The Chronic Progressive Repeated Measures (CPRM) Model for Clinical Trials Comparing Change Over Time in Quantitative Trait Outcomes

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Abstract: Repeated measures analysis is a common analysis plan for clinical trials comparing change over time in quantitative trait outcomes in treatment versus control. Mixed model for repeated measures (MMRM) assuming an unstructured covariance of repeated measures is the default statistical analysis plan, with alternative covariance structures specified in the event that the MMRM model with unstructured covariance does not converge. We here describe a parsimonious covariance structure for repeated measures analysis that is specifically appropriate for longitudinal repeated measures of chronic progressive conditions. This model has the parsimonious features of the mixed effects model with random slopes and intercepts, but without restricting the repeated measure means to be linear with time. We demonstrate with data from completed trials that this pattern of longitudinal trajectories spreading apart over time is typical of Alzheimer's disease. We further demonstrate that alternative covariance structures typically specified in statistical analysis plans using MMRM perform poorly for chronic progressive conditions, with the compound symmetry model being anticonservative, and the autoregressive model being poorly powered. Finally, we derive power calculation formulas for the chronic progressive repeated measures model that have the advantage of being independent of the design of the pilot studies informing the power calculations. When data follow the pattern of a chronic progressive condition. These power formulas are also appropriate for sizing clinical trials using MMRM analysis with unstructured covariance of repeated measures.

Keywords: Clinical trial design, Clinical trial sample size, Mixed model for repeated measures, Power calculations.

1. INTRODUCTION

A consistent feature of longitudinal studies of normal aging [1], mild cognitive impairment [2], and Alzheimer's disease (AD) [3, 4] is that longitudinal measures of cognition and function "fan out" over time. This is typical of chronic progressive conditions, where the rate of progression of symptoms is different for each person, so that persons who progress more quickly diverge from persons who progress more slowly over time. A standard statistical analysis used by clinical trialists to accommodate this pattern of progression is mixed model for repeated measures (MMRM) assuming an unstructured covariance matrix [5]. As a measure of the importance of the MMRM analysis plan, every pivotal phase 3 clinical trial of monoclonal antibody therapy for the treatment of Alzheimer's disease that filed a statistical analysis plan on clinicaltrials.gov (Table **1**) listed MMRM as the primary statistical analysis. Monoclonal antibody therapy is the first treatment proven to affect the course of Alzheimer's disease and be approved by the FDA, and MMRM was the the statistical analysis plan for each of the clinical trials supporting three recently approved treatments for early Alzheimer's disease [6-8]. A feature of MMRM is that the number of covariance parameters in the model increases quadratically with the number of repeated measures, and MMRM models may fail to converge. For this reason, regulatory trial statistical analysis plans include contingency analysis plans. Typically, MMRM analyses assume parsimonious compound symmetric (CS) or first order autoregression (AR1) covariance structures for the contingency analysis plan (Table **1**).

In this paper, we demonstrate that CS and AR1 models are not appropriate for chronic progressive data. In large-scale computer simulations of data typical of Alzheimer's disease, we found that both of these covariance structures performed poorly for chronic progressive data. The MMRM analysis with CS covariance is prone to type I error, with a type I error rate that greatly exceeds the nominal 5% type I error rate used in hypothesis testing. Hence this commonly applied covariance structure is not valid for data typical of Alzheimer's disease. In contrast, the MMRM analysis with AR1 covariance structure can result in a dramatic loss of statistical power, meaning that otherwise well-powered trials may miss effective treatments if a contingency analysis with AR1 is required. To address these concerns, we derived an alternative covariance structure that is more appropriate for chronic progressive data typical of Alzheimer's disease (Section 2). The model we propose is an MMRM model with arbitrary fixed effect means, but with a pattern of dispersion of longitudinal repeated measures more

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Table 1: Contingency Covariance Structures for Phase 3 Alzheimer's Disease Monoclonal Antibody Trials Listed on *clinicaltrials.gov*.

Trial	SAP	Contingency	N	Sponsor	Intervention
NCT03289143	MMRM	hetAR1	457	Genentech, Inc.	Semorinemab
NCT02484547	MMRM	hetAR1	1643	Biogen	Aducanumab
NCT02670083	MMRM	CS	813	Hoffmann-La Roche	Crenezumab
NCT03518073	MMRM	hetAR1, hetCS, CS	360	Eli Lilly and Company	Zagotenemab
NCT01224106	MMRM	not specified	799	Hoffmann-La Roche	Gantenerumab

SAP = Statistical Analysis Plan; MMRM = Mixed Model for Repeated Measures; hetAR1 = heterogeneous AR1; CS = compound symmetric; hetCS = heterogeneous CS.

consistent with the covariance structure of a chronic progressive condition. We call this alternative covariance structure the chronic progressive (CP) covariance structure, and the corresponding MMRM analysis the chronic progressive repeated measures (CPRM) analysis.

Unlike the unstructured covariance model, the CP covariance model, formally defined in Section 2, requires only four parameters for estimation regardless of the number of repeated measures. Critical to confirming the potential applicability of the CPRM analysis, we demonstrate using data from completed clinical trials that the CP covariance assumption holds for longitudinal cognitive data in Alzheimer's disease (Section 3). Section 4 reports computer simulations demonstrating how MMRM with a CS or AR1 covariance structures dramatically mis-represent treatment associations with disease. These limitations of the CS and AR1 models are relevant to any condition with a chronic progressive pattern of decline. Finally, we derive power formulas for the CPRM model (Section 5). A unique advantage of the CPRM parameterization is that power formulas are more flexible in that they can be used to power future clinical trials of arbitrary design (with arbitrary number and interval between followup visits) regardless of the design of the pilot study used to inform power calculations. It is often the case that available data to inform sample size calculations are from studies with a different length of follow-up than the planned future clinical trial. These formulas will allow power calculations that fully utilize available data regardless of the design of prior studies. Moreover, for chronic progressive data the CP and unstructure covariance estimate have the same expected value, meaning CPRM power formulas can be used to power clinical trial where MMRM with unstructure covariance is the primary statistical analysis plan.

2. THE CHRONIC PROGRESSIVE REPEATED MEASURES (CPRM) MODEL

The CPRM model is a modification of the commonly applied parameterization of the Laird and Ware [9] mixed effects model of longitudinal data

$$y_{ij} = \beta_0 + \beta_1 t_j + b_{0i} + b_{1i} t_j + e_{ij}, \quad (1)$$

where y_{ij} is the response for subject i ($i = 1,2,...,n$) at time j ($j = 1,2,...,m$), $t_1, t_2, ..., t_m$ are times at which measurements $\mathbf{y_i}$ are made, $\beta = (\beta_0, \beta_1)$ are the fixed effect coefficients describing the mean longitudinal trajectory, $(b_{0i}, b_{1i}) \sim N(\mathbf{0}, \mathbf{D})$ are random, subject-specific intercepts and slopes, and $\mathbf{e_i} \sim N(\mathbf{0}, \mathbf{R})$ is residual variation about the individual trajectories. Where convenient, we will represent the diagonal elements of $\mathbf{D}$ as σ^2_{b0} and σ^2_{b1}, and the off-diagonal elements as σ_{b_0, b_1} in derivations to follow. This model, familiarly called the random slopes model, has proved to be useful for modeling longitudinal cohort study data, where the linearity assumptions generally hold if the length of longitudinal follow-up is small relative to the full time course of the disease. The linearity assumption can be problematic for clinical trials, however, even when the period of follow-up is relatively short, because the pattern of progression under the alternative in the treatment arm cannot be known a priori. For example, treatment effects may be acute but not long lasting (e.g., Figure **1**, top panel), or, there may be some delay before treatment effects are realized (e.g., Figure **1**, bottom panel). We will demonstrate in simulations below how the random slope model can lead to dramatically anticonservative hypothesis testing when the fixed effect mean pattern of progression is consistent with the top panel of Figure **1**. To accommodate non-linear patterns of fixed effect mean change, we propose the CPRM model (equation (2)).

The CPRM model parameterization replaces the fixed effects intercept and slope in equation (1) with m

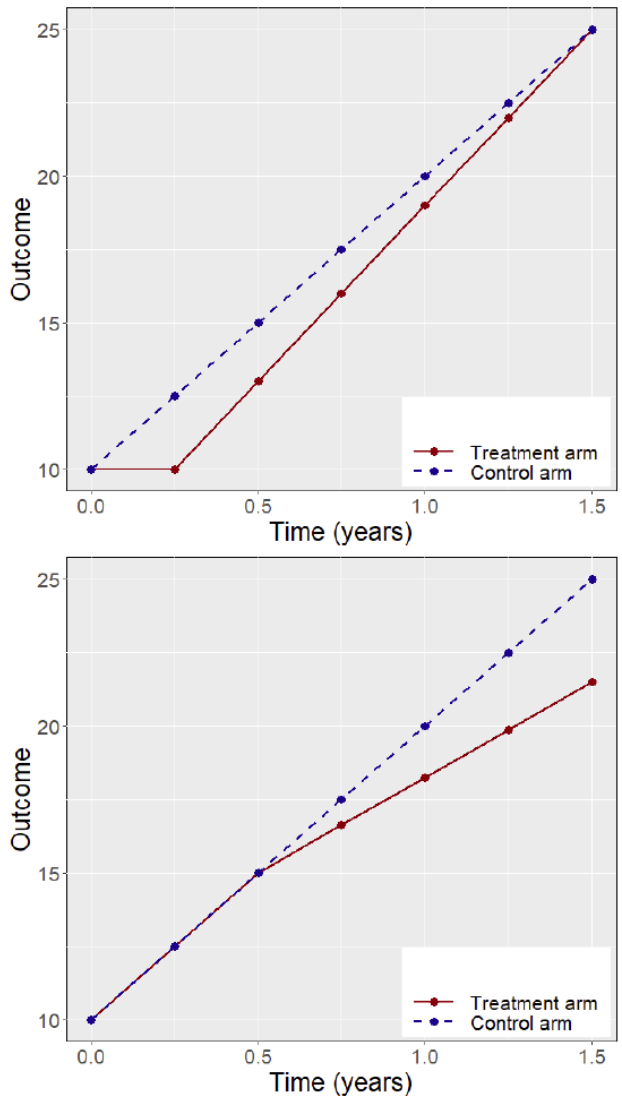

Figure 1: *Top panel.* Hypothetical trajectory of expected values by arm for a treatment with short term efficacy but no difference in treatment versus control at the end of the trial. *Bottom panel.* Hypothetical trajectory of expected values for a treatment with positive effect starting after the third observation and persisting to the end of the trial.

means, one for each repeated measurement time, and can be written as

$$y_{ij} = \alpha_j + b_{0i} + b_{1i}t_j + e_{ij}, \quad (2)$$

where $\alpha_j, j = 1,...,m$ are mean levels at each visit, $(b_{0i}, b_{1i}) \sim N(\mathbf{0},\mathbf{D})$ as above are random intercepts and slopes modeling the dispersion of the longitudinal trajectories, and $\mathbf{e_i} \sim N(\mathbf{0},\mathbf{R})$ are residual errors. The alternative parameterizations of fixed effects by the two models is illustrated with a toy example in Figure **2**.

Estimation of the parameters in equation (2) is by maximum likelihood or restricted maximum likelihood (REML). Derivation of the asymptotic variance of the fixed effect estimates for power calculation formulas proceeds analogously to the derivation of the variance of the fixed effects parameters under the random slopes model [10].

Writing equation (2) in matrix notation, we have

$$\mathbf{y_i} = \mathbf{X_i}\alpha + \mathbf{Z_i}\mathbf{b_i} + \varepsilon_i, \quad (3)$$

where identity matrix $\mathbf{X_i}$ is the fixed effects design matrix for subject i, and $\mathbf{Z_i} = (\mathbf{1},\mathbf{t_i})$ is the random effects design matrix for subject i. More generally, $\mathbf{X_i}$ can include additional fixed effect covariates.

Under this model, the covariance $\mathbf{V_i}$ for subject i with data completion pattern $\mathbf{t_i}$ is

$$\mathbf{V_i} = Cov(\mathbf{y_i}) = \mathbf{Z_i}\mathbf{D}\mathbf{Z_i}' + \mathbf{R_i}. \quad (4)$$

Assuming independent and identically distributed (iid) residual error σ_ε^2, $\mathbf{R_i} = \sigma_\varepsilon^2\mathbf{I}$, and the elements of $\mathbf{V_i}$ are a function of the pattern $\mathbf{t_i}$ of observations obtained for subject i, the residual error variance σ_ε^2, and the covariance parameters $\sigma_{b_0}^2$, $\sigma_{b_1}^2$, and $\sigma_{b_0b_1}$. Specifically, $\mathbf{V_i}$ are matrices with off diagonal elements u,v equal to $\sigma_{b_0}^2 + (t_u + t_v)\sigma_{b_0,b_1} + t_u t_v \sigma_{b_1}^2$ and diagonal elements u,u equal to $\sigma_{b_0}^2 + 2t_u\sigma_{b_0b_1} + t_u^2\sigma_{b_1}^2 + \sigma_\varepsilon^2$. See reference [10] for a formal derivation.

Given $\mathbf{V_i}$ and $\mathbf{X_i}$, when data are missing at random the asymptotic variance of REML estimates of the coefficients in equation (3) is

$$\mathbf{V}(\hat{\alpha}) = \left(\sum_i (\mathbf{X_i}'\mathbf{V_i}^{-1}\mathbf{X_i})\right)^{-1}. \quad (5)$$

Note that there is a finite set of missing value patterns defining $\mathbf{X_i}$ and $\mathbf{V_i}$. Indexing these missing value patterns by k and summing over participants with the same dropout pattern k, equation (5) can be expressed as

$$\mathbf{V}(\hat{\alpha}) = \left(\sum_k n_k(\mathbf{X_k}'\mathbf{V_k}^{-1}\mathbf{X_k})\right)^{-1} = \left(n\sum_k p_k(\mathbf{X_k}'\mathbf{V_k}^{-1}\mathbf{X_k})\right)^{-1} \quad (6)$$

where the n_k are counts of subjects in each set and sum to n, and $p_k = n_k / n$. Equation (6) will be useful for power calculation formulas for the CPRM model derived in Section 4 below.

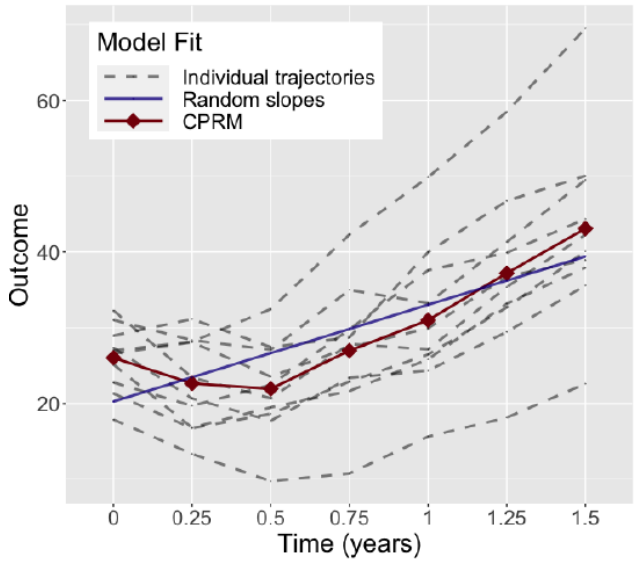

Figure 2: Fixed effect estimates by a repeated measures model (red) and a random slopes model (blue). The repeated measures model estimates the expect level at each time point while the random slopes model assumes a linear trajectory of fixed effect levels as a function of time.

3. EMPIRICAL VALIDATION OF THE CHRONIC PROGRESSIVE COVARIANCE STRUCTURE FOR ALZHEIMER'S DISEASE DATA

We explore the relevance of the CPRM model for modeling cognitive decline in Alzheimer's disease using placebo arm data from representative clinical trials performed by the National Institute of Aging funded Alzheimer's Disease Cooperative Study (ADCS). Alzheimer's disease is a chronic progressive condition characterized by gradual loss of short term memory and other cognitive faculties. The primary outcome measures for Alzheimer's disease clinical trials are typically so called global cognitive measures, meaning neuropsychometric instruments querying multiple domains of cognitive function affected by the disease. We here report data from two representative clinical trials, an Alzheimer's treatment trial of vitamins to reduce homocysteine levels using the Alzheimer's Disease Assessment Scale - cognitive domain (the ADAS-cog) as the primary outcome [11], and a prodromal Alzheimer's disease trial of vitamin E or donepezil using the Mini-Mental Status Exam (MMSE) as a secondary outcome [12]. The vitamin E arm was null in the prodromal Alzheimer trial [12], and therefore we pooled the placebo and vitamin E arm data from this trial to increase the available sample size.

Tables **2** and **3** report empirical covariance matrices and covariance matrices estimates by the CPRM model for the two trials. The empirical covariance matrices for these trials represent the covariance pattern one would expect for longitudinal trajectories that are fanning apart as a function of time. Under this pattern, we observe two phenomena. First, the variance increases over time, as reflected in the diagonal terms. Second, the covariance of neighboring observations increases over time, as reflected in the off-diagonal terms. The CPRM covariance model consistently recapitulates the empirical covariance observed in these data (Tables **2** and **3**). For comparison, we have included covariance matrices for

Table 2: Covariance Matrices Estimated from the ADCS Homocysteine Trial (ADAS-cog Data, n=330 Subjects, Quarterly Observations for One and One Half Years).

Empirical covariance matrix

$$\begin{pmatrix} 68.6 & 61.8 & 60.6 & 66.0 & 67.7 & 73.9 & 78.4 \\ 61.8 & 80.4 & 67.2 & 74.8 & 75.4 & 84.5 & 89.6 \\ 60.6 & 67.2 & 79.5 & 76.9 & 77.4 & 84.6 & 93.2 \\ 66.0 & 74.8 & 76.9 & 102.7 & 91.0 & 96.1 & 106.1 \\ 67.7 & 75.4 & 77.4 & 91.0 & 104.9 & 102.8 & 112.4 \\ 73.9 & 84.5 & 84.6 & 96.1 & 102.8 & 123.7 & 123.7 \\ 78.4 & 89.6 & 93.2 & 106.1 & 112.4 & 123.7 & 155.6 \end{pmatrix}$$

Covariance assuming the CPRM model

$$\begin{pmatrix} 69.1 & 58.8 & 62.3 & 65.7 & 69.1 & 72.5 & 76.0 \\ 58.8 & 76.9 & 67.7 & 72.1 & 76.5 & 80.9 & 85.3 \\ 62.3 & 67.7 & 86.7 & 78.5 & 83.9 & 89.3 & 94.7 \\ 65.7 & 72.1 & 78.5 & 98.5 & 91.3 & 97.6 & 104.0 \\ 69.1 & 76.5 & 83.9 & 91.3 & 112.3 & 106.0 & 113.4 \\ 72.5 & 80.9 & 89.3 & 97.6 & 106.0 & 128.0 & 122.8 \\ 76.0 & 85.3 & 94.7 & 104.0 & 113.4 & 122.8 & 145.8 \end{pmatrix}$$

Covariance assuming heterogeneous CS

$$\begin{pmatrix} 72.7 & 64.4 & 63.5 & 72.2 & 72.2 & 78.2 & 89.2 \\ 64.4 & 81.6 & 67.2 & 76.5 & 76.5 & 82.9 & 94.5 \\ 63.5 & 67.2 & 79.2 & 75.4 & 75.3 & 81.6 & 93.1 \\ 72.2 & 76.5 & 75.4 & 102.5 & 85.7 & 92.9 & 105.9 \\ 72.2 & 76.5 & 75.3 & 85.7 & 102.4 & 92.8 & 105.9 \\ 78.2 & 82.9 & 81.6 & 92.9 & 92.8 & 120.2 & 114.7 \\ 89.2 & 94.5 & 93.1 & 105.9 & 105.9 & 114.7 & 156.3 \end{pmatrix}$$

Covariance assuming heterogeneous AR1

$$\begin{pmatrix} 78.1 & 73.6 & 62.1 & 58.8 & 49.3 & 45.5 & 44.6 \\ 73.6 & 92.1 & 77.7 & 73.5 & 61.7 & 57.0 & 55.8 \\ 62.1 & 77.7 & 87.1 & 82.4 & 69.1 & 63.9 & 62.6 \\ 58.8 & 73.5 & 82.4 & 103.4 & 86.7 & 80.1 & 78.6 \\ 49.3 & 61.7 & 69.1 & 86.7 & 96.6 & 89.2 & 87.5 \\ 45.5 & 57.0 & 63.9 & 80.1 & 89.2 & 109.5 & 107.3 \\ 44.6 & 55.8 & 62.6 & 78.6 & 87.5 & 107.3 & 139.6 \end{pmatrix}$$

the heterogeneous CS and heterogeneous AR1 MMRM model fits to the ADCS homocysteine trial data (Table **2**). In these data, the CS model overestimates covariance terms away from the diagonal and the AR1 model underestimates these terms. Similar CS and AR1 covariance patterns were observed in the prodromal Alzheimer's disease trial (data not shown). Critically, in both data sets the covariance of the first and last observations, a critical component of the standard error of change first to last, is misrepresented by these models. Bias in estimates of the standard error of change can dramatically effect the performance of hypothesis testing by MMRM, as will be illustrated in Section 4.

Table 3: Covariance Matrices Estimated from the ADCS Clinical Trial of Vitamin E and Donepezil (MMSE Data, n = 510, Biannual Observations for Three Years)

Empirical covariance matrix

3.46	2.08	2.00	2.52	2.30	2.76	3.20
2.08	4.88	2.92	3.97	3.52	4.34	5.18
2.00	2.92	5.41	4.47	4.22	4.91	6.25
2.52	3.97	4.47	9.13	6.15	8.19	10.02
2.30	3.52	4.22	6.15	8.87	8.25	9.89
2.76	4.34	4.91	8.19	8.25	13.44	14.55
3.20	5.18	6.25	10.02	9.89	14.55	21.69

Covariance assuming the CPRM model

5.13	2.20	2.50	2.81	3.12	3.42	3.73
2.20	6.12	3.56	4.24	4.93	5.61	6.29
2.50	3.56	7.86	5.68	6.74	7.80	8.85
2.81	4.24	5.68	10.36	8.55	9.98	11.42
3.12	4.93	6.74	8.55	13.60	12.17	13.98
3.42	5.61	7.80	9.98	12.17	17.60	16.54
3.73	6.29	8.85	11.42	13.98	16.54	22.34

4. PERFORMANCE OF MMRM ON CHRONIC PROGRESSIVE DATA

We use computer simulations to empirically characterize the performance of MMRM applied to chronic progressive data under null and alternative scenarios. We consider MMRM analyses assuming unstructured, chronic progressive, compound symmetric (standard and heterogeneous), and first order autoregressive (standard and heterogeneous) covariance structures. We also consider the random slopes analysis in the simulations. MMRM models were fit using the *gls* function within the R nlme package [13]. Random slopes and CPRM models were fit using the *lme* function within the same package. The random slopes models were constrained to have a single fixed effect intercept shared by both groups as recommended for randomized clinical trials [14].

Simulations under the null. Longitudinal repeat measures were generated following a CPRM model using covariance and residual error variance parameters estimated from the placebo arm of the ADCS homocysteine trial [11], and using fixed effects means under the hypothetical scenario of a treatment with short term palliative effect that washes out by the end of the study period (Figure **1**, top panel). A total of 10,000 simulated samples were performed (n=80 per group, 18 month trial with quarterly observations, and a nominal p-value for hypothesis testing of 0.05).

Type I error rate estimates under the different model fits are listed in Table **4**. The CPRM model and unstructured MMRM met the nominal five percent type I error rate to within the accuracy of simulations. The compound symmetry and heterogeneous compound symmetry MMRM models had type I error rates of 13.4 percent and 9.6 percent respectively, meaning these two models are invalid and not appropriate for data that follow the chronic progressive pattern. The mixed effects model with random slopes was likewise anticonservative, with a type I error rate of nearly 15% (Table **4**). This result clearly illustrates the concern of regulatory agencies that analyses imposing assumptions about the shape of the mean trajectory, such as the random slopes model with linear fixed effect mean illustrated here, can result in positive trial findings even when the treatment has no persistent efficacy. Finally, we observe that the AR1 and heterogeneous AR1 models (Table **4**) had type I error rates much less than 0.05 (i.e., were substantively conservative).

Simulations under the alternative. We next simulated data following the CPRM model as above, but under the alternative scenario depicted in Figure **1**, bottom panel, and with an effect size chosen to ensured an expected power of 80 percent under the CPRM analysis. The unstructured MMRM and the CPRM models acheived the expected 80 percent power, while power for the AR1 MMRM models was close to 50 percent (Table **4**). We do not report power for the compound symmetry models because type I error rates for these models are substantially greater than 0.05, meaning these models are invalid for chronic progressive longitudinal data. We also do not report power for the random slopes model because the type I error rate for this model (15%) is likewise greater than

the nominal 5% error rate under the null, meaning the random slopes model is invalid for plausible scenarios relevant to regulatory agencies.

Table 4: Type I error rate under the null (Figure 1, Top panel), and power under the alternative (Figure 1, Bottom panel). (10,000 simulations each, with effect size under the alternative chosen to achieve 80% power for the CPRM model). Power is not reported for models that did not meet the nominal 5% type I error rate under the null.

	α error rate	Power
CPRM	0.0536	0.7981
random slopes	0.1499	-
MMRM, CS	0.1343	-
MMRM, hetCS	0.0955	-
MMRM, AR1	0.0069	0.5187
MMRM, hetAR1	0.0058	0.4997
MMRM, UN	0.0539	0.7989

CS = compound symmetric; hetCS = heterogeneous CS; AR1 = autoregressive; hetAR1 = heterogeneous AR1; UN = unstructured.

5. SAMPLE SIZE CALCULATIONS FOR THE CPRM MODEL

Derivation of sample size formulas for the CPRM model follows directly from derivations for the random slopes model [10]. Power is a function of the sample size in each arm, the covariance of repeated measures in each arm, the study design (the study length and interval between followups), the missing data pattern, and the effect size. To simplify presentation, we begin by describing power formulas for the common circumstance of equal allocation to arms and equivalent covariance structure in the two arms. In this case, the variance of change first to last visit in each arm is $\mathbf{V}(\hat{\alpha}_m - \hat{\alpha}_1)$, and the sample size required to detect a difference Δ in change scores between arms at last visit with power $1-\beta$ and type I error rate α is given by the familiar formula

$$N / Arm = 2(z_{\alpha/2} + z_\beta)^2 \mathbf{V}(\hat{\alpha}_m - \hat{\alpha}_1) / \Delta^2. \quad (7)$$

We use this formula to demonstrate two power calculation approaches commonly used when sizing a clinical trial, a conservative estimate of required sample size informed by the power of a completers-only analysis, and a less conservation estimate that explicitly adjusts for the anticipated missing data pattern to be obtained by the trial. We describe each of these in turn.

Completers-only approach. A conservative approach is to determine the sample size required to power a completers-only analysis and then increase the sample size to ensure this many subjects complete the trial. This method has the advantages of relying on a straightforward power calculation formula and resulting in statistically conservative sample size estimates. For completers, there are no missing data and $\mathbf{X_i}$ and $\mathbf{Z_i}$ are equivalent full matrices for all subjects so that

$$\mathbf{V}(\hat{\alpha}_m - \hat{\alpha}_1) = \frac{2\sigma_\varepsilon^2 + (t_m - t_1)^2 \sigma_{b1}^2}{n}. \quad (8)$$

See the Appendix for derivation of this result. Equation (6) then reduces to

$$N_{completers} / Arm = 2(z_{\alpha/2} + z_\beta)^2 [2\sigma_\varepsilon^2 + (t_m - t_1)^2 \sigma_{b1}^2] / \Delta^2. \quad (9)$$

If p_m is the proportion of subjects who will complete the trial, then setting total N / Arm to $N_{completers} / p_m$ will ensure an expected $N_{completers}$ complete the planned trial.

Study subject attrition approach. Alternatively, one can use equation (6) to directly account for the anticipated dropout pattern expected in a study. Setting $\mathbf{W} = n\mathbf{V}(\hat{\alpha})$, under equal allocation to study arm and assuming equivalent repeated measures covariance across arms, the sample size required to detect treatment effect Δ with power $1-\beta$ and type I error rate α is

$$N / Arm = 2(z_{\alpha/2} + z_\beta)^2 \left(\mathbf{W}_{mm} + \mathbf{W}_{11} - 2\mathbf{W}_{1m}\right) / \Delta^2. \quad (10)$$

As a practical matter, investigators restrict to the m missing data patterns determined by study subject dropout [15]. Given iid residual error variance σ_ε^2, $\mathbf{W}$ and by extension equation (9) are simple linear functions of the variance parameters σ_ε^2, $\sigma_{b_0}^2$, $\sigma_{b_1}^2$, and $\sigma_{b_0 b_1}$, and the design vector $\mathbf{t}$ (see Appendix). Given these four parameters as input, equation (10) can be used to determine sample size as a function of power ($1-\beta$), type I error rate α, and effect size Δ.

Implementation. Formula (8) and the study subject attrition approach formula (9) under the usual assumption of iid residual error are implemented in the *CPRM.power* function within the R package *longpower* [16]. Generalizing these formulas to allow unequal allocation and to the case where the covariance structure is different in the two groups is straightforward [10], and has also been implemented for the CPRM model in the *CPRM.power* function. Different covariance structures may be anticipated across groups. For example, in clinical trials a greater variance of change may occur within the treatment arm because

the change observed in the treatment arm reflects both normal background variability in change and the variability in response to treatment [5]. The formulas provided in *CPRM.power* can be used to perform sensitivity analyses of the potential magnitude of this effect on trial power. Note that the variance parameters required for the power calculation formulas can be estimated from prior data of arbitrary design. Stated differently, if we have variance parameter estimates from pilot studies or prior trials, we can use these values to power a future trial of arbitrary design (with arbitrary number and interval between followup visits). Furthermore, for chronic progressive data, the CPRM covariance estimate is a consistent estimate of the unstructure covariance, meaning these power calculation formulas are appropriate for trials using MMRM with unstructured covariance as the primary *a priori* analysis plan.

5.1. Validation of Sample Size Formulas by Computer Simulation

We used computer simulations to evaluate the performance of equation (6). We simulated data following a CPRM model (equation (1)) using parameters estimated from the ADCS homocysteine trial described above, assuming an 18 month trial with quarterly observations and a 25% shift in mean change in treatment versus control. Power observed in simulations closely matches predicted power (Figure **3**).

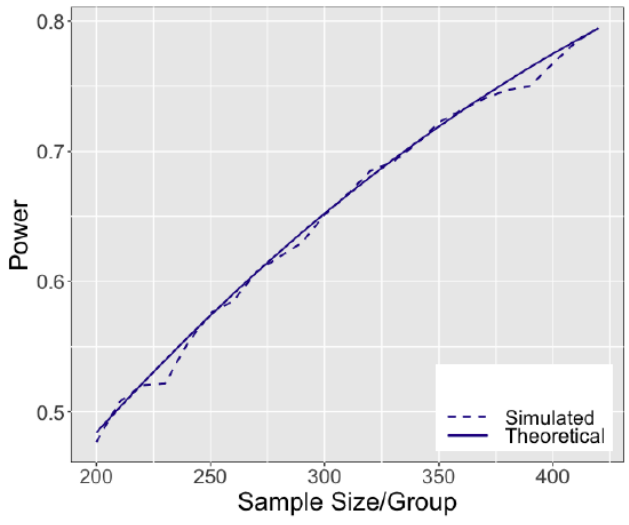

Figure 3: Theoretical power curve versus power estimated by computer simulation (10,000 simulations per sample size, two-sided test, type I error $\alpha = 0.05$).

6. DISCUSSION

We have introduced a novel parsimonious parameterization of the covariance structure of longitudinal repeated measures appropriate for chronic progressive conditions. We have demonstrated that alternative parsimonious parameterizations typically used in MMRM analysis are not appropriate for this pattern of longitudinal data that fan apart over time. In application, the MMRM analysis assuming compound symmetry is anticonservative, and the MMRM analysis assuming AR1 is underpowered for this type of data, while the CPRM analysis is both valid (maintaining its nominal type I error rate) and has equivalent power to MMRM with unstructured covariance when applied to chronic progressive data.

Further, we have derived power calculation formulas for the CPRM model that are independent of pilot study design. This is helpful when the design of pilot studies available to inform power calculations does not match the design of the future trial being powered.

The CPRM model has the heuristic advantage of testing treatment efficacy based explicitly on differences in response at the end of the trial period without any assumptions about the shape of mean trajectories of response over time. Model results are therefore unambiguous and easier to describe to a non-technical audience. We illustrated with computer simulations the concern of regulators and clinical trialists that false positive findings are possible under the random slopes analysis plan (Table **4**). Recent advances in analytic methods, including natural cubic spline [17] and progression repeated measures [18] models, may be less susceptible to type I error concerns, and this is an area of future research. However, MMRM remains the de facto standard for Alzheimer's disease treatment trials [6-8], and has the distinct advantage of providing an unambiguous characterization of treatment effect independent of any assumptions about the pattern of mean progression in the treatment or control arm. Finally we note that a current limitation of the CPRM model is that it has not been implemented as an option to MMRM functions contained in standard statistical analysis packages. Although the model parameters can be estimated with a linear mixed effect model, it would be more convenient and useful to include CP in the panoply of covariance structures available to the functions typically used for MMRM analysis. This is an area of future research.

The suitability of CPRM for data beyond the longitudinal Alzheimer data considered here will have to be examined on an individual basis. However, we note that *the CPRM model assumptions hold for any*

scenario where the mixed effects model with random slopes is appropriate, so applications of CPRM are equally as broad as this common analytic approach.

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APPENDIX

A. Proofs

A.1. Derivation of Equation (8)

Restricting to completers only, there is only one drop-out pattern in equation (6) (the complete data pattern, with design matrix $\mathbf{X}$, an m by m identity matrix). Hence, the asymptotic variance of $\hat{\alpha}$ reduces to

$$(n\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1} = (n\mathbf{I}'\mathbf{V}^{-1}\mathbf{I})^{-1} = \mathbf{V}/n,$$

where

$$\mathbf{V} = \mathbf{ZDZ}' + \sigma_\varepsilon^2\mathbf{I}$$

$$= \begin{pmatrix} 1 & t_1 \\ \vdots & \ddots \\ 1 & t_m \end{pmatrix} \begin{pmatrix} \sigma_{b_0}^2 & \sigma_{b_0b_1} \\ \sigma_{b_0b_1} & \sigma_{b_1}^2 \end{pmatrix} \begin{pmatrix} 1 & \dots & 1 \\ t_1 & \dots & t_m \end{pmatrix} + \sigma_\varepsilon^2\mathbf{I}$$

$$= \left(\sigma_{b_0}^2 + t_i\sigma_{b_0b_1} + t_j\sigma_{b_0b_1} + t_it_j\sigma_{b_1}^2 \right)_{i,j=1\dots m} + \sigma_\varepsilon^2\mathbf{I} \qquad \text{(A1)}$$

Applying elements of this matrix to the variance of $\hat{\alpha}_m - \hat{\alpha}_1$, we obtain

$$var(\hat{\alpha}_m - \hat{\alpha}_1) = var(\hat{\alpha}_m) + var(\hat{\alpha}_1) - 2cov(\hat{\alpha}_m, \hat{\alpha}_1)$$

$$= \frac{1}{n}[\sigma_{b_0}^2 + 2t_m\sigma_{b_0b_1} + t_m^2\sigma_{b_1}^2 + \sigma_\varepsilon^2$$

$$+\sigma_{b_0}^2 + 2t_1\sigma_{b_0b_1} + t_1^2\sigma_{b_0}^2 + \sigma_\varepsilon^2$$

$$-2(\sigma_{b_0}^2 + t_1\sigma_{b_0b_1} + t_m\sigma_{b_0b_1} + t_1t_m\sigma_{b_1}^2)]$$

$$= \frac{1}{n}[2\sigma_\varepsilon^2 + (t_m - t_1)^2\sigma_{b_1}^2].$$

This completes the proof.

A.2. Explicit Expression of W in Equation (10)

Let $\mathbf{V_m}$ be the covariance of repeated measures of completers defined above. Study subject dropout defines $m-1$ additional covariance matrices

$$\mathbf{V_k} = \begin{pmatrix} \mathbf{U_k} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{pmatrix},$$

$k = 1,...,m-1$ Where $\mathbf{U_k}$ are the k by k upper left submatrices of the completers' covariance matrix $\mathbf{V_m}$. Then by equation (6)

$$\mathbf{W} = n\mathbf{V}(\hat{\alpha}) = \left(\sum_k p_k \mathbf{V_k^{-1}} \right)^{-1}. \qquad \text{(A2)}$$

The indexing in equation (A1) defines the elements of $\mathbf{V_k}$ as a function of the variance parameters $\sigma_{b_0}^2$, $\sigma_{b_1}^2$, $\sigma_{b_0b_1}$, and σ_ε^2. Calculation of $\mathbf{W}$ involves setting the elements of $\mathbf{V_k}$ to values determined by these four parameters, and applying the matrix operations specified in equation (A2).

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