A Bayesian Analysis of Disease Modification Using Doubly Randomized Delayed-Start and Matched-Control Design Paradigms

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Temple University

Outline

- Introduction
- Scientific/Regulatory Considerations
- Existing Trial Designs and Statistical Methods
- Research Initiatives
- Discussion

How do Disease Progression and Disease Modification Differ?

- Disease progression: worsening of a disease in terms of symptom severity, underlying pathology, or outcome. The term "disease progression" is most commonly used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis

- Disease modification: alteration of the underlying disease pathophysiology that results in a beneficial outcome

Neurodegenerative Disease

- Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease
- Multiple sclerosis (MS)
- Parkinson's disease (PD)
- Alzheimer's disease (AD)

Introduction

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Challenges to Drug Development

- Unmet need for efficacious disease modification drugs over management of symptoms
- Driven by fruitful scientific research and discoveries
- Additional research objectives
  - To establish disease mediation biomarkers
  - To demonstrate clinical evidence of disease modifications

Basic Research in Disease Biology

- Associations of biomarkers and clinical outcomes from observational studies
- Causality via designed experiments
- Targeted drugs with effects on mediation biomarkers

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Mediation Biomarkers

- Direct measure of biological or physiological state of disease progression associated with clinical outcomes
- Direct targeted drug effects on biomarkers
- Indirect drug effects on clinical outcomes
- Indirect drug effects on clinical outcomes explained by direct biomarker effects

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?

Existing Trial Designs and Statistical Methods

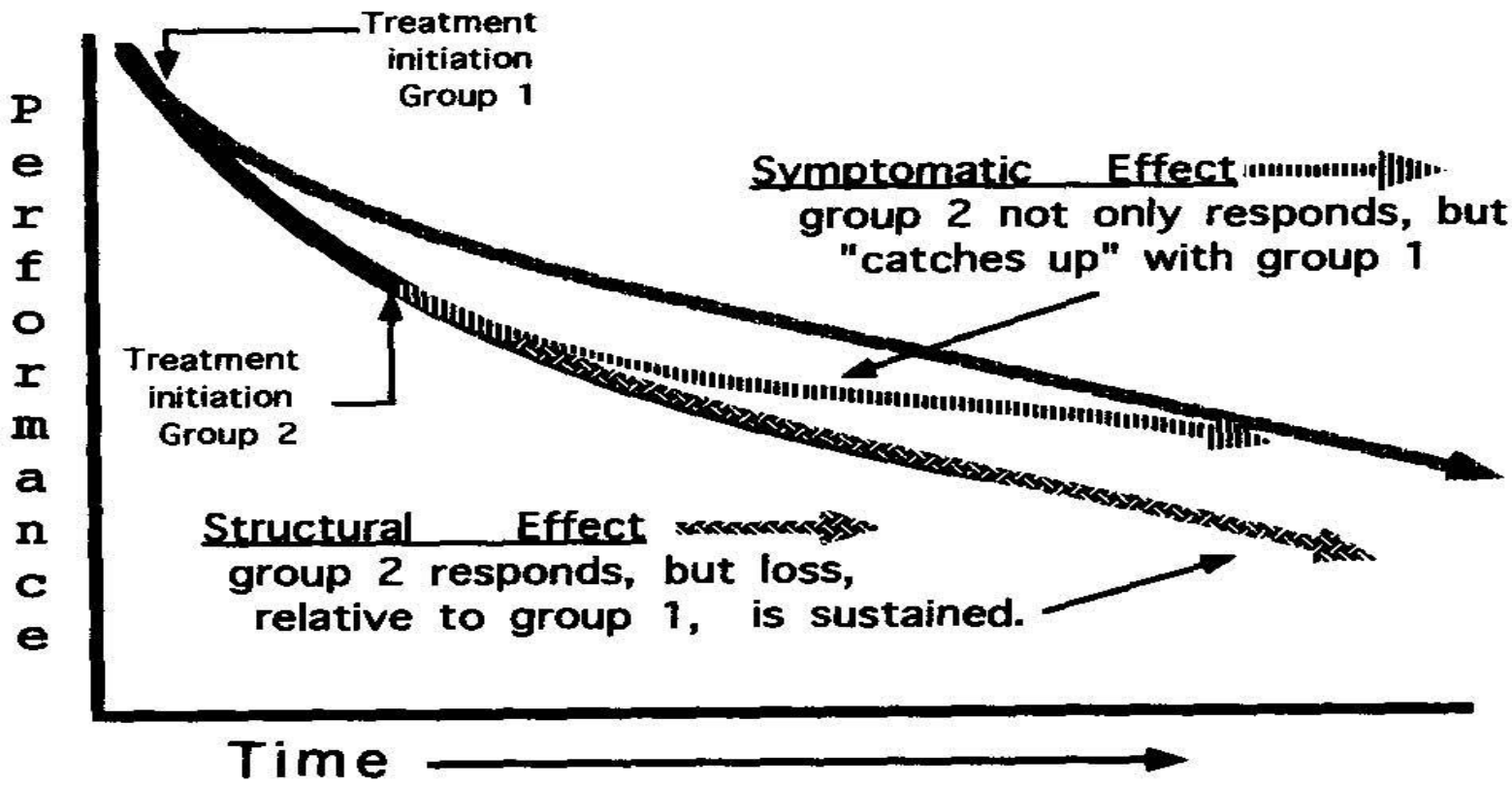

FIG. 2. Randomized start design.

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

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  - 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 dropouts

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- 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

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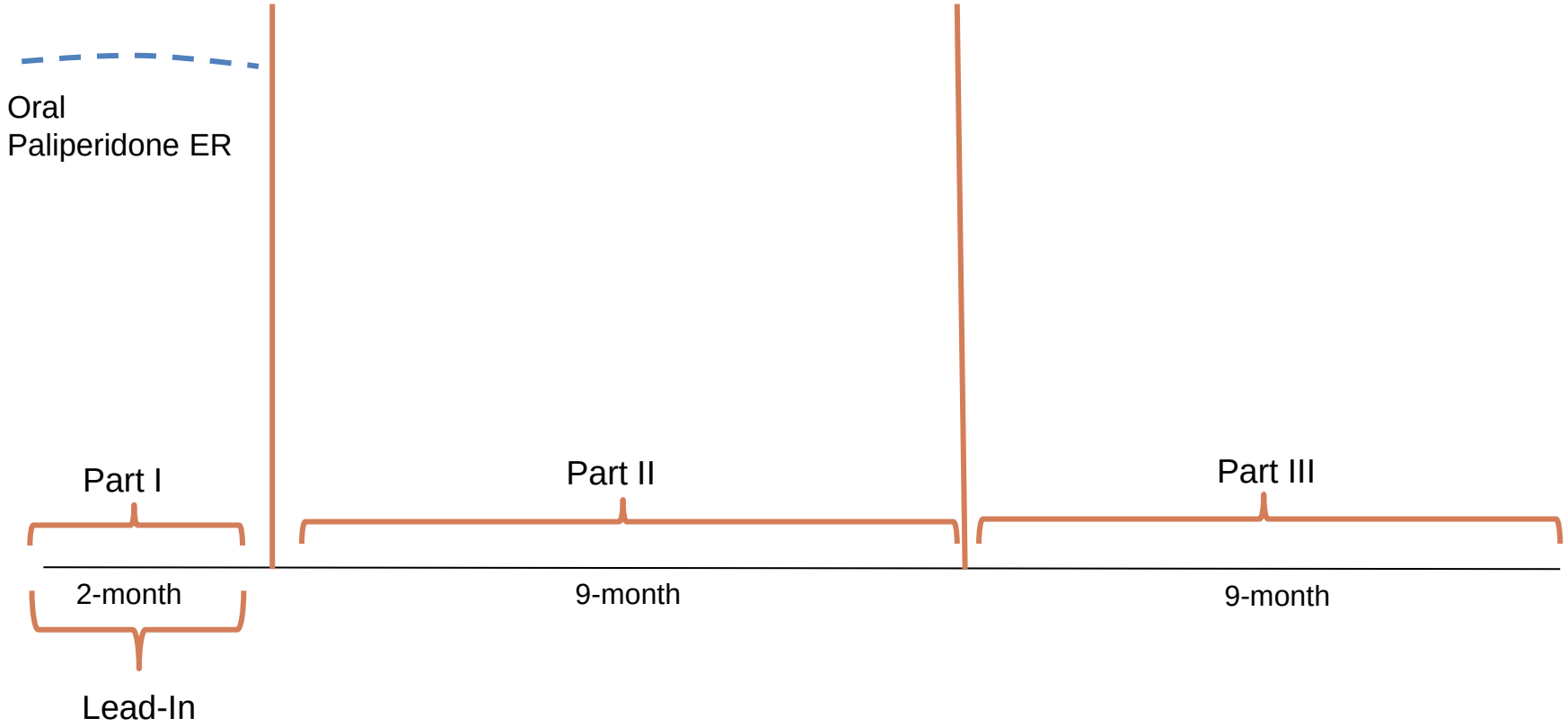
Adaptations with Potential Mediation Biomarkers

- Early futility, modification of enrollment criteria, or sample size adjustment
- Bias mediation analysis
- Validity of design established mathematically, not via limited and potentially biased simulation studies

Research Initiatives

Case 1: Disease Modification Effects



Research Initiatives

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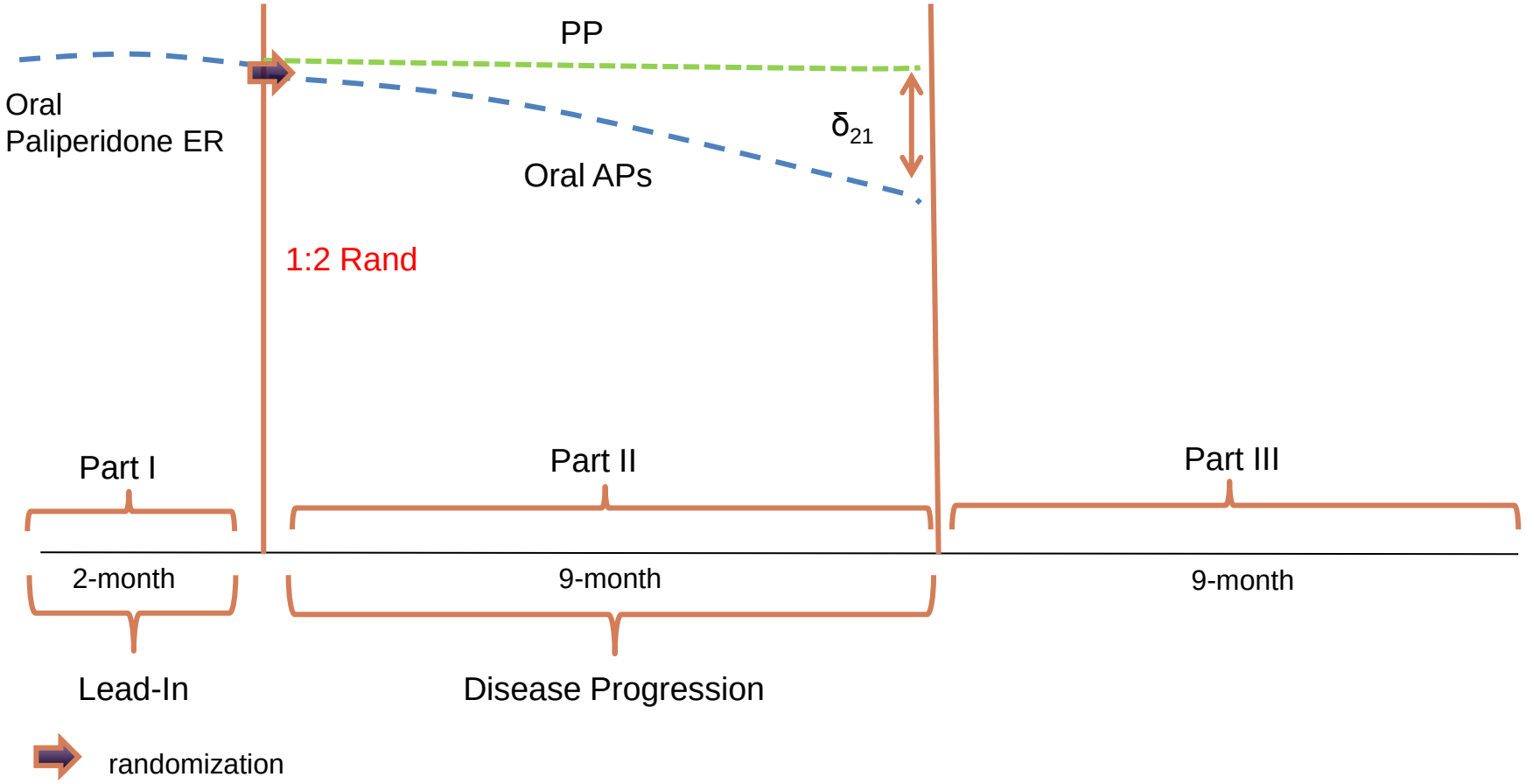

δ_{21}:Treatment effect on disease progression;

Research Initiatives

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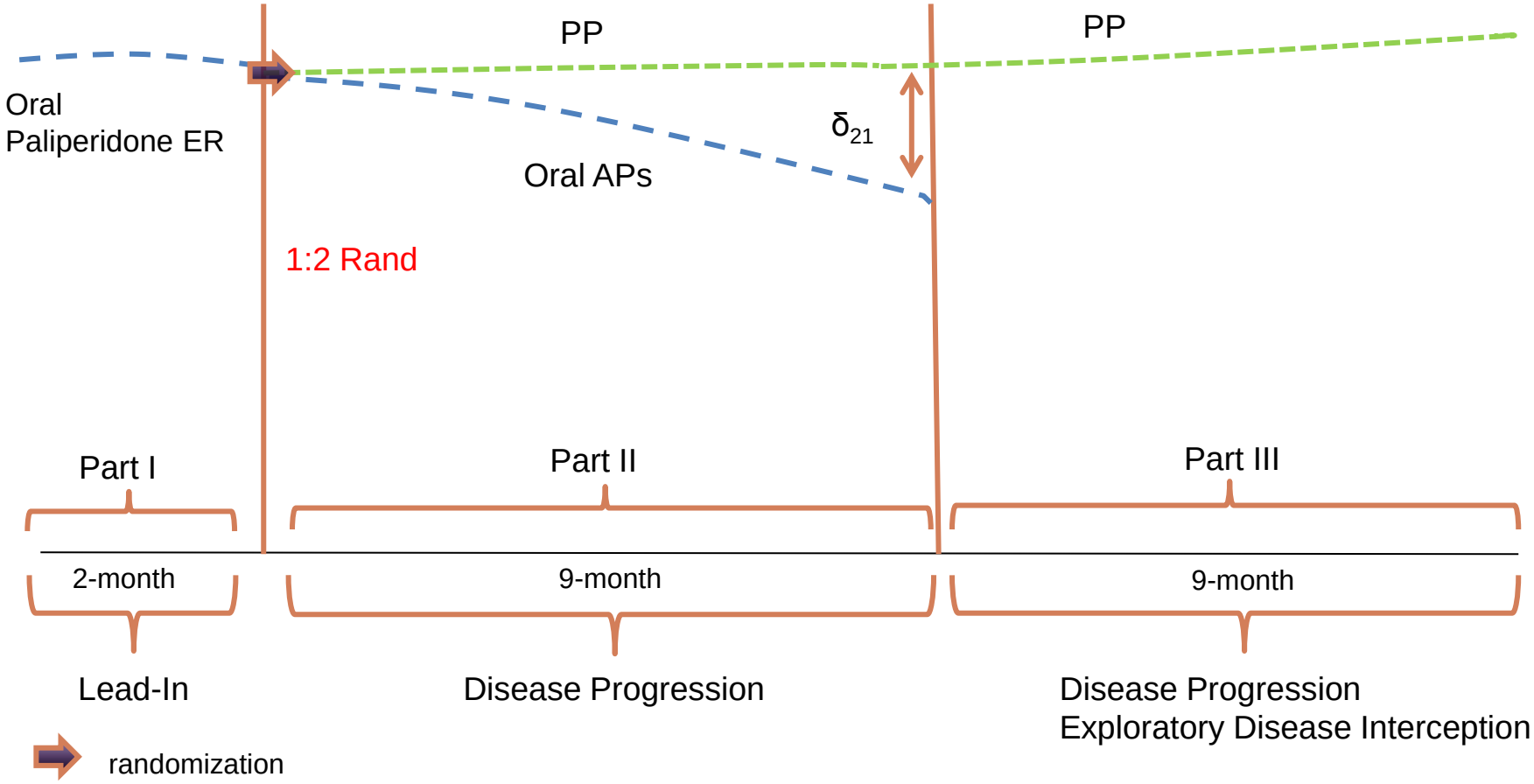

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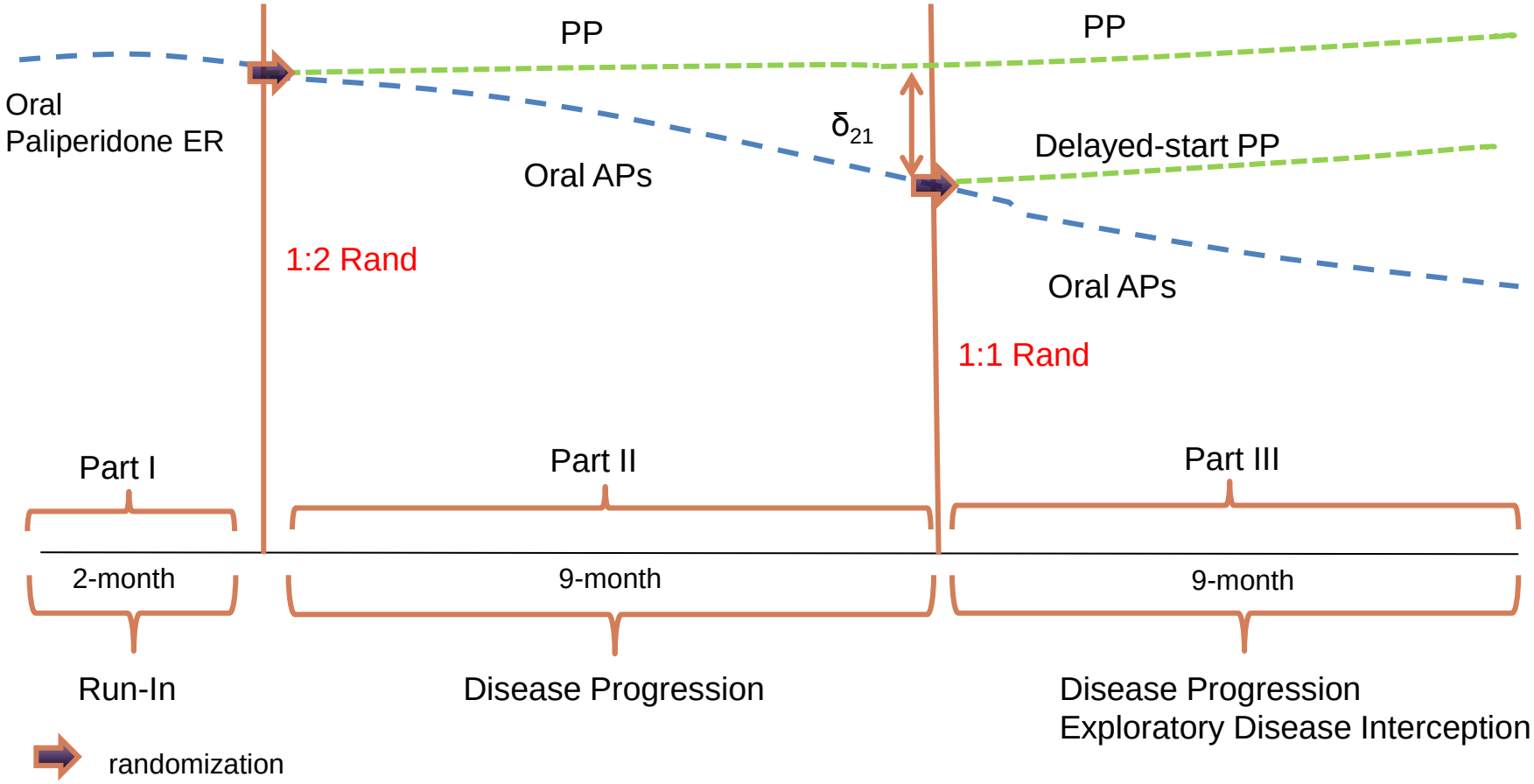

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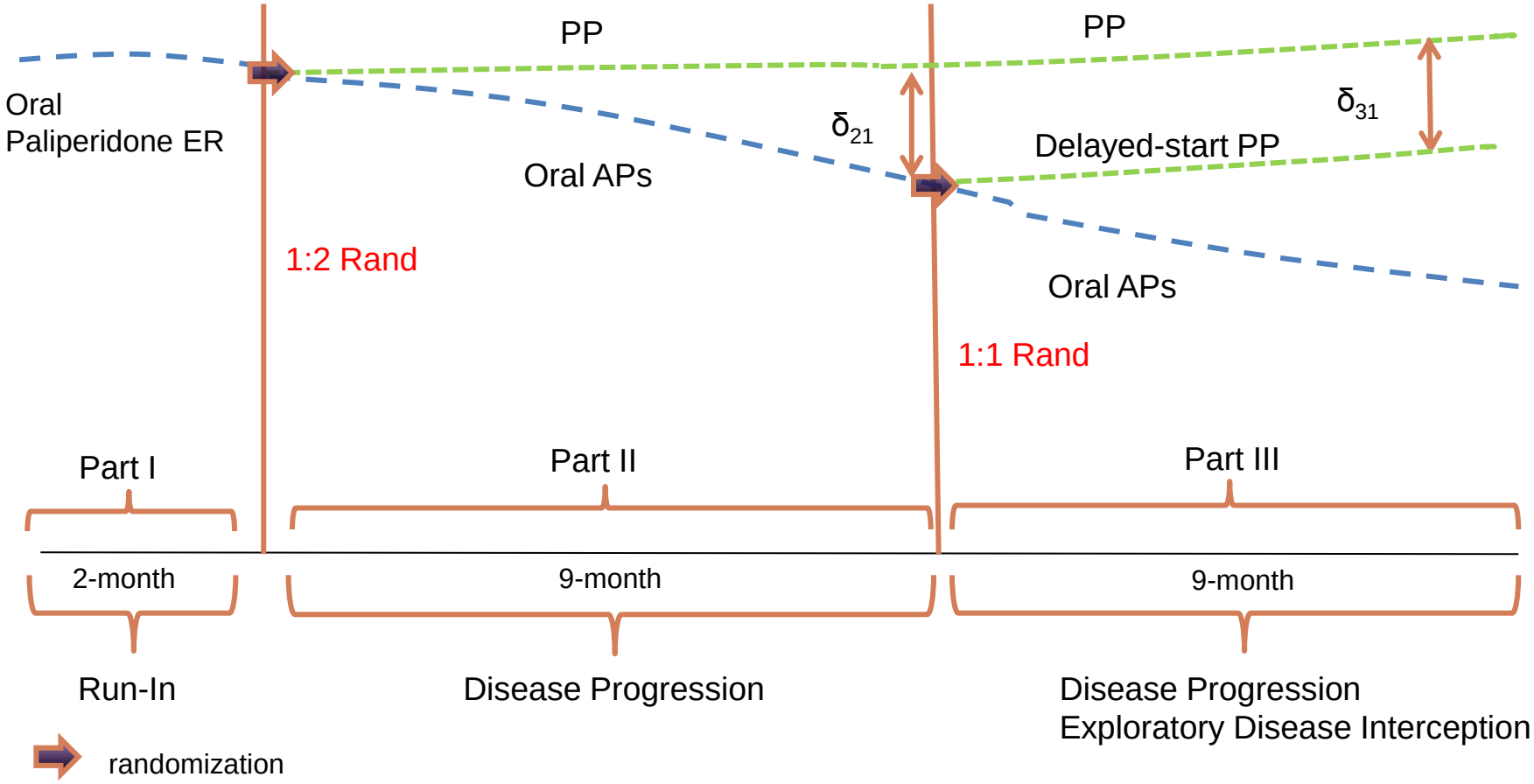

δ_{21}:Treatment effect on disease progression; δ_{31}:Lead treatment effect;

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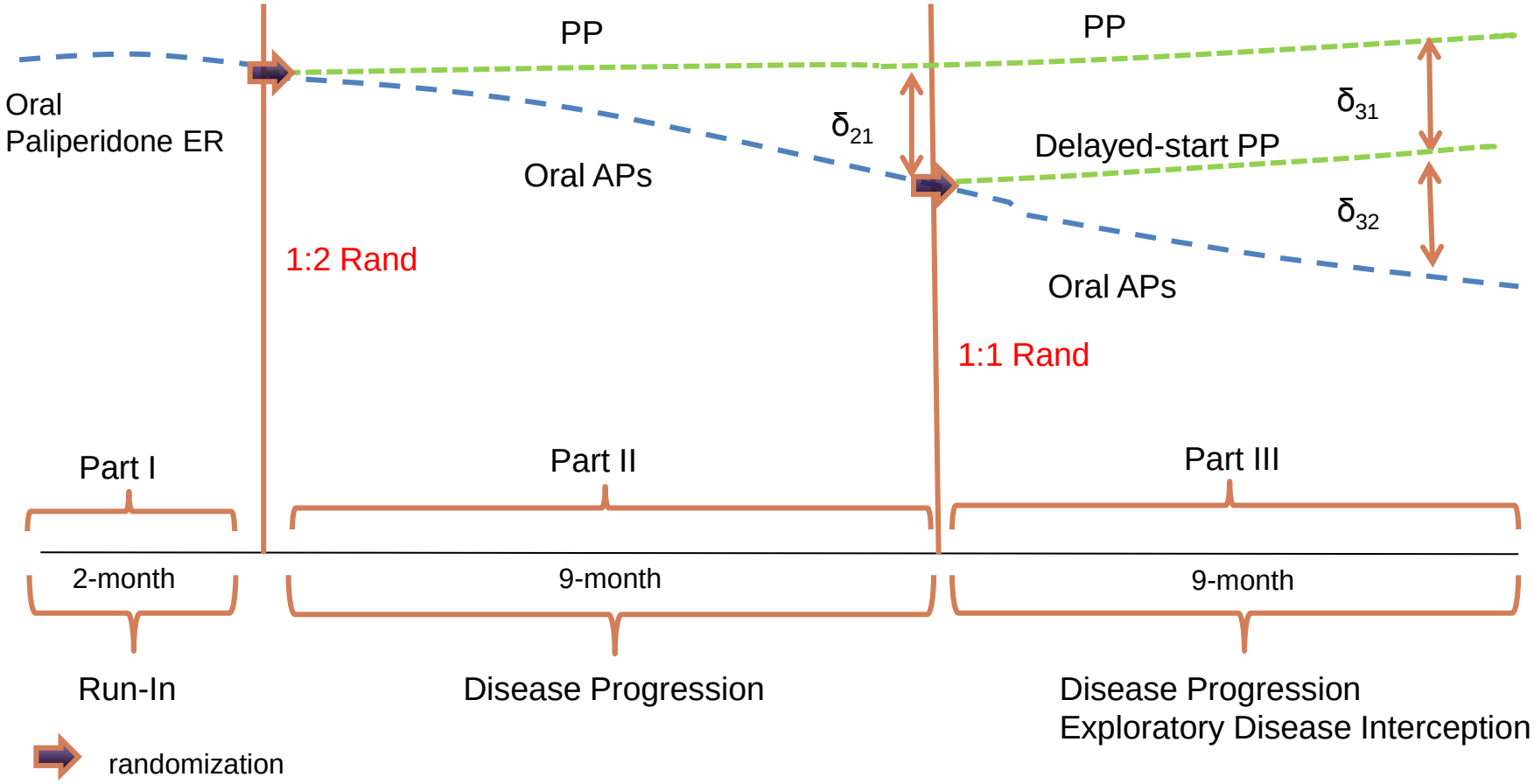

δ_{21}:Treatment effect on disease progression; δ_{31}:Lead treatment effect; δ_{32}:Delayed-start treatment effect on disease progression;

Research Initiatives

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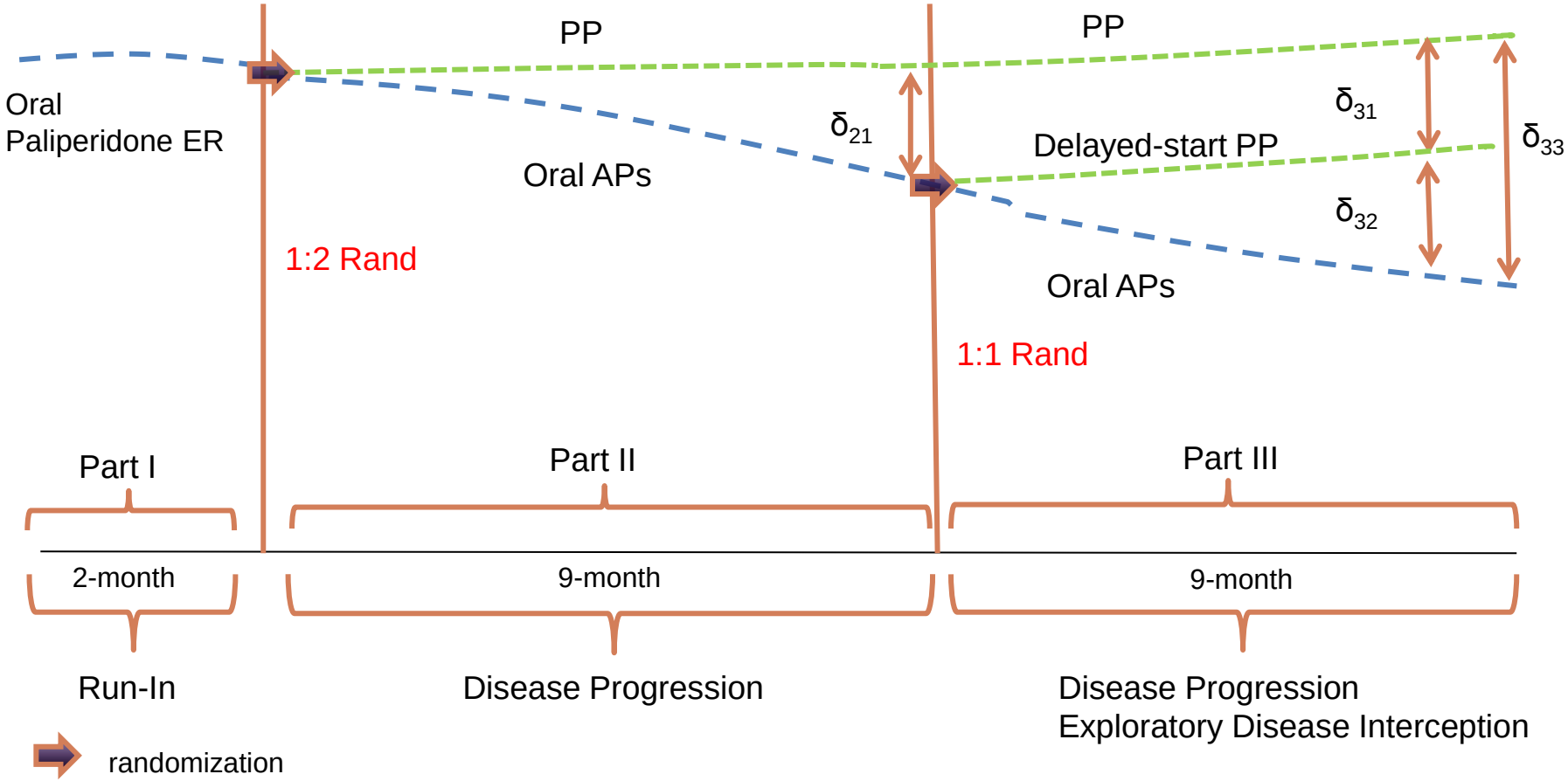

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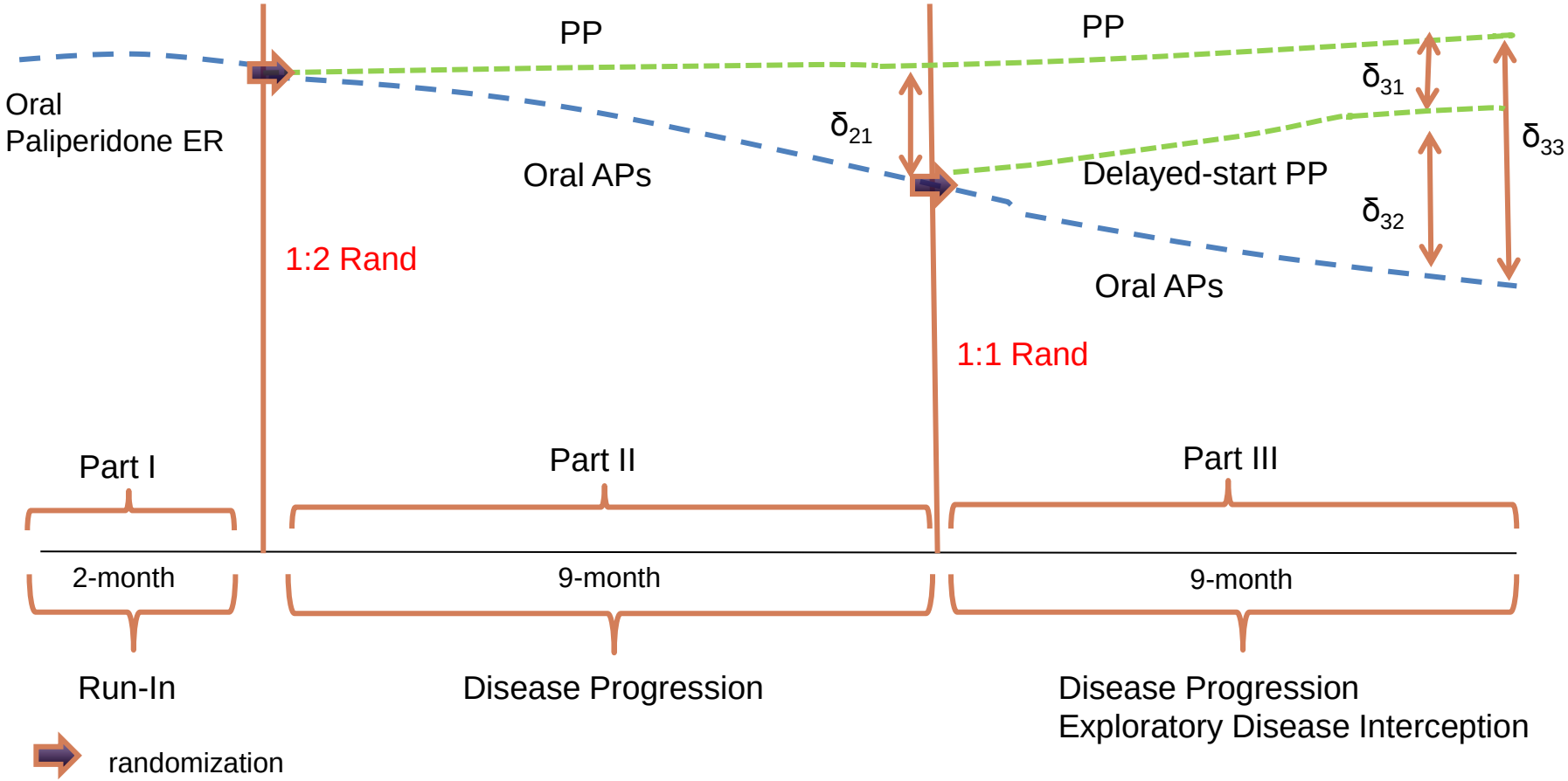
Case 2: Delayed-Start Effects



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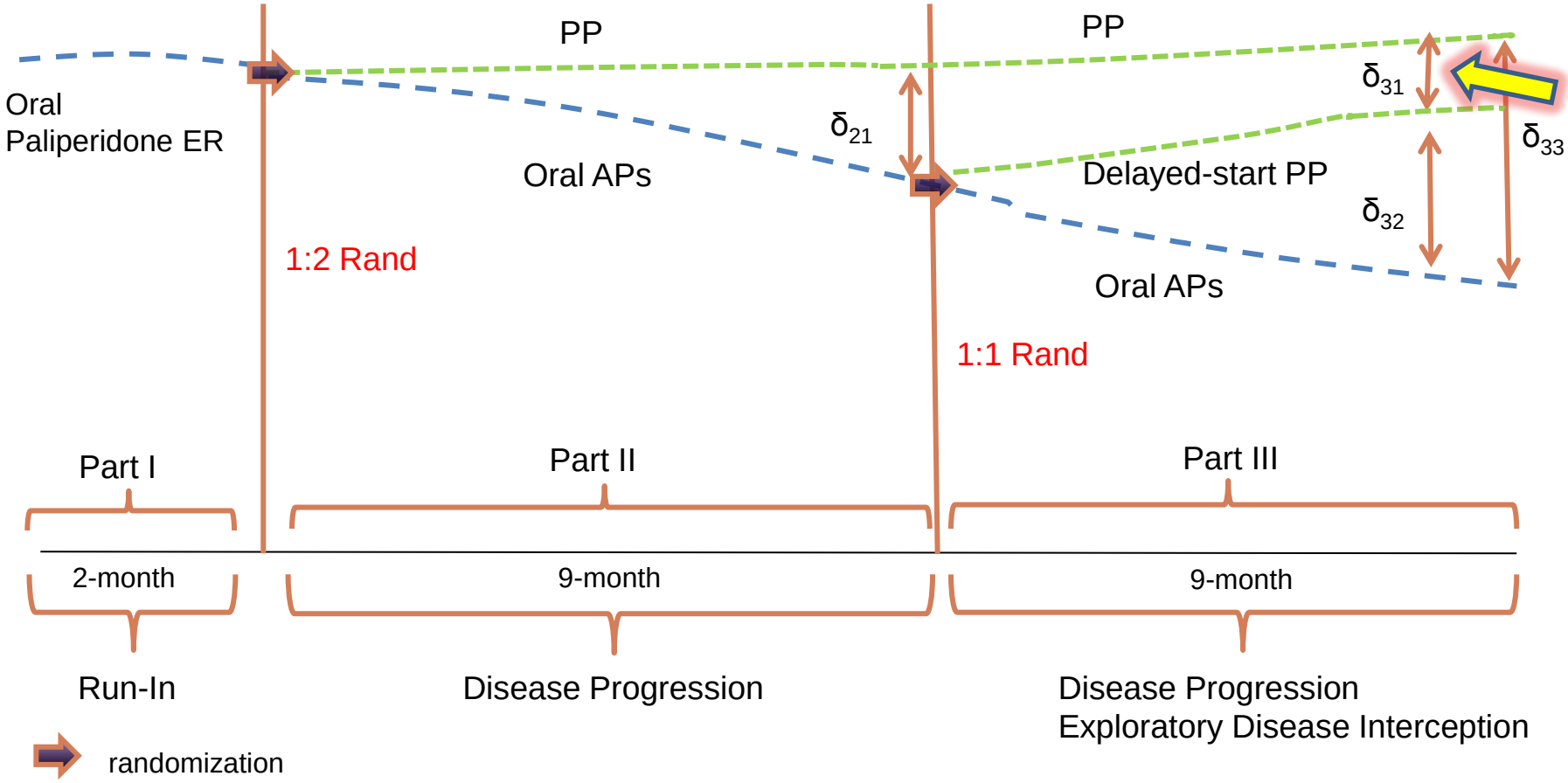

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Biomarkers

- Brain MRI Scans
- ICM volume will be measured - Cortical thickness, gray matter and white matter volumes

- No correlations
- No path analysis

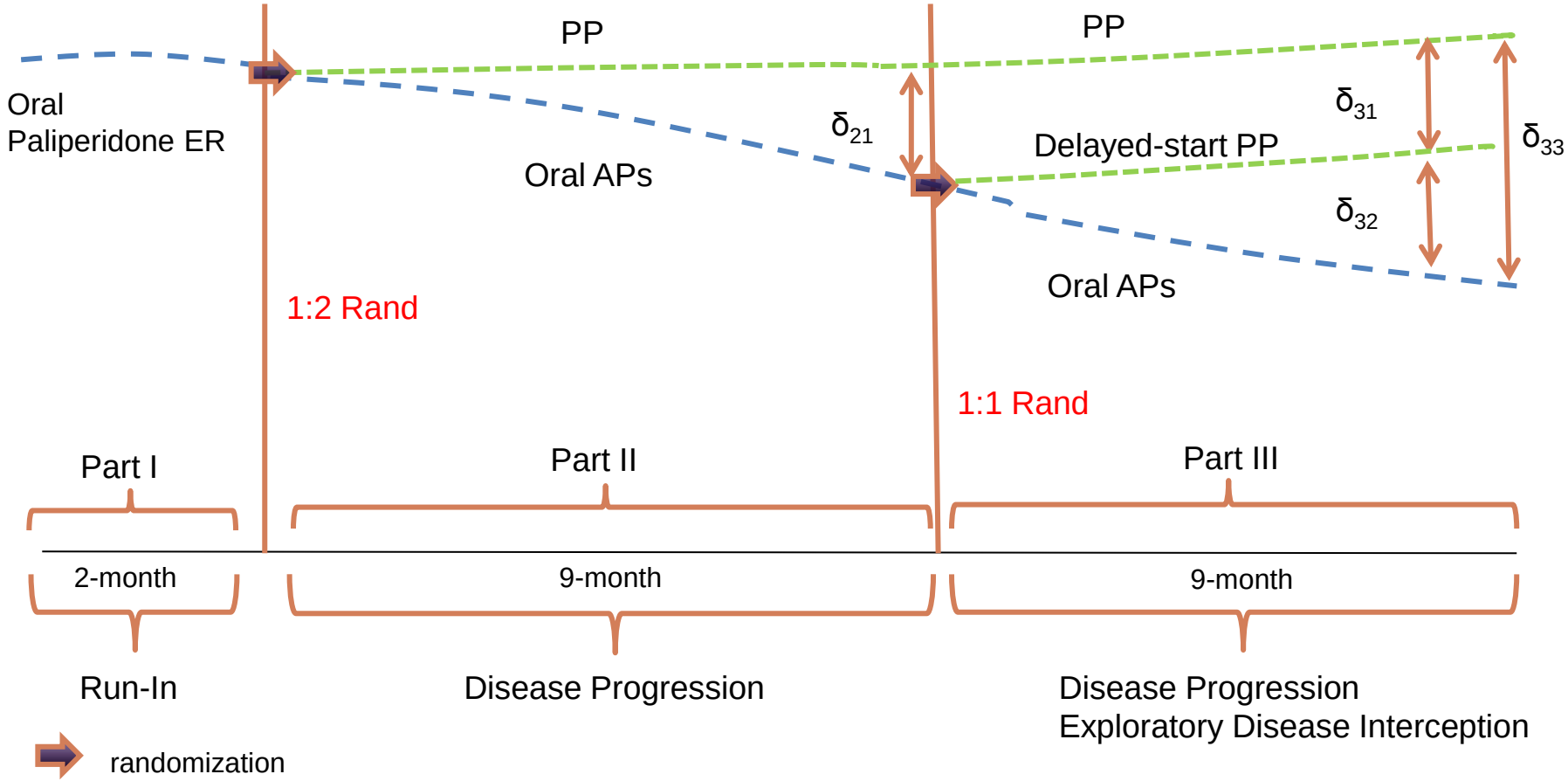
Lingering Issues

- Missing data
- Multiplicity

Three Key Innovations

- Randomized Matched Controls
  - Prospective run-in with static and dynamic prognostic factors
  - Matched control or causal inference to quantify retention effect
- Managed Withdrawal with Re-entry
  - Patients who decide to drop out are given necessary medicine(s) other than the study drug for best possible care, and are allowed to re-enter into Part III
  - On-going trials
- Randomized Delayed-Start
  - Verification and quantification of delayed-start effect
  - Disease modification as a clinical judgment based on the totality of evidence (i.e., effect on progress δ_{21}, lead effect after early-start δ_{31}, delayed-start effect δ_{32}, cumulative effect on progression δ_{33}, and biomarker effects)

Recall: Disease Modification



δ_{21}:Treatment effect on disease progression; δ_{31}:Lead treatment effect; δ_{32}:Delayed-start treatment effect on disease progression; δ_{33}:Overall effect of treatment.

Objective

- δ_{21} is the month 9 treatment effect on disease progression

  $\delta_{21} = \mu_9^{(PP)} - \mu_9^{(AP)}$

- δ_{31} is a measure of how much the AP / PP (delayed start with PP or lead treatment effect) subjects caught to the PP/PP subjects

  $\delta_{31} = \mu_{18}^{(PP,PP)} - \mu_{18}^{(AP,PP)}$

- δ_{32} is delayed start treatment effect on disease progression. The amount you may gain switching to PP

  $\delta_{32} = \mu_{18}^{(AP,PP)} - \mu_{18}^{(AP,AP)}$

- δ_{33} is the overall effect of treatment

  $\delta_{33} = \mu_{18}^{(PP,PP)} - \mu_{18}^{(AP,AP)}$

Objective

- We will examine catching up by estimating the posterior probabilities:

$P(\delta_{31} > 0.75\delta_{21})$; $P(\delta_{31} > 0.50\delta_{21})$; $P(\delta_{31} > 0.25\delta_{21})$

This is like

H_0: $\delta_{31} \leq 0.75\delta_{21}$

H_1: $\delta_{31} > 0.75\delta_{21}$ indicating that at least 75% of the treatment difference observed at the end of the Part II has been preserved at the end of delayed start period.

- We will also examine Significant Treatment differences by estimating the posterior probabilities:

$P(\delta_{21} > 0)$; $P(\delta_{31} > 0)$; $P(\delta_{32} > 0)$; $P(\delta_{33} > 0)$

Notation

- We observe $Y_{ij}^{(AP)}$, $Y_{ij}^{(PP)}$, and $Y_{ij}^{(APPP)}$; for subject i $(i = 1, \ldots, n)$

$$Y_{ij} = \mu_{ij} + \varepsilon_{ij} \;;\quad \varepsilon_{ij} \sim N(0,\ \tau_j^2) \qquad j = 0, 3, 6, 9, 12, 15, 18$$
$$\mu_{ij} = \theta + \alpha_i + \beta_{ij} M_j$$
$$\beta_{ij} = \beta_j + f_{ij} \;;\quad f_{i,\bullet} \sim N(0,\ \Sigma)$$

- μ_{ij} is the average response of patient i at month j
- α_i is the random intercept for patient i
- θ is the baseline response
- β_{ij} is the rate of change exhibited by patient i at month j
- β_j is the aggregated average rate of change
- ε_{ij} is the residual error for response Y_{ij}
- τ_j is the standard deviation of the error
- f_{ij} is the residual error for the rate of change exhibited by patient i at month j
- Σ is the covarinace matrix for residual errors

Notation

- Likelihood for the general model under a generic treatment regime

$$L \propto \exp\left\{-\frac{\sum (Y_{ij}-\mu_{ij})^2}{2\tau_j^2}\right\}$$

$$\times \exp\left\{-\frac{\sum_i (\beta_{i,\bullet}-\beta_{\bullet})'\Sigma^{-1}(\beta_{i,\bullet}-\beta_{\bullet})'}{2}\right\}$$

$$\times \frac{1}{|\Sigma|^{\frac{n+8}{2}}} \exp\left\{-\frac{\sum_j (\beta_j-\mu_\beta-\psi(\beta_{j-1}-\mu_\beta))^2}{2\sigma^2}\right\}$$

Models of Interest

- 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 Evaluation

- Deviance Information Criterion (DIC)

$$D(\mu,\tau)=\sum_{i,j}\frac{(Y_{ij}-\mu_{ij})^2}{\tau_j^2},\quad D(\bar{\mu},\bar{\tau})=\sum_{i,j}\frac{(Y_{ij}-\bar{\mu}_{ij})^2}{\bar{\tau}_j^2}$$

DIC is defined as the posterior average of:

$$DIC^*=2\times D(\mu,\tau)-D(\bar{\mu},\bar{\tau})$$

- Bayesian p-value is based on comparing predictive posterior residual with their observed counterparts

Predicted Residuals $resid_{ij}^*=\frac{(Y_{ij}^*-\mu_{ij})}{\tau_j}$, Observed Residuals $resid_{ij}=\frac{(Y_{ij}-\mu_{ij})}{\tau_j}$

Bayesian p-value $$P\left\{\sum_{i,j}\frac{(Y_{ij}^*-\mu_{ij})^2}{\tau_j^2}>\sum_{i,j}\frac{(Y_{ij}-\mu_{ij})^2}{\tau_j^2}\right\}$$

Central parameters have the prior distributions

$$\Sigma \sim IW(8, \frac{I}{\varepsilon})$$

$$\beta_j \sim N(0, \frac{I}{\varepsilon})$$

$$\tau_j^2 \sim \frac{\varepsilon}{\chi_1^2}; \quad \sigma^2 \sim \frac{\varepsilon}{\chi_1^2}$$

Posteriors

Posteriors will be computed for

θ

α_i

β_{ij}

β_j aggregated rate of change for treatment groups

Σ

τ_j^2

Linear Model under generic treatment regime

- We assume that

$$Y_{ij} = \mu_j + \varepsilon_{ij} \; ; \quad \varepsilon_{ij} \sim N(0, \; \tau_j^2)$$
$$\mu_{ij} = \theta I(j = 0) + \beta_{j>0} M_{j>0}$$

- θ is the means for subjects at month 0
- β_j is the rate of change for monh j
- εij is the residual error assumed to be normal with standard deviation τ_j
- Priors: We assume standard normal indifference priors for θ and β_j, and standard chi-square indifference priors for τ_j

Linear Model under generic treatment regime, Likelihood

$$Y_{ij} = \mu_j + \varepsilon_{ij}$$

$$\mu_{ij} = \theta I(j=0) + \beta_j M_j$$

$$L \propto \frac{1}{\prod_{j=1}^{7} \tau_j^n} \exp\left\{ -\sum_i \frac{\left(Y_{i0} - \theta\right)^2}{2\tau_0^2} - \sum_i \sum_{j>0} \frac{\left(Y_{ij} - \beta_j M_j\right)^2}{2\tau_j^2} \right\}$$

Linear Model under generic treatment regime, Posteriors

$$\theta \sim N\left\{ \frac{\sum_i \frac{Y_{i0}}{\tau_0^2}}{n/\tau_0^2},\ \sqrt{\frac{1}{n/\tau_0^2}} \right\}$$

$$\beta_j \sim N\left\{ \frac{M_j \frac{\sum_i Y_{ij}}{\tau_j^2}}{nM_j^2/\tau_j^2},\ \sqrt{\frac{1}{nM_j^2/\tau_j^2}} \right\}$$

$$\tau_0^2 \sim \frac{\sum_i (Y_{i0} - \theta)^2}{\chi_n^2}$$

$$\tau_j^2 \sim \frac{\sum_i (Y_{ij} - \beta_j M_j)^2}{\chi_n^2}$$

Linear Model under generic treatment regime, Model Check

- $DIC = 2 \times D(\theta, \beta, \tau) - D(\bar{\theta}, \bar{\beta}, \bar{\tau})$

$$D(\theta, \beta, \tau) = \sum_{ij} \frac{\left(Y_{ij} - \theta - \beta_j M_j\right)^2}{\tau_j^2}$$

$$D(\bar{\theta}, \bar{\beta}, \bar{\tau}) = \sum_{ij} \frac{\left(Y_{ij} - \bar{\theta} - \bar{\beta}_j M_j\right)^2}{\bar{\tau}_j^2}$$

- Bayesian p-value

$$P\left\{ \sum_{ij} \frac{\left(Y_{ij}^* - \theta - \beta_j M_j\right)^2}{\tau_j^2} > \sum_{ij} \frac{\left(Y_{ij} - \theta - \beta_j M_j\right)^2}{\tau_j^2} \right\}$$

Random Intercept

- $Y_{ij} = \mu_{ij} + \varepsilon_{ij}$

  $\mu_{ij} = \theta + \alpha_i + \beta_j M_j$

  $\uparrow$

α_i is the random intercept for patient i

β_j is the rate of change per month

ε_{ij} is the residual assumed to be normal with mean 0 and standard deviation τ_j

Here we assume standard normal indifference priors for α_i and β_j, and

standard chi-square indifferece priors for τ_j

Random Intercept and Random Slope

- $Y_{ij} = \mu_{ij} + \varepsilon_{ij}$

$$\mu_{ij} = \theta + \alpha_i + \beta_{ij} M_j$$

$$\uparrow \quad \uparrow$$

Random slope prior is $\beta_{ij} = \beta_j + e_{ij}$

$e_{ij} \sim N(0, \Sigma)$ and standard indifference priors on β_j and Σ

- $$L \propto \frac{1}{\prod_{j=1}^{7} \tau_j^n} \exp\left\{ -\sum_i \frac{(Y_{i0} - \theta - \alpha_i)^2}{2\tau_0^2} - \sum_i \sum_{j>0} \frac{(Y_{ij} - \alpha_i - \beta_{ij} M_j)^2}{2\tau_j^2} \right\}$$

$$\times \exp\left\{ -\frac{1}{2} \sum_i (\beta_{i,\bullet} - \beta_j)' \Sigma^{-1} (\beta_{i,\bullet} - \beta_j) \right\}$$

Random Intercept and Random Slope

- $Y_{ij} = \mu_{ij} + \varepsilon_{ij}$

  $\mu_{ij} = \theta + \alpha_i + \beta_{ij} M_j$

Random slope prior is $\beta_{ij} = \beta_j + e_{ij}$

$$e_{ij} \sim N(0, \Sigma)$$

Assume lower level correlation ψ and lower level mean μ_β

$$\beta_j = \begin{cases} \mu_\beta + \psi(\beta_{j-1} - \mu_\beta) + \varepsilon_j, & \text{if } j > 0 \\ \mu_\beta + \varepsilon_0, & \text{if } j = 0 \end{cases}$$

Autoregressive Model

- $$Y_{ij} = \begin{cases} \mu_j + \rho\left(Y_{i,j-1} - \mu_{j-1}\right) + \varepsilon_{i,j}, & \text{if } j > 0 \\ \mu_0 + \varepsilon_{i,0}, & \text{if } j = 0 \end{cases}$$

$$\mu_j = \theta + \beta_j M_j$$

The residual errors are assumed to be $\varepsilon_{i,j} \sim N(0, \tau_j^2)$

Assume indifference priors for the hyperparameters ρ, β, θ, τ_j.

Autoregressive Model

- $$Y_{ij} = \begin{cases} \mu_j + \rho\left(Y_{i,j-1} - \mu_{j-1}\right) + \varepsilon_{i,j}, & \text{if } j > 0 \\ \mu_0 + \varepsilon_{i,0}, & \text{if } j = 0 \end{cases}$$

$$\mu_j = \theta + \beta_j M_j$$

Compute posteriors for all the parameters

$$\rho \sim N_{-1,1}\left\{ \frac{\sum_{i,j=2:7} \left(Y_{i,j} - \mu_j\right)\left(Y_{i,j-1} - \mu_{j-1}\right)/\tau_j^2}{\sum_{i,j=2:7} \left(Y_{i,j-1} - \mu_{j-1}\right)/\tau_j^2}, \sqrt{\frac{1}{\sum_{i,j} \left(Y_{i,j-1} - \mu_{j-1}\right)/\tau_j^2}} \right\}$$

Generic Nonlinear Model

Peter Congdon, Applied Bayesian Modelling, Second Edition

Chapter 7: Analysis of Panel Data

The spline model of order q without random slopes or intercepts

$$Y_{ij} = \theta I(j=0) + \sum_{h=1}^{q} \beta_h M_j^h + \sum_{g=1}^{q} \gamma_g \left(M_j - \nu_g\right)_+^q + \varepsilon_{ij}$$

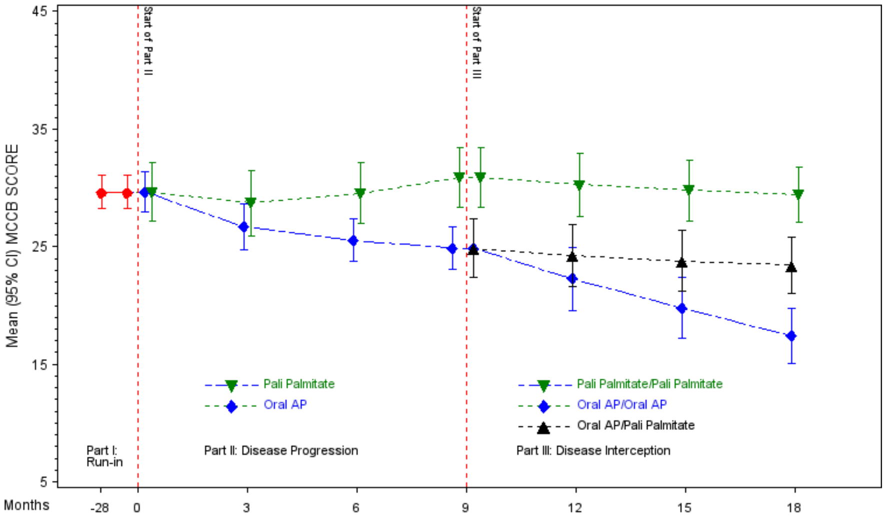
β_h is slope for polynomial M^h

γ_g is slope for spline polynomial

ν_g is the breakpoint (node)

α_i and β_{ih} can be included

Scenarios


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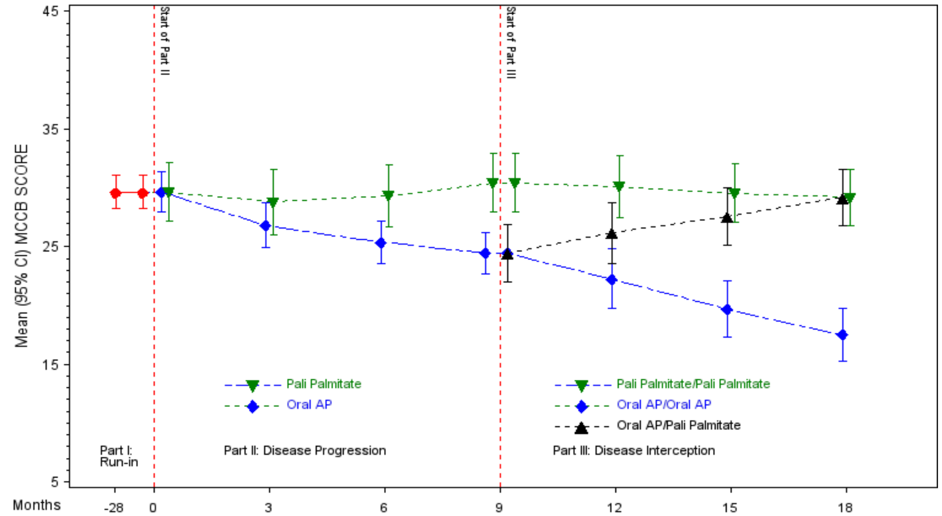
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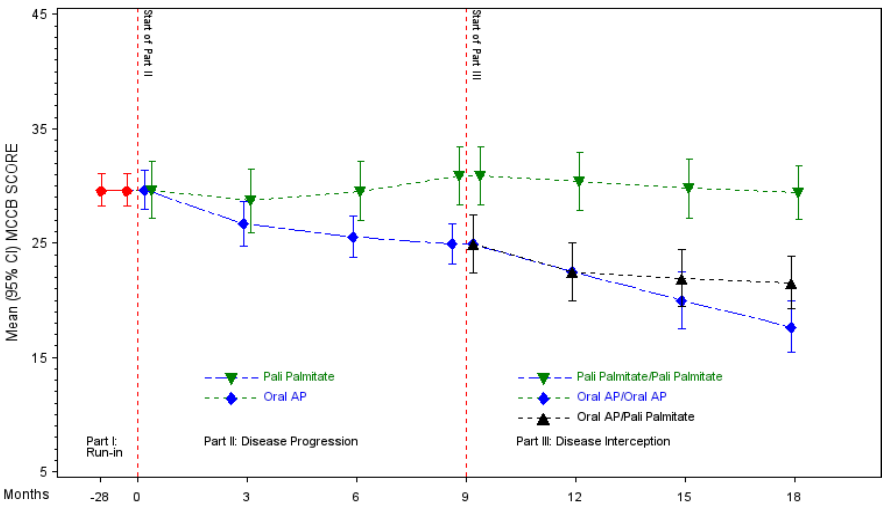
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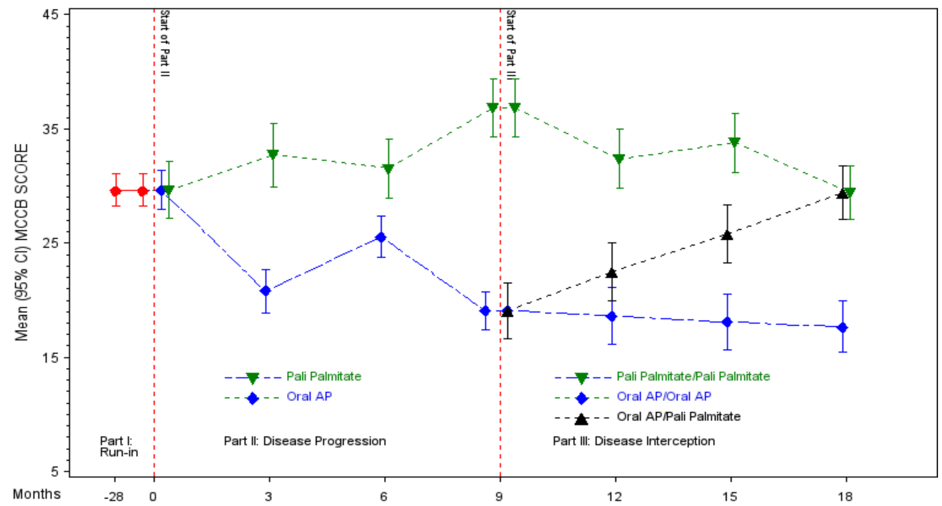
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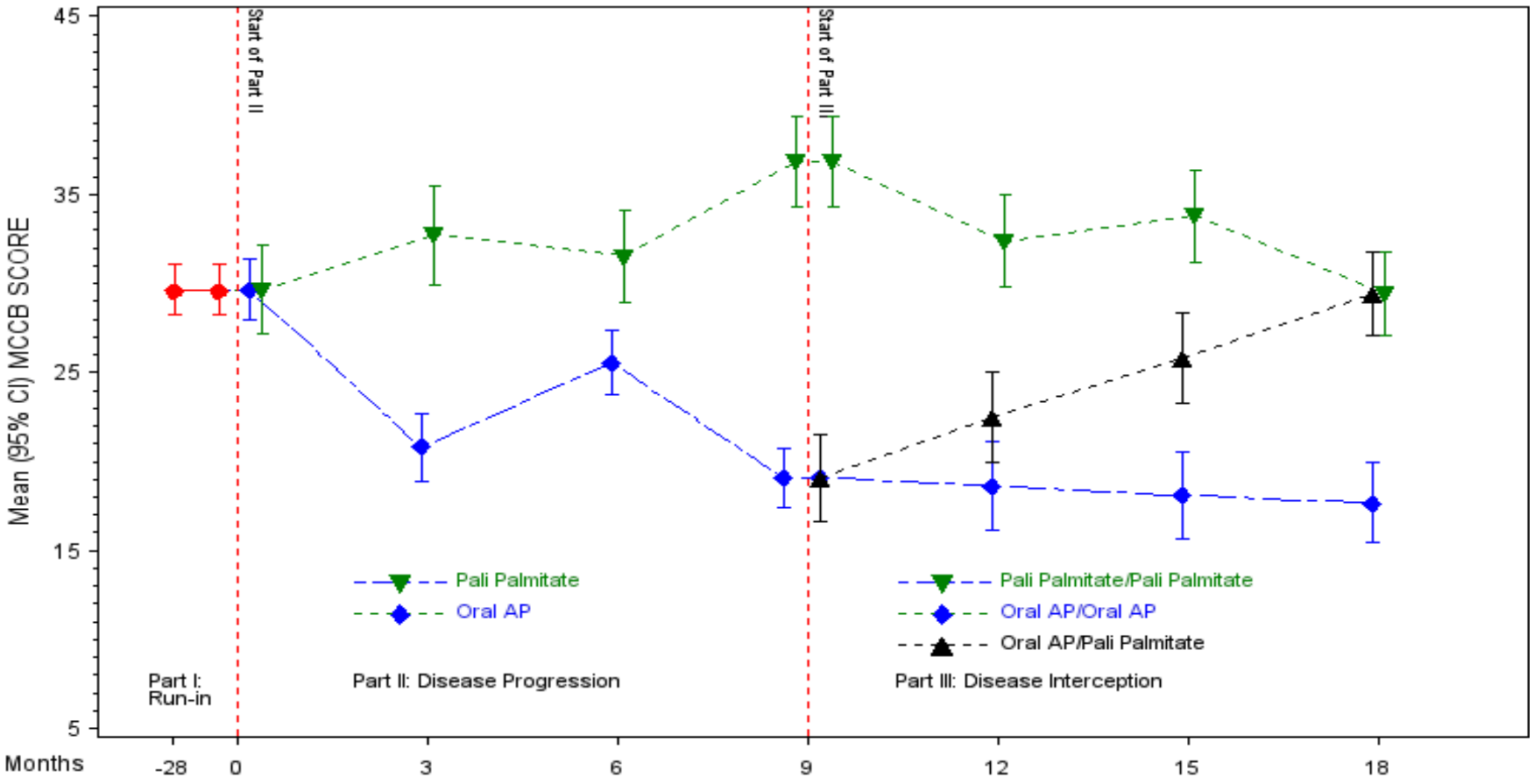
Part III: Disease Interception

Scenario – No Disease Modification



Scenario – No Disease Modification, Truth

Table 2 MCCB Score: Mixed Model Repeated Measures (MMRM) ANOVA, Actual Score and Difference at Each Visit Including Month 18 between PPPP and APAP; Subjects with Treatment PPPP or APAP

Parameter	PPPP Estimate(SE)	APAP Estimate(SE)	Difference (PPPP vs APAP) Estimate(SE)	95% CI	DF	p-value
Repeated Measures Model						
Treatment					1, 148	<0.001
Visit					6, 143	<0.001
Treatment*Visit Interaction					6, 143	<0.001
Model Estimates/Treatment Comparison (PPPP - APAP) at Each Visit						
Baseline	29.7 (1.25)	29.7 (1.25)	-0.0 (1.76)	(-3.49; 3.49)	148	1.000
Month 3	32.7 (1.39)	20.8 (1.39)	11.9 (1.97)	(8.03;15.81)	148	<0.001
Month 6	31.5 (1.30)	25.5 (1.30)	6.0 (1.84)	(2.36; 9.61)	148	0.001
Month 9	36.9 (1.25)	19.1 (1.25)	17.8 (1.76)	(14.32;21.28)	148	<0.001
Month 12	32.4 (1.26)	18.6 (1.26)	13.7 (1.79)	(10.17;17.26)	148	<0.001
Month 15	33.8 (1.26)	18.1 (1.26)	15.7 (1.78)	(12.17;19.21)	148	<0.001
Month 18	29.4 (1.16)	17.7 (1.16)	11.8 (1.64)	(8.52;15.00)	148	<0.001

Note: DF stands for degrees of freedom. The estimate, standard error, 95 percent CI, and p-value are based on a repeated measures mixed effects ANOVA model with treatment and visit as fixed effect (categorical) factors; and treatment-by-visit interaction. The correlation of the repeated measures is modeled with an unstructured covariance structure. Use DREAMSCENARIO5 dataset.

Scenario – No Disease Modification, Truth

Table 3.2 MCCB Score: Mixed Model Repeated Measures (MMRM) ANOVA, Actual Score and Difference at Each Visit including Month 18 between PPPP and APPP; Subjects with Treatment PPPP or APPP

Parameter	PPPP Estimate(SE)	APPP Estimate(SE)	Difference (PPPP vs APPP) Estimate(SE)	95% CI	DF	p-value
Repeated Measures Model						
Treatment					1, 148	<0.001
Visit					6, 143	0.091
Treatment*Visit Interaction					6, 143	<0.001
Model Estimates/Treatment Comparison (PPPP - APPP) at Each Visit						
Baseline	29.7 (1.25)	29.7 (1.25)	-0.0 (1.76)	(-3.49; 3.49)	148	1.000
Month 3	32.7 (1.39)	20.8 (1.39)	11.9 (1.97)	(8.03;15.81)	148	<0.001
Month 6	31.5 (1.30)	25.5 (1.30)	6.0 (1.84)	(2.36; 9.61)	148	0.001
Month 9	36.9 (1.25)	19.1 (1.25)	17.8 (1.76)	(14.32;21.28)	148	<0.001
Month 12	32.4 (1.28)	22.5 (1.28)	9.9 (1.81)	(6.30;13.43)	148	<0.001
Month 15	33.8 (1.29)	25.8 (1.29)	8.0 (1.83)	(4.38;11.59)	148	<0.001
Month 18	29.4 (1.19)	29.4 (1.19)	-0.0 (1.68)	(-3.32; 3.32)	148	1.000

Note: DF stands for degrees of freedom. The estimate, standard error, 95 percent CI, and p-value are based on a repeated measures mixed effects ANOVA model with treatment and visit as fixed effect (categorical) factors; and treatment-by-visit interaction. The correlation of the repeated measures is modeled with an unstructured covariance structure. Use DREAMSCENARIO5 dataset.

Scenario – No Disease Modification, Posterior Means

TSIMCCB03_C1: Estimated Means and 90% Credible Intervals for Generated Simulation Data; (Study R092670-SCH-3013)

	Linear			Random Intercept			Random Intercept and Slope			Autoregressive		
	OAP-OAP	PP-PP	OAP-PP	OAP-OAP	PP-PP	OAP-PP	OAP-OAP	PP-PP	OAP-PP	OAP-OAP	PP-PP	OAP-PP
BASELINE (PARTII)	29.8 (27.8-31.9)	29.7 (27.7-31.7)	29.7 (27.6-31.8)	29.7 (28.0-31.5)	29.7 (27.9-31.4)	29.7 (27.7-31.7)	29.7 (27.7-31.9)	29.7 (27.7-31.8)	29.7 (27.8-31.7)	32.7 (24.5-37.7)	32.7 (25.3-37.1)	32.8 (25.0-37.2)
MONTH 3 (PARTII)	20.8 (18.5-23.1)	32.7 (30.4-35.0)	20.8 (18.6-23.1)	23.2 (19.2-26.9)	32.1 (30.0-34.5)	23.2 (19.2-26.8)	19.9 (19.5-20.2)	30.4 (30.0-30.7)	19.5 (19.2-20.0)	22.7 (18.2-27.7)	33.9 (29.6-38.1)	22.0 (17.9-26.6)
MONTH 6 (PARTII)	25.5 (23.4-27.7)	31.6 (29.4-33.8)	25.5 (23.2-27.6)	18.8 (17.0-20.8)	34.6 (31.1-38.4)	20.8 (17.8-24.1)	26.8 (26.4-27.2)	32.3 (31.8-32.7)	27.2 (26.7-27.6)	26.7 (20.6-32.8)	31.7 (26.3-37.3)	25.9 (20.1-31.6)
MONTH 9 (PARTII)	19.1 (17.1-21.2)	36.9 (34.8-38.8)	19.1 (17.0-21.1)	17.9 (16.1-19.8)	31.6 (28.1-35.5)	27.6 (24.1-30.8)	19.8 (18.6-20.6)	36.3 (35.2-37.6)	20.3 (19.6-20.8)	19.9 (13.0-26.7)	36.9 (30.8-43.0)	19.2 (13.0-25.6)
BASELINE (PARTIII)	19.1 (17.1-21.2)	36.9 (34.8-38.8)	19.1 (17.0-21.1)	17.9 (16.1-19.8)	31.6 (28.1-35.5)	27.6 (24.1-30.8)	19.8 (18.6-20.6)	36.3 (35.2-37.6)	20.3 (19.6-20.8)	19.9 (13.0-26.7)	36.9 (30.8-43.0)	19.2 (13.0-25.6)
MONTH 12 (PARTIII)	18.6 (16.6-20.7)	32.4 (30.3-34.5)	22.5 (20.5-24.7)	23.2 (19.2-26.9)	32.1 (30.0-34.5)	23.2 (19.2-26.8)	19.3 (18.9-19.6)	33.1 (32.5-33.7)	21.9 (21.5-22.4)	19.2 (11.0-27.2)	32.4 (25.0-40.2)	22.3 (14.2-30.4)
MONTH 15 (PARTIII)	18.0 (15.9-20.2)	33.8 (31.6-36.1)	25.8 (23.6-27.9)	18.8 (17.0-20.8)	34.6 (31.1-38.4)	20.8 (17.8-24.1)	18.7 (18.2-19.2)	34.1 (33.6-34.6)	24.7 (24.4-25.3)	18.6 (10.2-26.9)	33.9 (25.6-42.7)	25.9 (17.9-33.8)
MONTH 18 (PARTIII)	17.6 (15.8-19.4)	29.4 (27.4-31.3)	29.5 (27.6-31.3)	17.9 (16.1-19.8)	31.6 (28.1-35.5)	27.6 (24.1-30.8)	16.8 (15.9-17.7)	30.8 (30.0-31.7)	30.6 (29.6-31.4)	18.0 (14.2-21.9)	29.5 (26.3-32.3)	29.4 (26.4-32.7)

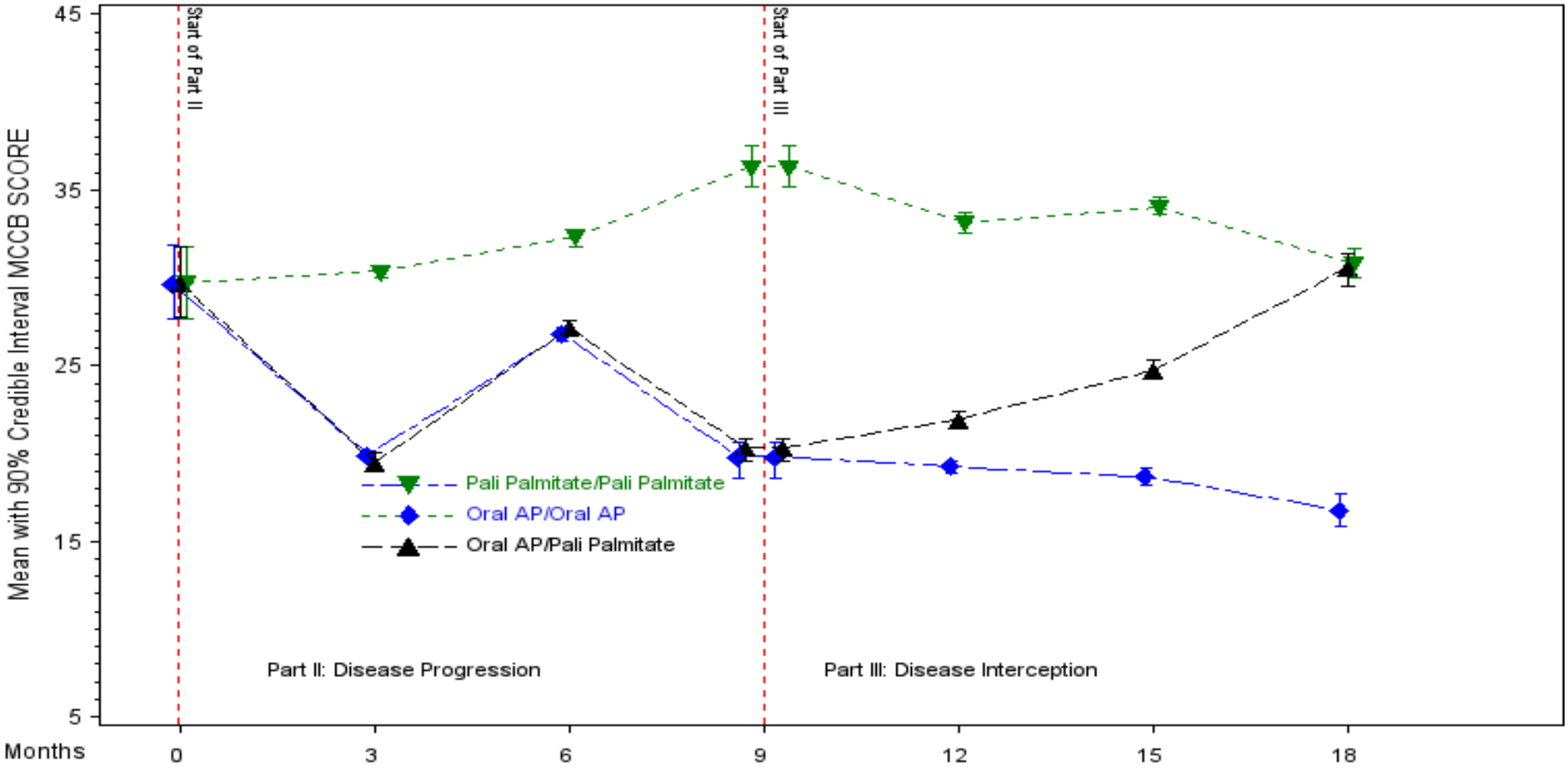
Scenario – No Disease Modification, Posterior Mean Diffs

TSIMCCB04_C1: Treatment Mean Differences and 90% Credible Intervals of 500 Selected Simulations of Generated Data; (Study R092670-SCH-3013)

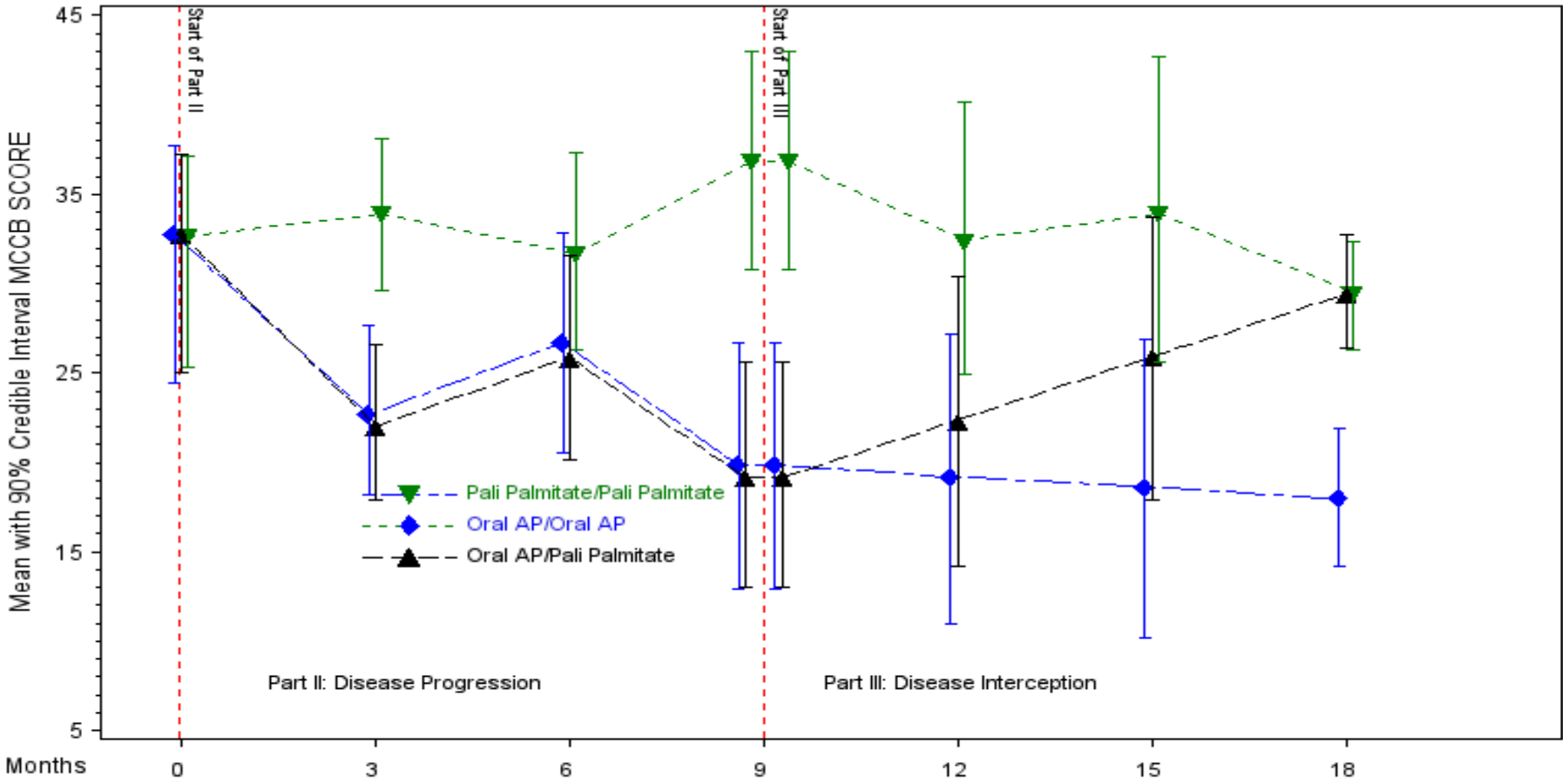
Contrasts	Linear Model	Random Intercept	Random Intercept and Slope	Autoregressive
DELTA21	-17.8 (-20.3, -15.3)	-8.8 (-13.7, -4.3)	-16.3 (-17.6, -14.7)	-17.4 (-25.0, -10.2)
DELTA31	-0.0 (-2.9, 2.6)	4.0 (-2.0, 10.2)	0.2 (-1.1, 2.1)	0.0 (-4.5, 4.3)
DELTA32	11.8 (9.3, 14.3)	9.7 (5.4, 13.7)	13.8 (12.1, 15.5)	11.5 (6.6, 16.5)
DELTA33	11.8 (9.0, 14.6)	13.7 (10.0, 17.9)	14.0 (13.1, 14.6)	11.5 (6.2, 16.5)

Note: Delta21: Treatment effect on disease progression; Delta31: Lead treatment effect; Delta32: Delayed-start treatment effect on disease progression; Delta33: Overall effect of treatment.

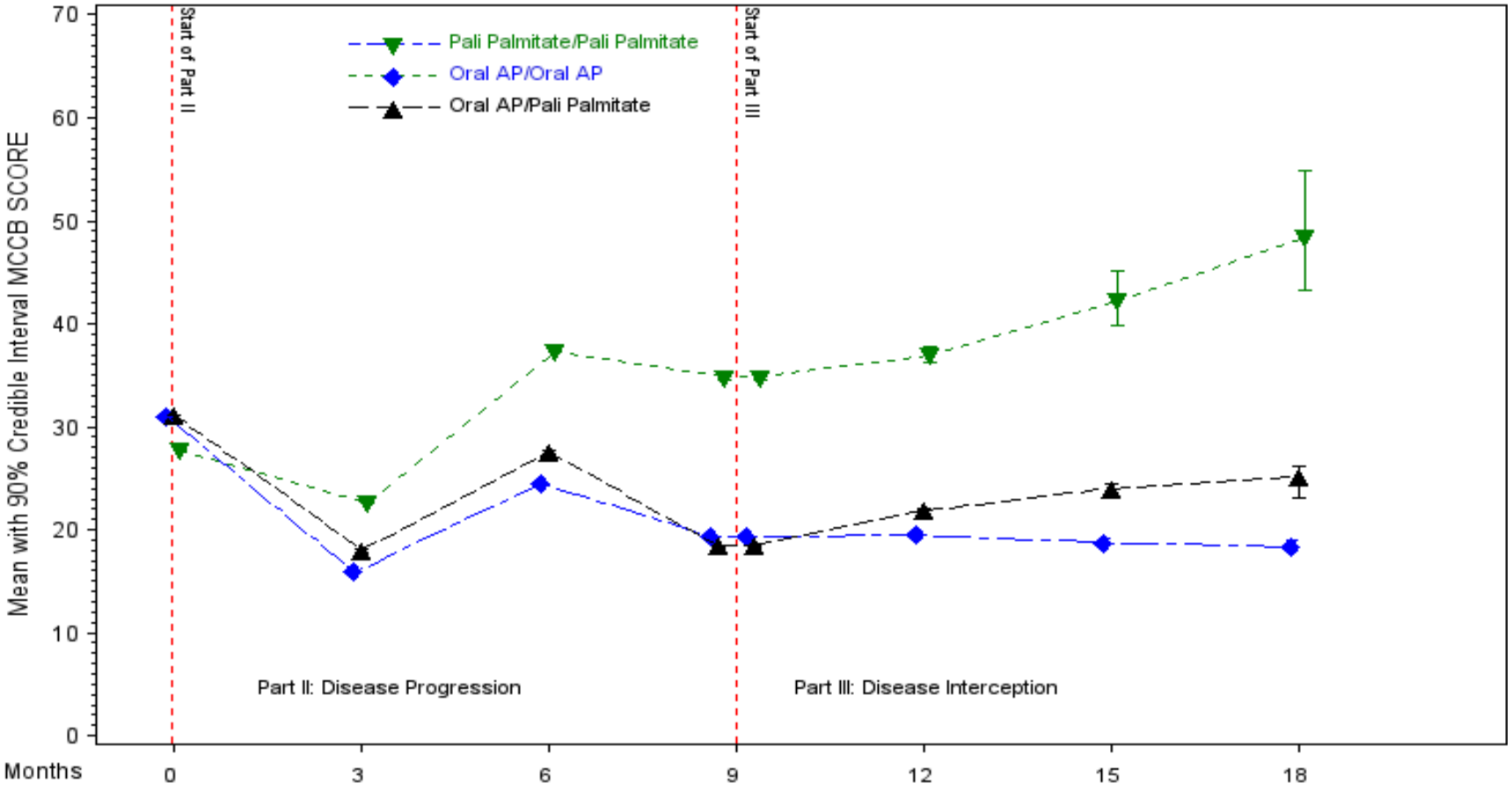
Scenario – No Disease Modification, RIRS Posterior Means



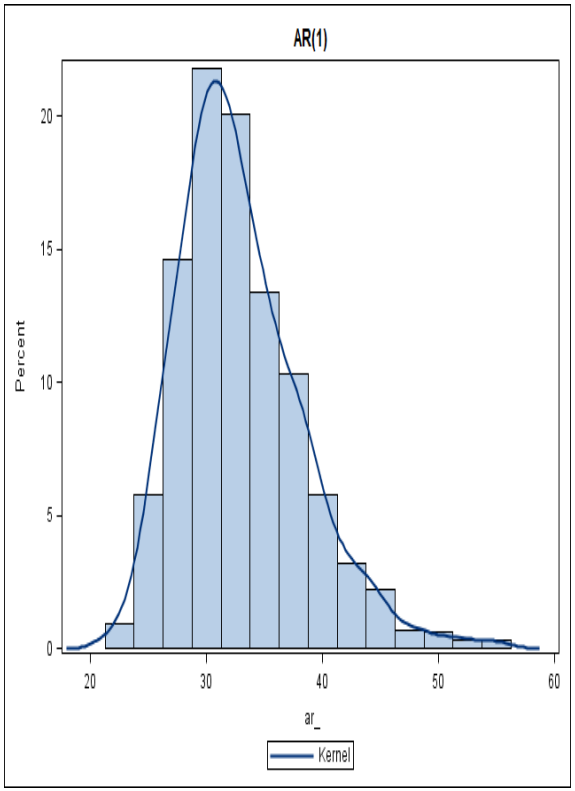
Scenario – No Disease Modification, AR(1) Posterior Means

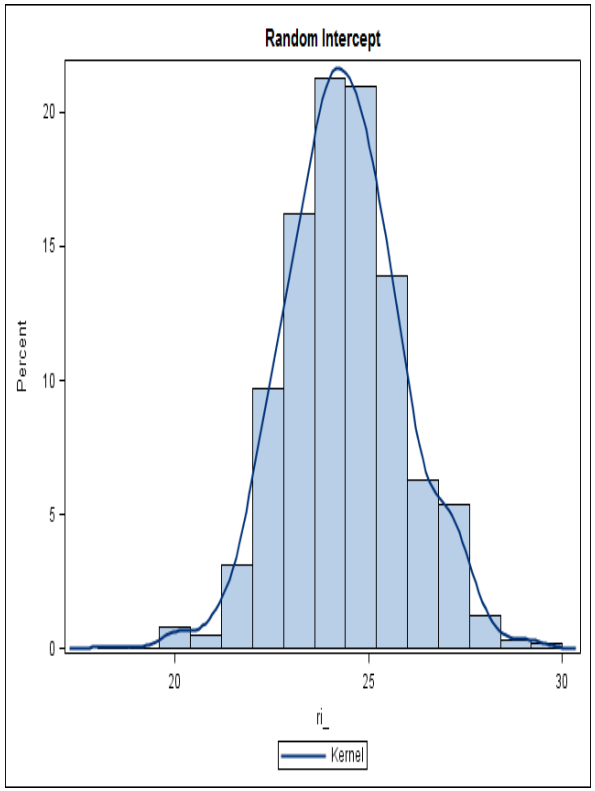


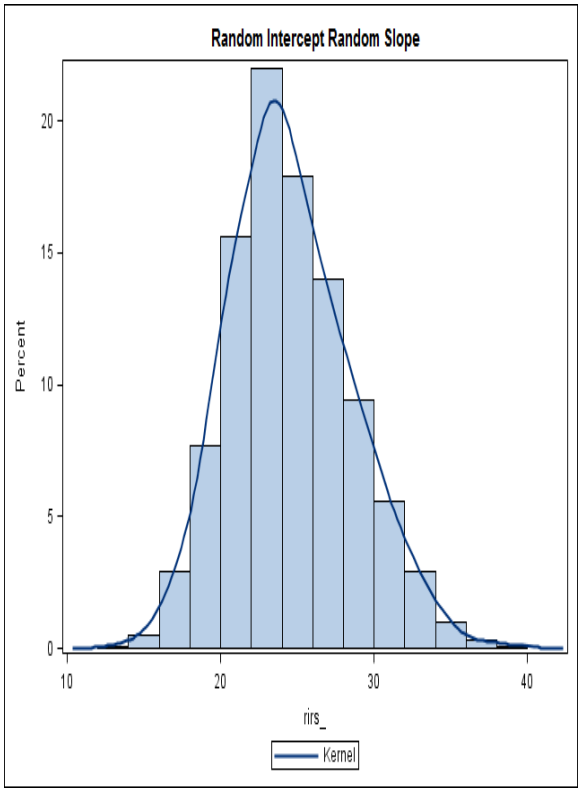
Scenario – No Disease Modification, 2 Nodes Posterior Means



Scenario – No Disease Modification, DIC







Means: 32.89 24.07 23.53

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
- Strong preference for simpler designs to establish mediation biomarkers, especially for drugs with modest effects