P9185 Project 1: Protocol of a Phase II MATIK Trial

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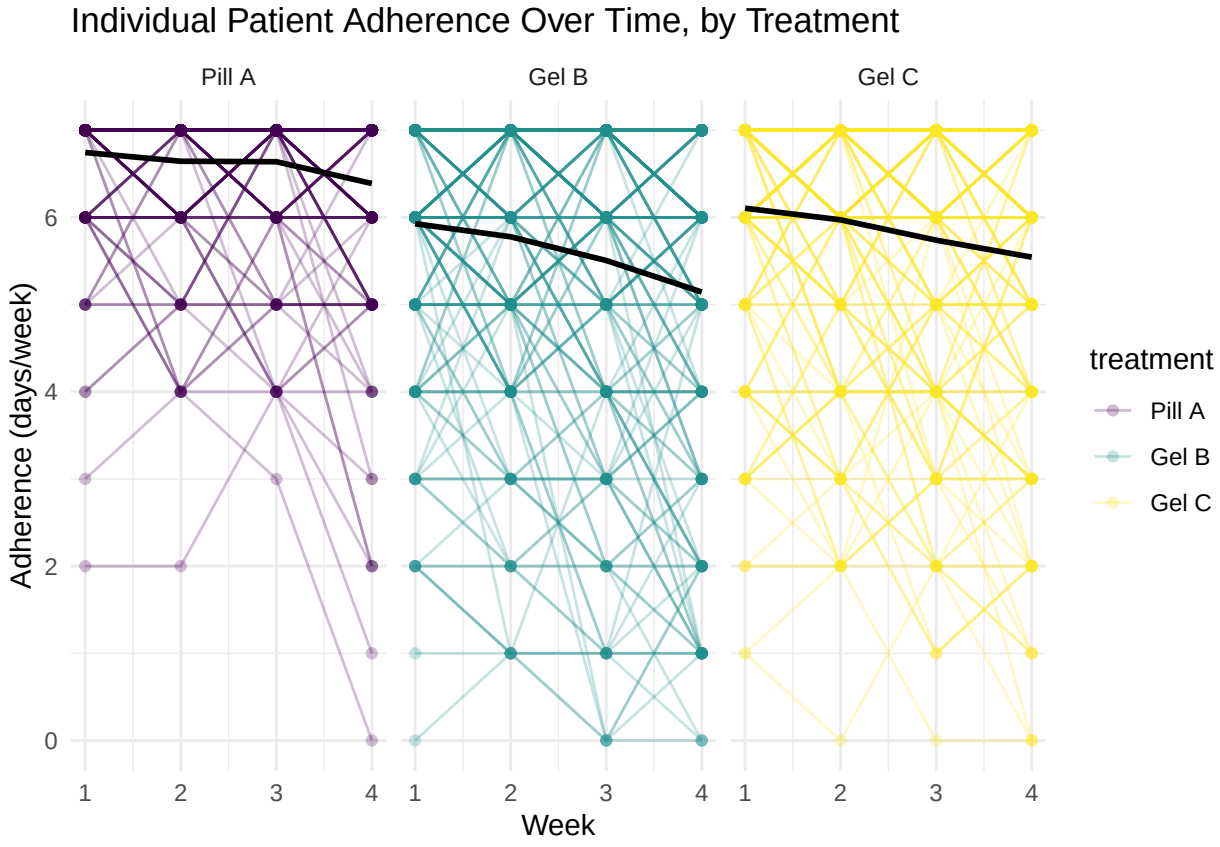
I. Introduction

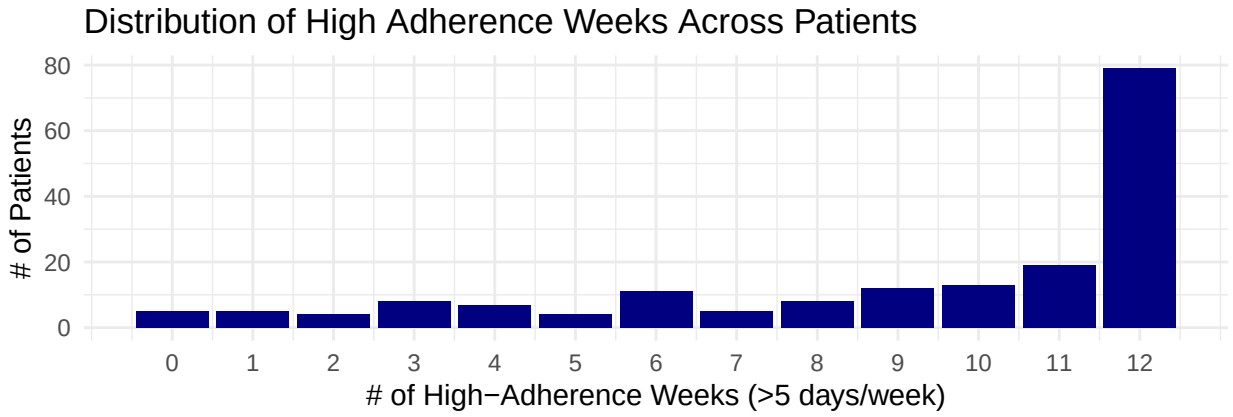
II. Methods

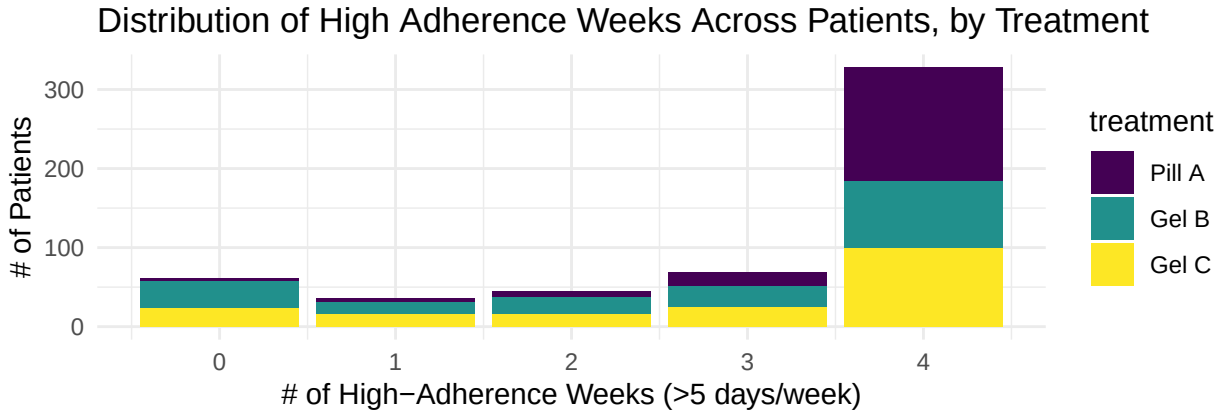
III. Results

3.1 Primary Objective 1

3.2 Primary Objective 2







Model

$$

$$Y_{hik} \sim \text{Binomial}\big(n = 7, p_{hik}\big), \tag{1}$$

$$\text{logit}(p_{hik}) = \mu + b_k + \pi_i + \tau_i + \lambda_j + \gamma * h, \tag{2}$$

$$b_k \sim \mathcal{N}(0, \sigma_b^2) \tag{3}$$

$$

Table 1: **GLMM Results of Treatment on Adherence**

Characteristic	OR	95% CI	p-value
Treatment			
Pill A	—	—	
Gel B	0.14	0.12, 0.17	**<0.001**
Gel C	0.21	0.17, 0.24	**<0.001**
Week	0.73	0.69, 0.76	**<0.001**
Period			
1	—	—	
2	1.15	1.00, 1.32	0.051
3	1.05	0.92, 1.20	0.5

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table 2: **Table 1. Baseline Characteristics**

Characteristic	**Overall** N = 180[1]	**ABC** N = 30[1]	**ACB** N = 30[1]	**BAC** N = 30[1]	**BCA** N = 30
Age (years)	32 (8) [18, 45]	33 (8) [19, 44]	31 (7) [18, 42]	31 (7) [20, 44]	33 (8) [19, 45]
Race					
Black	64 (36%)	12 (40%)	13 (43%)	12 (40%)	10 (33%)
White	52 (29%)	8 (27%)	9 (30%)	7 (23%)	7 (23%)
Other	64 (36%)	10 (33%)	8 (27%)	11 (37%)	13 (43%)
Female	81 (45%)	13 (43%)	11 (37%)	16 (53%)	14 (47%)

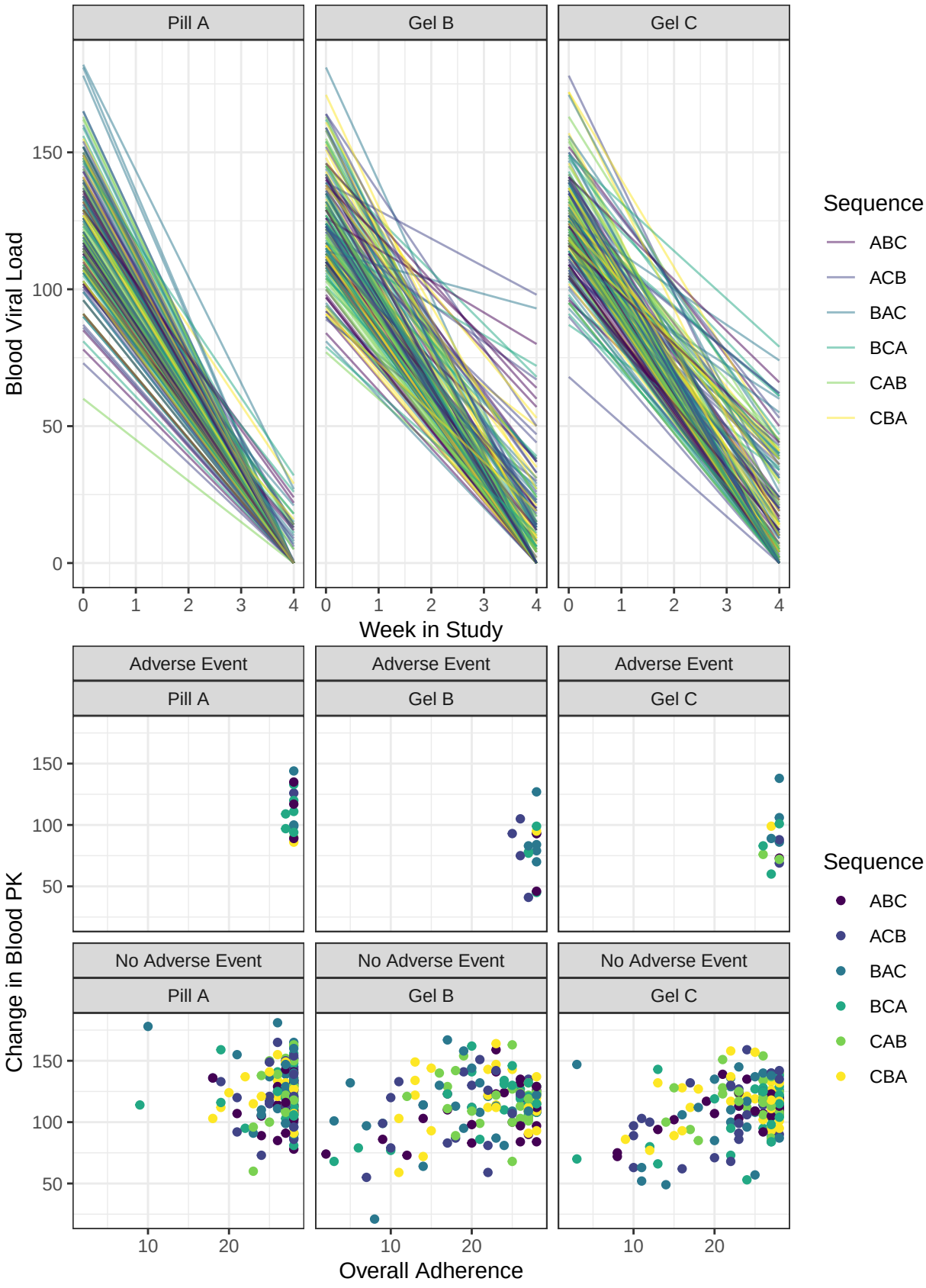
[1]Mean (SD) [Min, Max]; n (%)
[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

3.3 Secondary Objective 1

preliminary assessment and comparison of systemic and local Pharmacokinetics (PK) of Pill A, Gel B, and Gel C and the correlation of PK with adherence measures and the occurrence of adverse events

Blood PK

$$Y_{ik} = \mu + b_k + \pi_i + \tau_i + \lambda_i + \alpha_{ik} + \beta_{ik} + \varepsilon_{ik}, \quad b_k \sim N(0, \sigma_b^2), \quad \varepsilon_{ik} \sim N(0, \sigma^2)$$


Pill A
Gel B
Gel C
Blood Viral Load
150
100
50
0
0
1
2
3
4
Week in Study
Sequence
ABC
ACB
BAC
BCA
CAB
CBA
Adverse Event
No Adverse Event
Change in Blood PK
10
20
Overall Adherence

```
## Data: merged
```

```
## Models:
## model_blood: bloodVL_change ~ treatment + overall_adhere + overall_safety + period + (1 | ptid)
## model_large_blood: bloodVL_change ~ treatment + overall_adhere + overall_safety + sequence_ind + peri
##                   npar    AIC    BIC  logLik deviance  Chisq Df Pr(>Chisq)
## model_blood          9 4863.1 4901.7 -2422.6   4845.1
## model_large_blood   11 4866.5 4913.7 -2422.2   4844.5 0.6124  2     0.7362
```

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: bloodVL_change ~ treatment + overall_adhere + overall_safety +
##     period + (1 | ptid)
##    Data: merged
##
## REML criterion at convergence: 4827.4
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.5936 -0.5795  0.0153  0.6127  3.0873
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  ptid     (Intercept)  23.09    4.805
##  Residual             445.60   21.109
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##                                Estimate Std. Error       df t value
## (Intercept)                     73.4552     6.7058 419.7421  10.954
## treatmentGel B                  -6.7916     2.3555 417.1354  -2.883
## treatmentGel C                  -9.0880     2.2967 391.5595  -3.957
## overall_adhere                   0.9365     0.1882 269.4894   4.975
## overall_safetyNo Adverse Event  26.4624     3.4675 521.9424   7.632
## periodperiod2                   -2.3295     2.2271 356.0129  -1.046
## periodperiod3                   -1.5433     2.2252 355.4545  -0.694
##                                           Pr(>|t|)
## (Intercept)                    < 0.0000000000000002 ***
## treatmentGel B                              0.00414 **
## treatmentGel C                 0.000090106833739 ***
## overall_adhere                 0.000001161748206 ***
## overall_safetyNo Adverse Event 0.000000000000111 ***
## periodperiod2                               0.29629
## periodperiod3                               0.48842
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) trtmGB trtmGC ovrll_ ov_NAE prdpr2
## treatmntGlB -0.437
## treatmntGlC -0.359  0.538
## overall_dhr -0.832  0.328  0.247
## ovrll_sfNAE -0.616  0.080  0.032  0.196
## periodperd2 -0.129 -0.009 -0.006 -0.026 -0.038
## periodperd3 -0.173  0.001  0.001  0.004  0.009  0.499
```

```
##  treatment emmean   SE  df lower.CL upper.CL
```

Comparison	Beta	95% CI	p-value
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	73.5	60.3, 86.6	**<0.001**
Treatment			
Gel B vs Pill A	-6.8	-11.4, -2.2	**0.004**
Gel C vs Pill A	-9.1	-13.6, -4.6	**<0.001**
Additional Day of Adherence	0.9	0.6, 1.3	**<0.001**
Adverse Event			
No Adverse Event	26.5	19.7, 33.3	**<0.001**
Period			
Period 2 vs Period 1	-2.3	-6.7, 2.1	0.3
Period 3 vs Period 1	-1.5	-5.9, 2.8	0.5

Abbreviation: CI = Confidence Interval

```
##  Pill A     107.9 2.27 525    103.4      112
##  Gel B      101.1 2.13 523     96.9      105
##  Gel C       98.8 2.18 526     94.5      103
##
## Results are averaged over the levels of: overall_safety, period
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  contrast       estimate   SE  df t.ratio p.value
##  Pill A - Gel B     6.79 2.36 417   2.882  0.0115
##  Pill A - Gel C     9.09 2.30 391   3.956  0.0003
##  Gel B - Gel C      2.30 2.24 359   1.027  0.5602
##
## Results are averaged over the levels of: overall_safety, period
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```

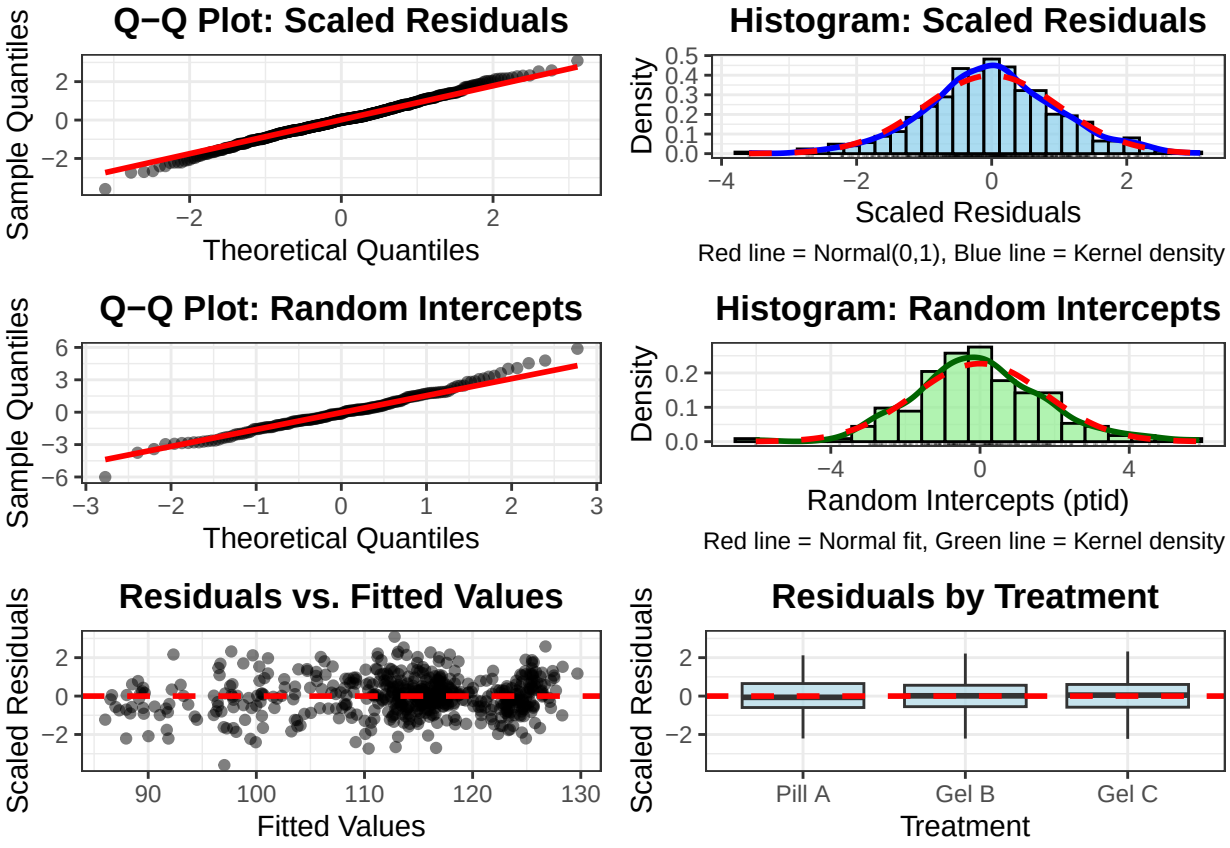
```
##  overall_adhere emmean   SE  df lower.CL upper.CL
##              24    103 1.75 411     99.2      106
##
## Results are averaged over the levels of: treatment, overall_safety, period
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  overall_safety   emmean   SE  df lower.CL upper.CL
##  Adverse Event      89.4 3.34 500     82.8     95.9
##  No Adverse Event  115.9 1.02 196    113.8    117.9
##
## Results are averaged over the levels of: treatment, period
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  period  emmean   SE  df lower.CL upper.CL
##  period1    104 2.16 527     99.7      108
##  period2    102 2.21 527     97.2      106
##  period3    102 2.14 527     98.2      107
##
## Results are averaged over the levels of: treatment, overall_safety
```

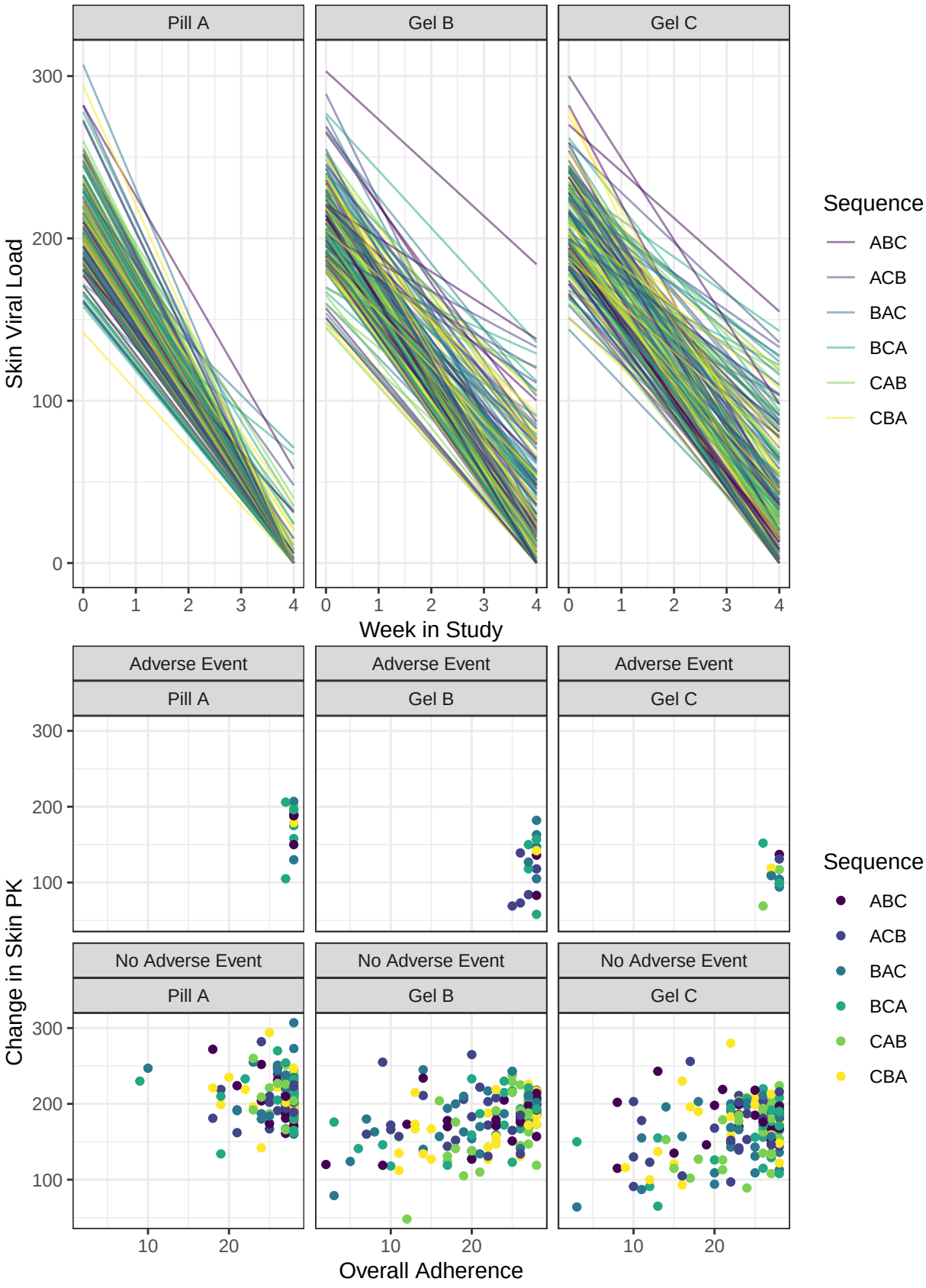
```
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  contrast          estimate   SE  df t.ratio p.value
##  period1 - period2    2.330 2.23 355   1.046  0.5484
##  period1 - period3    1.543 2.23 355   0.694  0.7674
##  period2 - period3   -0.786 2.23 356  -0.353  0.9337
##
## Results are averaged over the levels of: treatment, overall_safety
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```



Skin PK

Linear Model




```
## Analysis of Variance Table
```

```
##
## Model 1: skinVL_change ~ treatment + overall_adhere + overall_safety +
##     period
## Model 2: skinVL_change ~ treatment + overall_adhere + overall_safety +
##     sequence_ind + period
##   Res.Df    RSS Df Sum of Sq      F Pr(>F)
## 1    533 571160
## 2    531 568220  2    2940.4 1.3739  0.254
```

```
##
## Call:
## lm(formula = skinVL_change ~ treatment + overall_adhere + overall_safety +
##     period, data = merged)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -112.388  -22.128    1.035   20.921  115.662
##
## Coefficients:
##                                Estimate Std. Error t value             Pr(>|t|)
## (Intercept)                    105.6003     9.9680  10.594 < 0.0000000000000002
## treatmentGel B                 -24.4131     3.6314  -6.723       0.000000000046
## treatmentGel C                 -36.9951     3.5493 -10.423 < 0.0000000000000002
## overall_adhere                   1.8154     0.2753   6.594       0.000000000103
## overall_safetyNo Adverse Event  55.7940     5.2166  10.696 < 0.0000000000000002
## periodperiod2                    0.8567     3.4535   0.248                0.804
## periodperiod3                    1.6225     3.4507   0.470                0.638
##
## (Intercept)                    ***
## treatmentGel B                 ***
## treatmentGel C                 ***
## overall_adhere                 ***
## overall_safetyNo Adverse Event ***
## periodperiod2
## periodperiod3
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 32.74 on 533 degrees of freedom
## Multiple R-squared:  0.3581, Adjusted R-squared:  0.3508
## F-statistic: 49.55 on 6 and 533 DF,  p-value: < 0.00000000000000022
```

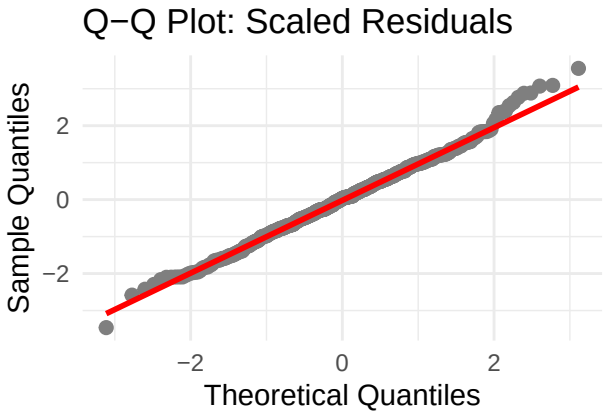
```
##  treatment emmean   SE  df lower.CL upper.CL
##  Pill A       178 3.42 533      171      185
##  Gel B        154 3.20 533      147      160
##  Gel C        141 3.29 533      135      147
##
## Results are averaged over the levels of: overall_safety, period
## Confidence level used: 0.95
```

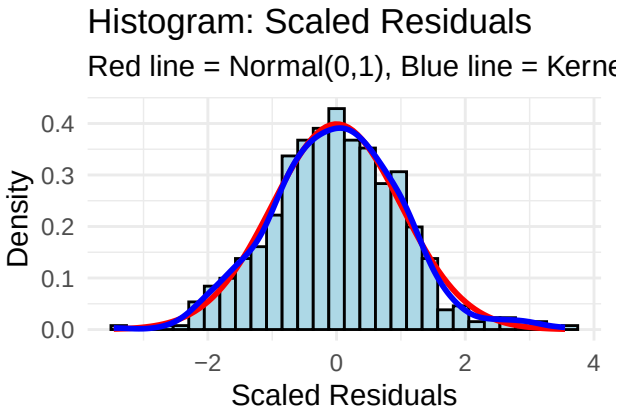
```
##  contrast       estimate   SE  df t.ratio p.value
##  Pill A - Gel B     24.4 3.63 533   6.723  <.0001
##  Pill A - Gel C     37.0 3.55 533  10.423  <.0001
##  Gel B - Gel C      12.6 3.47 533   3.631  0.0009
##
```

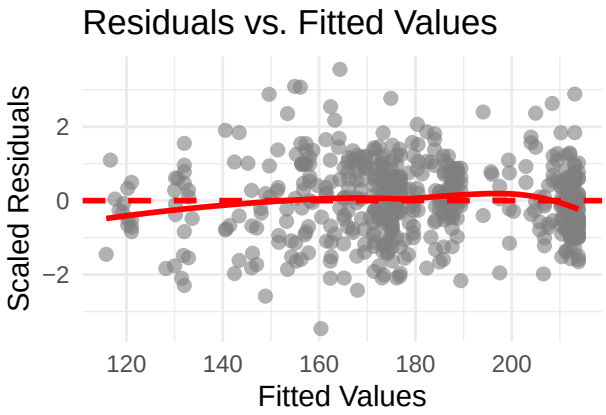
Comparison	Beta	95% CI	p-value
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	105.6	86.0, 125.2	**<0.001**
Treatment			
Gel B vs Pill A	-24.4	-31.5, -17.3	**<0.001**
Gel C vs Pill A	-37.0	-44.0, -30.0	**<0.001**
Additional Day of Adherence	1.8	1.3, 2.4	**<0.001**
Adverse Event			
No Adverse Event	55.8	45.5, 66.0	**<0.001**
Period			
Period 2 vs Period 1	0.9	-5.9, 7.6	0.8
Period 3 vs Period 1	1.6	-5.2, 8.4	0.6

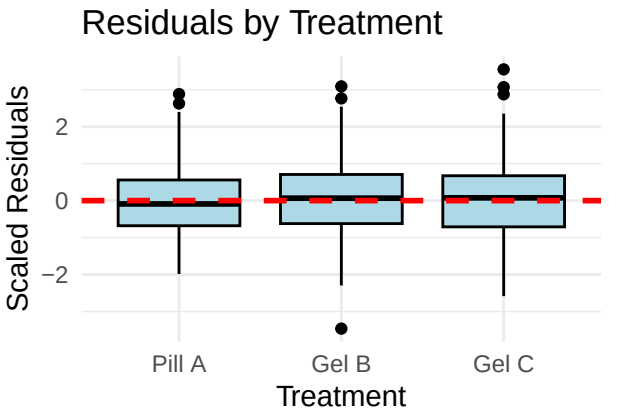
Abbreviation: CI = Confidence Interval

```
## Results are averaged over the levels of: overall_safety, period
## P value adjustment: tukey method for comparing a family of 3 estimates

##  overall_adhere emmean   SE  df lower.CL upper.CL
##              24    158 2.59 533      152      163
##
## Results are averaged over the levels of: treatment, overall_safety, period
## Confidence level used: 0.95

##  overall_safety   emmean   SE  df lower.CL upper.CL
##  Adverse Event       130 4.99 533      120      139
##  No Adverse Event    185 1.47 533      183      188
##
## Results are averaged over the levels of: treatment, period
## Confidence level used: 0.95

##  period  emmean   SE  df lower.CL upper.CL
##  period1    157 3.25 533      150      163
##  period2    158 3.33 533      151      164
##  period3    158 3.23 533      152      165
##
## Results are averaged over the levels of: treatment, overall_safety
## Confidence level used: 0.95

##  contrast          estimate   SE  df t.ratio p.value
##  period1 - period2   -0.857 3.45 533  -0.248  0.9666
##  period1 - period3   -1.623 3.45 533  -0.470  0.8853
##  period2 - period3   -0.766 3.45 533  -0.222  0.9733
##
## Results are averaged over the levels of: treatment, overall_safety
## P value adjustment: tukey method for comparing a family of 3 estimates
```









Linear Mixed Model

```
## Data: merged
## Models:
## model_skin: skinVL_change ~ treatment + overall_adhere + overall_safety + period + (1 | ptid)
## model_large_skin: skinVL_change ~ treatment + overall_adhere + overall_safety + sequence_ind + perio
##                  npar    AIC    BIC  logLik deviance  Chisq Df Pr(>Chisq)
## model_skin          9 5310.9 5349.6 -2646.5   5292.9
## model_large_skin   11 5312.1 5359.4 -2645.1   5290.1 2.7872  2     0.2482
```

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: skinVL_change ~ treatment + overall_adhere + overall_safety +
##     period + (1 | ptid)
##    Data: merged
##
## REML criterion at convergence: 5269.4
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.4333 -0.6760  0.0316  0.6391  3.5333
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  ptid     (Intercept)    0      0.00
##  Residual             1072     32.74
## Number of obs: 540, groups:  ptid, 180
##
```

Comparison	Beta	95% CI	p-value
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	105.6	86.0, 125.2	**<0.001**
Treatment			
Gel B vs Pill A	-24.4	-31.5, -17.3	**<0.001**
Gel C vs Pill A	-37.0	-44.0, -30.0	**<0.001**
Additional Day of Adherence	1.8	1.3, 2.4	**<0.001**
Adverse Event			
No Adverse Event	55.8	45.5, 66.0	**<0.001**
Period			
Period 2 vs Period 1	0.9	-5.9, 7.6	0.8
Period 3 vs Period 1	1.6	-5.2, 8.4	0.6

Abbreviation: CI = Confidence Interval

```
## Fixed effects:
##                                 Estimate Std. Error       df t value
## (Intercept)                     105.6003     9.9680 533.0000  10.594
## treatmentGel B                  -24.4131     3.6314 533.0000  -6.723
## treatmentGel C                  -36.9951     3.5493 533.0000 -10.423
## overall_adhere                    1.8154     0.2753 533.0000   6.594
## overall_safetyNo Adverse Event   55.7940     5.2166 533.0000  10.696
## periodperiod2                     0.8567     3.4535 533.0000   0.248
## periodperiod3                     1.6225     3.4507 533.0000   0.470
##                                           Pr(>|t|)
## (Intercept)                     < 0.0000000000000002 ***
## treatmentGel B                       0.000000000046 ***
## treatmentGel C                  < 0.0000000000000002 ***
## overall_adhere                       0.000000000103 ***
## overall_safetyNo Adverse Event < 0.0000000000000002 ***
## periodperiod2                                 0.804
## periodperiod3                                 0.638
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) trtmGB trtmGC ovrll_ ov_NAE prdpr2
## treatmntGlB -0.429
## treatmntGlC -0.354  0.534
## overall_dhr -0.826  0.311  0.234
## ovrll_sfNAE -0.627  0.079  0.033  0.206
## periodperd2 -0.137 -0.008 -0.005 -0.025 -0.037
## periodperd3 -0.180  0.001  0.001  0.004  0.009  0.499
## optimizer (nloptwrap) convergence code: 0 (OK)
## boundary (singular) fit: see help('isSingular')

##  treatment emmean   SE  df lower.CL upper.CL
##  Pill A       178 3.43 525      171      185
##  Gel B        154 3.21 525      147      160
##  Gel C        141 3.29 527      135      147
##
## Results are averaged over the levels of: overall_safety, period
```

```
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  contrast       estimate   SE  df t.ratio p.value
##  Pill A - Gel B     24.4 3.63 412   6.721  <.0001
##  Pill A - Gel C     37.0 3.55 388  10.422  <.0001
##  Gel B - Gel C      12.6 3.47 359   3.631  0.0009
##
## Results are averaged over the levels of: overall_safety, period
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
##  overall_adhere emmean  SE  df lower.CL upper.CL
##              24    158 2.6 401      152      163
##
## Results are averaged over the levels of: treatment, overall_safety, period
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

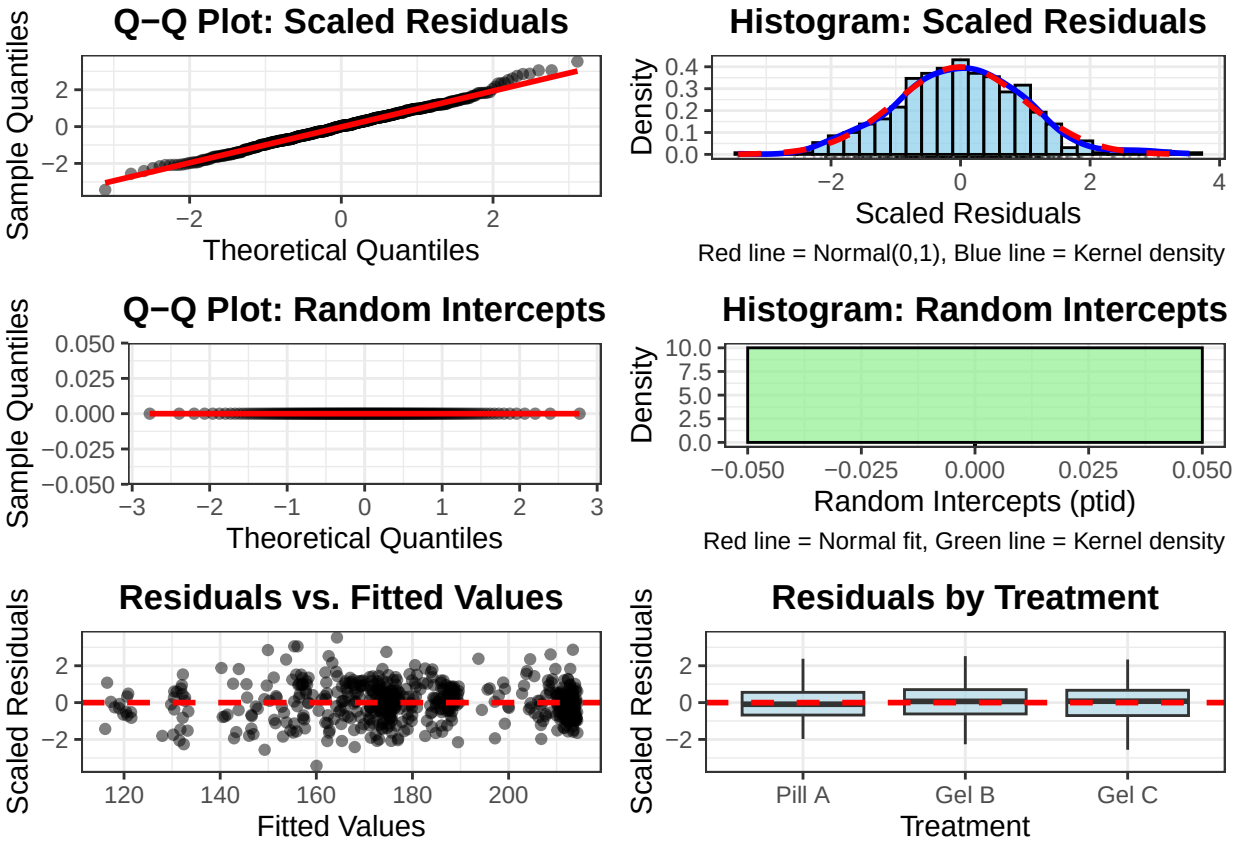
```
##  overall_safety   emmean   SE  df lower.CL upper.CL
##  Adverse Event       130 5.00 485      120      139
##  No Adverse Event    185 1.47 196      182      188
##
## Results are averaged over the levels of: treatment, period
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  period  emmean   SE  df lower.CL upper.CL
##  period1    157 3.25 528      150      163
##  period2    158 3.34 528      151      164
##  period3    158 3.23 528      152      165
##
## Results are averaged over the levels of: treatment, overall_safety
## Degrees-of-freedom method: kenward-roger
## Confidence level used: 0.95
```

```
##  contrast          estimate   SE  df t.ratio p.value
##  period1 - period2   -0.857 3.45 356  -0.248  0.9666
##  period1 - period3   -1.623 3.45 355  -0.470  0.8853
##  period2 - period3   -0.766 3.45 356  -0.222  0.9733
##
## Results are averaged over the levels of: treatment, overall_safety
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```

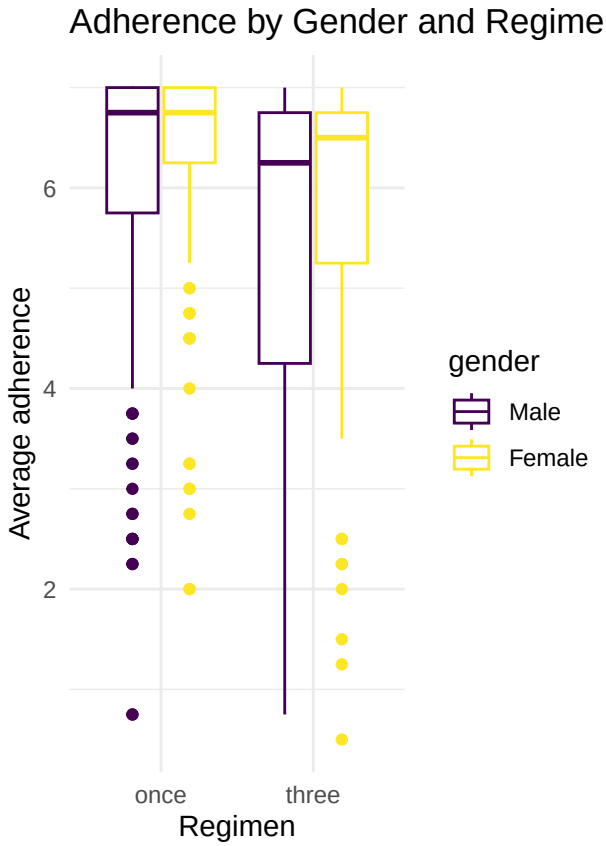
Comparison	Blood Viral Load			Skin	
	Beta	95% CI	p-value	Beta	95
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	73.5	60.3, 86.6	**<0.001**	105.6	86.
Treatment					
Gel B vs Pill A	-6.8	-11.4, -2.2	**0.004**	-24.4	-31
Gel C vs Pill A	-9.1	-13.6, -4.6	**<0.001**	-37.0	-44
Additional Day of Adherence	0.9	0.6, 1.3	**<0.001**	1.8	1
Adverse Event					
No Adverse Event	26.5	19.7, 33.3	**<0.001**	55.8	45
Period					
Period 2 vs Period 1	-2.3	-6.7, 2.1	0.3	0.9	-5
Period 3 vs Period 1	-1.5	-5.9, 2.8	0.5	1.6	-5

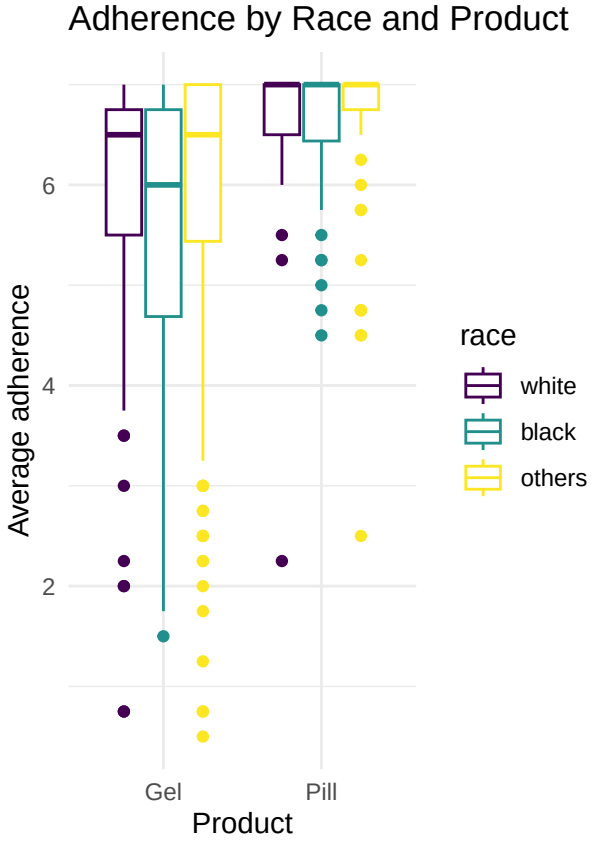
Abbreviation: CI = Confidence Interval

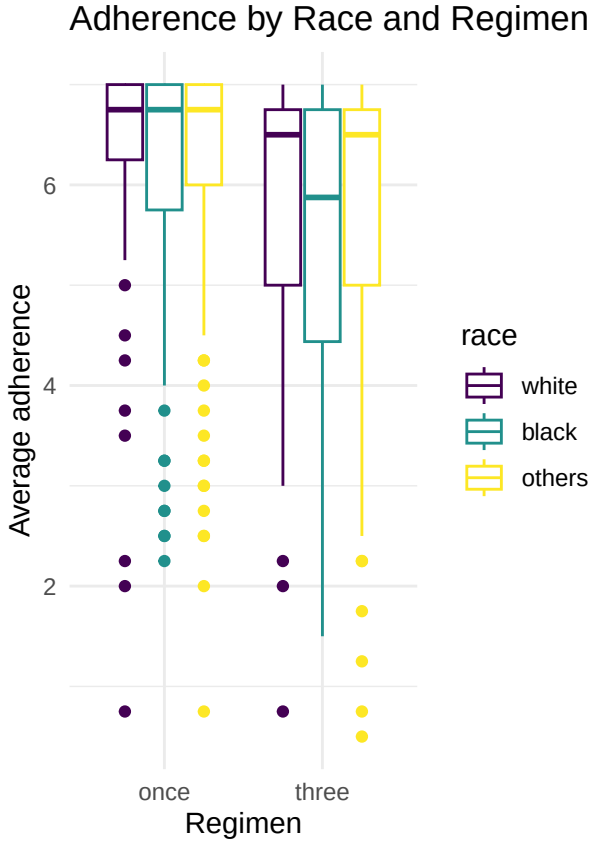


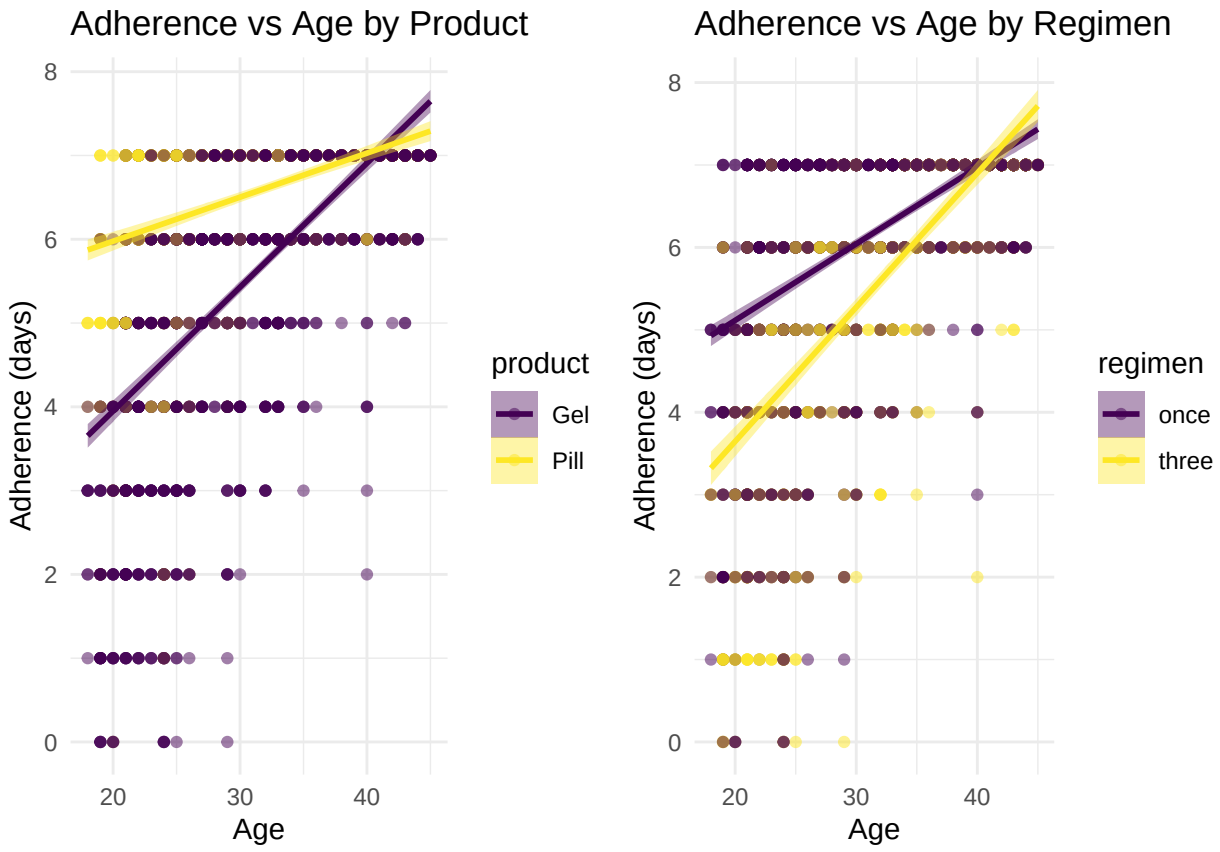
Combined Table

3.4 Secondary Objective 2









Model

$$

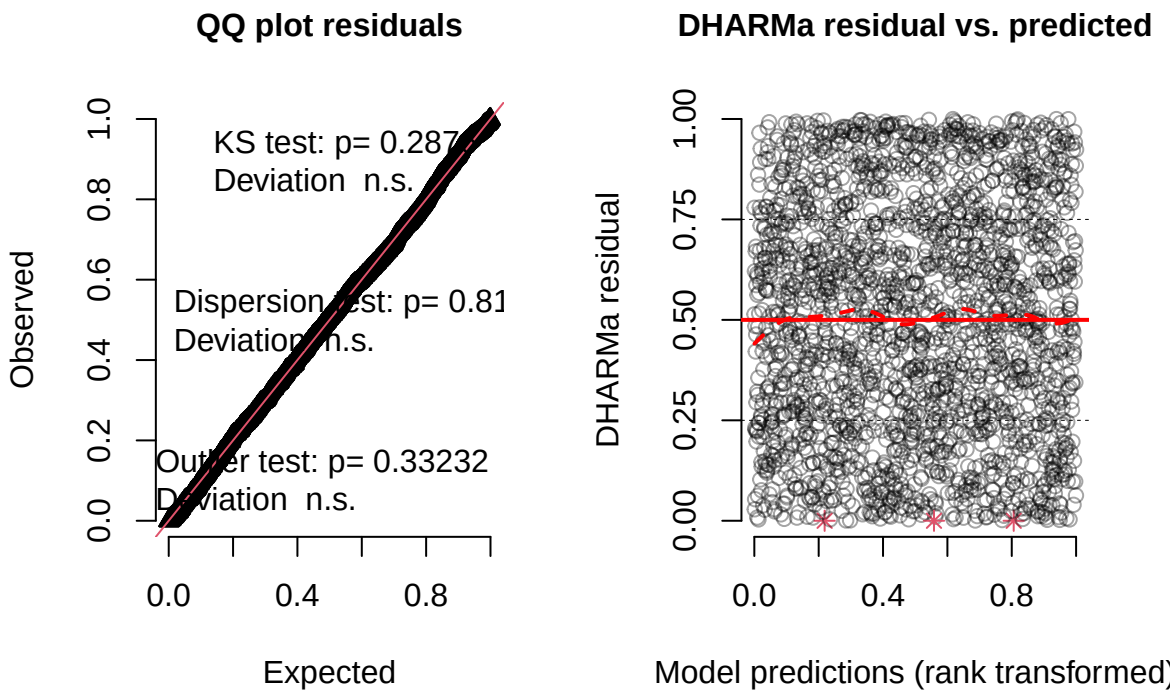
$$Y_{hik} \sim \text{Binomial}\big(n = 7, p_{hik}\big), \tag{4}$$

$$\text{logit}(p_{hik}) = \mu + b_k + \pi_i + \lambda_j + \gamma * h + \beta_d * d_k + \beta_r * regimen + \beta_p * product \tag{5}$$

$$+ \beta_{dr} * d_k * regimen + \beta_{dp} * d_k * product \tag{6}$$

$$b_k \sim \mathcal{N}(0, \sigma_b^2) \tag{7}$$

$$



IV. Discussion

V. Conclusion

VI. Appendix

Table 3: **Interaction Results of Demographic Variables on Adherence**

Characteristic	OR	95% CI	p-value
Age	1.21	1.18, 1.24	**<0.001**
Product			
Gel	—	—	
Pill	4.35	2.98, 6.35	**<0.001**
Gender			
Male	—	—	
Female	1.36	0.95, 1.95	0.10
Race			
white	—	—	
black	1.02	0.65, 1.60	>0.9
others	0.97	0.62, 1.53	0.9
Regimen			
once	—	—	
three	0.76	0.58, 1.00	**0.050**
Period			
1	—	—	
2	1.14	0.99, 1.32	0.073
3	1.03	0.89, 1.18	0.7
Week	0.73	0.69, 0.76	**<0.001**
Age * Product			
Age * Pill	1.00	0.97, 1.03	>0.9
Product * Gender			
Pill * Female	1.00	0.71, 1.40	>0.9
Product * Race			
Pill * black	1.23	0.81, 1.86	0.3
Pill * others	1.05	0.69, 1.61	0.8
Age * Regimen			
Age * three	1.02	1.00, 1.04	0.074
Gender * Regimen			
Female * three	0.89	0.69, 1.15	0.4
Race * Regimen			
black * three	1.14	0.84, 1.56	0.4
others * three	1.02	0.74, 1.41	0.9

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table 4: **Main Effect Results of Demographic Variables on Adherence**

Characteristic	OR	95% CI	p-value
Age	1.22	1.19, 1.25	**<0.001**
Gender			
Male	—	—	
Female	1.29	0.92, 1.80	0.14
Race			
white	—	—	
black	1.11	0.73, 1.69	0.6
others	0.99	0.65, 1.50	>0.9
Regimen			
once	—	—	
three	0.71	0.63, 0.80	**<0.001**
Product			
Gel	—	—	
Pill	4.84	4.12, 5.70	**<0.001**
Period			
1	—	—	
2	1.14	0.99, 1.32	0.065
3	1.04	0.91, 1.20	0.6
Week	0.73	0.69, 0.76	**<0.001**

Abbreviations: CI = Confidence Interval, OR = Odds Ratio