	27.3 (27.2-27.4)	18.1 (18.1-18.1)	33.8 (33.8-33.8)	25.8 (25.8-25.8)
MONTH 18 (PARTIII)	17.7 (15.8-19.7)	29.4 (27.6-31.3)	23.5 (21.6-25.3)	17.7 (15.8-19.7)	29.4 (27.6-31.3)	23.5 (21.6-25.3)	17.7 (17.7-17.9)	29.4 (29.2-29.6)	27.8 (27.6-28.1)	17.7 (17.7-17.7)	29.4 (29.4-29.4)	29.4 (29.4-29.4)
DIC SCORES		9.52 (9.38 – 9.81)						9.15 (8.66-9.50)				
AIC SCORES		9.30 (3.90 -15.42)			9.26 (4.95 -14.59)			18.57 (18.24-19.45)			8.79 (8.52-9.11)	

Discussion

Summary

- Huge unmet medical need for disease modification drugs
- Existing clinical development and trial design approaches are not adequate
- Doubly-randomized matched control design with proposed analytical plans addresses many existing issues for demonstrating clinical evidence of disease modification
- Bayesian inference is a natural fit
- Nonparametric models can be fit with ease

THANK YOU!!!