P9185 Statistical Practices and Research for Interdisciplinary Sciences (SPRIS)

Project II Report

Evaluation of the Safety and Adherence of 3 medications in Phase II MATIK Trial

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1 Introduction

An emerging highly contagious viral skin disease called MATIK has been discovered, which can cause severe skin rash and infections, and even pose a threat to life. Many scientific labs and drug companies are actively engaged in the development of drugs to combat this outbreak. From the results of biological and animal studies, three promising medications have been identified, which include Pill A (200 mg, once a day for 4 weeks), Gel B (1% gel concentration; three times a day on affected areas, daily use for 4 weeks), and Gel C (2% gel concentration; once a day on affected areas, daily use for 4 weeks). A phase II multi-site, randomized, open-label, three-arm crossover study has been completed. Individuals were randomly assigned a sequence of three-arm crossover treatments and each treatment period lasted for four weeks, during which the occurrence of adverse events and the number of adherence days are measured. All demographic information is measured at the baseline and virus loads in the skin and blood were measured at the beginning of each treatment period.

This report aimed to investigate the difference between different treatments regarding safety and adherence, as well as the association between outcomes and demographic information.

2 Exploratory Data Analysis

The dataset analyzed in this report was longitudinal and in a long format. It consisted of 180 clinically stable individuals who are randomly assigned to a sequence of three-arm crossover treatments. The outcome variables we

are concerned about are `AE` (binary) and `Adherence` (continuous), which represent the indicator for the occurrence of adverse events and the average number of adherence days during each treatment period, respectively. Additionally, we collected data about age, race, gender, virus load in the skin before the treatment period, and virus load in blood before the treatment period, represented by `age`, `race`, `gender`, `sviral`, and `bviral`, respectively. While `age`, `sviral`, and `bviral` are continuous variables, `gender` and `race` are categorical variables. To code the treatment, treatment sequence, and period information, we used three categorical variables: `treatment`, `sequence`, and `period`. The three levels of `treatment` included Pill A, Gel B, and Gel C. The six levels of `sequence` consists of treatment sequence "ABC", "CAB", "BCA", "BAC", "ACB", and "CBA". For `period`, the three levels were period 1, period 2 and period 3. The summary statistics can be found in Figure 1.

3 Methods

3.1 Notation

Consider a dataset consisting of n individuals, each with 3 repeated measures denoted by $\mathbf{AE}_i = (AE_{i1}, \ldots, AE_{i3})$ and $\mathbf{Adherence}_i = (Adherence_{i1}, \ldots, Adherence_{i3})$. Additionally, at each time period j, each individual has p covariates represented by the vector $\mathbf{X}_{ij} = (X_{ij1}, \ldots, X_{ijp})^\top$. We denote $\mathbf{AE} = (\mathbf{AE}_1, \ldots, \mathbf{AE}_n)$, $\mathbf{Adherence} = (\mathbf{Adherence}_1, \ldots, \mathbf{Adherence}_n)$ and $\mathbf{X} = (\mathbf{X}_1, \ldots, \mathbf{X}_n)$ and are interested in modeling the conditional distribution $f(\mathbf{AE}|\mathbf{X}, \theta_{\mathbf{AE}})$ and $f(\mathbf{Adherence}|\mathbf{X}, \theta_{\mathbf{Adherence}})$ with some unknown parameters $\theta_{\mathbf{AE}}$ and

$\theta_{\texttt{Adherence}}$ using statistical methods.

To make the problem more clearly, we denote the treatment effects for Pill A, Gel B, and Gel C as T_1, T_2, T_3 respectively. Also, we use P_1, P_2, P_3 to represent period effects for period 1, period 2 and period 3 respectively. In cross-over trial, we have to consider "carry-over" effects which will be discussed later. We use $\lambda_1, \lambda_2, \lambda_3$ to denote the "carry-over" effects from Pill A, Gel B, and Gel C in the last treatment period.

3.2 Bayesian Linear Mixed Effects Model

The linear mixed-effects model (LMM) is a widely used regression model for the longitudinal study. Bayesian LMM specifies the same likelihood function as frequentest's LMM, and then specifies hierarchical prior for each parameter. Bayesian LMM is easy to extend to data with different outcome types. The Bayesian LMM model for `AE` is specified as follows:

$$\begin{aligned} logit(AE_{ij}) &= \mathbf{X}\beta + \alpha_i + P_j + T_{ij} + \lambda_{ij} \\ T_{ij} &\in \{T_1, T_2, T_3\} \\ \lambda_{i1} = 0, \lambda_{ij} &\in \{\lambda_1, \lambda_2, \lambda_3\} \\ \alpha_i &\sim i.i.d\ N(0, \sigma^2) \\ \beta \propto 1, T_1, T_2, T_3 \propto 1, P_1, P_2, P_3 &\propto 1, \sigma^2 \propto \frac{1}{\sigma^2} \end{aligned} \tag{1}$$

where α_i is the random intercept for i-th individual, T_{ij} is the treatment effect for i-th individual at j-th period, P_j is the period effect at j-th period, λ_{ij} is the "carry-over" effect for i-th individual from (j-1)-th treatment period. The Bayesian LMM for `Adherence` can be found in Appendix. 1.

3.3 Carry-over Effects

In a cross-over trial, the effects of previous treatments can have an impact on subsequent periods of treatment. This effect is called the "carry-over" effect. We assume this effect only carries to one period, which means there is no "carry-over" effect from the first treatment period to the third treatment period.

To test if there are "carry-over" effects for `AE` and `Adherence`, we test if the posterior distribution of λ_1, λ_2, and λ_3 are the same or not. A way to establish whether two distributions are identical is by performing a Kolmogorov–Smirnov test [1], which compares the empirical distribution function of one sample to the cumulative distribution function of a theoretical distribution or that of another sample. Because we have to do the pairwise comparisons, we choose Bonferroni correction [2] to adjust the p-values. To test, we consider design matrix $\mathbf{X}$ only contains a column of $\mathbf{1}$. We also test the existence of period effects and treatment effects in the same models.

Once we had evaluated the "carry-over" effects, as well as the period effects and treatment effects, we proceeded to adjust the two Bayesian Linear Mixed Models by incorporating additional covariates along with the significant "carry-over" effects, period effects, and treatment effects.

4 Results

As shown in Appendix. 2, the pairwise p-values are all 1 for "carry-over" effects and period effects for `AE`, while there are significant differences between treatment 1 and treatment 2/3. For `Adherence`, the results are the

same.

Ignoring the "carry-over" effects and period effects, we refit the two Bayesian LMM with covariates, including `age`, `bviral`, `sviral`, `sequence`, and `treatment`. The posterior estimates for the model whose outcome variable is `AE` are in Figure 2. As we can see, `age`, `sequence = 3`, and `sequence = 4` are significant, whose 95% credible intervals exclude 0. The posterior means for these three variables are 0.256, 1.589, and 1.830, which indicates individuals are more likely to have adverse events as age increases or if they were assigned to sequence 3/4. Similarly, we summarized the posterior estimates of `Adherence` model in Figure 3. For `Adherence`, `age`, `gel B`, and `gel C` are significant. The posterior means for these three variables are 0.115, -1.02, and -0.768, which means individuals are more likely to adhere more days if they are old or taking pill A.

5 Conclusion

This report focuses on the safety and adherence of some sequences of three treatments in a cross-over trial to MATIK. We used a Bayesian LMM to investigate the existence of "carry-over" effects, as well as period effects and treatment effects. In the result, "carry-over" effects and period effects did not show up in this study. After adjusting for some covariates, we find individuals who are old or assigned to treatment sequences "BCA" or "BAC" are more likely to have adverse events. On the other hand, we also find individuals who are old or taking treatment pill A are more likely to adhere.

Appendices

The appendix includes all supplementary tables, formulas, and figures that are referred to in this report.

.1 Bayesian LMM for `Adherence` and regression models

The Bayesian LMM for **Adherence** is as follows:

$$\begin{aligned} Adherence_{ij} &= \mathbf{X}\beta + \alpha_i + P_j + T_{ij} + \lambda_{ij} \\ T_{ij} &\in \{T_1, T_2, T_3\} \\ \lambda_{i1} = 0, \lambda_{ij} &\in \{\lambda_1, \lambda_2, \lambda_3\} \\ \alpha_i &\sim i.i.d\ N(0, \sigma^2) \\ \beta \propto 1, T_1, T_2, T_3 \propto 1, P_1, P_2, P_3 &\propto 1, \sigma^2 \propto \frac{1}{\sigma^2} \end{aligned} \tag{2}$$

In the refitted models, our covariates consist of the `age`, `bviral`, `sviral` and two categorical variables `sequence` and `treatment`. For `treatment`, we choose pill A as the reference level and treatment sequence "ABC" for `sequence`. The analysis model for `AE` is:

$$\begin{aligned} logit(AE_{ij}) =& \beta_0 + \beta_1 * age + \beta_2 * bviral + \beta_3 * sviral + \beta_4 * I(sequence_{ij} = 2) + \\ & \beta_5 * I(sequence_{ij} = 3) + \beta_6 * I(sequence_{ij} = 4) + \beta_7 * I(sequence_{ij} = 5) + \\ & \beta_8 * I(sequence_{ij} = 6) + \beta_9 * I(treatment_{ij} = pillA) + \\ & \beta_{10} * I(treatment_{ij} = gelB) + \beta_{11} * I(treatment_{ij} = gelC) + \alpha_i, \\ & i = 1, 2, ..., n, j = 1, 2, 3. \end{aligned} \tag{3}$$

he analysis model for `Adherence` is:

$$\begin{aligned} Adherence_{ij} =& \beta_0 + \beta_1 * age + \beta_2 * bviral + \beta_3 * sviral + \beta_4 * I(sequence_{ij} = 2) + \\ & \beta_5 * I(sequence_{ij} = 3) + \beta_6 * I(sequence_{ij} = 4) + \beta_7 * I(sequence_{ij} = 5) + \\ & \beta_8 * I(sequence_{ij} = 6) + \beta_9 * I(treatment_{ij} = pillA) + \\ & \beta_{10} * I(treatment_{ij} = gelB) + \beta_{11} * I(treatment_{ij} = gelC) + \alpha_i + \epsilon_{ij}, \\ & i = 1, 2, ..., n, j = 1, 2, 3. \end{aligned} \tag{4}$$

.2 P-values for K-S test with Bonferroni correction

		`AE`	`Adherence`
"Carry-over" effects	λ_1 v.s λ_2	1	1
	λ_2 v.s λ_3	1	1
	λ_1 v.s λ_3	1	1
Period effects	P_1 v.s P_2	1	1
	P_2 v.s P_3	1	1
	P_1 v.s P_3	1	1
Treatment effects	T_1 v.s T_2	0.0072	0
	T_2 v.s T_3	1	1
	T_1 v.s T_3	0.0316	0

Table 1: P-values for K-S test with Bonferroni correction

.3 Figures

	ABC (N=30)	ACB (N=30)	BAC (N=30)	BCA (N=30)	CAB (N=30)	CBA (N=30)	Overall (N=180)
AE1							
0	27 (90.0%)	29 (96.7%)	25 (83.3%)	26 (86.7%)	28 (93.3%)	29 (96.7%)	164 (91.1%)
1	3 (10.0%)	1 (3.3%)	5 (16.7%)	4 (13.3%)	2 (6.7%)	1 (3.3%)	16 (8.9%)
AE2							
0	28 (93.3%)	28 (93.3%)	27 (90.0%)	27 (90.0%)	29 (96.7%)	29 (96.7%)	168 (93.3%)
1	2 (6.7%)	2 (6.7%)	3 (10.0%)	3 (10.0%)	1 (3.3%)	1 (3.3%)	12 (6.7%)
AE3							
0	29 (96.7%)	25 (83.3%)	26 (86.7%)	24 (80.0%)	30 (100%)	29 (96.7%)	163 (90.6%)
1	1 (3.3%)	5 (16.7%)	4 (13.3%)	6 (20.0%)	0 (0%)	1 (3.3%)	17 (9.4%)
Adhere1							
Mean (SD)	6.57 (0.679)	6.46 (0.756)	5.14 (1.88)	5.58 (1.76)	6.06 (1.01)	5.68 (1.39)	5.92 (1.41)
Median [Min, Max]	7.00 [4.00, 7.00]	7.00 [4.50, 7.00]	5.58 [0.500, 7.00]	6.50 [1.00, 7.00]	6.50 [3.50, 7.00]	6.50 [2.00, 7.00]	6.50 [0.500, 7.00]
Adhere2							
Mean (SD)	5.71 (1.59)	5.56 (1.50)	6.46 (0.907)	5.96 (1.48)	6.71 (0.433)	5.50 (1.52)	5.98 (1.37)
Median [Min, Max]	6.25 [0.500, 7.00]	6.00 [2.50, 7.00]	6.50 [2.33, 7.00]	6.50 [1.00, 7.00]	7.00 [5.50, 7.00]	6.00 [2.67, 7.00]	6.50 [0.500, 7.00]
Adhere3							
Mean (SD)	5.86 (1.41)	5.25 (1.64)	5.64 (1.49)	6.54 (0.992)	5.81 (1.17)	6.46 (0.794)	5.93 (1.34)
Median [Min, Max]	6.50 [2.00, 7.00]	5.75 [2.00, 7.00]	6.00 [1.00, 7.00]	7.00 [2.33, 7.00]	6.50 [2.33, 7.00]	6.75 [4.00, 7.00]	6.50 [1.00, 7.00]
age							
Mean (SD)	33.4 (8.29)	31.0 (7.14)	30.9 (7.23)	32.9 (8.44)	32.3 (6.82)	31.0 (7.39)	31.9 (7.54)
Median [Min, Max]	34.0 [19.0, 44.0]	29.0 [18.0, 42.0]	31.5 [20.0, 44.0]	32.0 [19.0, 45.0]	33.0 [21.0, 44.0]	31.5 [20.0, 44.0]	32.0 [18.0, 45.0]
race							
black	12 (40.0%)	13 (43.3%)	12 (40.0%)	10 (33.3%)	8 (26.7%)	9 (30.0%)	64 (35.6%)
others	10 (33.3%)	8 (26.7%)	11 (36.7%)	13 (43.3%)	10 (33.3%)	12 (40.0%)	64 (35.6%)
white	8 (26.7%)	9 (30.0%)	7 (23.3%)	7 (23.3%)	12 (40.0%)	9 (30.0%)	52 (28.9%)
gender							
0	17 (56.7%)	19 (63.3%)	14 (46.7%)	16 (53.3%)	18 (60.0%)	15 (50.0%)	99 (55.0%)
1	13 (43.3%)	11 (36.7%)	16 (53.3%)	14 (46.7%)	12 (40.0%)	15 (50.0%)	81 (45.0%)
bviral1							
Mean (SD)	120 (18.3)	123 (22.5)	119 (21.0)	123 (17.0)	128 (14.3)	127 (17.3)	123 (18.6)
Median [Min, Max]	122 [78.0, 152]	121 [73.0, 165]	114 [81.0, 181]	124 [79.0, 162]	125 [105, 163]	124 [95.0, 172]	122 [73.0, 181]
bviral2							
Mean (SD)	119 (18.8)	122 (20.7)	130 (25.6)	119 (17.1)	121 (22.6)	127 (20.9)	123 (21.2)
Median [Min, Max]	115 [84.0, 159]	124 [68.0, 178]	128 [90.0, 182]	121 [87.0, 149]	119 [60.0, 163]	122 [91.0, 171]	121 [60.0, 182]
bviral3							
Mean (SD)	120 (13.2)	127 (18.0)	126 (17.5)	121 (18.3)	120 (19.2)	125 (15.5)	123 (17.1)
Median [Min, Max]	117 [96.0, 152]	125 [89.0, 164]	126 [93.0, 171]	120 [81.0, 159]	118 [77.0, 163]	128 [91.0, 155]	122 [77.0, 171]
sviral1							
Mean (SD)	207 (29.0)	203 (24.3)	212 (30.1)	205 (23.3)	207 (23.6)	209 (29.9)	207 (26.7)
Median [Min, Max]	202 [161, 282]	203 [161, 282]	205 [154, 275]	199 [167, 277]	207 [160, 245]	204 [151, 280]	203 [151, 282]
sviral2							
Mean (SD)	211 (31.0)	211 (25.0)	217 (31.3)	203 (23.9)	211 (26.8)	210 (24.4)	210 (27.2)
Median [Min, Max]	213 [151, 303]	208 [159, 259]	213 [167, 307]	199 [163, 262]	204 [166, 260]	214 [147, 251]	211 [147, 307]
sviral3							
Mean (SD)	211 (34.3)	214 (23.3)	206 (28.0)	205 (29.8)	202 (28.9)	213 (27.1)	208 (28.7)
Median [Min, Max]	203 [165, 300]	206 [184, 289]	212 [144, 245]	206 [158, 278]	202 [145, 253]	214 [142, 294]	206 [142, 300]

AE1 means if the adverse event happened during 1st treatment period.
Adhere1 means the average number of adherence day during 1st treatment period.
bviral1 means the measurement of bviral at the beginning of 1st treatment period. The same for sviral1.

Figure 1: Summary statistics for each variable stratified by treatment sequence

	mean	2.5%	97.5%	25%	75%	sd
intercept	-14.968	-23.683	-7.471	-17.678	-12.151	4.126
age	0.256	0.160	0.373	0.217	0.289	0.055
bviral	0.014	-0.013	0.042	0.005	0.023	0.014
sviral	0.001	-0.021	0.022	-0.006	0.008	0.011
sequence_2	-0.661	-3.030	1.396	-1.333	0.087	1.125
sequence_3	1.589	0.025	3.488	0.994	2.105	0.873
sequence_4	1.830	0.265	3.670	1.222	2.412	0.874
sequence_5	1.291	-0.403	3.257	0.668	1.863	0.941
sequence_6	-0.262	-2.403	1.979	-1.001	0.378	1.077
treatment_gelB	0.200	-0.689	1.014	-0.112	0.503	0.441
treatment_gelC	-0.236	-1.233	0.636	-0.536	0.098	0.476

Figure 2: Posterior estimates for AE model

	mean	2.5%	97.5%	25%	75%	sd
intercept	2.960	1.863	4.026	2.591	3.333	0.550
age	0.115	0.095	0.132	0.109	0.121	0.009
bviral	0.000	-0.004	0.003	-0.002	0.001	0.002
sviral	0.000	-0.003	0.002	-0.001	0.001	0.001
sequence_2	0.288	-0.110	0.715	0.145	0.422	0.208
sequence_3	0.033	-0.382	0.461	-0.119	0.191	0.220
sequence_4	-0.037	-0.444	0.367	-0.172	0.104	0.208
sequence_5	-0.025	-0.453	0.408	-0.183	0.128	0.223
sequence_6	0.132	-0.272	0.552	-0.017	0.280	0.215
treatment_gelB	-1.020	-1.146	-0.901	-1.065	-0.974	0.066
treatment_gelC	-0.768	-0.894	-0.636	-0.812	-0.723	0.065

Figure 3: Posterior estimates for Adherence model

References

[1] Vance W Berger and YanYan Zhou. "Kolmogorov–smirnov test: Overview". In: *Wiley statsref: Statistics reference online* (2014).

[2] J Martin Bland and Douglas G Altman. "Multiple significance tests: the Bonferroni method". In: *Bmj* 310.6973 (1995), p. 170.