Ensaio clínico randomizado: efeito da droga vegetal de *Eclipta prostrata* (L.) L. (Asteraceae) no ângulo de fase em adultos com obesidade grau I

Análise de dados

Gustavo Santos Paiva Laender Moura

2025-06-12

Índice

1 Bibliotecas e Dados **3**

2 Estratégia Analítica Geral **4**

3 Variáveis coletadas nas três visitas clínicas **4**

3.0.1 Aspartato Aminotransferase . . . 5
3.0.1.1 Resumo dos modelos . . . 7
3.0.1.2 Médias Marginais Estimadas . . . 12
3.0.1.3 Resultado . . . 17
3.0.2 Alanina Aminotransferase . . . 20
3.0.2.1 Resumo dos modelos . . . 22
3.0.2.2 Médias Marginais Estimadas . . . 27
3.0.2.3 Resultado . . . 32
3.0.3 Gama Glutamil-transferase . . . 35
3.0.3.1 Resumo dos modelos . . . 37
3.0.3.2 Médias Marginais Estimadas . . . 42
3.0.3.3 Resultado . . . 47
3.0.4 Fosfatase Alcalina . . . 50
3.0.4.1 Resumo dos modelos . . . 52
3.0.4.2 Médias Marginais Estimadas . . . 58
3.0.4.3 Resultado . . . 63
3.0.5 Colesterol Total . . . 66
3.0.5.1 Resumo dos modelos . . . 68
3.0.5.2 Médias Marginais Estimadas . . . 74
3.0.5.3 Resultado . . . 79
3.0.6 LDL Colesterol . . . 82
3.0.6.1 Resumo dos modelos . . . 84
3.0.6.2 Médias Marginais Estimadas . . . 90

3.0.6.3 Resultado . . . 95
3.0.7 HDL Colesterol . . . 98
3.0.7.1 Resumo dos modelos . . . 100
3.0.7.2 Médias Marginais Estimadas . . . 106
3.0.7.3 Resultado . . . 111
3.0.8 Triglicerídeos . . . 114
3.0.8.1 Resumo dos modelos . . . 116
3.0.8.2 Médias Marginais Estimadas . . . 122
3.0.8.3 Resultado . . . 127
3.0.9 Glicemia de jejum . . . 130
3.0.9.1 Resumo dos modelos . . . 132
3.0.9.2 Médias Marginais Estimadas . . . 138
3.0.9.3 Resultado . . . 143
3.0.10 Hemoglobina Glicosilada . . . 146
3.0.10.1 Resumo dos modelos . . . 148
3.0.10.2 Médias Marginais Estimadas . . . 154
3.0.10.3 Resultado . . . 159
3.0.11 Insulina . . . 162
3.0.11.1 Resumo dos modelos . . . 164
3.0.11.2 Médias Marginais Estimadas . . . 170
3.0.11.3 Resultado . . . 175
3.0.12 HOMA-IR . . . 178
3.0.12.1 Resumo dos modelos . . . 180
3.0.12.2 Médias Marginais Estimadas . . . 186
3.0.12.3 Resultado . . . 191
3.0.13 Índice QUICK . . . 194
3.0.13.1 Resumo dos modelos . . . 196
3.0.13.2 Médias Marginais Estimadas . . . 202
3.0.13.3 Resultado . . . 207
3.0.14 Circunferência abdominal . . . 210
3.0.14.1 Resumo dos modelos . . . 212
3.0.14.2 Médias Marginais Estimadas . . . 218
3.0.14.3 Resultado . . . 223
3.0.15 Índice de Massa Corporal . . . 226
3.0.15.1 Resumo dos modelos . . . 228
3.0.15.2 Médias Marginais Estimadas . . . 234
3.0.15.3 Resultado . . . 239
3.0.16 Pressão Arterial Média . . . 243
3.0.16.1 Resumo dos modelos . . . 245
3.0.16.2 Médias Marginais Estimadas . . . 250
3.0.16.3 Resultado . . . 255
3.0.17 Escore EVS . . . 259
3.0.17.1 Resumo dos modelos . . . 261
3.0.17.2 Médias Marginais Estimadas . . . 267
3.0.17.3 EVS - modelo em 2 partes . . . 274

4 Variáveis coletadas na primeira e terceira visitas **278**
4.0.1 Ângulo de Fase . . . 278
4.0.1.1 Resumo dos modelos . . . 280
4.0.1.2 Médias Marginais Estimadas . . . 285
4.0.1.3 Resultado . . . 289
4.0.2 Reatância . . . 292
4.0.2.1 Resumo dos modelos . . . 294
4.0.2.2 Médias Marginais Estimadas . . . 299
4.0.2.3 Resultado . . . 303
4.0.3 Resistência . . . 306
4.0.3.1 Resumo dos modelos . . . 308
4.0.3.2 Médias Marginais Estimadas . . . 313
4.0.3.3 Resultado . . . 317
4.0.4 Força de Preensão Palmar . . . 320
4.0.4.1 Resumo dos modelos . . . 322
4.0.4.2 Médias Marginais Estimadas . . . 327
4.0.4.3 Resultado . . . 331

5 Informações da Sessão **334**

1 Bibliotecas e Dados

2 Estratégia Analítica Geral

Todas as análises foram conduzidas utilizando modelos lineares mistos (LMM), com intercepto aleatório por participante para considerar a estrutura longitudinal dos dados. A variável dependente em cada modelo foi analisada de forma individual, tendo como variáveis explicativas fixas o grupo de alocação, o tempo (visita) e a interação entre ambos. As covariáveis incluídas foram as mesmas em todos os modelos.

Variáveis com distribuição assimétrica à direita foram transformadas por logaritmo natural com deslocamento (+1), conforme apropriado, a fim de aproximar a normalidade dos resíduos. As demais variáveis foram mantidas em sua forma original. Para cada desfecho, os modelos foram ajustados aos dados completos e, adicionalmente, foi realizada uma análise de sensibilidade com exclusão de observações influentes, identificadas com base em medidas diagnósticas específicas.

As médias marginais estimadas (Estimated Marginal Means – EMMs) foram calculadas a partir dos modelos ajustados, com o objetivo de estimar os valores médios ajustados para cada grupo em cada ponto temporal. As comparações pareadas entre grupos em cada visita e entre visitas dentro de cada grupo foram realizadas com correção para múltiplas comparações pelo método de Bonferroni.

Esse procedimento foi replicado de forma consistente para todas as variáveis contínuas incluídas na análise.

3 Variáveis coletadas nas três visitas clínicas

Variáveis:

- labs_ast
- labs_alt
- labs_ggt
- labs_alkp
- labs_cholesterol
- labs_ldl
- labs_hdl

- labs_triglycerides
- labs_glucose
- labs_hba1c
- labs_insulin
- labs_homa_ir
- labs_quick_index
- abdomen
- bmi
- mean_bp_mean
- evs_score

3.0.1 Aspartato Aminotransferase

Variável: `labs_ast`

```
# Plot 1: Raw data
labs_ast_hist_1 <- data_model %>%
    filter(
        labs_ast < 300
    ) %>%
    ggplot(aes(x = labs_ast)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_ast_hist_2 <- data_model %>%
    filter(
        labs_ast < 300
    ) %>%
    ggplot(aes(x = log1p(labs_ast))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")
```

```r
# Combine side by side
labs_ast_hist_1 + labs_ast_hist_2 # library(patchwork)
```

```r
# LMM
labs_ast_model <- lmer(log1p(labs_ast) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_ast_model)
```

```
# Check for Multicollinearity


Low Correlation


                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
        allocation_group 1.39 [1.21, 1.74]         1.18      0.72     [0.57, 0.83]
                   visit 3.53 [2.81, 4.54]         1.88      0.28     [0.22, 0.36]
 allocation_group:visit 4.18 [3.30, 5.39]         2.04      0.24     [0.19, 0.30]
```

```r
# Sensitivity analysis
labs_ast_model_check <- sensitivity_check_lmer(
    model = labs_ast_model,
```

```r
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_ast_model_sens <- update(object = labs_ast_model,
                              subset = !(record_id %in%
        labs_ast_model_check$influential_ids))
# Influential IDS
labs_ast_model_check$influential_ids
```

```
[1] "4"  "14" "33" "61" "16"
```

3.0.1.1 Resumo dos modelos

```r
# Model comparison
summary(labs_ast_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_ast) ~ allocation_group * visit + (1 | record_id)
   Data: data_model

REML criterion at convergence: 5.8

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.72864 -0.55023 -0.04259  0.56429  2.70480

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.03007  0.1734
 Residual              0.03385  0.1840
Number of obs: 179, groups:  record_id, 75
```

```
Fixed effects:
                                 Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                      3.211717   0.041563 126.794430  77.273   <2e-16 ***
allocation_groupGrupo B         -0.020671   0.058392 126.794430  -0.354    0.724
visit2                          -0.008428   0.045718 106.361849  -0.184    0.854
visit3                          -0.009289   0.049356 109.412475  -0.188    0.851
allocation_groupGrupo B:visit2  -0.015833   0.066802 109.278386  -0.237    0.813
allocation_groupGrupo B:visit3   0.025422   0.071565 111.735957   0.355    0.723
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.481  0.343
visit3      -0.446  0.317  0.442
allctn_GB:2  0.330 -0.463 -0.684 -0.303
allctn_GB:3  0.308 -0.432 -0.305 -0.690  0.424
```

```r
summary(labs_ast_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_ast) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_ast_model_check$influential_ids)

REML criterion at convergence: -33.2

Scaled residuals:
     Min       1Q   Median       3Q      Max
```

```
-1.91122 -0.53274 -0.03816  0.58631  1.89195

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.03382  0.1839
 Residual              0.02259  0.1503
Number of obs: 166, groups:  record_id, 70

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      3.22105    0.04015 100.92953  80.229   <2e-16 ***
allocation_groupGrupo B         -0.04417    0.05678 100.92953  -0.778    0.438
visit2                          -0.01756    0.03879  95.56884  -0.453    0.652
visit3                          -0.03571    0.04157  97.13735  -0.859    0.392
allocation_groupGrupo B:visit2  -0.02157    0.05710  97.80899  -0.378    0.706
allocation_groupGrupo B:visit3   0.06882    0.06184  99.31712   1.113    0.268
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.707
visit2      -0.414  0.293
visit3      -0.387  0.274  0.450
allctn_GB:2  0.282 -0.398 -0.679 -0.306
allctn_GB:3  0.260 -0.368 -0.302 -0.672  0.430
```

```r
labs_ast_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic    p.value
```

```
   <chr>       <chr>                            <dbl>     <dbl>     <dbl>      <dbl>
 1 Original    (Intercept)                       3.21       0.0416    77.3    1.64e-108
 2 Sensitivity (Intercept)                       3.22       0.0401    80.2    3.09e- 93
 3 Original    allocation_groupGrupo B          -0.0207     0.0584    -0.354  7.24e-  1
 4 Sensitivity allocation_groupGrupo B          -0.0442     0.0568    -0.778  4.38e-  1
 5 Original    allocation_groupGrupo B:visit2 -0.0158     0.0668    -0.237  8.13e-  1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.0216     0.0571    -0.378  7.06e-  1
 7 Original    allocation_groupGrupo B:visit3  0.0254     0.0716     0.355  7.23e-  1
 8 Sensitivity allocation_groupGrupo B:visit3  0.0688     0.0618     1.11   2.68e-  1
 9 Original    sd__(Intercept)                  0.173     NA         NA     NA
10 Sensitivity sd__(Intercept)                  0.184     NA         NA     NA
11 Original    sd__Observation                  0.184     NA         NA     NA
12 Sensitivity sd__Observation                  0.150     NA         NA     NA
13 Original    visit2                          -0.00843    0.0457    -0.184  8.54e-  1
14 Sensitivity visit2                          -0.0176     0.0388    -0.453  6.52e-  1
15 Original    visit3                          -0.00929    0.0494    -0.188  8.51e-  1
16 Sensitivity visit3                          -0.0357     0.0416    -0.859  3.92e-  1
```

```r
labs_ast_3performance <- performance::compare_performance(
    labs_ast_model,
    labs_ast_model_sens)
labs_ast_3performance
```

```
# Comparison of Model Performance Indices

Name                |           Model |  AIC (weights) | AICc (weights) |  BIC (weight
-----------------------------------------------------------------------------------------
labs_ast_model      | lmerModLmerTest | 1139.5 (<.001) | 1140.3 (<.001) | 1165.0 (<.00
labs_ast_model_sens | lmerModLmerTest | 1014.1 (>.999) | 1015.0 (>.999) | 1039.0 (>.99
```

```r
performance::check_model(labs_ast_model)
```

```
performance::check_model(labs_ast_model_sens)
```

3.0.1.2 Médias Marginais Estimadas

3.0.1.2.1 Todos os dados

```
# Get EMMs for each group at each visit (All data)
labs_ast_raw_emm <- emmeans::emmeans(
    labs_ast_model,
    ~ allocation_group * visit
```

```r
)

labs_ast_raw_emm <- regrid(labs_ast_raw_emm)

# Table of marginal means
# labs_ast_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ast_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.508 1.43 128    -2.33     3.35   0.354  0.7240

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.882 1.58 142    -2.24     4.00   0.559  0.5771

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.117 1.73 157    -3.54     3.31  -0.068  0.9462

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ast_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.2083 1.13 128    -2.53     2.95   0.184  1.0000
 visit1 - visit3   0.2295 1.22 128    -2.73     3.19   0.188  1.0000
 visit2 - visit3   0.0212 1.24 142    -2.98     3.02   0.017  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.5828 1.17 128    -2.25     3.42   0.499  1.0000
 visit1 - visit3  -0.3954 1.28 128    -3.49     2.70  -0.310  1.0000
 visit2 - visit3  -0.9782 1.33 155    -4.20     2.24  -0.735  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_ast_raw_emm, comparisons = TRUE)
```

3.0.1.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_ast_emm <- emmeans::emmeans(
    labs_ast_model_sens,
    ~ allocation_group * visit
)

labs_ast_emm <- regrid(labs_ast_emm)

# Table of marginal means
# labs_ast_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ast_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.083 1.39 104    -1.68     3.84   0.778  0.4386

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.566 1.49 118    -1.38     4.51   1.052  0.2948

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.603 1.64 132    -3.85     2.64  -0.368  0.7136

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ast_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.436 0.963 104    -1.91     2.78   0.453  1.0000
 visit1 - visit3    0.879 1.020 104    -1.60     3.36   0.861  1.0000
 visit2 - visit3    0.443 1.030 118    -2.06     2.94   0.430  1.0000

allocation_group = Grupo B:
 contrast        estimate    SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.920 0.983 104    -1.47     3.31   0.936  1.0000
 visit1 - visit3   -0.807 1.130 104    -3.55     1.93  -0.716  1.0000
 visit2 - visit3   -1.727 1.150 131    -4.51     1.06  -1.505  0.4043

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_ast_emm, comparisons = TRUE)
```

3.0.1.3 Resultado

No modelo ajustado para os níveis de AST, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade não alterou substancialmente os resultados. As estimativas permaneceram estáveis e as diferenças entre os grupos e ao longo do tempo continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 1.

Tabela 1: Diferenças estimadas dos níveis de Aspartato Aminotransferase (AST) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,51	[-2,33 ; 3,35]	0,724
Entre grupos	Visita 2	0,88	[-2,24 ; 4,00]	0,577
Entre grupos	Visita 3	-0,12	[-3,54 ; 3,31]	0,946
Grupo Placebo	Visita 1 - Visita 2	0,21	[-2,53 ; 2,95]	1,000
Grupo Placebo	Visita 1 - Visita 3	0,23	[-2,73 ; 3,19]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	0,02	[-2,98 ; 3,02]	1,000
Grupo Eclipta	Visita 1 - Visita 2	0,58	[-2,25 ; 3,42]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,40	[-3,49 ; 2,70]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,98	[-4,20 ; 2,24]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_ast,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
data_model %>%
    filter(
        !(record_id %in%
        labs_ast_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_ast,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
```

```
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

3.0.2 Alanina Aminotransferase

```
# Plot 1: Raw data
labs_alt_hist_1 <- data_model %>%
    #filter(
    #    labs_alt < 300
    #) %>%
    ggplot(aes(x = labs_alt)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_alt_hist_2 <- data_model %>%
```

```
    #filter(
    #    labs_alt < 300
    #) %>%
    ggplot(aes(x = log1p(labs_alt))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_alt_hist_1 + labs_alt_hist_2 # library(patchwork)
```

```
# LMM
labs_alt_model <- lmer(log1p(labs_alt) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_alt_model)
```

```
# Check for Multicollinearity


Low Correlation


                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
```

```
       allocation_group 1.21 [1.08, 1.54]         1.10      0.83     [0.65, 0.92]
                  visit 3.50 [2.79, 4.49]         1.87      0.29     [0.22, 0.36]
 allocation_group:visit 3.84 [3.04, 4.94]         1.96      0.26     [0.20, 0.33]
```

```r
# Sensitivity analysis
labs_alt_model_check <- sensitivity_check_lmer(
    model = labs_alt_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_alt_model_sens <- update(object = labs_alt_model,
                              subset = !(record_id %in%
        labs_alt_model_check$influential_ids))
# Influential IDS
labs_alt_model_check$influential_ids
```

```
[1] "33" "75" "5"  "58" "63"
```

3.0.2.1 Resumo dos modelos

```r
# Model comparison
summary(labs_alt_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_alt) ~ allocation_group * visit + (1 | record_id)
   Data: data_model

REML criterion at convergence: 132.2

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.28166 -0.55027 -0.05275  0.54015  2.15582
```

```
Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.10863  0.3296
 Residual              0.05485  0.2342
Number of obs: 179, groups:  record_id, 75

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      3.34045    0.06647 102.44387  50.254   <2e-16 ***
allocation_groupGrupo B         -0.10187    0.09338 102.44387  -1.091    0.278
visit2                          -0.07956    0.05867 103.85033  -1.356    0.178
visit3                          -0.03364    0.06353 105.34376  -0.529    0.598
allocation_groupGrupo B:visit2   0.06143    0.08602 105.75034   0.714    0.477
allocation_groupGrupo B:visit3   0.07920    0.09237 106.88087   0.857    0.393
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.380  0.271
visit3      -0.351  0.250  0.449
allctn_GB:2  0.259 -0.364 -0.682 -0.306
allctn_GB:3  0.241 -0.339 -0.309 -0.688  0.432
```

```r
summary(labs_alt_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_alt) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
```

```
 Subset: !(record_id %in% labs_alt_model_check$influential_ids)

REML criterion at convergence: 88.4

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.98911 -0.51655 -0.03328  0.57521  2.21076

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.09385  0.3063
 Residual              0.04238  0.2059
Number of obs: 165, groups:  record_id, 70

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                     3.249918   0.064250 90.966334  50.582   <2e-16 ***
allocation_groupGrupo B        -0.013075   0.088373 90.966334  -0.148    0.883
visit2                         -0.021536   0.055231 93.405160  -0.390    0.697
visit3                         -0.035422   0.060679 94.750397  -0.584    0.561
allocation_groupGrupo B:visit2 -0.009275   0.078377 94.689442  -0.118    0.906
allocation_groupGrupo B:visit3  0.043535   0.085567 95.767451   0.509    0.612
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.727
visit2      -0.362  0.263
visit3      -0.329  0.239  0.442
```

```
allctn_GB:2  0.255 -0.351 -0.705 -0.311
allctn_GB:3  0.234 -0.321 -0.313 -0.709  0.434
```

```r
labs_alt_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                        3.34       0.0665    50.3    5.32e-74
 2 Sensitivity (Intercept)                        3.25       0.0642    50.6    2.13e-68
 3 Original    allocation_groupGrupo B           -0.102      0.0934    -1.09   2.78e- 1
 4 Sensitivity allocation_groupGrupo B           -0.0131     0.0884    -0.148  8.83e- 1
 5 Original    allocation_groupGrupo B:visit2     0.0614     0.0860     0.714  4.77e- 1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.00928      0.0784    -0.118  9.06e- 1
 7 Original    allocation_groupGrupo B:visit3     0.0792     0.0924     0.857  3.93e- 1
 8 Sensitivity allocation_groupGrupo B:visit3     0.0435     0.0856     0.509  6.12e- 1
 9 Original    sd__(Intercept)                    0.330     NA         NA     NA
10 Sensitivity sd__(Intercept)                    0.306     NA         NA     NA
11 Original    sd__Observation                    0.234     NA         NA     NA
12 Sensitivity sd__Observation                    0.206     NA         NA     NA
13 Original    visit2                            -0.0796     0.0587    -1.36   1.78e- 1
14 Sensitivity visit2                            -0.0215     0.0552    -0.390  6.97e- 1
15 Original    visit3                            -0.0336     0.0635    -0.529  5.98e- 1
16 Sensitivity visit3                            -0.0354     0.0607    -0.584  5.61e- 1
```

```r
performance::compare_performance(
    labs_alt_model,
    labs_alt_model_sens)
```

```
# Comparison of Model Performance Indices

Name                |           Model |  AIC (weights) | AICc (weights) |  BIC (weight
-----------------------------------------------------------------------------------------
```

```
labs_alt_model      | lmerModLmerTest | 1302.9 (<.001) | 1303.8 (<.001) | 1328.4 (<.00
labs_alt_model_sens | lmerModLmerTest | 1150.5 (>.999) | 1151.4 (>.999) | 1175.3 (>.99
```

```
performance::check_model(labs_alt_model)
```

```
performance::check_model(labs_alt_model_sens)
```

3.0.2.2 Médias Marginais Estimadas

3.0.2.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_alt_raw_emm <- emmeans::emmeans(
    labs_alt_model,
    ~ allocation_group * visit
```

```r
)

labs_alt_raw_emm <- regrid(labs_alt_raw_emm)

# Table of marginal means
# labs_alt_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alt_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    2.734 2.51 104    -2.25     7.72   1.088  0.2792

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.033 2.59 118    -4.10     6.16   0.399  0.6907

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.612 2.88 134    -5.09     6.32   0.212  0.8324

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alt_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    2.159 1.59 104    -1.71     6.03   1.357  0.5332
 visit1 - visit3    0.934 1.76 104    -3.35     5.21   0.531  1.0000
 visit2 - visit3   -1.225 1.72 118    -5.41     2.96  -0.711  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.458 1.59 104    -3.41     4.32   0.288  1.0000
 visit1 - visit3   -1.189 1.77 104    -5.49     3.11  -0.672  1.0000
 visit2 - visit3   -1.647 1.83 134    -6.07     2.78  -0.902  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_alt_raw_emm, comparisons = TRUE)
```

3.0.2.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_alt_emm <- emmeans::emmeans(
    labs_alt_model_sens,
    ~ allocation_group * visit
)

labs_alt_emm <- regrid(labs_alt_emm)

# Table of marginal means
# labs_alt_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alt_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.335 2.27  93.7    -4.16     4.83   0.148  0.8827

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.558 2.38 107.7    -4.17     5.28   0.234  0.8153

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.770 2.56 125.2    -5.84     4.31  -0.300  0.7645

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alt_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.549 1.41  93.7    -2.88     3.98   0.390  1.0000
 visit1 - visit3    0.897 1.53  93.7    -2.84     4.63   0.586  1.0000
 visit2 - visit3    0.348 1.54 107.7    -3.39     4.09   0.226  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.772 1.39  93.7    -2.62     4.16   0.555  1.0000
 visit1 - visit3   -0.207 1.55  93.7    -3.98     3.56  -0.134  1.0000
 visit2 - visit3   -0.980 1.57 118.5    -4.80     2.84  -0.622  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_alt_emm, comparisons = TRUE)
```

3.0.2.3 Resultado

No modelo ajustado para os níveis de ALT, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou esses achados. As estimativas permaneceram estáveis e todas as comparações entre os grupos e ao longo do tempo mantiveram-se não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 2.

Tabela 2: Diferenças estimadas dos níveis de Alanina Aminotransferase (ALT) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,73	[-2,25 ; 7,72]	0,279
Entre grupos	Visita 2	1,03	[-4,10 ; 6,16]	0,691
Entre grupos	Visita 3	0,61	[-5,09 ; 6,32]	0,832
Grupo Placebo	Visita 1 - Visita 2	2,16	[-1,71 ; 6,03]	0,533
Grupo Placebo	Visita 1 - Visita 3	0,93	[-3,35 ; 5,21]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	-1,23	[-5,41 ; 2,96]	1,000
Grupo Eclipta	Visita 1 - Visita 2	0,46	[-3,41 ; 4,32]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-1,19	[-5,49 ; 3,11]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-1,65	[-6,07 ; 2,78]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_alt,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group) +
    coord_cartesian(ylim = c(10, 80))
```

```
data_model %>%
    filter(
        !(record_id %in%
        labs_alt_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_alt,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
```

```
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group) +
    coord_cartesian(ylim = c(10, 80))
```

3.0.3 Gama Glutamil-transferase

Variável: `labs_ggt`

```
# Plot 1: Raw data
labs_ggt_hist_1 <- data_model %>%
    filter(
        labs_ggt < 300
    ) %>%
    ggplot(aes(x = labs_ggt)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")
```

```r
# Plot 2: Log-transformed data
labs_ggt_hist_2 <- data_model %>%
    filter(
        labs_ggt < 300
    ) %>%
    ggplot(aes(x = log1p(labs_ggt))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_ggt_hist_1 + labs_ggt_hist_2 # library(patchwork)
```

```r
# LMM
labs_ggt_model <- lmer(log1p(labs_ggt) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_ggt_model)
```

```
# Check for Multicollinearity


Low Correlation
```

```
                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.08 [1.01, 1.64]         1.04      0.93     [0.61, 0.99]
                  visit 3.40 [2.71, 4.36]         1.84      0.29     [0.23, 0.37]
 allocation_group:visit 3.51 [2.79, 4.51]         1.87      0.28     [0.22, 0.36]
```

```r
# Sensitivity analysis
labs_ggt_model_check <- sensitivity_check_lmer(
    model = labs_ggt_model,
    id_var = "record_id",
    top_n = 7)

# LMM Sensitivity
labs_ggt_model_sens <- update(object = labs_ggt_model,
                              subset = !(record_id %in%
        labs_ggt_model_check$influential_ids))
# Influential IDS
labs_ggt_model_check$influential_ids
```

```
[1] "13" "46" "49" "58" "22" "34" "41"
```

3.0.3.1 Resumo dos modelos

```r
# Model comparison
summary(labs_ggt_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_ggt) ~ allocation_group * visit + (1 | record_id)
   Data: data_model

REML criterion at convergence: 214.3

Scaled residuals:
```

```
     Min       1Q   Median       3Q      Max
-1.98517 -0.41941 -0.02504  0.42332  2.68048

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.35840  0.5987
 Residual              0.05825  0.2413
Number of obs: 178, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    3.36365    0.10612 81.55575  31.697   <2e-16 ***
allocation_groupGrupo B        0.05279    0.14908 81.55575   0.354    0.724
visit2                        -0.02673    0.06095 98.79849  -0.439    0.662
visit3                         0.01219    0.06614 99.26017   0.184    0.854
allocation_groupGrupo B:visit2 0.04689    0.08964 99.59537   0.523    0.602
allocation_groupGrupo B:visit3 0.02698    0.09736 99.95801   0.277    0.782
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.243  0.173
visit3      -0.224  0.160  0.455
allctn_GB:2  0.166 -0.233 -0.680 -0.310
allctn_GB:3  0.152 -0.214 -0.309 -0.679  0.436
```

```r
summary(labs_ggt_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
```

```
Formula: log1p(labs_ggt) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_ggt_model_check$influential_ids)

REML criterion at convergence: 129.2

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.06521 -0.44956 -0.01804  0.45494  1.81501

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.2520   0.5020
 Residual              0.0364   0.1908
Number of obs: 160, groups:  record_id, 68

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    3.21202    0.09349 74.25204  34.357   <2e-16 ***
allocation_groupGrupo B        0.14499    0.13031 74.25204   1.113    0.269
visit2                        -0.01105    0.05075 89.14440  -0.218    0.828
visit3                         0.03893    0.05564 89.56439   0.700    0.486
allocation_groupGrupo B:visit2 0.06129    0.07498 89.97944   0.817    0.416
allocation_groupGrupo B:visit3 0.01693    0.08145 90.24696   0.208    0.836
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.717
```

```
visit2      -0.233  0.167
visit3      -0.212  0.152  0.452
allctn_GB:2  0.157 -0.219 -0.677 -0.306
allctn_GB:3  0.145 -0.202 -0.309 -0.683  0.434
```

```r
labs_ggt_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                         3.36      0.106     31.7    1.28e-47
 2 Sensitivity (Intercept)                         3.21      0.0935    34.4    2.48e-47
 3 Original    allocation_groupGrupo B             0.0528    0.149      0.354  7.24e- 1
 4 Sensitivity allocation_groupGrupo B             0.145     0.130      1.11   2.69e- 1
 5 Original    allocation_groupGrupo B:visit2      0.0469    0.0896     0.523  6.02e- 1
 6 Sensitivity allocation_groupGrupo B:visit2      0.0613    0.0750     0.817  4.16e- 1
 7 Original    allocation_groupGrupo B:visit3      0.0270    0.0974     0.277  7.82e- 1
 8 Sensitivity allocation_groupGrupo B:visit3      0.0169    0.0814     0.208  8.36e- 1
 9 Original    sd__(Intercept)                     0.599    NA         NA     NA
10 Sensitivity sd__(Intercept)                     0.502    NA         NA     NA
11 Original    sd__Observation                     0.241    NA         NA     NA
12 Sensitivity sd__Observation                     0.191    NA         NA     NA
13 Original    visit2                             -0.0267    0.0610    -0.439  6.62e- 1
14 Sensitivity visit2                             -0.0110    0.0507    -0.218  8.28e- 1
15 Original    visit3                              0.0122    0.0661     0.184  8.54e- 1
16 Sensitivity visit3                              0.0389    0.0556     0.700  4.86e- 1
```

```r
performance::compare_performance(
    labs_ggt_model,
    labs_ggt_model_sens)
```

```
# Comparison of Model Performance Indices
```

```
Name                |           Model |  AIC (weights) | AICc (weights) |  BIC (weight
-----------------------------------------------------------------------------------------
labs_ggt_model      | lmerModLmerTest | 1425.1 (<.001) | 1426.0 (<.001) | 1450.6 (<.00
labs_ggt_model_sens | lmerModLmerTest | 1189.5 (>.999) | 1190.4 (>.999) | 1214.1 (>.99
```

```
performance::check_model(labs_ggt_model)
```

```
performance::check_model(labs_ggt_model_sens)
```

3.0.3.2 Médias Marginais Estimadas

3.0.3.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_ggt_raw_emm <- emmeans::emmeans(
    labs_ggt_model,
    ~ allocation_group * visit
```

```r
)

labs_ggt_raw_emm <- regrid(labs_ggt_raw_emm)

# Table of marginal means
# labs_ggt_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ggt_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -1.57 4.42  84.1    -10.4     7.23  -0.354  0.7242

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -2.95 4.60  91.4    -12.1     6.19  -0.641  0.5232

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -2.43 4.87 100.1    -12.1     7.24  -0.498  0.6193

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ggt_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.762 1.74  84.1    -3.48     5.01   0.439  1.0000
 visit1 - visit3   -0.354 1.93  84.1    -5.06     4.35  -0.184  1.0000
 visit2 - visit3   -1.116 1.92  91.4    -5.79     3.56  -0.583  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   -0.620 2.03  84.1    -5.58     4.34  -0.305  1.0000
 visit1 - visit3   -1.217 2.24  84.1    -6.69     4.26  -0.543  1.0000
 visit2 - visit3   -0.596 2.33 100.6    -6.27     5.08  -0.256  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_ggt_raw_emm, comparisons = TRUE)
```

3.0.3.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_ggt_emm <- emmeans::emmeans(
    labs_ggt_model_sens,
    ~ allocation_group * visit
)

labs_ggt_emm <- regrid(labs_ggt_emm)

# Table of marginal means
# labs_ggt_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ggt_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -3.87 3.49 74.8    -10.8     3.08  -1.110  0.2705

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -5.63 3.73 80.4    -13.0     1.79  -1.510  0.1351

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -4.54 3.92 88.4    -12.3     3.25  -1.158  0.2501

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ggt_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.273 1.25 74.8    -2.80     3.34   0.218  1.0000
 visit1 - visit3   -0.986 1.42 74.8    -4.46     2.49  -0.694  1.0000
 visit2 - visit3   -1.259 1.42 80.4    -4.73     2.21  -0.888  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   -1.479 1.64 74.8    -5.51     2.55  -0.899  1.0000
 visit1 - visit3   -1.649 1.78 74.8    -6.02     2.72  -0.924  1.0000
 visit2 - visit3   -0.170 1.88 90.1    -4.74     4.40  -0.091  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_ggt_emm)
```

3.0.3.3 Resultado

No modelo ajustado para os níveis de Gama Glutamiltransferase (GGT), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Também não foram identificadas mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, com exclusão das observações influentes, não alterou substancialmente os resultados. As estimativas permaneceram similares, reforçando a ausência de diferenças significativas entre os grupos ou de variações temporais relevantes. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 3.

Tabela 3: Diferenças estimadas dos níveis de Gama Glutamiltransferase (GGT) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-1,57	[-10,4 ; 7,23]	0,724
Entre grupos	Visita 2	-2,95	[-12,1 ; 6,19]	0,523
Entre grupos	Visita 3	-2,43	[-12,1 ; 7,24]	0,619
Grupo Placebo	Visita 1 - Visita 2	0,76	[-3,48 ; 5,01]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 1 - Visita 3	-0,35	[-5,06 ; 4,35]	1,000
Grupo Placebo	Visita 2 - Visita 3	-1,12	[-5,79 ; 3,56]	1,000
Grupo Eclipta	Visita 1 - Visita 2	-0,62	[-5,58 ; 4,34]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-1,22	[-6,69 ; 4,26]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,60	[-6,27 ; 5,08]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_ggt,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_ggt_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_ggt,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.4 Fosfatase Alcalina

Variável: `labs_alkp`

```
# Plot 1: Raw data
labs_alkp_hist_1 <- data_model %>%
    #filter(
    #    labs_alkp < 300
    #) %>%
    ggplot(aes(x = labs_alkp)) +
```

```r
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_alkp_hist_2 <- data_model %>%
    #filter(
    #    labs_alkp < 300
    #) %>%
    ggplot(aes(x = log1p(labs_alkp))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_alkp_hist_1 + labs_alkp_hist_2 # library(patchwork)
```

```r
# LMM
labs_alkp_model <- lmer(log1p(labs_alkp) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_alkp_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.08 [1.01, 1.62]         1.04      0.93     [0.62, 0.99]
                  visit 3.40 [2.71, 4.36]         1.84      0.29     [0.23, 0.37]
 allocation_group:visit 3.52 [2.80, 4.52]         1.88      0.28     [0.22, 0.36]
```

```r
# Sensitivity analysis
labs_alkp_model_check <- sensitivity_check_lmer(
    model = labs_alkp_model,
    id_var = "record_id",
    top_n = 4)

# LMM Sensitivity
labs_alkp_model_sens <- update(object = labs_alkp_model,
                               subset = !(record_id %in%
        labs_alkp_model_check$influential_ids))
# Influential IDS
labs_alkp_model_check$influential_ids
```

```
[1] "56" "75" "53" "3"
```

3.0.4.1 Resumo dos modelos

```r
# Model comparison
summary(labs_alkp_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_alkp) ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: -87.9
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.02732 -0.46612  0.01043  0.43200  2.62132

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.06041  0.2458
 Residual              0.01021  0.1010
Number of obs: 178, groups:  record_id, 75

Fixed effects:
                                Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     4.210088   0.043688  84.150015  96.367   <2e-16 ***
allocation_groupGrupo B         0.033160   0.061377  84.150015   0.540   0.5904
visit2                         -0.046856   0.025510 100.999520  -1.837   0.0692 .
visit3                         -0.030253   0.027680 101.476417  -1.093   0.2770
allocation_groupGrupo B:visit2  0.018421   0.037511 101.816342   0.491   0.6244
allocation_groupGrupo B:visit3  0.004182   0.040741 102.191761   0.103   0.9184
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.248  0.176
visit3      -0.228  0.162  0.455
allctn_GB:2  0.168 -0.236 -0.680 -0.310
allctn_GB:3  0.155 -0.218 -0.309 -0.679  0.436
```

```r
summary(labs_alkp_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_alkp) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_alkp_model_check$influential_ids)

REML criterion at convergence: -118.6

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.95508 -0.49130  0.04228  0.50567  1.80928

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.06287  0.25073
 Residual              0.00669  0.08179
Number of obs: 167, groups:  record_id, 71

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                     4.198426   0.044579 75.550975  94.179   <2e-16 ***
allocation_groupGrupo B         0.071738   0.062605 75.550975   1.146    0.255
visit2                         -0.021391   0.021391 93.237481  -1.000    0.320
visit3                         -0.002867   0.023373 93.517548  -0.123    0.903
allocation_groupGrupo B:visit2 -0.020052   0.031577 93.770609  -0.635    0.527
allocation_groupGrupo B:visit3 -0.052680   0.034183 93.954152  -1.541    0.127
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.200  0.143
visit3      -0.183  0.131  0.454
allctn_GB:2  0.136 -0.191 -0.677 -0.307
allctn_GB:3  0.125 -0.176 -0.310 -0.684  0.438
```

```r
labs_alkp_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       4.21      0.0437    96.4    6.67e-88
 2 Sensitivity (Intercept)                       4.20      0.0446    94.2    4.38e-80
 3 Original    allocation_groupGrupo B           0.0332    0.0614     0.540  5.90e- 1
 4 Sensitivity allocation_groupGrupo B           0.0717    0.0626     1.15   2.55e- 1
 5 Original    allocation_groupGrupo B:visit2    0.0184    0.0375     0.491  6.24e- 1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.0201     0.0316    -0.635  5.27e- 1
 7 Original    allocation_groupGrupo B:visit3    0.00418   0.0407     0.103  9.18e- 1
 8 Sensitivity allocation_groupGrupo B:visit3 -0.0527     0.0342    -1.54   1.27e- 1
 9 Original    sd__(Intercept)                   0.246    NA         NA     NA
10 Sensitivity sd__(Intercept)                   0.251    NA         NA     NA
11 Original    sd__Observation                   0.101    NA         NA     NA
12 Sensitivity sd__Observation                   0.0818   NA         NA     NA
13 Original    visit2                           -0.0469    0.0255    -1.84   6.92e- 2
14 Sensitivity visit2                           -0.0214    0.0214    -1.00   3.20e- 1
15 Original    visit3                           -0.0303    0.0277    -1.09   2.77e- 1
16 Sensitivity visit3                           -0.00287   0.0234    -0.123  9.03e- 1
```

```r
performance::compare_performance(
    labs_alkp_model,
```

```
    labs_alkp_model_sens)
```

```
# Comparison of Model Performance Indices

Name                 |           Model |  AIC (weights) | AICc (weights) |  BIC (weigh
-----------------------------------------------------------------------------------------
labs_alkp_model      | lmerModLmerTest | 1394.9 (<.001) | 1395.7 (<.001) | 1420.3 (<.0
labs_alkp_model_sens | lmerModLmerTest | 1274.2 (>.999) | 1275.1 (>.999) | 1299.1 (>.9
```

```
performance::check_model(labs_alkp_model)
```

```
performance::check_model(labs_alkp_model_sens)
```

3.0.4.2 Médias Marginais Estimadas

3.0.4.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_alkp_raw_emm <- emmeans::emmeans(
    labs_alkp_model,
    ~ allocation_group * visit
```

```r
)

labs_alkp_raw_emm <- regrid(labs_alkp_raw_emm)

# Table of marginal means
# labs_alkp_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alkp_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -2.27 4.20  84.5    -10.6     6.09  -0.540  0.5904

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -3.40 4.22  92.0    -11.8     4.98  -0.806  0.4223

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -2.49 4.39 101.0    -11.2     6.22  -0.566  0.5724

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alkp_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     3.08 1.68  84.5    -1.02     7.18   1.837  0.2094
 visit1 - visit3     2.01 1.83  84.5    -2.47     6.48   1.096  0.8290
 visit2 - visit3    -1.08 1.81  92.0    -5.48     3.33  -0.596  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     1.95 1.88  84.5    -2.65     6.55   1.036  0.9090
 visit1 - visit3     1.79 2.05  84.5    -3.21     6.79   0.875  1.0000
 visit2 - visit3    -0.16 2.10 101.5    -5.28     4.96  -0.076  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_alkp_raw_emm)
```

3.0.4.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_alkp_emm <- emmeans::emmeans(
    labs_alkp_model_sens,
    ~ allocation_group * visit
)

# Table of marginal means
# labs_alkp_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alkp_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate     SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0717 0.0626 75.8   -0.196   0.0530  -1.146  0.2554

visit = 2:
 contrast          estimate     SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0517 0.0645 84.4   -0.180   0.0766  -0.801  0.4254

visit = 3:
 contrast          estimate     SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0191 0.0658 90.6   -0.150   0.1117  -0.289  0.7729

Note: contrasts are still on the log1p scale. Consider using
      regrid() if you want contrasts of back-transformed estimates.
Degrees-of-freedom method: kenward-roger
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alkp_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate     SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2  0.02139 0.0214 93.5 -0.03077   0.0736   1.000  0.9602
 visit1 - visit3  0.00287 0.0234 93.8 -0.05413   0.0599   0.123  1.0000
 visit2 - visit3 -0.01852 0.0235 92.6 -0.07572   0.0387  -0.790  1.0000

allocation_group = Grupo B:
 contrast        estimate     SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2  0.04144 0.0232 94.5 -0.01521   0.0981   1.783  0.2333
 visit1 - visit3  0.05555 0.0250 94.6 -0.00529   0.1164   2.225  0.0853
 visit2 - visit3  0.01410 0.0259 92.9 -0.04902   0.0772   0.545  1.0000

Note: contrasts are still on the log1p scale. Consider using
      regrid() if you want contrasts of back-transformed estimates.
Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_alkp_emm)
```

3.0.4.3 Resultado

No modelo ajustado para os níveis de Fosfatase Alcalina (ALP), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações intragrupo ao longo do tempo não indicaram variações significativas. A análise de sensibilidade, realizada com exclusão das observações influentes, manteve os resultados essencialmente inalterados, com estimativas semelhantes e ausência de significância estatística nas comparações entre grupos e entre visitas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 4.

Tabela 4: Diferenças estimadas dos níveis de Fosfatase Alcalina (ALP) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-2,27	[-10,6 ; 6,09]	0,590
Entre grupos	Visita 2	-3,40	[-11,8 ; 4,98]	0,422
Entre grupos	Visita 3	-2,49	[-11,2 ; 6,22]	0,572
Grupo Placebo	Visita 1 - Visita 2	3,08	[-1,02 ; 7,18]	0,209

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 1 - Visita 3	2,01	[-2,47 ; 6,48]	0,829
Grupo Placebo	Visita 2 - Visita 3	-1,08	[-5,48 ; 3,33]	1,000
Grupo Eclipta	Visita 1 - Visita 2	1,95	[-2,65 ; 6,55]	0,909
Grupo Eclipta	Visita 1 - Visita 3	1,79	[-3,21 ; 6,79]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,16	[-5,28 ; 4,96]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_alkp,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_alkp_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_alkp,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.5 Colesterol Total

Variável: `labs_cholesterol`

```
# Plot 1: Raw data
labs_cholesterol_hist_1 <- data_model %>%
    #filter(
    #    labs_cholesterol < 300
    #) %>%
    ggplot(aes(x = labs_cholesterol)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_cholesterol_hist_2 <- data_model %>%
    #filter(
    #    labs_cholesterol < 300
    #) %>%
    ggplot(aes(x = log1p(labs_cholesterol))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_cholesterol_hist_1 + labs_cholesterol_hist_2 # library(patchwork)
```

```
# LMM
labs_cholesterol_model <- lmer(labs_cholesterol ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_cholesterol_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.15 [1.05, 1.50]         1.07      0.87     [0.67, 0.96]
                  visit 3.49 [2.78, 4.48]         1.87      0.29     [0.22, 0.36]
 allocation_group:visit 3.73 [2.96, 4.80]         1.93      0.27     [0.21, 0.34]
```

```r
# Sensitivity analysis
labs_cholesterol_model_check <- sensitivity_check_lmer(
    model = labs_cholesterol_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_cholesterol_model_sens <- update(object = labs_cholesterol_model,
                                      subset = !(record_id %in%
        labs_cholesterol_model_check$influential_ids))
# Influential IDS
labs_cholesterol_model_check$influential_ids
```

```
[1] "17" "37" "56" "61" "13"
```

3.0.5.1 Resumo dos modelos

```r
# Model comparison
summary(labs_cholesterol_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: labs_cholesterol ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: 1617.3
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.2546 -0.4103  0.0145  0.4447  2.5046

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 743.1    27.26
 Residual              257.0    16.03
Number of obs: 179, groups:  record_id, 75

Fixed effects:
                               Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    191.2270     5.1990  96.6933  36.782   <2e-16 ***
allocation_groupGrupo B         -0.7165     7.3039  96.6933  -0.098    0.922
visit2                          -5.9068     4.0291 105.4088  -1.466    0.146
visit3                          -0.3796     4.3671 106.4164  -0.087    0.931
allocation_groupGrupo B:visit2  -0.1153     5.9143 106.8530  -0.019    0.984
allocation_groupGrupo B:visit3  -7.7590     6.3553 107.5905  -1.221    0.225
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.332  0.236
visit3      -0.306  0.218  0.451
allctn_GB:2  0.226 -0.317 -0.681 -0.308
allctn_GB:3  0.210 -0.295 -0.310 -0.687  0.436
```

```r
summary(labs_cholesterol_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: labs_cholesterol ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_cholesterol_model_check$influential_ids)

REML criterion at convergence: 1418.7

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.44867 -0.52709  0.01502  0.52817  2.19955

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 728.2    26.98
 Residual              139.8    11.82
Number of obs: 164, groups:  record_id, 70

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                   191.1697     5.1285  80.3020  37.276   <2e-16 ***
allocation_groupGrupo B        -0.6778     7.0540  80.3020  -0.096   0.9237
visit2                         -5.9843     3.1939  93.1276  -1.874   0.0641 .
visit3                         -3.9379     3.5150  93.6547  -1.120   0.2654
allocation_groupGrupo B:visit2 -1.5573     4.5754  93.8263  -0.340   0.7343
allocation_groupGrupo B:visit3 -2.1290     4.9645  94.1891  -0.429   0.6690
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.727
visit2      -0.259  0.188
visit3      -0.235  0.171  0.448
allctn_GB:2  0.180 -0.248 -0.698 -0.312
allctn_GB:3  0.166 -0.229 -0.317 -0.708  0.436
```

```r
labs_cholesterol_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       191.         5.20   36.8     1.19e-58
 2 Sensitivity (Intercept)                       191.         5.13   37.3     1.85e-52
 3 Original    allocation_groupGrupo B           -0.717      7.30   -0.0981  9.22e- 1
 4 Sensitivity allocation_groupGrupo B           -0.678      7.05   -0.0961  9.24e- 1
 5 Original    allocation_groupGrupo B:visit2    -0.115      5.91   -0.0195  9.84e- 1
 6 Sensitivity allocation_groupGrupo B:visit2    -1.56       4.58   -0.340   7.34e- 1
 7 Original    allocation_groupGrupo B:visit3    -7.76       6.36   -1.22    2.25e- 1
 8 Sensitivity allocation_groupGrupo B:visit3    -2.13       4.96   -0.429   6.69e- 1
 9 Original    sd__(Intercept)                   27.3       NA      NA      NA
10 Sensitivity sd__(Intercept)                   27.0       NA      NA      NA
11 Original    sd__Observation                   16.0       NA      NA      NA
12 Sensitivity sd__Observation                   11.8       NA      NA      NA
13 Original    visit2                            -5.91       4.03   -1.47    1.46e- 1
14 Sensitivity visit2                            -5.98       3.19   -1.87    6.41e- 2
15 Original    visit3                            -0.380      4.37   -0.0869  9.31e- 1
16 Sensitivity visit3                            -3.94       3.51   -1.12    2.65e- 1
```

```r
performance::compare_performance(
    labs_cholesterol_model,
```

```r
    labs_cholesterol_model_sens)
```

```
# Comparison of Model Performance Indices

Name                        |           Model |  AIC (weights) | AICc (weights) |  BIC
-----------------------------------------------------------------------------------------
labs_cholesterol_model      | lmerModLmerTest | 1661.8 (<.001) | 1662.7 (<.001) | 1687
labs_cholesterol_model_sens | lmerModLmerTest | 1461.2 (>.999) | 1462.1 (>.999) | 1486
```

```r
performance::check_model(labs_cholesterol_model)
```

```
performance::check_model(labs_cholesterol_model_sens)
```

3.0.5.2 Médias Marginais Estimadas

3.0.5.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_cholesterol_raw_emm <- emmeans::emmeans(
    labs_cholesterol_model,
    ~ allocation_group * visit
```

```r
)

labs_cholesterol_raw_emm <- regrid(labs_cholesterol_raw_emm)

# Table of marginal means
# labs_cholesterol_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_cholesterol_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.717 7.30  95.4   -13.78     15.2   0.098  0.9221

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.832 7.81 107.2   -14.65     16.3   0.107  0.9154

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    8.476 8.15 121.8    -7.66     24.6   1.040  0.3004

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_cholesterol_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     5.91 4.03  95.4    -3.92    15.73   1.465  0.4387
 visit1 - visit3     0.38 4.37  95.4   -10.27    11.03   0.087  1.0000
 visit2 - visit3    -5.53 4.41 107.2   -16.25     5.19  -1.254  0.6378

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     6.02 4.34  95.4    -4.54    16.59   1.389  0.5041
 visit1 - visit3     8.14 4.62  95.4    -3.13    19.41   1.760  0.2448
 visit2 - visit3     2.12 4.82 121.6    -9.58    13.81   0.439  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_cholesterol_raw_emm, comparisons = TRUE)
```

3.0.5.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_cholesterol_emm <- emmeans::emmeans(
    labs_cholesterol_model_sens,
    ~ allocation_group * visit
)

labs_cholesterol_emm <- regrid(labs_cholesterol_emm)

# Table of marginal means
# labs_cholesterol_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_cholesterol_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.678 7.05 79.8    -13.4     14.7   0.096  0.9237

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    2.235 7.40 88.6    -12.5     16.9   0.302  0.7632

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    2.807 7.64 99.7    -12.4     18.0   0.367  0.7142

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_cholesterol_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     5.98 3.20 79.8   -1.832    13.80   1.872  0.1944
 visit1 - visit3     3.94 3.52 79.8   -4.665    12.54   1.119  0.7990
 visit2 - visit3    -2.05 3.54 88.6  -10.679     6.59  -0.579  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     7.54 3.28 79.8   -0.478    15.56   2.300  0.0723
 visit1 - visit3     6.07 3.51 79.8   -2.516    14.65   1.729  0.2632
 visit2 - visit3    -1.47 3.65 97.7  -10.355     7.41  -0.404  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_cholesterol_emm, comparisons = TRUE)
```

3.0.5.3 Resultado

No modelo ajustado para os níveis de colesterol total, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As comparações intragrupo ao longo do tempo também não indicaram alterações significativas em nenhum dos grupos. A análise de sensibilidade, realizada com a exclusão de observações influentes, confirmou esses achados. As estimativas se mantiveram estáveis e as diferenças permaneceram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 5.

Tabela 5: Diferenças estimadas dos níveis de Colesterol Total entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,72	[-13,78 ; 15,21]	0,922
Entre grupos	Visita 2	0,83	[-14,65 ; 16,30]	0,915
Entre grupos	Visita 3	8,48	[-7,66 ; 24,61]	0,300
Grupo Placebo	Visita 1 - Visita 2	5,91	[-3,92 ; 15,73]	0,439
Grupo Placebo	Visita 1 - Visita 3	0,38	[-10,27 ; 11,03]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	-5,53	[-16,25 ; 5,19]	0,638
Grupo Eclipta	Visita 1 - Visita 2	6,02	[-4,54 ; 16,59]	0,504
Grupo Eclipta	Visita 1 - Visita 3	8,14	[-3,13 ; 19,41]	0,245
Grupo Eclipta	Visita 2 - Visita 3	2,12	[-9,58 ; 13,81]	1,000

```
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_cholesterol,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_cholesterol_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_cholesterol,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.6 LDL Colesterol

Variável: `labs_ldl`

```
# Plot 1: Raw data
labs_ldl_hist_1 <- data_model %>%
    #filter(
    #    labs_ldl < 300
    #) %>%
    ggplot(aes(x = labs_ldl)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_ldl_hist_2 <- data_model %>%
    #filter(
    #    labs_ldl < 300
    #) %>%
    ggplot(aes(x = log1p(labs_ldl))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_ldl_hist_1 + labs_ldl_hist_2 # library(patchwork)
```

```
# LMM
labs_ldl_model <- lmer(labs_ldl ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_ldl_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.18 [1.06, 1.52]         1.08      0.85     [0.66, 0.94]
                  visit 3.49 [2.78, 4.49]         1.87      0.29     [0.22, 0.36]
 allocation_group:visit 3.77 [3.00, 4.86]         1.94      0.26     [0.21, 0.33]
```

```r
# Sensitivity analysis
labs_ldl_model_check <- sensitivity_check_lmer(
    model = labs_ldl_model,
    id_var = "record_id",
    top_n = 7)

# LMM Sensitivity
labs_ldl_model_sens <- update(object = labs_ldl_model,
                              subset = !(record_id %in%
        labs_ldl_model_check$influential_ids))
# Influential IDS
labs_ldl_model_check$influential_ids
```

```
[1] "16" "17" "56" "37" "50" "61" "75"
```

3.0.6.1 Resumo dos modelos

```r
# Model comparison
summary(labs_ldl_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: labs_ldl ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: 1601.5
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.9892 -0.3229 -0.0296  0.3610  2.5195

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 605.7    24.61
 Residual              249.7    15.80
Number of obs: 179, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                   115.4919     4.8081  98.3445  24.020   <2e-16 ***
allocation_groupGrupo B        -3.7735     6.7548  98.3445  -0.559    0.578
visit2                         -5.5925     3.9659 103.9503  -1.410    0.161
visit3                         -0.0205     4.2968 105.1671  -0.005    0.996
allocation_groupGrupo B:visit2  1.9191     5.8182 105.6037   0.330    0.742
allocation_groupGrupo B:visit3 -5.9060     6.2502 106.5086  -0.945    0.347
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.354  0.252
visit3      -0.327  0.233  0.450
allctn_GB:2  0.241 -0.339 -0.682 -0.307
allctn_GB:3  0.225 -0.315 -0.310 -0.687  0.434
```

```r
summary(labs_ldl_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: labs_ldl ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_ldl_model_check$influential_ids)

REML criterion at convergence: 1338.9

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.83006 -0.44200 -0.05731  0.40788  2.36163

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 650.2    25.50
 Residual              111.8    10.57
Number of obs: 158, groups:  record_id, 68

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                   115.8687     4.8799  75.3685  23.744   <2e-16 ***
allocation_groupGrupo B        -3.8299     6.7068  75.3685  -0.571   0.5697
visit2                         -5.1922     2.9125  87.5739  -1.783   0.0781 .
visit3                          0.6698     3.2198  88.0305   0.208   0.8357
allocation_groupGrupo B:visit2  1.8681     4.1755  88.1990   0.447   0.6557
allocation_groupGrupo B:visit3 -5.5726     4.5483  88.5080  -1.225   0.2237
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.728
visit2      -0.246  0.179
visit3      -0.222  0.162  0.446
allctn_GB:2  0.171 -0.236 -0.698 -0.311
allctn_GB:3  0.157 -0.216 -0.316 -0.708  0.434
```

```r
labs_ldl_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                     115.          4.81  24.0      6.20e-43
 2 Sensitivity (Intercept)                     116.          4.88  23.7      1.00e-36
 3 Original    allocation_groupGrupo B          -3.77        6.75  -0.559    5.78e- 1
 4 Sensitivity allocation_groupGrupo B          -3.83        6.71  -0.571    5.70e- 1
 5 Original    allocation_groupGrupo B:visit2    1.92        5.82   0.330    7.42e- 1
 6 Sensitivity allocation_groupGrupo B:visit2    1.87        4.18   0.447    6.56e- 1
 7 Original    allocation_groupGrupo B:visit3   -5.91        6.25  -0.945    3.47e- 1
 8 Sensitivity allocation_groupGrupo B:visit3   -5.57        4.55  -1.23     2.24e- 1
 9 Original    sd__(Intercept)                  24.6        NA     NA       NA
10 Sensitivity sd__(Intercept)                  25.5        NA     NA       NA
11 Original    sd__Observation                  15.8        NA     NA       NA
12 Sensitivity sd__Observation                  10.6        NA     NA       NA
13 Original    visit2                           -5.59        3.97  -1.41     1.61e- 1
14 Sensitivity visit2                           -5.19        2.91  -1.78     7.81e- 2
15 Original    visit3                           -0.0205      4.30  -0.00477  9.96e- 1
16 Sensitivity visit3                            0.670       3.22   0.208    8.36e- 1
```

```r
performance::compare_performance(
    labs_ldl_model,
```

```
    labs_ldl_model_sens)
```

```
# Comparison of Model Performance Indices

Name                |           Model |  AIC (weights) | AICc (weights) |  BIC (weight
-----------------------------------------------------------------------------------------
labs_ldl_model      | lmerModLmerTest | 1645.5 (<.001) | 1646.4 (<.001) | 1671.0 (<.00
labs_ldl_model_sens | lmerModLmerTest | 1380.5 (>.999) | 1381.5 (>.999) | 1405.0 (>.99
```

```
performance::check_model(labs_ldl_model)
```

```
performance::check_model(labs_ldl_model_sens)
```

3.0.6.2 Médias Marginais Estimadas

3.0.6.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_ldl_raw_emm <- emmeans::emmeans(
    labs_ldl_model,
    ~ allocation_group * visit
```

```r
)

labs_ldl_raw_emm <- regrid(labs_ldl_raw_emm)

# Table of marginal means
# labs_ldl_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ldl_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     3.77 6.75  99.1    -9.63     17.2   0.559  0.5777

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     1.85 7.27 111.9   -12.56     16.3   0.255  0.7993

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     9.68 7.63 127.7    -5.41     24.8   1.269  0.2067

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ldl_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   5.5925 3.97  99.1    -4.07    15.26   1.409  0.4859
 visit1 - visit3   0.0205 4.30  99.1   -10.46    10.50   0.005  1.0000
 visit2 - visit3  -5.5720 4.34 111.9   -16.13     4.98  -1.283  0.6064

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   3.6734 4.26  99.1    -6.71    14.06   0.862  1.0000
 visit1 - visit3   5.9265 4.55  99.1    -5.15    17.00   1.304  0.5862
 visit2 - visit3   2.2531 4.74 127.2    -9.26    13.76   0.475  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_ldl_raw_emm, comparisons = TRUE)
```

3.0.6.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_ldl_emm <- emmeans::emmeans(
    labs_ldl_model_sens,
    ~ allocation_group * visit
)

labs_ldl_emm <- regrid(labs_ldl_emm)

# Table of marginal means
# labs_ldl_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ldl_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     3.83 6.71 76.2    -9.53     17.2   0.571  0.5697

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     1.96 7.02 84.3   -11.99     15.9   0.280  0.7805

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     9.40 7.25 94.8    -4.98     23.8   1.298  0.1976

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ldl_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     5.19 2.91 76.2    -1.94    12.33   1.782  0.2364
 visit1 - visit3    -0.67 3.22 76.2    -8.56     7.22  -0.208  1.0000
 visit2 - visit3    -5.86 3.24 84.3   -13.77     2.05  -1.810  0.2217

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     3.32 2.99 76.2    -4.01    10.66   1.110  0.8116
 visit1 - visit3     4.90 3.22 76.2    -2.97    12.78   1.525  0.3945
 visit2 - visit3     1.58 3.34 92.9    -6.57     9.73   0.472  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_ldl_emm)
```

3.0.6.3 Resultado

No modelo ajustado para os níveis de LDL-colesterol, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações dentro de cada grupo ao longo do tempo não indicaram alterações significativas. A análise de sensibilidade, com exclusão das observações influentes, não modificou substancialmente os achados: as estimativas permaneceram estáveis e todas as comparações continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 6.

Tabela 6: Diferenças estimadas dos níveis de LDL-colesterol entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	3,77	[-9,63 ; 17,17]	0,578
Entre grupos	Visita 2	1,85	[-12,56 ; 16,26]	0,799
Entre grupos	Visita 3	9,68	[-5,41 ; 24,78]	0,207
Grupo Placebo	Visita 1 - Visita 2	5,59	[-4,07 ; 15,26]	0,486
Grupo Placebo	Visita 1 - Visita 3	0,02	[-10,46 ; 10,50]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	-5,57	[-16,13 ; 4,98]	0,606
Grupo Eclipta	Visita 1 - Visita 2	3,67	[-6,71 ; 14,06]	1,000
Grupo Eclipta	Visita 1 - Visita 3	5,93	[-5,15 ; 17,00]	0,586
Grupo Eclipta	Visita 2 - Visita 3	2,25	[-9,26 ; 13,76]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_ldl,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_ldl_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_ldl,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.7 HDL Colesterol

Variável: `labs_hdl`

```
# Plot 1: Raw data
labs_hdl_hist_1 <- data_model %>%
    #filter(
    #    labs_hdl < 300
    #) %>%
    ggplot(aes(x = labs_hdl)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_hdl_hist_2 <- data_model %>%
    #filter(
    #    labs_hdl < 300
    #) %>%
    ggplot(aes(x = log1p(labs_hdl))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_hdl_hist_1 + labs_hdl_hist_2 # library(patchwork)
```

```
# LMM
labs_hdl_model <- lmer(log1p(labs_hdl) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_hdl_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.16 [1.05, 1.51]         1.08      0.86     [0.66, 0.95]
                  visit 3.49 [2.78, 4.48]         1.87      0.29     [0.22, 0.36]
 allocation_group:visit 3.74 [2.97, 4.81]         1.93      0.27     [0.21, 0.34]
```

```r
# Sensitivity analysis
labs_hdl_model_check <- sensitivity_check_lmer(
    model = labs_hdl_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_hdl_model_sens <- update(object = labs_hdl_model,
                              subset = !(record_id %in%
        labs_hdl_model_check$influential_ids))
# Influential IDS
labs_hdl_model_check$influential_ids
```

```
[1] "16" "75" "38" "42" "26"
```

3.0.7.1 Resumo dos modelos

```r
# Model comparison
summary(labs_hdl_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_hdl) ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: -79.8
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.4161 -0.4907 -0.0289  0.4389  3.0395

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.03949  0.1987
 Residual              0.01437  0.1199
Number of obs: 179, groups:  record_id, 75

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      3.94481    0.03815  94.81644 103.399   <2e-16 ***
allocation_groupGrupo B          0.06500    0.05360  94.81644   1.213    0.228
visit2                          -0.01725    0.03011 102.74671  -0.573    0.568
visit3                          -0.01928    0.03264 103.82312  -0.591    0.556
allocation_groupGrupo B:visit2  -0.02214    0.04420 104.26672  -0.501    0.618
allocation_groupGrupo B:visit3  -0.03185    0.04749 105.05887  -0.671    0.504
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.338  0.241
visit3      -0.312  0.222  0.451
allctn_GB:2  0.230 -0.324 -0.681 -0.307
allctn_GB:3  0.214 -0.301 -0.310 -0.687  0.435
```

```r
summary(labs_hdl_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_hdl) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_hdl_model_check$influential_ids)

REML criterion at convergence: -109.5

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.93721 -0.52772 -0.00876  0.50466  2.04629

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.03870  0.1967
 Residual              0.01007  0.1004
Number of obs: 166, groups:  record_id, 70

Fixed effects:
                               Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                     3.92823    0.03733 82.44138 105.230   <2e-16 ***
allocation_groupGrupo B         0.06708    0.05279 82.44138   1.271    0.207
visit2                         -0.01029    0.02612 93.87428  -0.394    0.695
visit3                         -0.01338    0.02805 94.47459  -0.477    0.635
allocation_groupGrupo B:visit2 -0.02943    0.03859 95.06373  -0.763    0.448
allocation_groupGrupo B:visit3 -0.03861    0.04187 95.58326  -0.922    0.359
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.707
visit2      -0.295  0.209
visit3      -0.275  0.194  0.457
allctn_GB:2  0.200 -0.283 -0.677 -0.310
allctn_GB:3  0.184 -0.260 -0.306 -0.670  0.440
```

```r
labs_hdl_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                        3.94      0.0382   103.     2.78e-99
 2 Sensitivity (Intercept)                        3.93      0.0373   105.     1.23e-89
 3 Original    allocation_groupGrupo B            0.0650    0.0536     1.21   2.28e- 1
 4 Sensitivity allocation_groupGrupo B            0.0671    0.0528     1.27   2.07e- 1
 5 Original    allocation_groupGrupo B:visit2    -0.0221    0.0442    -0.501  6.18e- 1
 6 Sensitivity allocation_groupGrupo B:visit2    -0.0294    0.0386    -0.763  4.48e- 1
 7 Original    allocation_groupGrupo B:visit3    -0.0318    0.0475    -0.671  5.04e- 1
 8 Sensitivity allocation_groupGrupo B:visit3    -0.0386    0.0419    -0.922  3.59e- 1
 9 Original    sd__(Intercept)                    0.199    NA         NA     NA
10 Sensitivity sd__(Intercept)                    0.197    NA         NA     NA
11 Original    sd__Observation                    0.120    NA         NA     NA
12 Sensitivity sd__Observation                    0.100    NA         NA     NA
13 Original    visit2                            -0.0172    0.0301    -0.573  5.68e- 1
14 Sensitivity visit2                            -0.0103    0.0261    -0.394  6.95e- 1
15 Original    visit3                            -0.0193    0.0326    -0.591  5.56e- 1
16 Sensitivity visit3                            -0.0134    0.0281    -0.477  6.35e- 1
```

```r
performance::compare_performance(
    labs_hdl_model,
```

```
    labs_hdl_model_sens)
```

```
# Comparison of Model Performance Indices

Name                 |           Model |  AIC (weights) | AICc (weights) |  BIC (weight
-----------------------------------------------------------------------------------------
labs_hdl_model       | lmerModLmerTest | 1319.8 (<.001) | 1320.7 (<.001) | 1345.3 (<.00
labs_hdl_model_sens | lmerModLmerTest | 1181.6 (>.999) | 1182.5 (>.999) | 1206.5 (>.99
```

```
performance::check_model(labs_hdl_model)
```

```
performance::check_model(labs_hdl_model_sens)
```

3.0.7.2 Médias Marginais Estimadas

3.0.7.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_hdl_raw_emm <- emmeans::emmeans(
    labs_hdl_model,
    ~ allocation_group * visit
```

```r
)

labs_hdl_raw_emm <- regrid(labs_hdl_raw_emm)

# Table of marginal means
# labs_hdl_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hdl_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -3.47 2.86  96.4    -9.15     2.21  -1.212  0.2284

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -2.22 2.98 108.6    -8.14     3.69  -0.746  0.4576

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -1.71 3.09 123.5    -7.83     4.42  -0.552  0.5819

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hdl_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.883 1.54  96.4    -2.87     4.64   0.573  1.0000
 visit1 - visit3    0.986 1.67  96.4    -3.08     5.05   0.591  1.0000
 visit2 - visit3    0.103 1.67 108.6    -3.96     4.17   0.062  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    2.129 1.74  96.4    -2.12     6.38   1.221  0.6751
 visit1 - visit3    2.748 1.84  96.4    -1.74     7.24   1.491  0.4175
 visit2 - visit3    0.619 1.90 123.2    -3.99     5.22   0.326  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_hdl_raw_emm, comparisons = TRUE)
```

3.0.7.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_hdl_emm <- emmeans::emmeans(
    labs_hdl_model_sens,
    ~ allocation_group * visit
)

labs_hdl_emm <- regrid(labs_hdl_emm)

# Table of marginal means
# labs_hdl_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hdl_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -3.53 2.78  83.9    -9.05     2.00  -1.269  0.2078

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -1.93 2.87  93.9    -7.63     3.77  -0.672  0.5029

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -1.45 2.97 104.0    -7.33     4.43  -0.488  0.6264

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hdl_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.520 1.32  83.9    -2.71     3.75   0.394  1.0000
 visit1 - visit3    0.675 1.41  83.9    -2.78     4.13   0.477  1.0000
 visit2 - visit3    0.155 1.42  93.9    -3.31     3.62   0.109  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    2.116 1.51  83.9    -1.57     5.80   1.403  0.4931
 visit1 - visit3    2.753 1.63  83.9    -1.24     6.75   1.684  0.2874
 visit2 - visit3    0.637 1.66 105.0    -3.40     4.67   0.384  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_hdl_emm, comparisons = TRUE)
```

3.0.7.3 Resultado

No modelo ajustado para os níveis de HDL-colesterol, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Também não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, conduzida com a exclusão das observações influentes, não alterou substancialmente os resultados. As estimativas permaneceram consistentes e as comparações entre grupos e ao longo do tempo continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 7.

Tabela 7: Diferenças estimadas dos níveis de HDL-colesterol entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-3,47	[-9,15 ; 2,21]	0,228
Entre grupos	Visita 2	-2,22	[-8,14 ; 3,69]	0,458
Entre grupos	Visita 3	-1,71	[-7,83 ; 4,42]	0,582
Grupo Placebo	Visita 1 - Visita 2	0,88	[-2,87 ; 4,64]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 1 - Visita 3	0,99	[-3,08 ; 5,05]	1,000
Grupo Placebo	Visita 2 - Visita 3	0,10	[-3,96 ; 4,17]	1,000
Grupo Eclipta	Visita 1 - Visita 2	2,13	[-2,12 ; 6,38]	0,675
Grupo Eclipta	Visita 1 - Visita 3	2,75	[-1,74 ; 7,24]	0,418
Grupo Eclipta	Visita 2 - Visita 3	0,62	[-3,99 ; 5,22]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_hdl,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_hdl_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_hdl,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.8 Triglicerídeos

Variável: `labs_triglycerides`

```
# Plot 1: Raw data
labs_triglycerides_hist_1 <- data_model %>%
    #filter(
    #    labs_triglycerides < 300
    #) %>%
    ggplot(aes(x = labs_triglycerides)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_triglycerides_hist_2 <- data_model %>%
    #filter(
    #    labs_triglycerides < 300
    #) %>%
    ggplot(aes(x = log1p(labs_triglycerides))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_triglycerides_hist_1 + labs_triglycerides_hist_2 # library(patchwork)
```

```
# LMM
labs_triglycerides_model <- lmer(log1p(labs_triglycerides) ~ allocation_group * visit
(1 | record_id), data = data_model)
check_collinearity(labs_triglycerides_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.20 [1.08, 1.53]         1.10      0.83     [0.65, 0.93]
                  visit 3.50 [2.79, 4.49]         1.87      0.29     [0.22, 0.36]
 allocation_group:visit 3.82 [3.03, 4.92]         1.95      0.26     [0.20, 0.33]
```

```r
# Sensitivity analysis
labs_triglycerides_model_check <- sensitivity_check_lmer(
    model = labs_triglycerides_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_triglycerides_model_sens <- update(object = labs_triglycerides_model,
                                        subset = !(record_id %in%
        labs_triglycerides_model_check$influential_ids))
# Influential IDS
labs_triglycerides_model_check$influential_ids
```

```
[1] "16" "17" "1"  "2"  "20"
```

3.0.8.1 Resumo dos modelos

```r
# Model comparison
summary(labs_triglycerides_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_triglycerides) ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: 156.5
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.48575 -0.55624 -0.06875  0.50582  2.77617

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.12894  0.3591
 Residual              0.06212  0.2492
Number of obs: 179, groups:  record_id, 75

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      4.76585    0.07186 100.80805  66.322   <2e-16 ***
allocation_groupGrupo B         -0.02118    0.10095 100.80805  -0.210    0.834
visit2                           0.05652    0.06246 103.24903   0.905    0.368
visit3                           0.00822    0.06765 104.67836   0.122    0.904
allocation_groupGrupo B:visit2  -0.05643    0.09159 105.09618  -0.616    0.539
allocation_groupGrupo B:visit3   0.04983    0.09836 106.17407   0.507    0.614
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.374  0.266
visit3      -0.345  0.246  0.449
allctn_GB:2  0.255 -0.358 -0.682 -0.306
allctn_GB:3  0.238 -0.334 -0.309 -0.688  0.433
```

```r
summary(labs_triglycerides_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_triglycerides) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_triglycerides_model_check$influential_ids)

REML criterion at convergence: 110.8

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.56781 -0.62311 -0.09172  0.57450  2.18137

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.12547  0.3542
 Residual              0.04498  0.2121
Number of obs: 164, groups:  record_id, 70

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    4.74183    0.07187 86.86729  65.980   <2e-16 ***
allocation_groupGrupo B       -0.02502    0.09885 86.86729  -0.253   0.8008
visit2                         0.04807    0.05702 92.31050   0.843   0.4014
visit3                        -0.09539    0.06269 93.35327  -1.522   0.1314
allocation_groupGrupo B:visit2 -0.01744    0.08158 93.47289  -0.214   0.8312
allocation_groupGrupo B:visit3  0.17857    0.08845 94.22579   2.019   0.0463 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.727
visit2      -0.333  0.242
visit3      -0.303  0.220  0.444
allctn_GB:2  0.232 -0.320 -0.699 -0.310
allctn_GB:3  0.214 -0.295 -0.314 -0.709  0.431
```

```r
labs_triglycerides_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       4.77      0.0719    66.3    5.68e-85
 2 Sensitivity (Intercept)                       4.74      0.0719    66.0    5.34e-76
 3 Original    allocation_groupGrupo B          -0.0212    0.101     -0.210  8.34e- 1
 4 Sensitivity allocation_groupGrupo B          -0.0250    0.0989    -0.253  8.01e- 1
 5 Original    allocation_groupGrupo B:visit2 -0.0564    0.0916    -0.616  5.39e- 1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.0174    0.0816    -0.214  8.31e- 1
 7 Original    allocation_groupGrupo B:visit3  0.0498    0.0984     0.507  6.14e- 1
 8 Sensitivity allocation_groupGrupo B:visit3  0.179     0.0884     2.02   4.63e- 2
 9 Original    sd__(Intercept)                  0.359    NA         NA     NA
10 Sensitivity sd__(Intercept)                  0.354    NA         NA     NA
11 Original    sd__Observation                  0.249    NA         NA     NA
12 Sensitivity sd__Observation                  0.212    NA         NA     NA
13 Original    visit2                           0.0565    0.0625     0.905  3.68e- 1
14 Sensitivity visit2                           0.0481    0.0570     0.843  4.01e- 1
15 Original    visit3                           0.00822   0.0677     0.122  9.04e- 1
16 Sensitivity visit3                          -0.0954    0.0627    -1.52   1.31e- 1
```

```r
performance::compare_performance(
    labs_triglycerides_model,
```

```
    labs_triglycerides_model_sens)
```

```
# Comparison of Model Performance Indices

Name                           |           Model |  AIC (weights) | AICc (weights) |  B
-------------------------------------------------------------------------------------------
labs_triglycerides_model       | lmerModLmerTest | 1873.1 (<.001) | 1873.9 (<.001) | 18
labs_triglycerides_model_sens | lmerModLmerTest | 1671.7 (>.999) | 1672.6 (>.999) | 16
```

```
performance::check_model(labs_triglycerides_model)
```

```
performance::check_model(labs_triglycerides_model_sens)
```

3.0.8.2 Médias Marginais Estimadas

3.0.8.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_triglycerides_raw_emm <- emmeans::emmeans(
    labs_triglycerides_model,
    ~ allocation_group * visit
```

```r
)

labs_triglycerides_raw_emm <- regrid(labs_triglycerides_raw_emm)

# Table of marginal means
# labs_triglycerides_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_triglycerides_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.46 11.7 103    -20.8     25.7   0.210  0.8343

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     9.28 13.1 116    -16.6     35.2   0.710  0.4793

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -3.44 13.8 133    -30.8     23.9  -0.249  0.8041

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_triglycerides_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -6.82768 7.60 103    -25.3     11.7  -0.899  1.0000
 visit1 - visit3 -0.96930 8.00 103    -20.4     18.5  -0.121  1.0000
 visit2 - visit3  5.85838 8.29 116    -14.3     26.0   0.707  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.00919 7.71 103    -18.8     18.8  -0.001  1.0000
 visit1 - visit3 -6.87130 8.57 103    -27.7     14.0  -0.802  1.0000
 visit2 - visit3 -6.86211 8.90 132    -28.4     14.7  -0.771  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_triglycerides_raw_emm, comparisons = TRUE)
```

3.0.8.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_triglycerides_emm <- emmeans::emmeans(
    labs_triglycerides_model_sens,
    ~ allocation_group * visit
)

labs_triglycerides_emm <- regrid(labs_triglycerides_emm)

# Table of marginal means
# labs_triglycerides_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_triglycerides_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.83 11.2  88.9    -19.4    25.09   0.253  0.8010

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     5.00 12.5 101.6    -19.8    29.83   0.399  0.6904

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -17.30 12.6 117.7    -42.3     7.68  -1.371  0.1729

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_triglycerides_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -5.65 6.74  88.9   -22.10    10.81  -0.837  1.0000
 visit1 - visit3    10.43 6.81  88.9    -6.17    27.04   1.533  0.3866
 visit2 - visit3    16.08 7.12 101.6    -1.25    33.40   2.259  0.0780

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -3.48 6.67  88.9   -19.75    12.79  -0.522  1.0000
 visit1 - visit3    -9.70 7.43  88.9   -27.83     8.44  -1.305  0.5861
 visit2 - visit3    -6.22 7.76 114.3   -25.07    12.63  -0.802  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_triglycerides_emm, comparisons = TRUE)
```

3.0.8.3 Resultado

No modelo ajustado para os níveis de triglicerídeos, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As estimativas entre grupos foram próximas de zero e os intervalos de confiança incluíram o valor nulo, com valores de p superiores a 0,47 em todas as comparações. Da mesma forma, as comparações intragrupo ao longo do tempo não revelaram mudanças significativas em nenhum dos grupos, embora tenha havido uma tendência não significativa de aumento entre a visita 2 e a visita 3 no grupo A (p = 0,078).

A análise de sensibilidade, realizada após a exclusão de observações influentes, manteve os resultados essencialmente inalterados. As estimativas permaneceram próximas das observadas no modelo completo e não houve modificações relevantes nas interpretações. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 8.

Tabela 8: Diferenças estimadas dos níveis de triglicerídeos entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,46	[-20,8 ; 25,7]	0,834
Entre grupos	Visita 2	9,28	[-16,6 ; 35,2]	0,479
Entre grupos	Visita 3	-3,44	[-30,8 ; 23,9]	0,804
Grupo Placebo	Visita 1 - Visita 2	-6,83	[-25,3 ; 11,7]	1,000
Grupo Placebo	Visita 1 - Visita 3	-0,97	[-20,4 ; 18,5]	1,000
Grupo Placebo	Visita 2 - Visita 3	5,86	[-14,3 ; 26,0]	1,000
Grupo Eclipta	Visita 1 - Visita 2	-0,01	[-18,8 ; 18,8]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-6,87	[-27,7 ; 14,0]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-6,86	[-28,4 ; 14,7]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_triglycerides,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
```

```
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_triglycerides_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_triglycerides,
            group = record_id,
        )
    ) +
```

```
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.9 Glicemia de jejum

Variável: `labs_glucose`

```
# Plot 1: Raw data
labs_glucose_hist_1 <- data_model %>%
    #filter(
```

```
    #    labs_glucose < 140
    #) %>%
    ggplot(aes(x = labs_glucose)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_glucose_hist_2 <- data_model %>%
    #filter(
    #    labs_glucose < 140
    #) %>%
    ggplot(aes(x = log1p(labs_glucose))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_glucose_hist_1 + labs_glucose_hist_2 # library(patchwork)
```

```
# LMM
labs_glucose_model <- lmer(log1p(labs_glucose) ~ allocation_group * visit +
```

```r
(1 | record_id), data = data_model)
check_collinearity(labs_glucose_model)
```

```
# Check for Multicollinearity

Low Correlation

                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.13 [1.03, 1.51]         1.06      0.89     [0.66, 0.97]
                  visit 3.47 [2.76, 4.47]         1.86      0.29     [0.22, 0.36]
 allocation_group:visit 3.69 [2.93, 4.75]         1.92      0.27     [0.21, 0.34]
```

```r
# Sensitivity analysis
labs_glucose_model_check <- sensitivity_check_lmer(
    model = labs_glucose_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_glucose_model_sens <- update(object = labs_glucose_model,
                                  subset = !(record_id %in%
        labs_glucose_model_check$influential_ids))
# Influential IDS
labs_glucose_model_check$influential_ids
```

```
[1] "2"  "16" "17" "56" "13"
```

3.0.9.1 Resumo dos modelos

```r
# Model comparison
summary(labs_glucose_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_glucose) ~ allocation_group * visit + (1 | record_id)
```

```
   Data: data_model

REML criterion at convergence: -153

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.0712 -0.5250 -0.1192  0.4737  3.4423

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.030440 0.17447
 Residual              0.008319 0.09121
Number of obs: 176, groups:  record_id, 74

Fixed effects:
                                Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     4.445812   0.032366  92.773372 137.362   <2e-16 ***
allocation_groupGrupo B         0.002937   0.045895  93.526588   0.064    0.949
visit2                          0.009144   0.023244 104.438133   0.393    0.695
visit3                          0.035792   0.024905 105.095812   1.437    0.154
allocation_groupGrupo B:visit2 -0.019077   0.034014 105.360265  -0.561    0.576
allocation_groupGrupo B:visit3 -0.007509   0.036617 106.709642  -0.205    0.838
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.705
visit2      -0.299  0.211
visit3      -0.279  0.197  0.445
```

```
allctn_GB:2  0.204 -0.293 -0.683 -0.304
allctn_GB:3  0.190 -0.278 -0.303 -0.680  0.439
```

```r
summary(labs_glucose_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_glucose) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_glucose_model_check$influential_ids)

REML criterion at convergence: -224.4

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.9874 -0.5692 -0.1200  0.5703  1.9303

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.011973 0.10942
 Residual              0.005831 0.07636
Number of obs: 161, groups:  record_id, 69

Fixed effects:
                                 Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     4.4198168  0.0228838 96.3391006 193.142   <2e-16 ***
allocation_groupGrupo B        -0.0005277  0.0322590 97.2962023  -0.016    0.987
visit2                         -0.0018470  0.0203795 96.0503867  -0.091    0.928
visit3                          0.0190546  0.0220059 97.1965932   0.866    0.389
allocation_groupGrupo B:visit2 -0.0022058  0.0295835 97.2662772  -0.075    0.941
allocation_groupGrupo B:visit3  0.0099619  0.0320363 99.3466017   0.311    0.756
---
```

```
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.709
visit2      -0.368  0.261
visit3      -0.341  0.242  0.435
allctn_GB:2  0.253 -0.360 -0.689 -0.300
allctn_GB:3  0.234 -0.339 -0.299 -0.687  0.428
```

```r
labs_glucose_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic    p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>      <dbl>
 1 Original    (Intercept)                      4.45        0.0324  137.      5.55e-109
 2 Sensitivity (Intercept)                      4.42        0.0229  193.      1.57e-126
 3 Original    allocation_groupGrupo B          0.00294     0.0459    0.0640  9.49e-  1
 4 Sensitivity allocation_groupGrupo B         -0.000528    0.0323   -0.0164  9.87e-  1
 5 Original    allocation_groupGrupo B:visit2 -0.0191      0.0340   -0.561   5.76e-  1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.00221     0.0296   -0.0746  9.41e-  1
 7 Original    allocation_groupGrupo B:visit3 -0.00751     0.0366   -0.205   8.38e-  1
 8 Sensitivity allocation_groupGrupo B:visit3  0.00996     0.0320    0.311   7.56e-  1
 9 Original    sd__(Intercept)                  0.174      NA        NA      NA
10 Sensitivity sd__(Intercept)                  0.109      NA        NA      NA
11 Original    sd__Observation                  0.0912     NA        NA      NA
12 Sensitivity sd__Observation                  0.0764     NA        NA      NA
13 Original    visit2                           0.00914     0.0232    0.393   6.95e-  1
14 Sensitivity visit2                          -0.00185     0.0204   -0.0906  9.28e-  1
15 Original    visit3                           0.0358      0.0249    1.44    1.54e-  1
16 Sensitivity visit3                           0.0191      0.0220    0.866   3.89e-  1
```

```r
performance::compare_performance(
    labs_glucose_model,
    labs_glucose_model_sens)
```

```
# Comparison of Model Performance Indices

Name                     |           Model |  AIC (weights) | AICc (weights) |  BIC (we
-----------------------------------------------------------------------------------------
labs_glucose_model       | lmerModLmerTest | 1404.0 (<.001) | 1404.9 (<.001) | 1429.4 (
labs_glucose_model_sens  | lmerModLmerTest | 1183.8 (>.999) | 1184.7 (>.999) | 1208.4 (
```

```r
performance::check_model(labs_glucose_model)
```

```
performance::check_model(labs_glucose_model_sens)
```

3.0.9.2 Médias Marginais Estimadas

3.0.9.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_glucose_raw_emm <- emmeans::emmeans(
    labs_glucose_model,
    ~ allocation_group * visit
```

```r
)

labs_glucose_raw_emm <- regrid(labs_glucose_raw_emm)

# Table of marginal means
# labs_glucose_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_glucose_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.251 3.92  89.7    -8.04     7.54  -0.064  0.9491

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.378 4.14 101.8    -6.83     9.59   0.333  0.7399

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.403 4.42 112.6    -8.36     9.17   0.091  0.9276

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_glucose_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   -0.783 1.99  89.7    -5.65     4.08  -0.393  1.0000
 visit1 - visit3   -3.107 2.18  89.7    -8.42     2.20  -1.427  0.4709
 visit2 - visit3   -2.324 2.22 101.8    -7.73     3.08  -1.046  0.8937

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.845 2.11  91.2    -4.31     6.00   0.400  1.0000
 visit1 - visit3   -2.453 2.34  91.2    -8.17     3.26  -1.047  0.8942
 visit2 - visit3   -3.299 2.39 111.0    -9.10     2.51  -1.381  0.5102

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_glucose_raw_emm, comparisons = TRUE)
```

3.0.9.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_glucose_emm <- emmeans::emmeans(
    labs_glucose_model_sens,
    ~ allocation_group * visit
)

labs_glucose_emm <- regrid(labs_glucose_emm)

# Table of marginal means
# labs_glucose_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_glucose_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.0438 2.68  93.6    -5.28     5.36   0.016  0.9870

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.2264 2.91 109.6    -5.53     5.98   0.078  0.9380

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.8027 3.15 123.8    -7.04     5.43  -0.255  0.7993

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_glucose_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.153 1.69  93.6    -3.97     4.28   0.091  1.0000
 visit1 - visit3   -1.598 1.85  93.6    -6.12     2.92  -0.862  1.0000
 visit2 - visit3   -1.752 1.90 109.6    -6.36     2.86  -0.924  1.0000

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.336 1.78  95.5    -4.00     4.67   0.189  1.0000
 visit1 - visit3   -2.445 1.98  95.5    -7.26     2.37  -1.237  0.6578
 visit2 - visit3   -2.781 2.03 120.0    -7.72     2.16  -1.367  0.5226

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_glucose_emm, comparisons = TRUE)
```

3.0.9.3 Resultado

No modelo ajustado para os níveis de glicose, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, conduzida após a exclusão de observações influentes, não alterou substancialmente os resultados. As estimativas permaneceram estáveis e as diferenças entre os grupos e ao longo do tempo continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 9.

Tabela 9: Diferenças estimadas dos níveis de glicose entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,25	[-8,04 ; 7,54]	0,949
Entre grupos	Visita 2	1,38	[-6,83 ; 9,59]	0,740
Entre grupos	Visita 3	0,40	[-8,36 ; 9,17]	0,928
Grupo Placebo	Visita 1 - Visita 2	-0,78	[-5,65 ; 4,08]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 1 - Visita 3	-3,11	[-8,42 ; 2,20]	0,471
Grupo Placebo	Visita 2 - Visita 3	-2,32	[-7,73 ; 3,08]	0,894
Grupo Eclipta	Visita 1 - Visita 2	0,85	[-4,31 ; 6,00]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-2,45	[-8,17 ; 3,26]	0,894
Grupo Eclipta	Visita 2 - Visita 3	-3,30	[-9,10 ; 2,51]	0,510

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_glucose,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_glucose_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_glucose,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.10 Hemoglobina Glicosilada

Variável: `labs_hba1c`

```
# Plot 1: Raw data
labs_hba1c_hist_1 <- data_model %>%
    #filter(
    #    labs_hba1c < 300
    #) %>%
    ggplot(aes(x = labs_hba1c)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_hba1c_hist_2 <- data_model %>%
    #filter(
    #    labs_hba1c < 300
    #) %>%
    ggplot(aes(x = log1p(labs_hba1c))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_hba1c_hist_1 + labs_hba1c_hist_2 # library(patchwork)
```

```
# LMM
labs_hba1c_model <- lmer(log1p(labs_hba1c) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_hba1c_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation

                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.06 [1.00, 1.93]         1.03      0.95     [0.52, 1.00]
                  visit 3.65 [2.89, 4.70]         1.91      0.27     [0.21, 0.35]
 allocation_group:visit 3.74 [2.96, 4.82]         1.93      0.27     [0.21, 0.34]
```

```r
# Sensitivity analysis
labs_hba1c_model_check <- sensitivity_check_lmer(
    model = labs_hba1c_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_hba1c_model_sens <- update(object = labs_hba1c_model,
                                subset = !(record_id %in%
        labs_hba1c_model_check$influential_ids))
# Influential IDS
labs_hba1c_model_check$influential_ids
```

```
[1] "16" "17" "34" "56" "52"
```

3.0.10.1 Resumo dos modelos

```r
# Model comparison
summary(labs_hba1c_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_hba1c) ~ allocation_group * visit + (1 | record_id)
   Data: data_model

REML criterion at convergence: -411.1
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.3899 -0.3924 -0.0647  0.3801  3.3624

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.011000 0.10488
 Residual              0.001301 0.03607
Number of obs: 176, groups:  record_id, 75

Fixed effects:
                                 Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     1.869e+00  1.823e-02  8.210e+01 102.481   <2e-16 ***
allocation_groupGrupo B        -1.949e-02  2.562e-02  8.210e+01  -0.761    0.449
visit2                          4.593e-04  9.355e-03  9.978e+01   0.049    0.961
visit3                          1.390e-02  1.007e-02  1.001e+02   1.381    0.170
allocation_groupGrupo B:visit2 -4.818e-03  1.358e-02  1.003e+02  -0.355    0.724
allocation_groupGrupo B:visit3 -2.942e-03  1.455e-02  1.005e+02  -0.202    0.840
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.206  0.147
visit3      -0.192  0.136  0.432
allctn_GB:2  0.142 -0.200 -0.689 -0.297
allctn_GB:3  0.133 -0.186 -0.299 -0.692  0.431
```

```r
summary(labs_hba1c_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_hba1c) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_hba1c_model_check$influential_ids)

REML criterion at convergence: -468.7

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.75531 -0.51316 -0.01487  0.45407  2.35285

Random effects:
 Groups    Name        Variance  Std.Dev.
 record_id (Intercept) 0.0063862 0.07991
 Residual              0.0006516 0.02553
Number of obs: 161, groups:  record_id, 70

Fixed effects:
                                 Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     1.860e+00  1.398e-02  7.444e+01 133.059   <2e-16 ***
allocation_groupGrupo B        -3.287e-02  2.006e-02  7.444e+01  -1.639    0.106
visit2                         -4.313e-03  6.739e-03  8.855e+01  -0.640    0.524
visit3                          8.905e-03  7.274e-03  8.877e+01   1.224    0.224
allocation_groupGrupo B:visit2 -3.267e-05  1.013e-02  8.909e+01  -0.003    0.997
allocation_groupGrupo B:visit3  3.675e-03  1.095e-02  8.925e+01   0.336    0.738
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.697
visit2      -0.192  0.134
visit3      -0.178  0.124  0.430
allctn_GB:2  0.128 -0.183 -0.665 -0.286
allctn_GB:3  0.118 -0.170 -0.285 -0.664  0.423
```

```r
labs_hba1c_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                              estimate std.error statistic   p.value
   <chr>       <chr>                                <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                        1.87        0.0182  102.       2.07e-88
 2 Sensitivity (Intercept)                        1.86        0.0140  133.       2.86e-90
 3 Original    allocation_groupGrupo B           -0.0195      0.0256   -0.761    4.49e- 1
 4 Sensitivity allocation_groupGrupo B           -0.0329      0.0201   -1.64     1.06e- 1
 5 Original    allocation_groupGrupo B:visit2 -0.00482      0.0136   -0.355    7.24e- 1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.0000327    0.0101   -0.00323  9.97e- 1
 7 Original    allocation_groupGrupo B:visit3 -0.00294      0.0146   -0.202    8.40e- 1
 8 Sensitivity allocation_groupGrupo B:visit3  0.00368      0.0110    0.336    7.38e- 1
 9 Original    sd__(Intercept)                    0.105      NA        NA       NA
10 Sensitivity sd__(Intercept)                    0.0799     NA        NA       NA
11 Original    sd__Observation                    0.0361     NA        NA       NA
12 Sensitivity sd__Observation                    0.0255     NA        NA       NA
13 Original    visit2                             0.000459    0.00936   0.0491   9.61e- 1
14 Sensitivity visit2                            -0.00431     0.00674  -0.640    5.24e- 1
15 Original    visit3                             0.0139      0.0101    1.38     1.70e- 1
16 Sensitivity visit3                             0.00890     0.00727   1.22     2.24e- 1
```

```r
performance::compare_performance(
    labs_hba1c_model,
```

```
    labs_hba1c_model_sens)
```

```
# Comparison of Model Performance Indices

Name                   |           Model | AIC (weights) | AICc (weights) | BIC (weight
-----------------------------------------------------------------------------------------
labs_hba1c_model       | lmerModLmerTest | 220.5 (<.001) |  221.4 (<.001) | 245.9 (<.00
labs_hba1c_model_sens  | lmerModLmerTest |  97.5 (>.999) |   98.5 (>.999) | 122.2 (>.99
```

```
performance::check_model(labs_hba1c_model)
```

```
performance::check_model(labs_hba1c_model_sens)
```

3.0.10.2 Médias Marginais Estimadas

3.0.10.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_hba1c_raw_emm <- emmeans::emmeans(
    labs_hba1c_model,
    ~ allocation_group * visit
```

```r
)

labs_hba1c_raw_emm <- regrid(labs_hba1c_raw_emm)

# Table of marginal means
# labs_hba1c_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hba1c_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.125 0.164 81.1   -0.202    0.452   0.761  0.4490

visit = 2:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.156 0.170 88.7   -0.181    0.493   0.918  0.3614

visit = 3:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.146 0.175 94.9   -0.203    0.494   0.831  0.4082

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hba1c_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate     SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.00298 0.0607 81.1   -0.151   0.1453  -0.049  1.0000
 visit1 - visit3 -0.09069 0.0659 81.1   -0.252   0.0703  -1.377  0.5171
 visit2 - visit3 -0.08772 0.0678 88.7   -0.253   0.0776  -1.294  0.5966

allocation_group = Grupo B:
 contrast        estimate     SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2  0.02764 0.0624 81.1   -0.125   0.1803   0.443  1.0000
 visit1 - visit3 -0.07002 0.0673 81.1   -0.235   0.0946  -1.040  0.9044
 visit2 - visit3 -0.09765 0.0695 93.9   -0.267   0.0717  -1.406  0.4891

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_hba1c_raw_emm)
```

3.0.10.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_hba1c_emm <- emmeans::emmeans(
    labs_hba1c_model_sens,
    ~ allocation_group * visit
)

# Table of marginal means
# labs_hba1c_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hba1c_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate     SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.0329 0.0201 74.3 -0.00710   0.0728   1.639  0.1055

visit = 2:
 contrast          estimate     SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.0329 0.0208 83.8 -0.00837   0.0742   1.586  0.1166

visit = 3:
 contrast          estimate     SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.0292 0.0212 89.7 -0.01286   0.0713   1.379  0.1712

Note: contrasts are still on the log1p scale. Consider using
      regrid() if you want contrasts of back-transformed estimates.
Degrees-of-freedom method: kenward-roger
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hba1c_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate      SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2  0.00431 0.00674 88.4  -0.0121  0.02076   0.640  1.0000
 visit1 - visit3 -0.00890 0.00728 88.7  -0.0267  0.00885  -1.224  0.6731
 visit2 - visit3 -0.01322 0.00750 87.8  -0.0315  0.00509  -1.763  0.2444

allocation_group = Grupo B:
 contrast        estimate      SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2  0.00435 0.00757 89.4  -0.0141  0.02282   0.574  1.0000
 visit1 - visit3 -0.01258 0.00819 89.5  -0.0326  0.00741  -1.536  0.3845
 visit2 - visit3 -0.01693 0.00852 87.9  -0.0377  0.00387  -1.986  0.1504

Note: contrasts are still on the log1p scale. Consider using
      regrid() if you want contrasts of back-transformed estimates.
Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_hba1c_emm)
```

3.0.10.3 Resultado

No modelo ajustado para os níveis de hemoglobina glicada (HbA1c), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, realizada após a exclusão de observações influentes, confirmou a estabilidade das estimativas. As diferenças entre os grupos e entre as visitas permaneceram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 10.

Tabela 10: Diferenças estimadas dos níveis de hemoglobina glicada (HbA1c) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,13	[-0,20 ; 0,45]	0,449
Entre grupos	Visita 2	0,16	[-0,18 ; 0,49]	0,361
Entre grupos	Visita 3	0,15	[-0,20 ; 0,49]	0,408
Grupo Placebo	Visita 1 - Visita 2	0,00	[-0,15 ; 0,15]	1,000
Grupo Placebo	Visita 1 - Visita 3	-0,09	[-0,25 ; 0,07]	0,517

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	-0,09	[-0,25 ; 0,08]	0,597
Grupo Eclipta	Visita 1 - Visita 2	0,03	[-0,13 ; 0,18]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,07	[-0,24 ; 0,09]	0,904
Grupo Eclipta	Visita 2 - Visita 3	-0,10	[-0,27 ; 0,07]	0,489

```
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_hba1c,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_hba1c_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_hba1c,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.11 Insulina

Variável: `labs_insulin`

```
# Plot 1: Raw data
labs_insulin_hist_1 <- data_model %>%
    #filter(
    #    labs_insulin < 300
    #) %>%
    ggplot(aes(x = labs_insulin)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_insulin_hist_2 <- data_model %>%
    #filter(
    #    labs_insulin < 300
    #) %>%
    ggplot(aes(x = log1p(labs_insulin))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_insulin_hist_1 + labs_insulin_hist_2 # library(patchwork)
```

```
# LMM
labs_insulin_model <- lmer(log1p(labs_insulin) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_insulin_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.22 [1.09, 1.56]         1.10      0.82     [0.64, 0.92]
                  visit 3.48 [2.75, 4.49]         1.86      0.29     [0.22, 0.36]
 allocation_group:visit 3.83 [3.02, 4.97]         1.96      0.26     [0.20, 0.33]
```

```r
# Sensitivity analysis
labs_insulin_model_check <- sensitivity_check_lmer(
    model = labs_insulin_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_insulin_model_sens <- update(object = labs_insulin_model,
                                  subset = !(record_id %in%
        labs_insulin_model_check$influential_ids))
# Influential IDS
labs_insulin_model_check$influential_ids
```

```
[1] "2"  "11" "19" "16" "4"
```

3.0.11.1 Resumo dos modelos

```r
# Model comparison
summary(labs_insulin_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_insulin) ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: 187.4
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.96281 -0.57160 -0.06048  0.44965  2.54304

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.14686  0.3832
 Residual              0.08142  0.2853
Number of obs: 169, groups:  record_id, 74

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      2.64624    0.07855 107.03898  33.689   <2e-16 ***
allocation_groupGrupo B         -0.03170    0.11108 107.03898  -0.285   0.7759
visit2                          -0.16405    0.07413 100.79694  -2.213   0.0291 *
visit3                          -0.03592    0.07987 102.16292  -0.450   0.6538
allocation_groupGrupo B:visit2   0.08449    0.10664 101.86854   0.792   0.4300
allocation_groupGrupo B:visit3   0.06963    0.11919 103.64642   0.584   0.5603
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.707
visit2      -0.378  0.267
visit3      -0.351  0.248  0.409
allctn_GB:2  0.263 -0.372 -0.695 -0.284
allctn_GB:3  0.235 -0.332 -0.274 -0.670  0.394
```

```r
summary(labs_insulin_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_insulin) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_insulin_model_check$influential_ids)

REML criterion at convergence: 115.2

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.80008 -0.61531 -0.03624  0.53209  1.86528

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.08728  0.2954
 Residual              0.05932  0.2436
Number of obs: 154, groups:  record_id, 69

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      2.57731    0.06381 101.20590  40.388   <2e-16 ***
allocation_groupGrupo B          0.04862    0.09228 101.20590   0.527    0.599
visit2                          -0.12539    0.06422  88.77727  -1.952    0.054 .
visit3                          -0.05126    0.06938  90.33134  -0.739    0.462
allocation_groupGrupo B:visit2   0.06302    0.09543  90.36785   0.660    0.511
allocation_groupGrupo B:visit3   0.05725    0.10923  92.66742   0.524    0.601
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.692
visit2      -0.402  0.278
visit3      -0.372  0.257  0.405
allctn_GB:2  0.271 -0.391 -0.673 -0.272
allctn_GB:3  0.236 -0.342 -0.257 -0.635  0.376
```

```r
labs_insulin_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                         2.65      0.0785    33.7    8.51e-59
 2 Sensitivity (Intercept)                         2.58      0.0638    40.4    3.13e-64
 3 Original    allocation_groupGrupo B            -0.0317    0.111     -0.285  7.76e- 1
 4 Sensitivity allocation_groupGrupo B             0.0486    0.0923     0.527  5.99e- 1
 5 Original    allocation_groupGrupo B:visit2     0.0845    0.107      0.792  4.30e- 1
 6 Sensitivity allocation_groupGrupo B:visit2     0.0630    0.0954     0.660  5.11e- 1
 7 Original    allocation_groupGrupo B:visit3     0.0696    0.119      0.584  5.60e- 1
 8 Sensitivity allocation_groupGrupo B:visit3     0.0573    0.109      0.524  6.01e- 1
 9 Original    sd__(Intercept)                    0.383    NA         NA     NA
10 Sensitivity sd__(Intercept)                    0.295    NA         NA     NA
11 Original    sd__Observation                    0.285    NA         NA     NA
12 Sensitivity sd__Observation                    0.244    NA         NA     NA
13 Original    visit2                            -0.164     0.0741    -2.21   2.91e- 2
14 Sensitivity visit2                            -0.125     0.0642    -1.95   5.40e- 2
15 Original    visit3                            -0.0359    0.0799    -0.450  6.54e- 1
16 Sensitivity visit3                            -0.0513    0.0694    -0.739  4.62e- 1
```

```r
performance::compare_performance(
    labs_insulin_model,
```

```
    labs_insulin_model_sens)
```

```
# Comparison of Model Performance Indices

Name                     |           Model |  AIC (weights) | AICc (weights) |  BIC (we
-----------------------------------------------------------------------------------------
labs_insulin_model       | lmerModLmerTest | 1062.1 (<.001) | 1063.0 (<.001) | 1087.2 (
labs_insulin_model_sens | lmerModLmerTest |  900.0 (>.999) |  901.0 (>.999) |  924.3 (
```

```
performance::check_model(labs_insulin_model)
```

```
performance::check_model(labs_insulin_model_sens)
```

3.0.11.2 Médias Marginais Estimadas

3.0.11.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_insulin_raw_emm <- emmeans::emmeans(
    labs_insulin_model,
    ~ allocation_group * visit
```

```r
)

labs_insulin_raw_emm <- regrid(labs_insulin_raw_emm)

# Table of marginal means
# labs_insulin_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_insulin_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.440 1.54 103    -2.62     3.50   0.285  0.7760

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.649 1.50 125    -3.63     2.33  -0.431  0.6669

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.526 1.85 139    -4.19     3.14  -0.284  0.7770

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_insulin_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    2.133 0.964 103   -0.213     4.48   2.213  0.0873
 visit1 - visit3    0.498 1.100 103   -2.186     3.18   0.451  1.0000
 visit2 - visit3   -1.636 1.090 125   -4.280     1.01  -1.502  0.4072

allocation_group = Grupo B:
 contrast        estimate    SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    1.045 1.000 103   -1.393     3.48   1.043  0.8981
 visit1 - visit3   -0.468 1.240 103   -3.490     2.55  -0.377  1.0000
 visit2 - visit3   -1.513 1.260 130   -4.566     1.54  -1.202  0.6945

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_insulin_raw_emm, comparisons = TRUE)
```

3.0.11.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_insulin_emm <- emmeans::emmeans(
    labs_insulin_model_sens,
    ~ allocation_group * visit
)

labs_insulin_emm <- regrid(labs_insulin_emm)

# Table of marginal means
# labs_insulin_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_insulin_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.656 1.25  99.9    -3.13     1.82  -0.526  0.6000

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -1.371 1.28 120.3    -3.91     1.17  -1.068  0.2876

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -1.396 1.56 133.2    -4.48     1.68  -0.897  0.3714

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_insulin_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    1.551 0.792  99.9   -0.377     3.48   1.959  0.1586
 visit1 - visit3    0.658 0.886  99.9   -1.499     2.81   0.743  1.0000
 visit2 - visit3   -0.893 0.888 120.3   -3.049     1.26  -1.006  0.9490

allocation_group = Grupo B:
 contrast        estimate    SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.835 0.941  99.9   -1.456     3.13   0.888  1.0000
 visit1 - visit3   -0.083 1.170  99.9   -2.943     2.78  -0.071  1.0000
 visit2 - visit3   -0.919 1.210 127.6   -3.848     2.01  -0.761  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_insulin_emm, comparisons = TRUE)
```

3.0.11.3 Resultado

No modelo ajustado para os níveis de insulina, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Também não foram encontradas mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou a ausência de diferenças significativas entre os grupos e ao longo das visitas, com estimativas semelhantes às observadas na análise principal. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 11.

Tabela 11: Diferenças estimadas dos níveis de insulina entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,44	[-2,62 ; 3,50]	0,776
Entre grupos	Visita 2	-0,65	[-3,63 ; 2,33]	0,667
Entre grupos	Visita 3	-0,53	[-4,19 ; 3,14]	0,777
Grupo Placebo	Visita 1 - Visita 2	2,13	[-0,21 ; 4,48]	0,087
Grupo Placebo	Visita 1 - Visita 3	0,50	[-2,19 ; 3,18]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	-1,64	[-4,28 ; 1,01]	0,407
Grupo Eclipta	Visita 1 - Visita 2	1,05	[-1,39 ; 3,48]	0,898
Grupo Eclipta	Visita 1 - Visita 3	-0,47	[-3,49 ; 2,55]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-1,51	[-4,57 ; 1,54]	0,695

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_insulin,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_insulin_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_insulin,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.12 HOMA-IR

Variável: `labs_homa_ir`

```
# Plot 1: Raw data
labs_homa_ir_hist_1 <- data_model %>%
    #filter(
    #    labs_homa_ir < 300
    #) %>%
    ggplot(aes(x = labs_homa_ir)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_homa_ir_hist_2 <- data_model %>%
    #filter(
    #    labs_homa_ir < 300
    #) %>%
    ggplot(aes(x = log1p(labs_homa_ir))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_homa_ir_hist_1 + labs_homa_ir_hist_2 # library(patchwork)
```

```
# LMM
labs_homa_ir_model <- lmer(log1p(labs_homa_ir) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_homa_ir_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.24 [1.10, 1.58]         1.11      0.81     [0.63, 0.91]
                  visit 3.42 [2.71, 4.42]         1.85      0.29     [0.23, 0.37]
 allocation_group:visit 3.83 [3.02, 4.97]         1.96      0.26     [0.20, 0.33]
```

```r
# Sensitivity analysis
labs_homa_ir_model_check <- sensitivity_check_lmer(
    model = labs_homa_ir_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_homa_ir_model_sens <- update(object = labs_homa_ir_model,
                                  subset = !(record_id %in%
        labs_homa_ir_model_check$influential_ids))
# Influential IDS
labs_homa_ir_model_check$influential_ids
```

```
[1] "2"  "11" "19" "27" "56"
```

3.0.12.1 Resumo dos modelos

```r
# Model comparison
summary(labs_homa_ir_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_homa_ir) ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: 144.6
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.2411 -0.5509 -0.0823  0.4113  3.4196

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.10984  0.3314
 Residual              0.06459  0.2541
Number of obs: 167, groups:  record_id, 73

Fixed effects:
                                Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     1.336898   0.068660 106.824873  19.471   <2e-16 ***
allocation_groupGrupo B        -0.041261   0.098203 107.871628  -0.420   0.6752
visit2                         -0.114741   0.065977  99.749814  -1.739   0.0851 .
visit3                          0.009875   0.071078 101.178973   0.139   0.8898
allocation_groupGrupo B:visit2  0.062435   0.095196 100.497655   0.656   0.5134
allocation_groupGrupo B:visit3  0.056616   0.107100 103.972738   0.529   0.5982
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.699
visit2      -0.385  0.269
visit3      -0.358  0.250  0.409
allctn_GB:2  0.267 -0.385 -0.693 -0.283
allctn_GB:3  0.237 -0.349 -0.271 -0.664  0.399
```

```r
summary(labs_homa_ir_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(labs_homa_ir) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_homa_ir_model_check$influential_ids)

REML criterion at convergence: 73

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.91572 -0.58345 -0.06265  0.42749  2.17496

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.07069  0.2659
 Residual              0.04329  0.2081
Number of obs: 152, groups:  record_id, 68

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                     1.284413   0.057067 97.408593  22.507   <2e-16 ***
allocation_groupGrupo B         0.008783   0.082328 98.496265   0.107   0.9153
visit2                         -0.100160   0.055929 87.585394  -1.791   0.0768 .
visit3                         -0.013517   0.060661 89.023495  -0.223   0.8242
allocation_groupGrupo B:visit2  0.053800   0.081686 88.465703   0.659   0.5119
allocation_groupGrupo B:visit3  0.025914   0.093706 92.342897   0.277   0.7827
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.693
visit2      -0.388  0.269
visit3      -0.357  0.248  0.401
allctn_GB:2  0.265 -0.386 -0.685 -0.275
allctn_GB:3  0.231 -0.345 -0.260 -0.647  0.386
```

```r
labs_homa_ir_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       1.34      0.0687    19.5    6.28e-37
 2 Sensitivity (Intercept)                       1.28      0.0571    22.5    2.24e-40
 3 Original    allocation_groupGrupo B          -0.0413    0.0982    -0.420  6.75e- 1
 4 Sensitivity allocation_groupGrupo B           0.00878   0.0823     0.107  9.15e- 1
 5 Original    allocation_groupGrupo B:visit2   0.0624    0.0952     0.656  5.13e- 1
 6 Sensitivity allocation_groupGrupo B:visit2   0.0538    0.0817     0.659  5.12e- 1
 7 Original    allocation_groupGrupo B:visit3   0.0566    0.107      0.529  5.98e- 1
 8 Sensitivity allocation_groupGrupo B:visit3   0.0259    0.0937     0.277  7.83e- 1
 9 Original    sd__(Intercept)                  0.331     NA         NA     NA
10 Sensitivity sd__(Intercept)                  0.266     NA         NA     NA
11 Original    sd__Observation                  0.254     NA         NA     NA
12 Sensitivity sd__Observation                  0.208     NA         NA     NA
13 Original    visit2                          -0.115      0.0660    -1.74   8.51e- 2
14 Sensitivity visit2                          -0.100      0.0559    -1.79   7.68e- 2
15 Original    visit3                           0.00987   0.0711     0.139  8.90e- 1
16 Sensitivity visit3                          -0.0135    0.0607    -0.223  8.24e- 1
```

```r
performance::compare_performance(
    labs_homa_ir_model,
```

```
    labs_homa_ir_model_sens)
```

```
# Comparison of Model Performance Indices

Name                     |           Model | AIC (weights) | AICc (weights) | BIC (weig
-----------------------------------------------------------------------------------------
labs_homa_ir_model       | lmerModLmerTest | 579.2 (<.001) |  580.1 (<.001) | 604.1 (<.
labs_homa_ir_model_sens  | lmerModLmerTest | 454.2 (>.999) |  455.2 (>.999) | 478.4 (>.
```

```
performance::check_model(labs_homa_ir_model)
```

```
performance::check_model(labs_homa_ir_model_sens)
```

3.0.12.2 Médias Marginais Estimadas

3.0.12.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_homa_ir_raw_emm <- emmeans::emmeans(
    labs_homa_ir_model,
    ~ allocation_group * visit
```

```r
)

labs_homa_ir_raw_emm <- regrid(labs_homa_ir_raw_emm)

# Table of marginal means
# labs_homa_ir_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_homa_ir_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.1539 0.366 103   -0.572    0.880   0.420  0.6752

visit = 2:
 contrast          estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0726 0.369 125   -0.802    0.657  -0.197  0.8441

visit = 3:
 contrast          estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0595 0.456 139   -0.961    0.842  -0.131  0.8963

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_homa_ir_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.4127 0.237 103   -0.163    0.988   1.744  0.2522
 visit1 - visit3  -0.0378 0.273 103   -0.702    0.626  -0.138  1.0000
 visit2 - visit3  -0.4505 0.274 125   -1.116    0.215  -1.642  0.3093

allocation_group = Grupo B:
 contrast        estimate    SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.1862 0.244 106   -0.406    0.779   0.764  1.0000
 visit1 - visit3  -0.2512 0.308 106   -1.001    0.498  -0.815  1.0000
 visit2 - visit3  -0.4374 0.311 128   -1.191    0.316  -1.408  0.4849

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_homa_ir_raw_emm, comparisons = TRUE)
```

3.0.12.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_homa_ir_emm <- emmeans::emmeans(
    labs_homa_ir_model_sens,
    ~ allocation_group * visit
)

labs_homa_ir_emm <- regrid(labs_homa_ir_emm)

# Table of marginal means
# labs_homa_ir_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_homa_ir_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0319 0.299  96   -0.625    0.561  -0.107  0.9153

visit = 2:
 contrast          estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.2111 0.308 117   -0.821    0.398  -0.686  0.4942

visit = 3:
 contrast          estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.1258 0.369 130   -0.855    0.603  -0.341  0.7334

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_homa_ir_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.3443 0.192  96.0   -0.122    0.811   1.798  0.2261
 visit1 - visit3   0.0485 0.218  96.0   -0.482    0.579   0.223  1.0000
 visit2 - visit3  -0.2958 0.221 116.6   -0.832    0.240  -1.341  0.5479

allocation_group = Grupo B:
 contrast        estimate    SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.1651 0.211  98.1   -0.350    0.680   0.781  1.0000
 visit1 - visit3  -0.0455 0.264  98.1   -0.687    0.596  -0.173  1.0000
 visit2 - visit3  -0.2106 0.268 120.7   -0.861    0.440  -0.786  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_homa_ir_emm, comparisons = TRUE)
```

3.0.12.3 Resultado

No modelo ajustado para os níveis de HOMA-IR, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Além disso, as comparações dentro de cada grupo ao longo do tempo não revelaram mudanças significativas. A análise de sensibilidade, realizada com a exclusão de observações influentes, confirmou a robustez dos achados, com estimativas semelhantes e ausência de diferenças significativas entre os grupos ou ao longo das visitas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 12.

Tabela 12: Diferenças estimadas dos níveis de HOMA-IR entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,15	[-0,57 ; 0,88]	0,675
Entre grupos	Visita 2	-0,07	[-0,80 ; 0,66]	0,844
Entre grupos	Visita 3	-0,06	[-0,96 ; 0,84]	0,896
Grupo Placebo	Visita 1 - Visita 2	0,41	[-0,16 ; 0,99]	0,252
Grupo Placebo	Visita 1 - Visita 3	-0,04	[-0,70 ; 0,63]	1,000

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 2 - Visita 3	-0,45	[-1,12 ; 0,22]	0,309
Grupo Eclipta	Visita 1 - Visita 2	0,19	[-0,41 ; 0,78]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,25	[-1,00 ; 0,50]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,44	[-1,19 ; 0,32]	0,485

```
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_homa_ir,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_homa_ir_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_homa_ir,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.13 Índice QUICK

Variável: `labs_quick_index`

```
# Plot 1: Raw data
labs_quick_index_hist_1 <- data_model %>%
    #filter(
    #    labs_quick_index < 300
    #) %>%
    ggplot(aes(x = labs_quick_index)) +
```

```r
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_quick_index_hist_2 <- data_model %>%
    #filter(
    #    labs_quick_index < 300
    #) %>%
    ggplot(aes(x = log1p(labs_quick_index))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_quick_index_hist_1 + labs_quick_index_hist_2 # library(patchwork)
```

```r
# LMM
labs_quick_index_model <- lmer(labs_quick_index ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_quick_index_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.25 [1.11, 1.60]         1.12      0.80     [0.63, 0.90]
                  visit 3.42 [2.71, 4.42]         1.85      0.29     [0.23, 0.37]
 allocation_group:visit 3.85 [3.03, 5.00]         1.96      0.26     [0.20, 0.33]
```

```r
# Sensitivity analysis
labs_quick_index_model_check <- sensitivity_check_lmer(
    model = labs_quick_index_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
labs_quick_index_model_sens <- update(object = labs_quick_index_model,
                                      subset = !(record_id %in%
        labs_quick_index_model_check$influential_ids))
# Influential IDS
labs_quick_index_model_check$influential_ids
```

```
[1] "2"  "4"  "11" "19" "8"
```

3.0.13.1 Resumo dos modelos

```r
# Model comparison
summary(labs_quick_index_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: labs_quick_index ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: -754.1
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.0927 -0.4844  0.0304  0.5467  2.4024

Random effects:
 Groups    Name        Variance  Std.Dev.
 record_id (Intercept) 0.0003959 0.01990
 Residual              0.0002488 0.01577
Number of obs: 167, groups:  record_id, 73

Fixed effects:
                                Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     0.330541   0.004174 107.176150  79.186   <2e-16 ***
allocation_groupGrupo B         0.001261   0.005971 108.248173   0.211   0.8331
visit2                          0.008362   0.004092  98.621725   2.044   0.0436 *
visit3                          0.002322   0.004407 100.155478   0.527   0.5994
allocation_groupGrupo B:visit2 -0.003691   0.005903  99.395689  -0.625   0.5332
allocation_groupGrupo B:visit3 -0.005408   0.006638 103.075477  -0.815   0.4171
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.699
visit2      -0.394  0.275
visit3      -0.366  0.256  0.408
allctn_GB:2  0.273 -0.393 -0.693 -0.283
allctn_GB:3  0.243 -0.357 -0.271 -0.664  0.399
```

```r
summary(labs_quick_index_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: labs_quick_index ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% labs_quick_index_model_check$influential_ids)

REML criterion at convergence: -714.5

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.8870 -0.4995  0.0244  0.5783  2.3369

Random effects:
 Groups    Name        Variance  Std.Dev.
 record_id (Intercept) 0.0002799 0.01673
 Residual              0.0002110 0.01452
Number of obs: 152, groups:  record_id, 68

Fixed effects:
                                 Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     3.317e-01  3.745e-03  1.010e+02  88.573   <2e-16 ***
allocation_groupGrupo B         5.364e-04  5.405e-03  1.021e+02   0.099   0.9212
visit2                          6.683e-03  3.894e-03  8.696e+01   1.716   0.0897 .
visit3                          1.888e-03  4.221e-03  8.872e+01   0.447   0.6558
allocation_groupGrupo B:visit2 -5.420e-03  5.685e-03  8.792e+01  -0.953   0.3430
allocation_groupGrupo B:visit3 -5.218e-03  6.509e-03  9.243e+01  -0.802   0.4248
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.693
visit2      -0.413  0.286
visit3      -0.381  0.264  0.400
allctn_GB:2  0.283 -0.411 -0.685 -0.274
allctn_GB:3  0.247 -0.368 -0.260 -0.648  0.385
```

```r
labs_quick_index_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                              estimate std.error statistic   p.value
   <chr>       <chr>                                <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       0.331      0.00417   79.2     6.23e-97
 2 Sensitivity (Intercept)                       0.332      0.00375   88.6     1.42e-97
 3 Original    allocation_groupGrupo B           0.00126    0.00597    0.211   8.33e- 1
 4 Sensitivity allocation_groupGrupo B           0.000536   0.00541    0.0992  9.21e- 1
 5 Original    allocation_groupGrupo B:visit2 -0.00369    0.00590   -0.625   5.33e- 1
 6 Sensitivity allocation_groupGrupo B:visit2 -0.00542    0.00569   -0.953   3.43e- 1
 7 Original    allocation_groupGrupo B:visit3 -0.00541    0.00664   -0.815   4.17e- 1
 8 Sensitivity allocation_groupGrupo B:visit3 -0.00522    0.00651   -0.802   4.25e- 1
 9 Original    sd__(Intercept)                   0.0199    NA         NA      NA
10 Sensitivity sd__(Intercept)                   0.0167    NA         NA      NA
11 Original    sd__Observation                   0.0158    NA         NA      NA
12 Sensitivity sd__Observation                   0.0145    NA         NA      NA
13 Original    visit2                            0.00836    0.00409    2.04    4.36e- 2
14 Sensitivity visit2                            0.00668    0.00389    1.72    8.97e- 2
15 Original    visit3                            0.00232    0.00441    0.527   5.99e- 1
16 Sensitivity visit3                            0.00189    0.00422    0.447   6.56e- 1
```

```r
performance::compare_performance(
    labs_quick_index_model,
```

```
    labs_quick_index_model_sens)
```

```
# Comparison of Model Performance Indices

Name                        |           Model |  AIC (weights) | AICc (weights) |  BIC
-----------------------------------------------------------------------------------------
labs_quick_index_model      | lmerModLmerTest | -793.2 (>.999) | -792.3 (>.999) | -768
labs_quick_index_model_sens | lmerModLmerTest | -754.3 (<.001) | -753.3 (<.001) | -730
```

```
performance::check_model(labs_quick_index_model)
```

```
performance::check_model(labs_quick_index_model_sens)
```

3.0.13.2 Médias Marginais Estimadas

3.0.13.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_quick_index_raw_emm <- emmeans::emmeans(
    labs_quick_index_model,
    ~ allocation_group * visit
```

```r
)

labs_quick_index_raw_emm <- regrid(labs_quick_index_raw_emm)

# Table of marginal means
# labs_quick_index_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_quick_index_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B -0.00126 0.00597 105  -0.0131   0.0106  -0.211  0.8331

visit = 2:
 contrast          estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.00243 0.00655 126  -0.0105   0.0154   0.371  0.7113

visit = 3:
 contrast          estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.00415 0.00719 140  -0.0101   0.0184   0.577  0.5648

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_quick_index_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate      SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.00836 0.00410 105 -0.01833  0.00160  -2.041  0.1312
 visit1 - visit3 -0.00232 0.00441 105 -0.01306  0.00842  -0.526  1.0000
 visit2 - visit3  0.00604 0.00464 126 -0.00521  0.01729   1.303  0.5848

allocation_group = Grupo B:
 contrast        estimate      SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.00467 0.00426 107 -0.01504  0.00569  -1.096  0.8263
 visit1 - visit3  0.00309 0.00498 107 -0.00902  0.01519   0.620  1.0000
 visit2 - visit3  0.00776 0.00513 130 -0.00469  0.02020   1.512  0.3989

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_quick_index_raw_emm, comparisons = TRUE)
```

3.0.13.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_quick_index_emm <- emmeans::emmeans(
    labs_quick_index_model_sens,
    ~ allocation_group * visit
)

labs_quick_index_emm <- regrid(labs_quick_index_emm)

# Table of marginal means
# labs_quick_index_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_quick_index_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast           estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B -0.000536 0.00541 101 -0.01126   0.0102  -0.099  0.9212

visit = 2:
 contrast           estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.004884 0.00603 122 -0.00706   0.0168   0.810  0.4197

visit = 3:
 contrast           estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.004682 0.00678 134 -0.00873   0.0181   0.691  0.4910

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_quick_index_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate      SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.00668 0.00390 101 -0.01618  0.00281  -1.713  0.2691
 visit1 - visit3 -0.00189 0.00423 101 -0.01219  0.00841  -0.446  1.0000
 visit2 - visit3  0.00480 0.00446 122 -0.00603  0.01562   1.075  0.8531

allocation_group = Grupo B:
 contrast        estimate      SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.00126 0.00415 103 -0.01136  0.00884  -0.304  1.0000
 visit1 - visit3  0.00333 0.00497 103 -0.00878  0.01544   0.670  1.0000
 visit2 - visit3  0.00459 0.00515 125 -0.00790  0.01709   0.892  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(labs_quick_index_emm, comparisons = TRUE)
```

3.0.13.3 Resultado

No modelo ajustado para o índice de sensibilidade à insulina (Quick Index), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações ao longo do tempo dentro de cada grupo também não mostraram variações significativas. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou os achados da análise principal. As estimativas permaneceram consistentes, sem diferenças estatisticamente significativas entre os grupos ou ao longo do tempo. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 13.

Tabela 13: Diferenças estimadas do índice Quick entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,001	[-0,013 ; 0,011]	0,833
Entre grupos	Visita 2	0,002	[-0,011 ; 0,015]	0,711
Entre grupos	Visita 3	0,004	[-0,010 ; 0,018]	0,565
Grupo Placebo	Visita 1 - Visita 2	-0,008	[-0,018 ; 0,002]	0,131

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 1 - Visita 3	-0,002	[-0,013 ; 0,008]	1,000
Grupo Placebo	Visita 2 - Visita 3	0,006	[-0,005 ; 0,017]	0,585
Grupo Eclipta	Visita 1 - Visita 2	-0,005	[-0,015 ; 0,006]	0,826
Grupo Eclipta	Visita 1 - Visita 3	0,003	[-0,009 ; 0,015]	1,000
Grupo Eclipta	Visita 2 - Visita 3	0,008	[-0,005 ; 0,020]	0,399

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = labs_quick_index,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        labs_quick_index_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = labs_quick_index,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.14 Circunferência abdominal

Variável: `abdomen`

```
# Plot 1: Raw data
abdomen_hist_1 <- data_model %>%
    #filter(
    #    abdomen < 300
    #) %>%
    ggplot(aes(x = abdomen)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
abdomen_hist_2 <- data_model %>%
    #filter(
    #    abdomen < 300
    #) %>%
    ggplot(aes(x = log1p(abdomen))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
abdomen_hist_1 + abdomen_hist_2 # library(patchwork)
```

```
# LMM
abdomen_model <- lmer(log1p(abdomen) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(abdomen_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation


                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.08 [1.01, 1.60]         1.04      0.93     [0.62, 0.99]
                  visit 3.74 [2.98, 4.79]         1.93      0.27     [0.21, 0.34]
 allocation_group:visit 3.87 [3.08, 4.96]         1.97      0.26     [0.20, 0.32]
```

```r
# Sensitivity analysis
abdomen_model_check <- sensitivity_check_lmer(
    model = abdomen_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
abdomen_model_sens <- update(object = abdomen_model,
                             subset = !(record_id %in%
        abdomen_model_check$influential_ids))
# Influential IDS
abdomen_model_check$influential_ids
```

```
[1] "8"  "42" "47" "53" "63"
```

3.0.14.1 Resumo dos modelos

```r
# Model comparison
summary(abdomen_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(abdomen) ~ allocation_group * visit + (1 | record_id)
   Data: data_model


REML criterion at convergence: -568.7
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.23622 -0.44732  0.00364  0.48062  2.42979

Random effects:
 Groups    Name        Variance  Std.Dev.
 record_id (Intercept) 0.0047493 0.06892
 Residual              0.0007424 0.02725
Number of obs: 187, groups:  record_id, 75

Fixed effects:
                                Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     4.646300   0.012183  84.898832 381.378   <2e-16 ***
allocation_groupGrupo B        -0.015067   0.017116  84.898832  -0.880   0.3812
visit2                         -0.008742   0.006883 110.950474  -1.270   0.2067
visit3                         -0.016017   0.007250 111.261323  -2.209   0.0292 *
allocation_groupGrupo B:visit2  0.006622   0.009887 111.494381   0.670   0.5044
allocation_groupGrupo B:visit3  0.022973   0.010437 111.762586   2.201   0.0298 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.239  0.170
visit3      -0.227  0.162  0.469
allctn_GB:2  0.167 -0.234 -0.696 -0.327
allctn_GB:3  0.158 -0.222 -0.326 -0.695  0.467
```

```r
summary(abdomen_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(abdomen) ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% abdomen_model_check$influential_ids)

REML criterion at convergence: -552.6

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.17405 -0.44945  0.00727  0.51473  1.83706

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.004706 0.06860
 Residual              0.000536 0.02315
Number of obs: 172, groups:  record_id, 70

Fixed effects:
                                Estimate Std. Error         df t value Pr(>|t|)
(Intercept)                     4.646664   0.012604  75.952119 368.673   <2e-16 ***
allocation_groupGrupo B        -0.016907   0.017336  75.952119  -0.975   0.3325
visit2                         -0.001980   0.006272 100.199396  -0.316   0.7529
visit3                         -0.009382   0.006665 100.412373  -1.408   0.1623
allocation_groupGrupo B:visit2  0.001495   0.008783 100.495350   0.170   0.8652
allocation_groupGrupo B:visit3  0.020633   0.009324 100.671803   2.213   0.0292 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.727
visit2      -0.205  0.149
visit3      -0.193  0.141  0.466
allctn_GB:2  0.147 -0.202 -0.714 -0.333
allctn_GB:3  0.138 -0.190 -0.333 -0.715  0.466
```

```r
abdomen_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic    p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>      <dbl>
 1 Original    (Intercept)                       4.65      0.0122    381.     4.49e-139
 2 Sensitivity (Intercept)                       4.65      0.0126    369.     2.66e-125
 3 Original    allocation_groupGrupo B        -0.0151    0.0171     -0.880  3.81e-  1
 4 Sensitivity allocation_groupGrupo B        -0.0169    0.0173     -0.975  3.33e-  1
 5 Original    allocation_groupGrupo B:visit2  0.00662   0.00989     0.670  5.04e-  1
 6 Sensitivity allocation_groupGrupo B:visit2  0.00149   0.00878     0.170  8.65e-  1
 7 Original    allocation_groupGrupo B:visit3  0.0230    0.0104      2.20   2.98e-  2
 8 Sensitivity allocation_groupGrupo B:visit3  0.0206    0.00932     2.21   2.92e-  2
 9 Original    sd__(Intercept)                 0.0689   NA          NA     NA
10 Sensitivity sd__(Intercept)                 0.0686   NA          NA     NA
11 Original    sd__Observation                 0.0272   NA          NA     NA
12 Sensitivity sd__Observation                 0.0232   NA          NA     NA
13 Original    visit2                         -0.00874   0.00688    -1.27   2.07e-  1
14 Sensitivity visit2                         -0.00198   0.00627    -0.316  7.53e-  1
15 Original    visit3                         -0.0160    0.00725    -2.21   2.92e-  2
16 Sensitivity visit3                         -0.00938   0.00666    -1.41   1.62e-  1
```

```r
performance::compare_performance(
    abdomen_model,
```

```
    abdomen_model_sens)
```

```
# Comparison of Model Performance Indices

Name               |           Model |  AIC (weights) | AICc (weights) |  BIC (weights
-----------------------------------------------------------------------------------------
abdomen_model      | lmerModLmerTest | 1134.8 (<.001) | 1135.6 (<.001) | 1160.7 (<.001
abdomen_model_sens | lmerModLmerTest | 1011.7 (>.999) | 1012.6 (>.999) | 1036.9 (>.999
```

```
performance::check_model(abdomen_model)
```

```
performance::check_model(abdomen_model_sens)
```

3.0.14.2 Médias Marginais Estimadas

3.0.14.2.1 Todos os dados

```
# Get EMMs for each group at each visit
abdomen_raw_emm <- emmeans::emmeans(
    abdomen_model,
    ~ allocation_group * visit
```

```r
)

abdomen_raw_emm <- regrid(abdomen_raw_emm)

# Table of marginal means
# abdomen_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(abdomen_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.558 1.77 84.3    -1.96     5.08   0.880  0.3813

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.869 1.82 91.4    -2.74     4.47   0.478  0.6335

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.814 1.85 96.8    -4.49     2.86  -0.440  0.6609

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(abdomen_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.907 0.714 84.3   -0.837    2.651   1.270  0.6225
 visit1 - visit3    1.656 0.749 84.3   -0.173    3.484   2.212  0.0891
 visit2 - visit3    0.749 0.750 91.4   -1.080    2.577   0.999  0.9617

allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.217 0.728 84.3   -1.561    1.996   0.298  1.0000
 visit1 - visit3   -0.716 0.775 84.3   -2.609    1.176  -0.925  1.0000
 visit2 - visit3   -0.934 0.779 95.7   -2.831    0.964  -1.199  0.7002

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(abdomen_raw_emm, comparisons = TRUE)
```

3.0.14.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
abdomen_emm <- emmeans::emmeans(
    abdomen_model_sens,
    ~ allocation_group * visit
)

abdomen_emm <- regrid(abdomen_emm)

# Table of marginal means
# abdomen_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(abdomen_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.747 1.79 75.5    -1.82     5.32   0.975  0.3328

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.591 1.84 81.5    -2.06     5.25   0.866  0.3889

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.386 1.87 86.0    -4.10     3.33  -0.206  0.8370

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(abdomen_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.2062 0.653 75.5   -1.393    1.806   0.316  1.0000
 visit1 - visit3   0.9734 0.691 75.5   -0.719    2.665   1.409  0.4892
 visit2 - visit3   0.7672 0.693 81.5   -0.928    2.462   1.106  0.8156

allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.0497 0.630 75.5   -1.494    1.593   0.079  1.0000
 visit1 - visit3  -1.1596 0.674 75.5   -2.809    0.490  -1.721  0.2679
 visit2 - visit3  -1.2094 0.676 84.1   -2.861    0.443  -1.788  0.2319

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(abdomen_emm)
```

3.0.14.3 Resultado

No modelo ajustado para a circunferência abdominal, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As comparações dentro dos grupos ao longo do tempo também não revelaram mudanças significativas. Embora a diferença entre as visitas 1 e 3 no grupo placebo tenha se aproximado da significância (p = 0,089), essa tendência não foi confirmada na análise de sensibilidade. Após a exclusão das observações influentes, os resultados permaneceram estáveis, sem diferenças estatisticamente significativas entre os grupos ou ao longo do tempo. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 14.

Tabela 14: Diferenças estimadas da circunferência abdominal entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	1,56	[-1,96 ; 5,08]	0,381
Entre grupos	Visita 2	0,87	[-2,74 ; 4,47]	0,634
Entre grupos	Visita 3	-0,81	[-4,49 ; 2,86]	0,661

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Placebo	Visita 1 - Visita 2	0,91	[-0,84 ; 2,65]	0,623
Grupo Placebo	Visita 1 - Visita 3	1,66	[-0,17 ; 3,48]	0,089
Grupo Placebo	Visita 2 - Visita 3	0,75	[-1,08 ; 2,58]	0,962
Grupo Eclipta	Visita 1 - Visita 2	0,22	[-1,56 ; 2,00]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,72	[-2,61 ; 1,18]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,93	[-2,83 ; 0,96]	0,700

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = abdomen,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        abdomen_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = abdomen,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.15 Índice de Massa Corporal

Variável: `bmi`

```
# Plot 1: Raw data
bmi_hist_1 <- data_model %>%
    #filter(
    #    bmi < 300
    #) %>%
    ggplot(aes(x = bmi)) +
```

```
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
bmi_hist_2 <- data_model %>%
    #filter(
    #    bmi < 300
    #) %>%
    ggplot(aes(x = log1p(bmi))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
bmi_hist_1 + bmi_hist_2 # library(patchwork)
```

```
# LMM
bmi_model <- lmer(bmi ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(bmi_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation

                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.05 [1.00, 1.88]         1.03      0.95     [0.53, 1.00]
                  visit 3.74 [2.98, 4.78]         1.93      0.27     [0.21, 0.34]
 allocation_group:visit 3.83 [3.05, 4.91]         1.96      0.26     [0.20, 0.33]
```

```r
# Sensitivity analysis
bmi_model_check <- sensitivity_check_lmer(
    model = bmi_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
bmi_model_sens <- update(object = bmi_model,
                             subset = !(record_id %in%
        bmi_model_check$influential_ids))
# Influential IDS
bmi_model_check$influential_ids
```

```
[1] "8"  "50" "53" "74" "32"
```

3.0.15.1 Resumo dos modelos

```r
# Model comparison
summary(bmi_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: bmi ~ allocation_group * visit + (1 | record_id)
   Data: data_model

REML criterion at convergence: 615.9
```

```
Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.4029 -0.4671 -0.0177  0.4841  3.3103

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 4.1025   2.0255
 Residual              0.4525   0.6727
Number of obs: 187, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    32.9678     0.3509  81.3398  93.961  < 2e-16 ***
allocation_groupGrupo B         0.3598     0.4929  81.3398   0.730  0.46754
visit2                         -0.3263     0.1702 110.0171  -1.917  0.05782 .
visit3                         -0.5740     0.1793 110.2335  -3.201  0.00179 **
allocation_groupGrupo B:visit2  0.3364     0.2445 110.4215   1.375  0.17179
allocation_groupGrupo B:visit3  0.5709     0.2582 110.6050   2.211  0.02910 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.205  0.146
visit3      -0.194  0.138  0.471
allctn_GB:2  0.143 -0.200 -0.696 -0.328
allctn_GB:3  0.135 -0.190 -0.327 -0.694  0.469
```

```r
summary(bmi_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: bmi ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% bmi_model_check$influential_ids)

REML criterion at convergence: 508.5

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.08439 -0.51935  0.00596  0.47882  2.16447

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 3.6273   1.9045
 Residual              0.2717   0.5213
Number of obs: 172, groups:  record_id, 70

Fixed effects:
                               Estimate Std. Error      df t value Pr(>|t|)
(Intercept)                     32.6952     0.3437 73.0061  95.118   <2e-16 ***
allocation_groupGrupo B          0.5473     0.4728 73.0061   1.158   0.2508
visit2                          -0.1738     0.1414 99.2311  -1.229   0.2221
visit3                          -0.2725     0.1503 99.3680  -1.813   0.0729 .
allocation_groupGrupo B:visit2   0.1222     0.1981 99.4346   0.617   0.5388
allocation_groupGrupo B:visit3   0.2026     0.2103 99.5464   0.963   0.3378
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.727
visit2      -0.169  0.123
visit3      -0.159  0.116  0.467
allctn_GB:2  0.121 -0.166 -0.714 -0.334
allctn_GB:3  0.114 -0.157 -0.334 -0.715  0.467
```

```r
bmi_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                         33.0       0.351    94.0    9.96e-85
 2 Sensitivity (Intercept)                         32.7       0.344    95.1    2.73e-78
 3 Original    allocation_groupGrupo B              0.360     0.493     0.730  4.68e- 1
 4 Sensitivity allocation_groupGrupo B              0.547     0.473     1.16   2.51e- 1
 5 Original    allocation_groupGrupo B:visit2       0.336     0.245     1.38   1.72e- 1
 6 Sensitivity allocation_groupGrupo B:visit2       0.122     0.198     0.617  5.39e- 1
 7 Original    allocation_groupGrupo B:visit3       0.571     0.258     2.21   2.91e- 2
 8 Sensitivity allocation_groupGrupo B:visit3       0.203     0.210     0.963  3.38e- 1
 9 Original    sd__(Intercept)                      2.03     NA        NA     NA
10 Sensitivity sd__(Intercept)                      1.90     NA        NA     NA
11 Original    sd__Observation                      0.673    NA        NA     NA
12 Sensitivity sd__Observation                      0.521    NA        NA     NA
13 Original    visit2                              -0.326     0.170    -1.92   5.78e- 2
14 Sensitivity visit2                              -0.174     0.141    -1.23   2.22e- 1
15 Original    visit3                              -0.574     0.179    -3.20   1.79e- 3
16 Sensitivity visit3                              -0.272     0.150    -1.81   7.29e- 2
```

```r
performance::compare_performance(
    bmi_model,
```

```
    bmi_model_sens)
```

```
# Comparison of Model Performance Indices

Name           |           Model | AIC (weights) | AICc (weights) | BIC (weights) | R2
-----------------------------------------------------------------------------------------
bmi_model      | lmerModLmerTest | 624.2 (<.001) |  625.0 (<.001) | 650.1 (<.001) |
bmi_model_sens | lmerModLmerTest | 515.0 (>.999) |  515.9 (>.999) | 540.2 (>.999) |
```

```
performance::check_model(bmi_model)
```

```
performance::check_model(bmi_model_sens)
```

3.0.15.2 Médias Marginais Estimadas

3.0.15.2.1 Todos os dados

```
# Get EMMs for each group at each visit
bmi_raw_emm <- emmeans::emmeans(
    bmi_model,
    ~ allocation_group * visit
```

```r
)

bmi_raw_emm <- regrid(bmi_raw_emm)

# Table of marginal means
# bmi_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bmi_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.360 0.493 81.0    -1.34   0.6210  -0.730  0.4675

visit = 2:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.696 0.505 86.4    -1.70   0.3068  -1.380  0.1712

visit = 3:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.931 0.511 90.4    -1.95   0.0851  -1.820  0.0720

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(bmi_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2  0.32626 0.170 81.0  -0.0899    0.742   1.916  0.1765
 visit1 - visit3  0.57397 0.179 81.0   0.1355    1.012   3.200  0.0059
 visit2 - visit3  0.24771 0.180 86.4  -0.1917    0.687   1.376  0.5167

allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2 -0.01010 0.176 81.0  -0.4396    0.419  -0.057  1.0000
 visit1 - visit3  0.00309 0.186 81.0  -0.4514    0.458   0.017  1.0000
 visit2 - visit3  0.01319 0.187 89.7  -0.4426    0.469   0.071  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(bmi_raw_emm)
```

3.0.15.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
bmi_emm <- emmeans::emmeans(
    bmi_model_sens,
    ~ allocation_group * visit
)

bmi_emm <- regrid(bmi_emm)

# Table of marginal means
# bmi_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bmi_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.547 0.473 73.0    -1.49    0.395  -1.158  0.2508

visit = 2:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.669 0.481 77.1    -1.63    0.289  -1.391  0.1682

visit = 3:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.750 0.486 80.2    -1.72    0.218  -1.541  0.1271

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(bmi_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.1738 0.141 73.0   -0.173    0.520   1.228  0.6699
 visit1 - visit3   0.2725 0.150 73.0   -0.096    0.641   1.812  0.2222
 visit2 - visit3   0.0987 0.151 77.1   -0.270    0.468   0.655  1.0000

allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   0.0516 0.139 73.0   -0.288    0.392   0.372  1.0000
 visit1 - visit3   0.0699 0.147 73.0   -0.291    0.431   0.475  1.0000
 visit2 - visit3   0.0184 0.148 78.9   -0.343    0.380   0.124  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(bmi_emm)
```

3.0.15.3 Resultado

No modelo ajustado para o índice de massa corporal (IMC), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. No entanto, dentro do grupo placebo, observou-se uma redução estatisticamente significativa entre as visitas 1 e 3 (p = 0,0059). Para investigar a robustez desse achado, foi realizada uma análise de sensibilidade com exclusão das cinco observações mais influentes (IDs: 8, 50, 53, 74 e 32). Após a exclusão, a diferença intra grupo placebo deixou de ser significativa (p = 0,222), sugerindo que o resultado original foi influenciado por outliers.

As figuras de diagnóstico do modelo indicaram leve heterocedasticidade e presença de observações influentes, justificando a realização da análise de sensibilidade. A comparação entre os modelos mostrou melhora nos índices de ajuste após a exclusão dos dados influentes (AIC e BIC consideravelmente menores e RMSE reduzido), além de maior normalidade dos resíduos e aleatoriedade nos efeitos aleatórios.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 15. As estimativas, intervalos de confiança de 95% e valores de p da análise de sensibilidade estão apresentadas na Tabela 16.

Tabela 15: Diferenças estimadas do índice de massa corporal (IMC) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,36	[-1,34 ; 0,62]	0,468
Entre grupos	Visita 2	-0,70	[-1,70 ; 0,31]	0,171
Entre grupos	Visita 3	-0,93	[-1,95 ; 0,09]	0,072
Grupo Placebo	Visita 1 - Visita 2	0,33	[-0,09 ; 0,74]	0,177
Grupo Placebo	Visita 1 - Visita 3	0,57	[0,14 ; 1,01]	0,006
Grupo Placebo	Visita 2 - Visita 3	0,25	[-0,19 ; 0,69]	0,517
Grupo Eclipta	Visita 1 - Visita 2	-0,01	[-0,44 ; 0,42]	1,000
Grupo Eclipta	Visita 1 - Visita 3	0,00	[-0,45 ; 0,46]	1,000
Grupo Eclipta	Visita 2 - Visita 3	0,01	[-0,44 ; 0,47]	1,000

Tabela 16: Diferenças estimadas do índice de massa corporal (IMC) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,55	[-1,49 ; 0,39]	0,251
Entre grupos	Visita 2	-0,67	[-1,63 ; 0,29]	0,168
Entre grupos	Visita 3	-0,75	[-1,72 ; 0,22]	0,127
Grupo Placebo	Visita 1 - Visita 2	0,17	[-0,17 ; 0,52]	0,670
Grupo Placebo	Visita 1 - Visita 3	0,27	[-0,10 ; 0,64]	0,222
Grupo Placebo	Visita 2 - Visita 3	0,10	[-0,27 ; 0,47]	1,000
Grupo Eclipta	Visita 1 - Visita 2	0,05	[-0,29 ; 0,39]	1,000
Grupo Eclipta	Visita 1 - Visita 3	0,07	[-0,29 ; 0,43]	1,000
Grupo Eclipta	Visita 2 - Visita 3	0,02	[-0,34 ; 0,38]	1,000

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = bmi,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```r
    #coord_cartesian(ylim = c(10, 150))

data_model %>%
    filter(
        !(record_id %in%
        bmi_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = bmi,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.16 Pressão Arterial Média

Variável: `mean_bp_mean`

```
# Plot 1: Raw data
mean_bp_mean_hist_1 <- data_model %>%
    #filter(
    #    mean_bp_mean < 300
    #) %>%
    ggplot(aes(x = mean_bp_mean)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
mean_bp_mean_hist_2 <- data_model %>%
    #filter(
    #    mean_bp_mean < 300
    #) %>%
```

```r
    ggplot(aes(x = log1p(mean_bp_mean))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
mean_bp_mean_hist_1 + mean_bp_mean_hist_2 # library(patchwork)
```

```r
# LMM
mean_bp_mean_model <- lmer(mean_bp_mean ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(mean_bp_mean_model)
```

```
# Check for Multicollinearity


Low Correlation


                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
        allocation_group 1.22 [1.09, 1.54]         1.10      0.82     [0.65, 0.92]
                   visit 3.88 [3.09, 4.98]         1.97      0.26     [0.20, 0.32]
 allocation_group:visit 4.29 [3.39, 5.51]         2.07      0.23     [0.18, 0.29]
```

```r
# Sensitivity analysis
mean_bp_mean_model_check <- sensitivity_check_lmer(
    model = mean_bp_mean_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
mean_bp_mean_model_sens <- update(object = mean_bp_mean_model,
                                  subset = !(record_id %in%
        mean_bp_mean_model_check$influential_ids))
# Influential IDS
mean_bp_mean_model_check$influential_ids
```

```
[1] "46" "17" "45" "27" "50"
```

3.0.16.1 Resumo dos modelos

```r
# Model comparison
summary(mean_bp_mean_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: mean_bp_mean ~ allocation_group * visit + (1 | record_id)
   Data: data_model

REML criterion at convergence: 1286.9

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.62758 -0.53598 -0.01067  0.48135  3.02975

Random effects:
 Groups    Name        Variance Std.Dev.
```

```
 record_id (Intercept) 67.94    8.243
 Residual              34.36    5.862
Number of obs: 185, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error      df t value Pr(>|t|)
(Intercept)                     89.595      1.663 104.881  53.882   <2e-16 ***
allocation_groupGrupo B          2.775      2.336 104.881   1.188   0.2375
visit2                          -1.208      1.504 111.576  -0.803   0.4238
visit3                          -3.713      1.545 112.106  -2.403   0.0179 *
allocation_groupGrupo B:visit2  -2.813      2.130 112.538  -1.321   0.1893
allocation_groupGrupo B:visit3   1.435      2.220 113.267   0.647   0.5192
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.371  0.264
visit3      -0.362  0.257  0.448
allctn_GB:2  0.262 -0.368 -0.706 -0.317
allctn_GB:3  0.252 -0.353 -0.312 -0.696  0.451
```

```r
summary(mean_bp_mean_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: mean_bp_mean ~ allocation_group * visit + (1 | record_id)
   Data: data_model
 Subset: !(record_id %in% mean_bp_mean_model_check$influential_ids)

REML criterion at convergence: 1154
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.93844 -0.57618 -0.01579  0.55161  1.94113

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 66.38    8.147
 Residual              25.49    5.049
Number of obs: 171, groups:  record_id, 70

Fixed effects:
                               Estimate Std. Error      df t value Pr(>|t|)
(Intercept)                      88.940      1.668  90.996  53.307  < 2e-16 ***
allocation_groupGrupo B           3.765      2.295  90.996   1.641  0.10434
visit2                           -2.137      1.375 101.567  -1.554  0.12337
visit3                           -4.528      1.440 102.162  -3.144  0.00218 **
allocation_groupGrupo B:visit2   -2.666      1.911 102.226  -1.395  0.16591
allocation_groupGrupo B:visit3    1.794      2.012 102.825   0.892  0.37455
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.727
visit2      -0.337  0.245
visit3      -0.321  0.234  0.451
allctn_GB:2  0.242 -0.333 -0.720 -0.324
allctn_GB:3  0.230 -0.316 -0.323 -0.716  0.453
```

```r
mean_bp_mean_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       89.6       1.66    53.9    2.88e-78
 2 Sensitivity (Intercept)                       88.9       1.67    53.3    2.03e-70
 3 Original    allocation_groupGrupo B            2.78      2.34     1.19   2.37e- 1
 4 Sensitivity allocation_groupGrupo B            3.76      2.29     1.64   1.04e- 1
 5 Original    allocation_groupGrupo B:visit2    -2.81      2.13    -1.32   1.89e- 1
 6 Sensitivity allocation_groupGrupo B:visit2    -2.67      1.91    -1.40   1.66e- 1
 7 Original    allocation_groupGrupo B:visit3     1.44      2.22     0.647  5.19e- 1
 8 Sensitivity allocation_groupGrupo B:visit3     1.79      2.01     0.892  3.75e- 1
 9 Original    sd__(Intercept)                    8.24     NA       NA     NA
10 Sensitivity sd__(Intercept)                    8.15     NA       NA     NA
11 Original    sd__Observation                    5.86     NA       NA     NA
12 Sensitivity sd__Observation                    5.05     NA       NA     NA
13 Original    visit2                            -1.21      1.50    -0.803  4.24e- 1
14 Sensitivity visit2                            -2.14      1.38    -1.55   1.23e- 1
15 Original    visit3                            -3.71      1.54    -2.40   1.79e- 2
16 Sensitivity visit3                            -4.53      1.44    -3.14   2.18e- 3
```

```r
performance::compare_performance(
    mean_bp_mean_model,
    mean_bp_mean_model_sens)
```

```
# Comparison of Model Performance Indices

Name                     |           Model |  AIC (weights) | AICc (weights) |  BIC (we
-----------------------------------------------------------------------------------------
mean_bp_mean_model       | lmerModLmerTest | 1318.4 (<.001) | 1319.2 (<.001) | 1344.2 (
mean_bp_mean_model_sens | lmerModLmerTest | 1184.7 (>.999) | 1185.6 (>.999) | 1209.8 (
```

```r
performance::check_model(mean_bp_mean_model)
```

Normality of Random Effects (record_id)
Dots should be plotted along the line


```r
performance::check_model(mean_bp_mean_model_sens)
```

3.0.16.2 Médias Marginais Estimadas

3.0.16.2.1 Todos os dados

```
# Get EMMs for each group at each visit
mean_bp_mean_raw_emm <- emmeans::emmeans(
    mean_bp_mean_model,
    ~ allocation_group * visit
```

```r
)

mean_bp_mean_raw_emm <- regrid(mean_bp_mean_raw_emm)

# Table of marginal means
# mean_bp_mean_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(mean_bp_mean_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -2.7754 2.34 105    -7.41    1.856  -1.188  0.2375

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.0381 2.52 125    -4.95    5.022   0.015  0.9880

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -4.2106 2.59 131    -9.34    0.922  -1.623  0.1070

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(mean_bp_mean_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     1.21 1.51 105  -2.4559     4.87   0.802  1.0000
 visit1 - visit3     3.71 1.55 105  -0.0494     7.48   2.401  0.0543
 visit2 - visit3     2.51 1.60 125  -1.3844     6.39   1.563  0.3618

allocation_group = Grupo B:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     4.02 1.51 105   0.3469     7.70   2.662  0.0269
 visit1 - visit3     2.28 1.60 105  -1.6056     6.16   1.427  0.4697
 visit2 - visit3    -1.74 1.62 127  -5.6828     2.20  -1.074  0.8549

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(mean_bp_mean_raw_emm, comparisons = TRUE)
```

3.0.16.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
mean_bp_mean_emm <- emmeans::emmeans(
    mean_bp_mean_model_sens,
    ~ allocation_group * visit
)

mean_bp_mean_emm <- regrid(mean_bp_mean_emm)

# Table of marginal means
# mean_bp_mean_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(mean_bp_mean_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -3.76 2.29  91.4    -8.32    0.793  -1.641  0.1043

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -1.10 2.45 107.3    -5.96    3.758  -0.448  0.6548

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -5.56 2.53 115.6   -10.57   -0.548  -2.197  0.0300

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(mean_bp_mean_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     2.14 1.38  91.4   -1.221     5.49   1.552  0.3722
 visit1 - visit3     4.53 1.44  91.4    1.012     8.04   3.141  0.0068
 visit2 - visit3     2.39 1.48 107.3   -1.202     5.98   1.619  0.3254

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     4.80 1.33  91.4    1.565     8.04   3.617  0.0015
 visit1 - visit3     2.73 1.41  91.4   -0.698     6.17   1.943  0.1654
 visit2 - visit3    -2.07 1.43 110.3   -5.540     1.40  -1.450  0.4495

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(mean_bp_mean_emm, comparisons = TRUE)
```

3.0.16.3 Resultado

No modelo ajustado para a média da pressão arterial, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. No entanto, observou-se uma redução da pressão arterial entre as visitas 1 e 2 no grupo Eclipta (diferença média de 4,02 mmHg; IC 95%: 0,35 a 7,70), e uma tendência à redução entre as visitas 1 e 3 no grupo placebo (diferença média de 3,71 mmHg; IC 95%: -0,05 a 7,48).

Na análise de sensibilidade, realizada com exclusão das observações mais influentes, foi identificada uma diferença significativa entre os grupos na visita 3, com o grupo Eclipta apresentando pressão arterial média 5,56 mmHg inferior ao grupo placebo (IC 95%: -10,57 a -0,55). A redução entre as visitas 1 e 3 no grupo placebo tornou-se significativa e mais pronunciada, com diferença de 4,53 mmHg (IC 95%: 1,01 a 8,04), e a diferença entre as visitas 1 e 2 no grupo Eclipta foi mantida (diferença de 4,80 mmHg; IC 95%: 1,57 a 8,04). Essas mudanças foram acompanhadas por melhora nos indicadores de ajuste do modelo. As melhorias nos indicadores de ajuste (AIC, BIC, RMSE e R^2) reforçam a adequação do modelo sensível.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentadas nas Tabelas Tabela 17 e Tabela 18.

Tabela 17: Diferenças estimadas da pressão arterial média entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-2,78	[-7,41 ; 1,86]	0,238
Entre grupos	Visita 2	0,04	[-4,95 ; 5,02]	0,988
Entre grupos	Visita 3	-4,21	[-9,34 ; 0,92]	0,107
Grupo Placebo	Visita 1 - Visita 2	1,21	[-2,46 ; 4,87]	1,000
Grupo Placebo	Visita 1 - Visita 3	3,71	[-0,05 ; 7,48]	0,054
Grupo Placebo	Visita 2 - Visita 3	2,51	[-1,38 ; 6,39]	0,362
Grupo Eclipta	Visita 1 - Visita 2	4,02	[0,35 ; 7,70]	0,027
Grupo Eclipta	Visita 1 - Visita 3	2,28	[-1,61 ; 6,16]	0,470
Grupo Eclipta	Visita 2 - Visita 3	-1,74	[-5,68 ; 2,20]	0,855

Tabela 18: Diferenças estimadas da pressão arterial média entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-3,76	[-8,32 ; 0,79]	0,104
Entre grupos	Visita 2	-1,10	[-5,96 ; 3,76]	0,655
Entre grupos	Visita 3	-5,56	[-10,57 ; -0,55]	0,030
Grupo Placebo	Visita 1 - Visita 2	2,14	[-1,22 ; 5,49]	0,372
Grupo Placebo	Visita 1 - Visita 3	4,53	[1,01 ; 8,04]	0,007
Grupo Placebo	Visita 2 - Visita 3	2,39	[-1,20 ; 5,98]	0,325
Grupo Eclipta	Visita 1 - Visita 2	4,80	[1,57 ; 8,04]	0,002
Grupo Eclipta	Visita 1 - Visita 3	2,73	[-0,70 ; 6,17]	0,165
Grupo Eclipta	Visita 2 - Visita 3	-2,07	[-5,54 ; 1,40]	0,450

```r
ggplot(
    data = data_model,
    aes(
        x = as.factor(visit),
        y = mean_bp_mean,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model %>%
    filter(
        !(record_id %in%
        mean_bp_mean_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = mean_bp_mean,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.17 Escore EVS

Variável: `evs_score`

```
# Plot 1: Raw data
evs_score_hist_1 <- data_model %>%
    filter(
        evs_score >0
    ) %>%
    ggplot(aes(x = evs_score)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
evs_score_hist_2 <- data_model %>%
     filter(
        evs_score >0
    ) %>%
```

```
    ggplot(aes(x = log1p(evs_score))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
evs_score_hist_1 + evs_score_hist_2 # library(patchwork)
```

```
# LMM

data_model_evs <- data_model %>%
  filter(evs_score > 0)

evs_score_model <- lmer(log1p(evs_score) ~ allocation_group * visit +
(1 | record_id), data = data_model_evs)
check_collinearity(evs_score_model)
```

```
# Check for Multicollinearity

Low Correlation
```

```
             Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
 allocation_group 2.02 [1.62, 2.66]         1.42      0.50     [0.38, 0.62]
            visit 3.96 [3.02, 5.35]         1.99      0.25     [0.19, 0.33]

Moderate Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
 allocation_group:visit 5.59 [4.18, 7.61]         2.36      0.18     [0.13, 0.24]
```

```r
# Sensitivity analysis
evs_score_model_check <- sensitivity_check_lmer(
    model = evs_score_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
evs_score_model_sens <- update(object = evs_score_model,
                               subset = !(record_id %in%
        evs_score_model_check$influential_ids))
# Influential IDS
evs_score_model_check$influential_ids
```

```
[1] "18" "44" "68" "50" "12"
```

3.0.17.1 Resumo dos modelos

```r
# Model comparison
summary(evs_score_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(evs_score) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_evs
```

```
REML criterion at convergence: 196.5

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.5002 -0.4282  0.1341  0.4983  1.9054

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.1002   0.3166
 Residual              0.1919   0.4380
Number of obs: 123, groups:  record_id, 56

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      5.45023    0.12407 113.97017  43.927   <2e-16 ***
allocation_groupGrupo B         -0.07889    0.16813 112.03406  -0.469    0.640
visit2                          -0.06127    0.14094  79.06500  -0.435    0.665
visit3                           0.09117    0.14936  76.96426   0.610    0.543
allocation_groupGrupo B:visit2   0.12742    0.19735  80.22191   0.646    0.520
allocation_groupGrupo B:visit3  -0.01678    0.20995  78.03049  -0.080    0.937
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.738
visit2      -0.678  0.501
visit3      -0.621  0.458  0.554
allctn_GB:2  0.484 -0.644 -0.714 -0.396
allctn_GB:3  0.442 -0.587 -0.394 -0.711  0.520
```

```r
summary(evs_score_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(evs_score) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_evs
 Subset: !(record_id %in% evs_score_model_check$influential_ids)

REML criterion at convergence: 136.4

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.47567 -0.51463  0.07711  0.49472  2.15838

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.06004  0.2450
 Residual              0.13788  0.3713
Number of obs: 109, groups:  record_id, 51

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                      5.57355    0.10898 100.91854  51.145   <2e-16 ***
allocation_groupGrupo B         -0.12141    0.14669  99.63237  -0.828    0.410
visit2                          -0.12042    0.12666  66.59739  -0.951    0.345
visit3                           0.06011    0.13576  64.41769   0.443    0.659
allocation_groupGrupo B:visit2   0.09871    0.17636  68.03387   0.560    0.578
allocation_groupGrupo B:visit3  -0.05185    0.18957  65.91159  -0.274    0.785
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.743
visit2      -0.689  0.512
visit3      -0.623  0.463  0.543
allctn_GB:2  0.495 -0.658 -0.718 -0.390
allctn_GB:3  0.446 -0.594 -0.389 -0.716  0.513
```

```r
evs_score_model_check$comparison_table
```

```
# A tibble: 16 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                         5.45      0.124   43.9     2.81e-73
 2 Sensitivity (Intercept)                         5.57      0.109   51.1     5.58e-74
 3 Original    allocation_groupGrupo B          -0.0789     0.168   -0.469   6.40e- 1
 4 Sensitivity allocation_groupGrupo B          -0.121      0.147   -0.828   4.10e- 1
 5 Original    allocation_groupGrupo B:visit2    0.127      0.197    0.646   5.20e- 1
 6 Sensitivity allocation_groupGrupo B:visit2    0.0987     0.176    0.560   5.78e- 1
 7 Original    allocation_groupGrupo B:visit3   -0.0168     0.210   -0.0799  9.37e- 1
 8 Sensitivity allocation_groupGrupo B:visit3   -0.0519     0.190   -0.274   7.85e- 1
 9 Original    sd__(Intercept)                   0.317     NA       NA      NA
10 Sensitivity sd__(Intercept)                   0.245     NA       NA      NA
11 Original    sd__Observation                   0.438     NA       NA      NA
12 Sensitivity sd__Observation                   0.371     NA       NA      NA
13 Original    visit2                           -0.0613     0.141   -0.435   6.65e- 1
14 Sensitivity visit2                           -0.120      0.127   -0.951   3.45e- 1
15 Original    visit3                            0.0912     0.149    0.610   5.43e- 1
16 Sensitivity visit3                            0.0601     0.136    0.443   6.59e- 1
```

```r
performance::compare_performance(
    evs_score_model,
```

```
    evs_score_model_sens)
```

```
# Comparison of Model Performance Indices

Name                 |           Model |  AIC (weights) | AICc (weights) |  BIC (weigh
-----------------------------------------------------------------------------------------
evs_score_model      | lmerModLmerTest | 1532.6 (<.001) | 1533.9 (<.001) | 1555.1 (<.0
evs_score_model_sens | lmerModLmerTest | 1332.9 (>.999) | 1334.3 (>.999) | 1354.4 (>.9
```

```
performance::check_model(evs_score_model)
```

```
performance::check_model(evs_score_model_sens)
```

3.0.17.2 Médias Marginais Estimadas

3.0.17.2.1 Todos os dados

```
# Get EMMs for each group at each visit
evs_score_raw_emm <- emmeans::emmeans(
    evs_score_model,
    ~ allocation_group * visit
```

```r
)

evs_score_raw_emm <- regrid(evs_score_raw_emm)

# Table of marginal means
# evs_score_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(evs_score_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     17.7 38.0 109    -57.6     92.9   0.465  0.6426

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -10.9 35.2 104    -80.8     59.0  -0.309  0.7579

visit = 3:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     23.3 42.9 113    -61.8    108.3   0.542  0.5889

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(evs_score_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     13.8 32.2 104    -64.5     92.2   0.430  1.0000
 visit1 - visit3    -22.2 36.6 113   -111.1     66.7  -0.607  1.0000
 visit2 - visit3    -36.1 33.2 104   -116.9     44.7  -1.086  0.8402

allocation_group = Grupo B:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -14.7 30.9 108    -89.9     60.4  -0.476  1.0000
 visit1 - visit3    -16.6 33.4 109    -97.7     64.5  -0.498  1.0000
 visit2 - visit3     -1.9 33.6 108    -83.7     79.9  -0.057  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(evs_score_raw_emm, comparisons = TRUE)
```

3.0.17.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
evs_score_emm <- emmeans::emmeans(
    evs_score_model_sens,
    ~ allocation_group * visit
)

evs_score_emm <- regrid(evs_score_emm)

# Table of marginal means
# evs_score_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(evs_score_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    30.11 36.9  98.3    -43.1    103.3   0.816  0.4163

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     5.24 31.5  94.7    -57.4     67.8   0.166  0.8684

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    44.49 40.5 101.1    -35.9    124.9   1.098  0.2750

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
```

```
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(evs_score_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    29.88 32.1  94.7    -48.3    108.0   0.932  1.0000
 visit1 - visit3   -16.32 37.1 101.1   -106.6     73.9  -0.440  1.0000
 visit2 - visit3   -46.20 33.1  94.7   -127.0     34.6  -1.394  0.5001

allocation_group = Grupo B:
 contrast        estimate   SE    df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     5.01 28.5  97.7    -64.4     74.4   0.176  1.0000
 visit1 - visit3    -1.93 31.2  98.3    -77.9     74.0  -0.062  1.0000
 visit2 - visit3    -6.95 30.4  97.7    -80.9     67.0  -0.229  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```r
# Plot of marginal means
plot(evs_score_emm, comparisons = TRUE)
```

```
ggplot(
    data = data_model_evs,
    aes(
        x = as.factor(visit),
        y = evs_score,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
```

```
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))


data_model_evs %>%
    filter(
        !(record_id %in%
        evs_score_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = evs_score,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
```

```
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
    #coord_cartesian(ylim = c(10, 150))
```

3.0.17.3 EVS - modelo em 2 partes

```
data_model_evs <- data_model %>%
  mutate(
    exercised = if_else(evs_score > 0, 1, 0)
  )


model_part1 <- glmer(
```

```r
  exercised ~ allocation_group * visit + (1 | record_id),
  data = data_model_evs,
  family = binomial
)

summary(model_part1)
```

```
What factors are associated with whether someone exercises at all during the week? Ger
What factors are associated with whether someone exercises at all during the week?  Fa
What factors are associated with whether someone exercises at all during the week? For
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? Sca
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? -2.
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? Ran
What factors are associated with whether someone exercises at all during the week?  Gr
What factors are associated with whether someone exercises at all during the week?  re
What factors are associated with whether someone exercises at all during the week? Num
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? Fix
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? (In
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? vis
```

```
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? ---
What factors are associated with whether someone exercises at all during the week? Sig
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? Cor
What factors are associated with whether someone exercises at all during the week?
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? all
```

```r
data_model_evs_active <- data_model_evs %>%
  filter(evs_score > 0)

model_part2 <- lmer(
  log(evs_score) ~ allocation_group * visit + (1 | record_id),
  data = data_model_evs_active
)

summary(model_part2)
```

```
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
```

Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (
Among those who do exercise, what factors are associated with how much they exercise (

3.0.17.3.1 Resultado

Para analisar o escore de atividade física semanal (evs_score), que representa o produto entre os dias por semana e os minutos por dia de exercício relatados por cada participante, foi adotado um

modelo em dois estágios. Esta abordagem se mostrou mais adequada devido à presença de 33.9% de valores iguais a zero (pacientes inativos) e à distribuição assimétrica dos valores positivos (pacientes ativos).

No primeiro estágio, foi ajustado um modelo de regressão logística mista com intercepto aleatório por participante para estimar a probabilidade de o participante relatar qualquer atividade física (evs_score > 0). Observou-se que, independentemente do grupo, a chance de relatar exercício aumentou significativamente na visita 2 (OR ≈ 24, p = 0,002) e, em menor grau, na visita 3 (p = 0,046) em comparação à visita 1. No entanto, não houve efeito significativo do grupo de intervenção (Grupo B) nem interações significativas entre grupo e visita, indicando que o aumento da atividade física ao longo do tempo pode estar relacionado a outros fatores (por exemplo, efeito de acompanhamento ou motivação decorrente da participação no estudo).

No segundo estágio, foi ajustado um modelo linear misto com intercepto aleatório por participante, incluindo apenas os participantes que relataram evs_score > 0, utilizando a transformação logarítmica dos minutos semanais de exercício como variável dependente. Neste modelo, nenhuma diferença significativa foi observada entre os grupos ou ao longo do tempo em relação à quantidade de exercício realizada entre os participantes ativos. Ou seja, embora mais participantes tenham relatado prática de atividade física nas visitas seguintes, a duração total semanal entre aqueles que se exercitavam permaneceu estável.

Esses resultados sugerem que o efeito observado ao longo do tempo se concentrou em uma maior adesão à prática de atividade física, mas não em um aumento da quantidade entre os que já praticavam.

4 Variáveis coletadas na primeira e terceira visitas

4.0.1 Ângulo de Fase

Variável: `phase_angle`

```
# Plot 1: Raw data
phase_angle_hist_1 <- data_model_V1V3 %>%
    filter(
```

```
        phase_angle < 300
    ) %>%
    ggplot(aes(x = phase_angle)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
phase_angle_hist_2 <- data_model_V1V3 %>%
    filter(
        phase_angle < 300
    ) %>%
    ggplot(aes(x = log1p(phase_angle))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
phase_angle_hist_1 + phase_angle_hist_2 # library(patchwork)
```

```
# LMM
phase_angle_model <- lmer(log1p(phase_angle) ~ allocation_group * visit +
```

```r
(1 | record_id), data = data_model_V1V3)
check_collinearity(phase_angle_model)
```

```
# Check for Multicollinearity

Low Correlation

                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.07 [1.01, 1.97]         1.04      0.93     [0.51, 0.99]
                  visit 1.86 [1.51, 2.46]         1.37      0.54     [0.41, 0.66]
 allocation_group:visit 1.93 [1.55, 2.54]         1.39      0.52     [0.39, 0.64]
```

```r
# Sensitivity analysis
phase_angle_model_check <- sensitivity_check_lmer(
    model = phase_angle_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
phase_angle_model_sens <- update(object = phase_angle_model,
                                 subset = !(record_id %in%
        phase_angle_model_check$influential_ids))
# Influential IDS
phase_angle_model_check$influential_ids
```

```
[1] "38" "46" "50" "74" "58"
```

4.0.1.1 Resumo dos modelos

```r
# Model comparison
summary(phase_angle_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(phase_angle) ~ allocation_group * visit + (1 | record_id)
```

```
   Data: data_model_V1V3

REML criterion at convergence: -221.5

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.3340 -0.3586  0.0353  0.3389  3.5151

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.010030 0.10015
 Residual              0.002521 0.05021
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                     2.021165   0.018418 82.634225 109.738   <2e-16 ***
allocation_groupGrupo B        -0.045637   0.025875 82.634225  -1.764   0.0815 .
visit3                         -0.011701   0.013479 49.678850  -0.868   0.3895
allocation_groupGrupo B:visit3  0.007182   0.019804 50.362921   0.363   0.7184
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.712
visit3      -0.274  0.195
allctn_GB:3  0.187 -0.262 -0.681
```

```r
summary(phase_angle_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(phase_angle) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3
 Subset: !(record_id %in% phase_angle_model_check$influential_ids)

REML criterion at convergence: -274.5

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.89890 -0.42265  0.07545  0.42996  1.44461

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.006874 0.08291
 Residual              0.001001 0.03163
Number of obs: 116, groups:  record_id, 70

Fixed effects:
                                Estimate Std. Error        df t value Pr(>|t|)
(Intercept)                     2.008697   0.015448 74.173320 130.033   <2e-16 ***
allocation_groupGrupo B        -0.045312   0.021248 74.173320  -2.133   0.0363 *
visit3                         -0.018047   0.009238 46.006589  -1.954   0.0569 .
allocation_groupGrupo B:visit3  0.017523   0.013049 46.227426   1.343   0.1859
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
```

```
allctn_grGB -0.727
visit3      -0.212  0.154
allctn_GB:3  0.150 -0.207 -0.708
```

```r
phase_angle_model_check$comparison_table
```

```
# A tibble: 12 x 6
   Model       term                           estimate std.error statistic   p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                       2.02      0.0184    110.     2.68e-91
 2 Sensitivity (Intercept)                       2.01      0.0154    130.     2.82e-89
 3 Original    allocation_groupGrupo B        -0.0456    0.0259     -1.76   8.15e- 2
 4 Sensitivity allocation_groupGrupo B        -0.0453    0.0212     -2.13   3.63e- 2
 5 Original    allocation_groupGrupo B:visit3  0.00718   0.0198      0.363  7.18e- 1
 6 Sensitivity allocation_groupGrupo B:visit3  0.0175    0.0130      1.34   1.86e- 1
 7 Original    sd__(Intercept)                  0.100    NA          NA     NA
 8 Sensitivity sd__(Intercept)                  0.0829   NA          NA     NA
 9 Original    sd__Observation                  0.0502   NA          NA     NA
10 Sensitivity sd__Observation                  0.0316   NA          NA     NA
11 Original    visit3                         -0.0117    0.0135     -0.868  3.90e- 1
12 Sensitivity visit3                         -0.0180    0.00924    -1.95   5.69e- 2
```

```r
performance::compare_performance(
    phase_angle_model,
    phase_angle_model_sens)
```

```
# Comparison of Model Performance Indices

Name                    |           Model | AIC (weights) | AICc (weights) | BIC (weigh
-----------------------------------------------------------------------------------------
phase_angle_model       | lmerModLmerTest | 262.3 (<.001) |  263.0 (<.001) | 279.3 (<.0
phase_angle_model_sens  | lmerModLmerTest | 168.0 (>.999) |  168.8 (>.999) | 184.5 (>.9
```

```r
performance::check_model(phase_angle_model)
```

```r
performance::check_model(phase_angle_model_sens)
```

4.0.1.2 Médias Marginais Estimadas

4.0.1.2.1 Todos os dados

```
# Get EMMs for each group at each visit
phase_angle_raw_emm <- emmeans::emmeans(
    phase_angle_model,
    ~ allocation_group * visit
```

```r
)

phase_angle_raw_emm <- regrid(phase_angle_raw_emm)

# Table of marginal means
# phase_angle_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(phase_angle_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.337 0.191 83.6  -0.0432    0.717   1.762  0.0817

visit = 3:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.281 0.206 99.1  -0.1277    0.691   1.365  0.1754

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(phase_angle_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   0.0878 0.101 83.6   -0.113    0.289   0.868  0.3880
```

```
allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   0.0325 0.105 83.6   -0.175    0.240   0.311  0.7566

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(phase_angle_raw_emm, comparisons = TRUE)
```

4.0.1.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
phase_angle_emm <- emmeans::emmeans(
    phase_angle_model_sens,
    ~ allocation_group * visit
)

phase_angle_emm <- regrid(phase_angle_emm)
```

```r
# Table of marginal means
# phase_angle_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(phase_angle_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.330 0.155 73.9   0.0211    0.639   2.129  0.0366

visit = 3:
 contrast          estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.201 0.163 86.3  -0.1229    0.524   1.233  0.2210

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(phase_angle_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate     SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3  0.13331 0.0682 73.9 -0.00255    0.269   1.955  0.0543

allocation_group = Grupo B:
 contrast        estimate     SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3  0.00373 0.0657 73.9 -0.12725    0.135   0.057  0.9549
```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(phase_angle_emm)
```

4.0.1.3 Resultado

No modelo ajustado para o desfecho primário do estudo, o ângulo de fase, observou-se uma tendência à diferença entre os grupos na visita 1 (estimativa = 0,34; IC 95% [-0,04 ; 0,72]), embora sem significância estatística. Na visita 3, as médias estimadas também foram semelhantes entre os grupos (estimativa = 0,28; IC 95% [-0,13 ; 0,69]). Dentro de cada grupo, não foram detectadas mudanças significativas ao longo do tempo.

A análise de sensibilidade, com exclusão de observações influentes, revelou um aumento da magnitude do efeito entre os grupos na visita 1, com significância estatística (estimativa = 0,33; IC 95% [0,02 ; 0,64]), sugerindo que o grupo placebo apresentou valores de ângulo de fase ligeiramente superiores no início do estudo. As demais comparações permaneceram não significativas, e as estimativas dentro dos grupos ao longo do tempo se mantiveram estáveis.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 19 e Tabela 20

Tabela 19: Diferenças estimadas do ângulo de fase entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo (todos os dados)

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,34	[-0,04 ; 0,72]	0,082
Entre grupos	Visita 3	0,28	[-0,13 ; 0,69]	0,175
Grupo Placebo	Visita 1 - Visita 3	0,09	[-0,11 ; 0,29]	0,388
Grupo Eclipta	Visita 1 - Visita 3	0,03	[-0,18 ; 0,24]	0,757

Tabela 20: Diferenças estimadas do ângulo de fase entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo (Análise de sensibilidade)

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,33	[0,02 ; 0,64]	0,037
Entre grupos	Visita 3	0,20	[-0,12 ; 0,52]	0,221
Grupo Placebo	Visita 1 - Visita 3	0,13	[-0,00 ; 0,27]	0,054
Grupo Eclipta	Visita 1 - Visita 3	0,00	[-0,13 ; 0,14]	0,955

```
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = phase_angle,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
```

```
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        phase_angle_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = phase_angle,
            group = record_id,
```

```
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

4.0.2 Reatância

Variável: `reactance`

```
# Plot 1: Raw data
reactance_hist_1 <- data_model_V1V3 %>%
```

```
    #filter(
    #    reactance < 300
    #) %>%
    ggplot(aes(x = reactance)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
reactance_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    reactance < 300
    #) %>%
    ggplot(aes(x = log1p(reactance))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
reactance_hist_1 + reactance_hist_2 # library(patchwork)
```

```r
# LMM
reactance_model <- lmer(log1p(reactance) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(reactance_model)
```

```
# Check for Multicollinearity

Low Correlation

                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.12 [1.02, 1.68]         1.06      0.90     [0.60, 0.98]
                  visit 1.87 [1.52, 2.47]         1.37      0.53     [0.41, 0.66]
 allocation_group:visit 1.97 [1.58, 2.60]         1.40      0.51     [0.38, 0.63]
```

```r
# Sensitivity analysis
reactance_model_check <- sensitivity_check_lmer(
    model = reactance_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
reactance_model_sens <- update(object = reactance_model,
                               subset = !(record_id %in%
        reactance_model_check$influential_ids))
# Influential IDS
reactance_model_check$influential_ids
```

```
[1] "22" "50" "74" "1"  "31"
```

4.0.2.1 Resumo dos modelos

```r
# Model comparison
summary(reactance_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(reactance) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: -154.5

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.01721 -0.46574  0.01052  0.54712  2.07167

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.013481 0.11611
 Residual              0.005657 0.07522
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    4.10499    0.02274 86.69858 180.493   <2e-16 ***
allocation_groupGrupo B       -0.01206    0.03195 86.69858  -0.377    0.707
visit3                        -0.01119    0.02006 49.12966  -0.558    0.579
allocation_groupGrupo B:visit3  0.01600    0.02942 50.14982   0.544    0.589
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.712
visit3      -0.335  0.239
allctn_GB:3  0.229 -0.321 -0.682
```

```r
summary(reactance_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(reactance) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3
 Subset: !(record_id %in% reactance_model_check$influential_ids)

REML criterion at convergence: -179.8

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.59721 -0.57888  0.01363  0.51723  1.65081

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.008423 0.09177
 Residual              0.004527 0.06728
Number of obs: 116, groups:  record_id, 70

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    4.12073    0.01924 85.06056 214.231   <2e-16 ***
allocation_groupGrupo B       -0.02913    0.02720 85.06056  -1.071    0.287
visit3                        -0.01607    0.01855 47.78854  -0.866    0.391
allocation_groupGrupo B:visit3  0.02453    0.02730 48.84683   0.899    0.373
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
```

```
allctn_grGB -0.707
visit3      -0.363  0.256
allctn_GB:3  0.246 -0.348 -0.680
```

```r
reactance_model_check$comparison_table
```

```
# A tibble: 12 x 6
   Model       term                           estimate std.error statistic    p.value
   <chr>       <chr>                             <dbl>     <dbl>     <dbl>      <dbl>
 1 Original    (Intercept)                        4.10    0.0227   180.     1.83e-113
 2 Sensitivity (Intercept)                        4.12    0.0192   214.     5.10e-118
 3 Original    allocation_groupGrupo B         -0.0121    0.0320    -0.377  7.07e-  1
 4 Sensitivity allocation_groupGrupo B         -0.0291    0.0272    -1.07   2.87e-  1
 5 Original    allocation_groupGrupo B:visit3   0.0160    0.0294     0.544  5.89e-  1
 6 Sensitivity allocation_groupGrupo B:visit3   0.0245    0.0273     0.899  3.73e-  1
 7 Original    sd__(Intercept)                   0.116   NA         NA     NA
 8 Sensitivity sd__(Intercept)                   0.0918  NA         NA     NA
 9 Original    sd__Observation                   0.0752  NA         NA     NA
10 Sensitivity sd__Observation                   0.0673  NA         NA     NA
11 Original    visit3                          -0.0112    0.0201    -0.558  5.79e-  1
12 Sensitivity visit3                          -0.0161    0.0185    -0.866  3.91e-  1
```

```r
performance::compare_performance(
    reactance_model,
    reactance_model_sens)
```

```
# Comparison of Model Performance Indices

Name                  |           Model | AIC (weights) | AICc (weights) | BIC (weights
-----------------------------------------------------------------------------------------
reactance_model       | lmerModLmerTest | 856.3 (<.001) |  857.0 (<.001) | 873.3 (<.001
reactance_model_sens | lmerModLmerTest | 758.9 (>.999) |  759.7 (>.999) | 775.5 (>.999
```

```
performance::check_model(reactance_model)
```

```
performance::check_model(reactance_model_sens)
```

4.0.2.2 Médias Marginais Estimadas

4.0.2.2.1 Todos os dados

```
# Get EMMs for each group at each visit
reactance_raw_emm <- emmeans::emmeans(
    reactance_model,
    ~ allocation_group * visit
```

```r
)

reactance_raw_emm <- regrid(reactance_raw_emm)

# Table of marginal means
# reactance_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(reactance_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.727 1.93  89.2    -3.10     4.55   0.377  0.7068

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.237 2.16 107.1    -4.51     4.04  -0.110  0.9128

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(reactance_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    0.675 1.21 89.2    -1.73     3.08   0.558  0.5785
```

```
allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.288 1.30 89.2    -2.87     2.29  -0.222  0.8247

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(reactance_raw_emm, comparisons = TRUE)
```

4.0.2.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
reactance_emm <- emmeans::emmeans(
    reactance_model_sens,
    ~ allocation_group * visit
)

reactance_emm <- regrid(reactance_emm)
```

```r
# Table of marginal means
# reactance_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(reactance_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.769 1.65  85.8    -1.52     5.05   1.071  0.2874

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.278 1.89 103.4    -3.46     4.02   0.147  0.8830

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(reactance_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    0.982 1.13 85.8    -1.27     3.24   0.865  0.3892

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.508 1.21 85.8    -2.91     1.90  -0.420  0.6756
```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(reactance_emm, comparisons = TRUE)
```

4.0.2.3 Resultado

No modelo ajustado para os valores de reatância, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados. As estimativas de diferença entre os grupos na visita 1 (estimativa = 0,73; IC 95% [-3,10 ; 4,55]) e na visita 3 (estimativa = -0,24; IC 95% [-4,51 ; 4,04]) apresentaram ampla sobreposição dos intervalos de confiança com zero. Da mesma forma, não foram identificadas mudanças significativas ao longo do tempo dentro de cada grupo.

A análise de sensibilidade não alterou substancialmente os resultados. Embora tenha havido um leve aumento da estimativa de diferença entre os grupos na visita 1 (estimativa = 1,77; IC 95% [-1,52 ; 5,05]), essa diferença continuou não significativa. As demais comparações permaneceram estáveis, sem alterações relevantes nas conclusões.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 21.

Tabela 21: Diferenças estimadas da reatância entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,73	[-3,10 ; 4,55]	0,707
Entre grupos	Visita 3	-0,24	[-4,51 ; 4,04]	0,913
Grupo Placebo	Visita 1 - Visita 3	0,68	[-1,73 ; 3,08]	0,579
Grupo Eclipta	Visita 1 - Visita 3	-0,29	[-2,87 ; 2,29]	0,825

```
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = reactance,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        reactance_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = reactance,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
```

```
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

4.0.3 Resistência

Variável: `resistance`

```
# Plot 1: Raw data
resistance_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    resistance < 300
    #) %>%
    ggplot(aes(x = resistance)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
```

```r
resistance_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    resistance < 300
    #) %>%
    ggplot(aes(x = log1p(resistance))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
resistance_hist_1 + resistance_hist_2 # library(patchwork)
```

```r
# LMM
resistance_model <- lmer(resistance ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(resistance_model)
```

```
# Check for Multicollinearity


Low Correlation
```

```
                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.09 [1.01, 1.82]         1.04      0.92     [0.55, 0.99]
                  visit 1.87 [1.51, 2.46]         1.37      0.54     [0.41, 0.66]
 allocation_group:visit 1.94 [1.56, 2.56]         1.39      0.52     [0.39, 0.64]
```

```r
# Sensitivity analysis
resistance_model_check <- sensitivity_check_lmer(
    model = resistance_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
resistance_model_sens <- update(object = resistance_model,
                                subset = !(record_id %in%
        resistance_model_check$influential_ids))
# Influential IDS
resistance_model_check$influential_ids
```

```
[1] "1"  "34" "46" "64" "4"
```

4.0.3.1 Resumo dos modelos

```r
# Model comparison
summary(resistance_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: resistance ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: 1326.5

Scaled residuals:
     Min       1Q   Median       3Q      Max
```

```
-3.15014 -0.38120  0.03119  0.40613  3.07461

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 3316.7   57.59
 Residual               992.1   31.50
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error      df t value Pr(>|t|)
(Intercept)                    524.476     10.791  85.554  48.601   <2e-16 ***
allocation_groupGrupo B         20.506     15.161  85.554   1.353    0.180
visit3                           2.234      8.438  51.500   0.265    0.792
allocation_groupGrupo B:visit3   4.651     12.392  52.296   0.375    0.709
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.712
visit3      -0.294  0.210
allctn_GB:3  0.201 -0.282 -0.681
```

```r
summary(resistance_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: resistance ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3
 Subset: !(record_id %in% resistance_model_check$influential_ids)

REML criterion at convergence: 1182.7
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.70853 -0.47972  0.04526  0.42531  1.76454

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 2489.5   49.90
 Residual               572.8   23.93
Number of obs: 116, groups:  record_id, 70

Fixed effects:
                              Estimate Std. Error      df t value Pr(>|t|)
(Intercept)                    531.866      9.354  77.137  56.860   <2e-16 ***
allocation_groupGrupo B          9.586     13.228  77.137   0.725    0.471
visit3                          -3.225      6.679  46.655  -0.483    0.631
allocation_groupGrupo B:visit3  10.852      9.855  47.200   1.101    0.276
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.707
visit3      -0.262  0.185
allctn_GB:3  0.178 -0.251 -0.678
```

```
resistance_model_check$comparison_table
```

```
# A tibble: 12 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
```

```
 1 Original    (Intercept)                      524.       10.8     48.6    4.33e-64
 2 Sensitivity (Intercept)                      532.        9.35    56.9    9.89e-65
 3 Original    allocation_groupGrupo B           20.5      15.2      1.35   1.80e- 1
 4 Sensitivity allocation_groupGrupo B            9.59     13.2      0.725  4.71e- 1
 5 Original    allocation_groupGrupo B:visit3     4.65     12.4      0.375  7.09e- 1
 6 Sensitivity allocation_groupGrupo B:visit3    10.9       9.85     1.10   2.76e- 1
 7 Original    sd__(Intercept)                   57.6      NA       NA     NA
 8 Sensitivity sd__(Intercept)                   49.9      NA       NA     NA
 9 Original    sd__Observation                   31.5      NA       NA     NA
10 Sensitivity sd__Observation                   23.9      NA       NA     NA
11 Original    visit3                             2.23      8.44     0.265  7.92e- 1
12 Sensitivity visit3                            -3.22      6.68    -0.483  6.31e- 1
```

```r
performance::compare_performance(
    resistance_model,
    resistance_model_sens)
```

```
# Comparison of Model Performance Indices

Name                   |           Model |  AIC (weights) | AICc (weights) |  BIC (weig
-----------------------------------------------------------------------------------------
resistance_model       | lmerModLmerTest | 1363.8 (<.001) | 1364.5 (<.001) | 1380.8 (<.
resistance_model_sens | lmerModLmerTest | 1218.5 (>.999) | 1219.3 (>.999) | 1235.0 (>.
```

```r
performance::check_model(resistance_model)
```

```
performance::check_model(resistance_model_sens)
```

4.0.3.2 Médias Marginais Estimadas

4.0.3.2.1 Todos os dados

```
# Get EMMs for each group at each visit
resistance_raw_emm <- emmeans::emmeans(
    resistance_model,
    ~ allocation_group * visit
```

```r
)

resistance_raw_emm <- regrid(resistance_raw_emm)

# Table of marginal means
# resistance_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(resistance_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -20.5 15.2  85.3    -50.6     9.64  -1.353  0.1798

visit = 3:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -25.2 16.7 101.9    -58.2     7.93  -1.508  0.1346

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(resistance_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    -2.23 8.45 85.3      -19     14.6  -0.264  0.7922
```

```
allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    -6.88 9.10 85.3      -25     11.2  -0.757  0.4514

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(resistance_raw_emm, comparisons = TRUE)
```

4.0.3.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
resistance_emm <- emmeans::emmeans(
    resistance_model_sens,
    ~ allocation_group * visit
)

resistance_emm <- regrid(resistance_emm)
```

```r
# Table of marginal means
# resistance_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(resistance_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -9.59 13.2 77.0    -35.9    16.76  -0.725  0.4709

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -20.44 14.4 91.8    -49.0     8.14  -1.420  0.1589

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(resistance_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE df lower.CL upper.CL t.ratio p.value
 visit1 - visit3     3.22 6.69 77    -10.1    16.55   0.482  0.6312

allocation_group = Grupo B:
 contrast        estimate   SE df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    -7.63 7.27 77    -22.1     6.84  -1.050  0.2970
```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(resistance_emm, comparisons = TRUE)
```

4.0.3.3 Resultado

No modelo ajustado para os valores de resistência bioelétrica corporal, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados. As estimativas de diferença entre os grupos foram de -20,5 ohms (IC 95%: -50,6 a 9,6) na visita 1 e -25,2 ohms (IC 95%: -58,2 a 7,9) na visita 3. Tampouco foram observadas mudanças significativas ao longo do tempo dentro de cada grupo.

A análise de sensibilidade, com exclusão das observações mais influentes, não alterou substancialmente os resultados. As estimativas permaneceram similares, com diferença entre os grupos de -9,6 ohms (IC 95%: -35,9 a 16,8) na visita 1 e -20,4 ohms (IC 95%: -49,0 a 8,1) na visita 3, também sem significância estatística. Da mesma forma, não houve mudanças significativas entre as visitas dentro de cada grupo. As estimativas e intervalos de confiança de 95% estão apresentados na Tabela Tabela 22.

Tabela 22: Diferenças estimadas nos valores de resistência elétrica entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-20,5	[-50,6 ; 9,6]	0,180
Entre grupos	Visita 3	-25,2	[-58,2 ; 7,9]	0,135
Grupo Placebo	Visita 1 - Visita 3	-2,23	[-19,0 ; 14,6]	0,792
Grupo Eclipta	Visita 1 - Visita 3	-6,88	[-25,0 ; 11,2]	0,451

```
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = resistance,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        resistance_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = resistance,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
```

```
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

4.0.4 Força de Preensão Palmar

Variável: `handgrip`

```
# Plot 1: Raw data
handgrip_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    handgrip < 300
    #) %>%
    ggplot(aes(x = handgrip)) +
    geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
```

```
handgrip_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    handgrip < 300
    #) %>%
    ggplot(aes(x = log1p(handgrip))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
handgrip_hist_1 + handgrip_hist_2 # library(patchwork)
```

```
# LMM
handgrip_model <- lmer(log1p(handgrip) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(handgrip_model)
```

```
# Check for Multicollinearity


Low Correlation
```

```
                    Term  VIF   VIF 95% CI Increased SE Tolerance Tolerance 95% CI
       allocation_group 1.06 [1.00, 2.22]         1.03      0.94     [0.45, 1.00]
                  visit 1.93 [1.56, 2.55]         1.39      0.52     [0.39, 0.64]
 allocation_group:visit 1.99 [1.60, 2.62]         1.41      0.50     [0.38, 0.62]
```

```r
# Sensitivity analysis
handgrip_model_check <- sensitivity_check_lmer(
    model = handgrip_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
handgrip_model_sens <- update(object = handgrip_model,
                              subset = !(record_id %in%
        handgrip_model_check$influential_ids))
# Influential IDS
handgrip_model_check$influential_ids
```

```
[1] "16" "23" "31" "72" "56"
```

4.0.4.1 Resumo dos modelos

```r
# Model comparison
summary(handgrip_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(handgrip) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: -36.3

Scaled residuals:
    Min      1Q  Median      3Q     Max
```

```
-3.2121 -0.2737  0.0096  0.3023  2.3599

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.05291  0.2300
 Residual              0.01046  0.1023
Number of obs: 127, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    3.51478    0.04138 81.97737  84.934   <2e-16 ***
allocation_groupGrupo B       -0.09908    0.05814 81.97737  -1.704   0.0921 .
visit3                         0.02794    0.02752 52.37961   1.015   0.3146
allocation_groupGrupo B:visit3 -0.07741    0.03962 52.70060  -1.954   0.0561 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.712
visit3      -0.248  0.177
allctn_GB:3  0.172 -0.242 -0.694
```

```r
summary(handgrip_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: log1p(handgrip) ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3
 Subset: !(record_id %in% handgrip_model_check$influential_ids)

REML criterion at convergence: -112.4
```

```
Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.07607 -0.35838  0.02018  0.31173  2.01345

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.037729 0.19424
 Residual              0.003193 0.05651
Number of obs: 117, groups:  record_id, 70

Fixed effects:
                              Estimate Std. Error       df t value Pr(>|t|)
(Intercept)                    3.49708    0.03372 70.87133 103.723   <2e-16 ***
allocation_groupGrupo B       -0.06327    0.04838 70.87133  -1.308    0.195
visit3                         0.02342    0.01559 45.19417   1.503    0.140
allocation_groupGrupo B:visit3 -0.01675    0.02329 45.40129  -0.719    0.476
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.697
visit3      -0.169  0.118
allctn_GB:3  0.113 -0.162 -0.669
```

```
handgrip_model_check$comparison_table
```

```
# A tibble: 12 x 6
   Model       term                            estimate std.error statistic   p.value
   <chr>       <chr>                              <dbl>     <dbl>     <dbl>     <dbl>
```

```
 1 Original    (Intercept)                      3.51      0.0414    84.9    1.11e-81
 2 Sensitivity (Intercept)                      3.50      0.0337   104.     3.80e-79
 3 Original    allocation_groupGrupo B         -0.0991    0.0581    -1.70   9.21e- 2
 4 Sensitivity allocation_groupGrupo B         -0.0633    0.0484    -1.31   1.95e- 1
 5 Original    allocation_groupGrupo B:visit3  -0.0774    0.0396    -1.95   5.61e- 2
 6 Sensitivity allocation_groupGrupo B:visit3  -0.0167    0.0233    -0.719  4.76e- 1
 7 Original    sd__(Intercept)                  0.230    NA         NA     NA
 8 Sensitivity sd__(Intercept)                  0.194    NA         NA     NA
 9 Original    sd__Observation                  0.102    NA         NA     NA
10 Sensitivity sd__Observation                  0.0565   NA         NA     NA
11 Original    visit3                           0.0279    0.0275     1.02   3.15e- 1
12 Sensitivity visit3                           0.0234    0.0156     1.50   1.40e- 1
```

```r
performance::compare_performance(
    handgrip_model,
    handgrip_model_sens)
```

```
# Comparison of Model Performance Indices

Name                |           Model | AIC (weights) | AICc (weights) | BIC (weights)
---------------------------------------------------------------------------------------
handgrip_model      | lmerModLmerTest | 834.9 (<.001) |  835.6 (<.001) | 851.9 (<.001)
handgrip_model_sens | lmerModLmerTest | 689.5 (>.999) |  690.3 (>.999) | 706.1 (>.999)
```

```r
performance::check_model(handgrip_model)
```

```
performance::check_model(handgrip_model_sens)
```

4.0.4.2 Médias Marginais Estimadas

4.0.4.2.1 Todos os dados

```
# Get EMMs for each group at each visit
handgrip_raw_emm <- emmeans::emmeans(
    handgrip_model,
    ~ allocation_group * visit
```

```r
)

handgrip_raw_emm <- regrid(handgrip_raw_emm)

# Table of marginal means
# handgrip_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(handgrip_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     3.17 1.87 81.9   -0.541     6.88   1.700  0.0930

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     5.59 1.97 95.8    1.672     9.51   2.832  0.0056

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(handgrip_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.952 0.943 81.9   -2.829    0.924  -1.009  0.3157
```

```
allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    1.469 0.844 81.9   -0.209    3.147   1.742  0.0853

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(handgrip_raw_emm)
```

4.0.4.2.2 Análise de sensibilidade

```r
# Get EMMs for each group at each visit (Sensitivity Analysis)
handgrip_emm <- emmeans::emmeans(
    handgrip_model_sens,
    ~ allocation_group * visit
)

handgrip_emm <- regrid(handgrip_emm)
```

```r
# Table of marginal means
# handgrip_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(handgrip_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.02 1.55 71.7   -1.061     5.11   1.308  0.1951

visit = 3:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.60 1.63 79.0   -0.644     5.84   1.595  0.1147

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(handgrip_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.782 0.523 71.7    -1.83    0.261  -1.495  0.1394

allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.208 0.540 71.7    -1.28    0.868  -0.385  0.7017
```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
```

```r
# Plot of marginal means
plot(handgrip_emm)
```

4.0.4.3 Resultado

No modelo ajustado para a força de preensão manual, observou-se uma diferença estatisticamente significativa entre os grupos na visita 3, com o grupo placebo apresentando força média 5,59 kgf superior ao grupo Eclipta (IC 95%: 1,67 a 9,51). Na visita 1, a diferença entre os grupos foi de 3,17 kgf (IC 95%: -0,54 a 6,88), sem alcançar significância estatística. Dentro de cada grupo, não foram observadas mudanças significativas ao longo do tempo.

Na análise de sensibilidade, os efeitos observados foram atenuados e perderam significância estatística. A diferença entre os grupos na visita 3 reduziu-se para 2,60 kgf (IC 95%: -0,64 a 5,84), e na visita 1 para 2,02 kgf (IC 95%: -1,06 a 5,11). Também não houve mudanças significativas entre as visitas dentro de cada grupo. Esses achados sugerem que os resultados observados no modelo completo podem ter sido influenciados por observações com alto impacto.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentadas nas Tabelas Tabela 23 e Tabela 24.

Tabela 23: Diferenças estimadas da força de preensão manual entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	3,17	[-0,54 ; 6,88]	0,093
Entre grupos	Visita 3	5,59	[1,67 ; 9,51]	0,006
Grupo Placebo	Visita 1 - Visita 3	-0,95	[-2,83 ; 0,92]	0,316
Grupo Eclipta	Visita 1 - Visita 3	1,47	[-0,21 ; 3,15]	0,085

Tabela 24: Diferenças estimadas da força de preensão manual entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,02	[-1,06 ; 5,11]	0,195
Entre grupos	Visita 3	2,60	[-0,64 ; 5,84]	0,115
Grupo Placebo	Visita 1 - Visita 3	-0,78	[-1,83 ; 0,26]	0,139
Grupo Eclipta	Visita 1 - Visita 3	-0,21	[-1,28 ; 0,87]	0,702

```
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = handgrip,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
```

```
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        handgrip_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = handgrip,
            group = record_id,
        )
    ) +
```

```
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

5 Informações da Sessão

```
sessionInfo()
```

```
R version 4.4.1 (2024-06-14)
Platform: aarch64-apple-darwin20
Running under: macOS 15.5
```

```
Matrix products: default
BLAS:   /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRblas.0.dy
LAPACK: /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRlapack.dy

locale:
[1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8

time zone: America/Sao_Paulo
tzcode source: internal

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] kableExtra_1.4.0.12 knitr_1.50          broom.mixed_0.2.9.6 influence.ME_0.9-9  e
 [9] skimr_2.1.5         lmerTest_3.1-3      lme4_1.1-37         Matrix_1.7-0        h
[17] stringr_1.5.1       dplyr_1.1.4.9000    purrr_1.0.4         readr_2.1.5         t

loaded via a namespace (and not attached):
 [1] tidyselect_1.2.1    viridisLite_0.4.2   farver_2.1.2        fastmap_1.2.0       T
 [9] estimability_1.5.1  lifecycle_1.0.4     survival_3.7-0      magrittr_2.0.3      c
[17] yaml_2.3.10         labeling_0.4.3      xml2_1.3.8          repr_1.1.7          m
[25] grid_4.4.1          xtable_1.8-4        colorspace_2.1-1    future_1.34.0       g
[33] cli_3.6.5           mvtnorm_1.3-3       rmarkdown_2.29      reformulas_0.4.1    g
[41] splines_4.4.1       parallel_4.4.1      cellranger_1.1.0    base64enc_0.1-3     v
[49] hms_1.1.3           pbkrtest_0.5.4      ggrepel_0.9.6       listenv_0.9.1       s
[57] nloptr_2.2.1        codetools_0.2-20    stringi_1.8.7       gtable_0.3.6        m
[65] R6_2.6.1            textshaping_0.4.0   Rdpack_2.6.4        rprojroot_2.0.4     e
[73] broom_1.0.7         Rcpp_1.0.14         svglite_2.2.1       coda_0.19-4.1       r
```

[81] pkgconfig_2.0.3