Supplement 3

Descriptive statistics on participant follow-up

Peter Kamerman and Prinisha Pillay

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Contents

This analysis describes the follow-up pattern of participants in the study.

Import data

```
data <- read_rds('data-cleaned/clean_data.rds') %>%
    # Select columns
    select(ID, visit_number, visit_day, visit_months, hivsn_present)
```

Process data

Add a column indicating whether a participant developed SN at any time during the follow-up period.

```
# Identify andf extract information on SN development (at anytime)
# by looking at the presence of SN at the final visit
data_sn <- data %>%
    select(ID, visit_number, hivsn_present) %>%
    group_by(ID) %>%
    mutate(max_visit = max(visit_number)) %>%
    filter(visit_number == max_visit) %>%
    select(ID, hivsn_present) %>%
    rename(sn = hivsn_present)
```

```
# Join data_sn to data
data %<>%
    left_join(data_sn)
```

Inspect data

```
# Dimensions
dim(data)
```

```
## [1] 371   6
```

```
# Column names
names(data)
```

```
## [1] "ID"            "visit_number"  "visit_day"     "visit_months"
## [5] "hivsn_present" "sn"
```

```
# Head and tail
head(data)
```

```
## # A tibble: 6 x 6
##   ID    visit_number visit_day visit_months hivsn_present sn
##   <chr>        <int>     <int>        <dbl> <fct>         <fct>
## 1 001              1         0            0 no            no
## 2 001              2        40            1 no            no
## 3 001              3       210            7 no            no
## 4 002              1         0            0 no            no
## 5 002              2        71            2 no            no
## 6 002              3       191            6 no            no
```

```
tail(data)
```

```
## # A tibble: 6 x 6
##   ID    visit_number visit_day visit_months hivsn_present sn
##   <chr>        <int>     <int>        <dbl> <fct>         <fct>
## 1 119              1         0            0 no            no
## 2 119              2        72            2 no            no
## 3 119              3       132            4 no            no
## 4 120              1         0            0 no            no
## 5 120              2        88            3 no            no
## 6 120              3       124            4 no            no
```

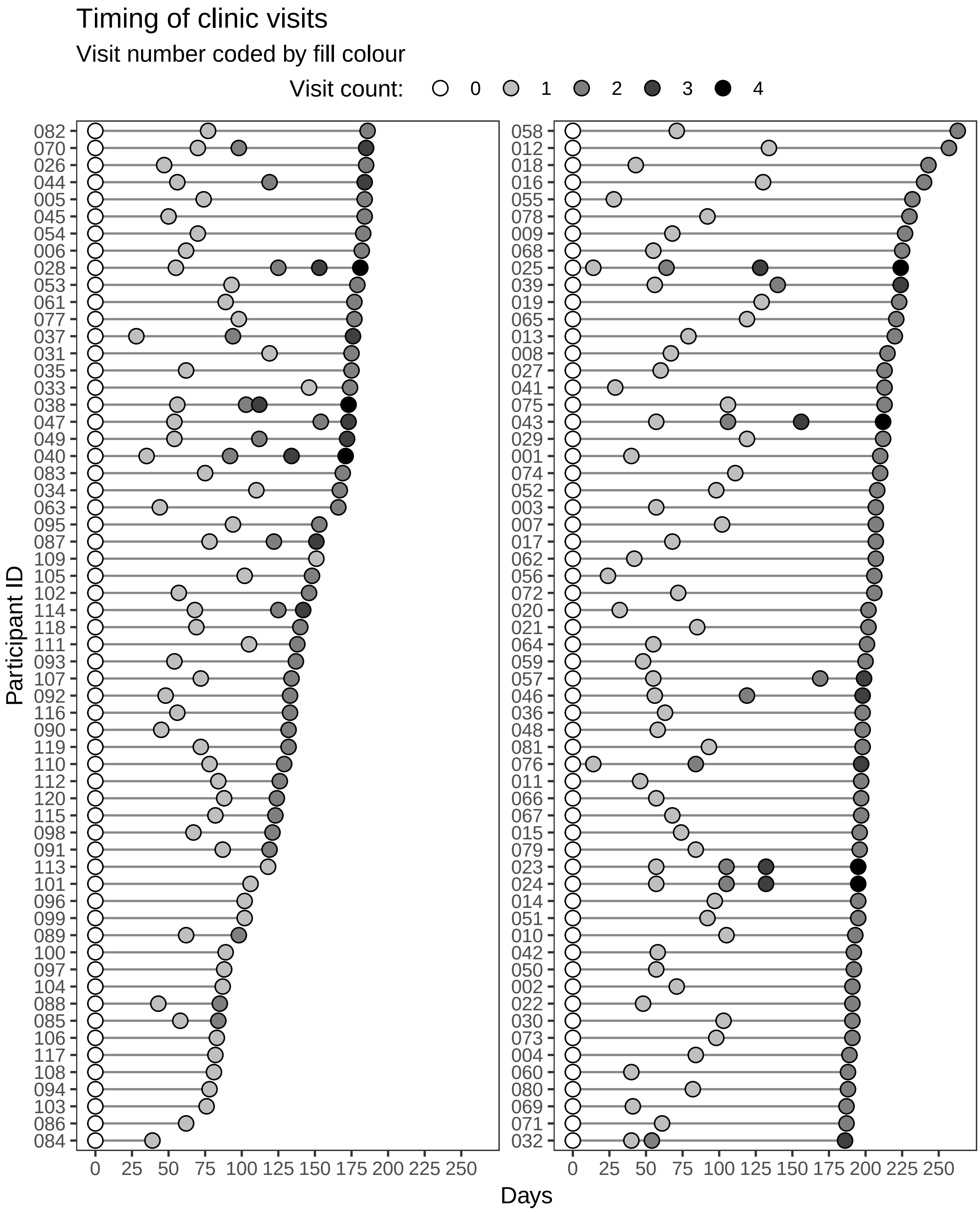
```
# Data structure
glimpse(data)
```

```
## Observations: 371
## Variables: 6
## $ ID            <chr> "001", "001", "001", "002", "002", "002", "003",...
## $ visit_number  <int> 1, 2, 3, 1, 2, 3, 1, 2, 3, 1, 2, 3, 1, 2, 3, 1, ...
## $ visit_day     <int> 0, 40, 210, 0, 71, 191, 0, 57, 207, 0, 84, 189, ...
## $ visit_months  <dbl> 0, 1, 7, 0, 2, 6, 0, 2, 7, 0, 3, 6, 0, 2, 6, 0, ...
## $ hivsn_present <fct> no, no, no, no, no, no, no, no, no, no, no, no, ...
## $ sn            <fct> no, no, no, no, no, no, no, no, no, no, no, no, ...
```

Clinic visits

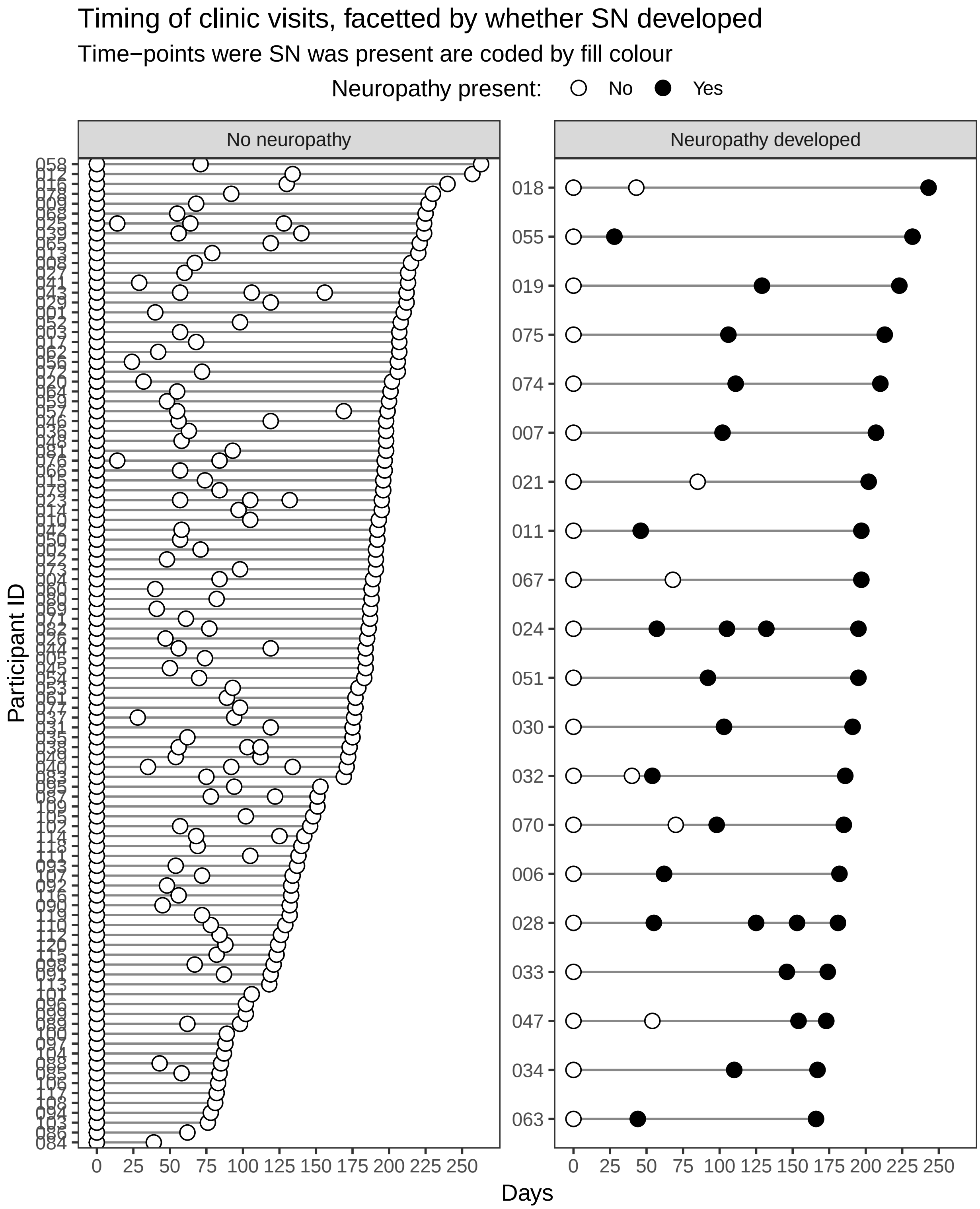
Whole cohort

```
data %>%
    # Process data for plotting
    group_by(ID) %>%
    mutate(visit = ifelse(visit_day > 0,
                          yes = 1,
                          no = 0),
           visit_count = cumsum(visit),
           max_visits = max(visit_count),
           max_duration = max(visit_day)) %>%
    ungroup() %>%
    select(ID, visit_day, visit_months,
           visit_count, max_visits,
           max_duration) %>%
    # Clean-up and order dataframe
    arrange(max_duration, max_visits, desc(ID)) %>%
    mutate(ID = as_factor(ID),
           visit_count = as.character(visit_count)) %>%
    complete(ID, visit_months) %>%
    # Add a dummy variable for faceting
    bind_cols(facet = c(rep('Panel 1', 600), rep('Panel 2', 1202-600))) %>%
    # Clean-up and order dataframe
    filter(complete.cases(.)) %>%
    # Plot
    ggplot(data = .) +
    aes(x = visit_day,
        y = ID) +
    geom_path(colour = '#888888') +
    geom_point(aes(fill = visit_count),
               shape = 21,
               size = 3) +
    scale_x_continuous(breaks = seq(0, 250, 25)) +
    scale_fill_manual(name = 'Visit count: ', values = grey_pal) +
    labs(title = 'Timing of clinic visits',
         subtitle = 'Visit number coded by fill colour',
         y = 'Participant ID',
         x = 'Days') +
    facet_wrap(~facet,
               ncol = 2,
               scales = 'free_y') +
    theme(legend.position = 'top',
          legend.margin = margin(t = -0.3,
                                 r = 0,
                                 b = -0.3,
                                 l = 0, 'lines'),
          panel.grid = element_blank(),
          strip.background = element_blank(),
          strip.text = element_blank())
```



By SN status

```
data_plot <- data %>%
    # Process data for plotting
    group_by(ID) %>%
    mutate(visit = ifelse(visit_day > 0,
                          yes = 1,
                          no = 0),
           visit_count = cumsum(visit),
           max_visits = max(visit_count),
           max_duration = max(visit_day)) %>%
    ungroup() %>%
    select(ID, hivsn_present, visit_day, visit_months,
           visit_count, max_visits,
           max_duration, sn) %>%
    # Clean-up and order dataframe
    arrange(max_duration, max_visits, desc(ID)) %>%
    mutate(ID = as_factor(ID),
           visit_count = as.character(visit_count)) %>%
    complete(ID, visit_months) %>%
    # Clean-up and order dataframe
    filter(complete.cases(.)) %>%
    # Recode facetting column
    mutate(sn = as.character(sn),
           sn = ifelse(sn == 'yes',
                       yes = 'Neuropathy developed',
                       no = 'No neuropathy'),
           sn = factor(sn,
                       levels = c('No neuropathy', 'Neuropathy developed'),
                       ordered = TRUE)) %>%
    mutate(hivsn_present = str_to_title(hivsn_present))

# Plot
ggplot(data = data_plot) +
    aes(x = visit_day,
        y = ID) +
    geom_path(colour = '#888888') +
    geom_point(aes(fill = hivsn_present),
               shape = 21,
               size = 3) +
    labs(title = 'Timing of clinic visits, facetted by whether SN developed',
         subtitle = 'Time-points were SN was present are coded by fill colour',
         x = 'Days',
         y = 'Participant ID') +
    scale_x_continuous(breaks = seq(0, 250, 25)) +
    scale_fill_manual(name = 'Neuropathy present: ',
                      values = c('#FFFFFF', '#000000')) +
    facet_wrap(~ sn,
               ncol = 2,
               scales = 'free_y') +
    theme(legend.position = 'top',
          legend.margin = margin(t = -0.3,
                                 r = 0,
                                 b = -0.3,
                                 l = 0, 'lines'),
          panel.grid = element_blank())
```



```
# Publication plot
gg_plot <- data_plot %>%
    ggplot(data = .) +
    aes(x = visit_day,
        y = ID) +
    geom_path(colour = '#888888') +
    geom_point(aes(fill = hivsn_present),
               shape = 21,
               size = 3) +
    labs(x = 'Days',
         y = 'Participant ID') +
    scale_x_continuous(breaks = seq(0, 250, 25)) +
    scale_fill_manual(name = 'Neuropathy present: ',
                      values = c('#FFFFFF', '#000000')) +
    facet_wrap(~ sn,
               ncol = 2,
               scales = 'free_y') +
    theme(legend.position = 'top',
          legend.text = element_text(size = 11),
          legend.title = element_text(size = 11),
          axis.text.y = element_text(colour = '#000000'),
          axis.text.x = element_text(colour = '#000000',
                                     size = 12),
          axis.title = element_text(size = 14),
          panel.grid = element_blank(),
          panel.border = element_rect(size = 1),
          strip.text = element_text(size = 12))

ggsave(filename = 'figures/follow-up.png',
       plot = gg_plot,
       width = 9,
       height = 11)
```

Analysis

Process data

```
# Generate visit data
data_v1 <- data %>%
    # Calculations per individual
    group_by(ID) %>%
    mutate(# Extract the max number of visits
           max_visits = max(visit_number),
           # Time from visit 1 to the last visit
           max_duration = max(visit_day),
           # Time between successive visits
           visit_break = visit_day - lag(visit_day),
           # Running mean time (days) between visits
           cummulative_mean = round(cummean(visit_day))) %>%
    ungroup() %>%
    # Select required columns
    select(ID, visit_number, visit_day, visit_break, max_visits,
           max_duration, cummulative_mean) %>%
    left_join(data_sn)

# Filter based on maximum number of visits
data_v2 <- data_v1 %>%
    # Per individual
    group_by(ID) %>%
    # Get maximum number of visits
    filter(visit_number == max_visits) %>%
    ungroup()
```

Number of clinic visits

```
# Summary table
data_v2 %>%
    summarise(n = n(),
              Median.visits = median(max_visits),
              Q25 = quantile(max_visits, 0.25),
              Q75 = quantile(max_visits, 0.75),
              min = min(max_visits),
              max = max(max_visits))
```

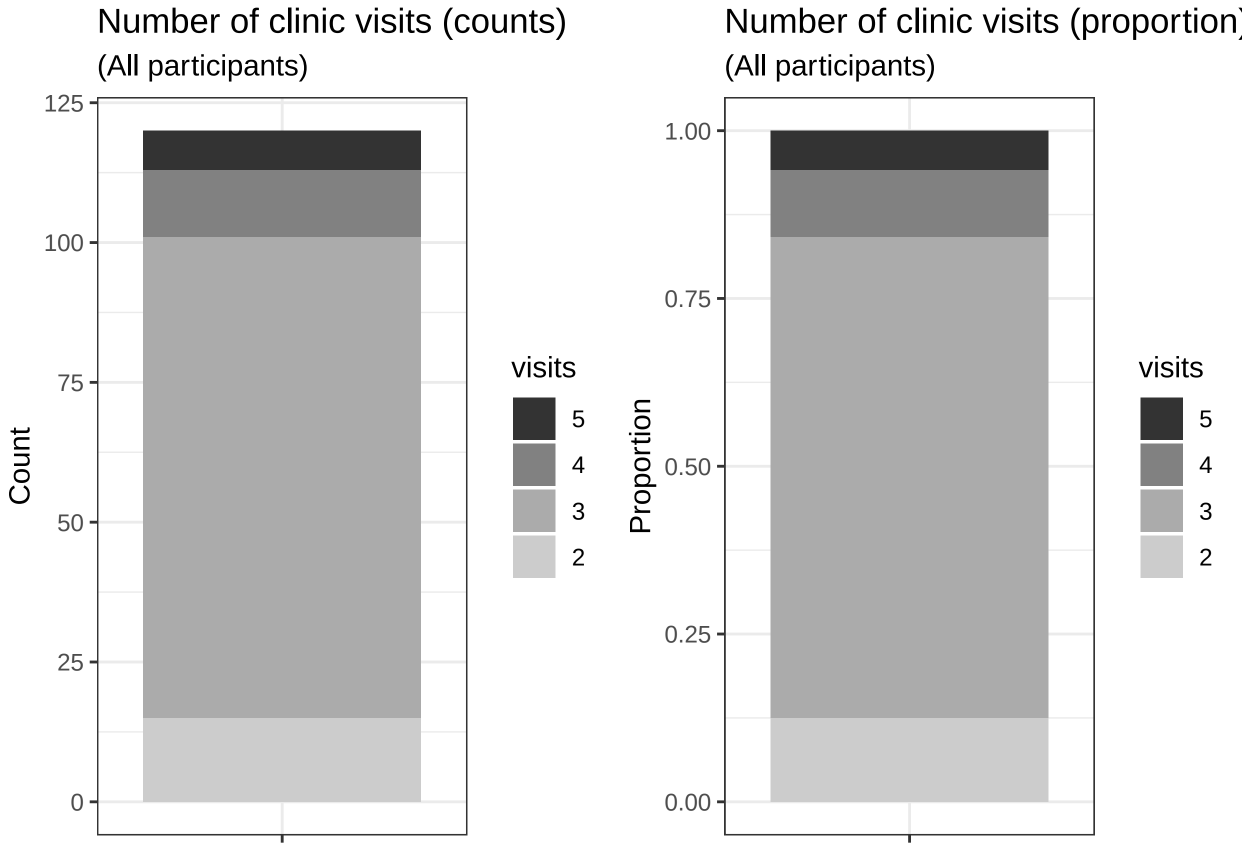
```
## # A tibble: 1 x 6
##       n Median.visits   Q25   Q75   min   max
##   <int>         <dbl> <dbl> <dbl> <dbl> <dbl>
## 1   120             3     3     3     2     5
```

```
# Summary table (conditioned on sn)
data_v2 %>%
    group_by(sn) %>%
    summarise(n = n(),
              Median.visits = median(max_visits),
              Q25 = quantile(max_visits, 0.25),
              Q75 = quantile(max_visits, 0.75),
              min = min(max_visits),
              max = max(max_visits))
```

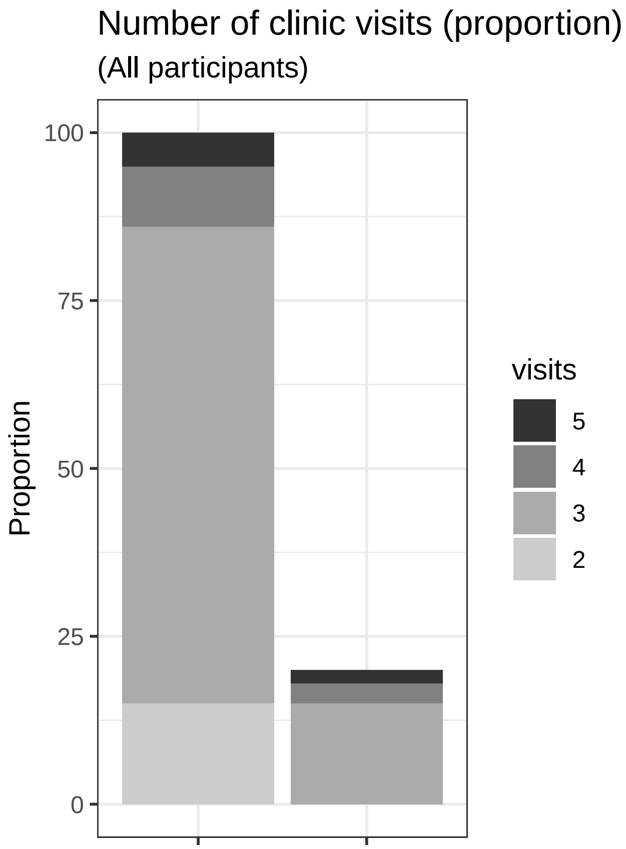
```
## # A tibble: 2 x 7
##   sn        n Median.visits   Q25   Q75   min   max
##   <fct> <int>         <dbl> <dbl> <dbl> <dbl> <dbl>
## 1 no      100             3     3  3        2     5
## 2 yes      20             3     3  3.25     3     5
```

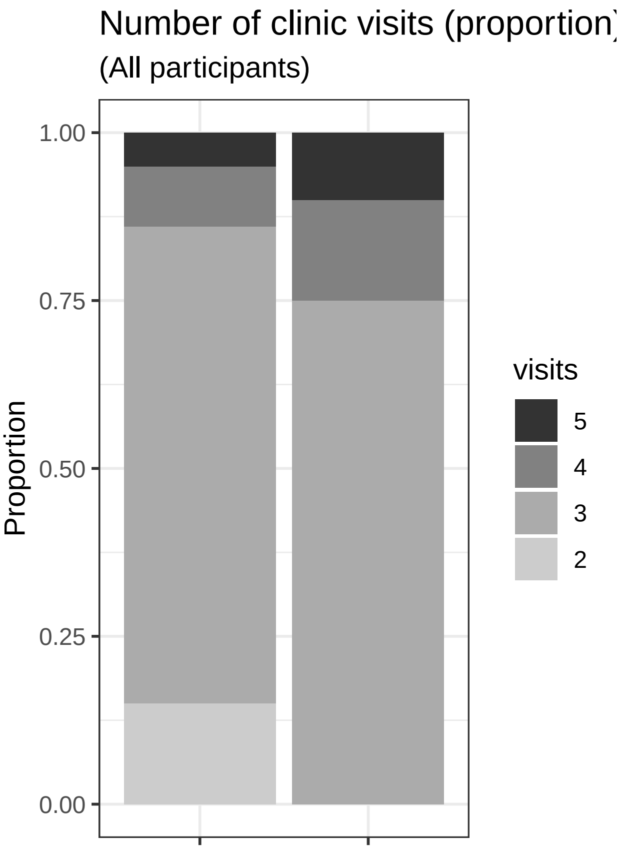
```
# Plots
gg_v2a <- data_v2 %>%
    group_by(max_visits) %>%
    summarise(count = n()) %>%
    mutate(visits = fct_relevel(factor(max_visits), '5', '4', '3')) %>%
    ggplot(data = .) +
    aes(y = count,
        x = 'all',
        fill = visits) +
    geom_bar(stat = 'identity') +
    scale_fill_grey() +
    labs(title = 'Number of clinic visits (counts)',
         subtitle = '(All participants)',
         y = 'Count') +
    theme(axis.title.x = element_blank(),
          axis.text.x = element_blank())
```

```
gg_v2b <- data_v2 %>%
    group_by(max_visits) %>%
    summarise(count = n()) %>%
    mutate(visits = fct_relevel(factor(max_visits), '5', '4', '3')) %>%
    ggplot(data = .) +
    aes(y = count,
        x = 'all',
        fill = visits) +
    geom_bar(stat = 'identity',
             position = position_fill()) +
    scale_fill_grey() +
    labs(title = 'Number of clinic visits (proportion)',
         subtitle = '(All participants)',
         y = 'Proportion') +
    theme(axis.title.x = element_blank(),
          axis.text.x = element_blank())

# Plot next to each other using patchwork package
gg_v2a + gg_v2b
```



```
## Conditional on SN
gg_v2c <- data_v2 %>%
    group_by(sn, max_visits) %>%
    summarise(count = n()) %>%
    mutate(visits = factor(max_visits,
                           levels = c('5', '4', '3', '2'),
                           ordered = TRUE)) %>%
    ggplot(data = .) +
    aes(y = count,
        x = sn,
        fill = visits) +
    geom_bar(stat = 'identity') +
    scale_fill_grey() +
    labs(title = 'Number of clinic visits (proportion)',
         subtitle = '(All participants)',
         y = 'Proportion') +
    theme(axis.title.x = element_blank(),
          axis.text.x = element_blank())

gg_v2d <- data_v2 %>%
    group_by(sn, max_visits) %>%
    summarise(count = n()) %>%
    mutate(visits = factor(max_visits,
                           levels = c('5', '4', '3', '2'),
                           ordered = TRUE)) %>%
    ggplot(data = .) +
    aes(y = count,
        x = sn,
        fill = visits) +
    geom_bar(stat = 'identity',
             position = position_fill()) +
    scale_fill_grey() +
    labs(title = 'Number of clinic visits (proportion)',
         subtitle = '(All participants)',
         y = 'Proportion') +
    theme(axis.title.x = element_blank(),
          axis.text.x = element_blank())

# Plot next to each other using patchwork package
gg_v2c + gg_v2d
```





```
# Stats
chisq_test(xtabs(~ sn + visit_number,
                 data = data_v2),
           distribution = approximate(B = 10000))
```

```
##
##  Approximative Pearson Chi-Squared Test
##
## data:  visit_number by sn (no, yes)
## chi-squared = 4.3515, p-value = 0.2209
```

Time between first and last visit

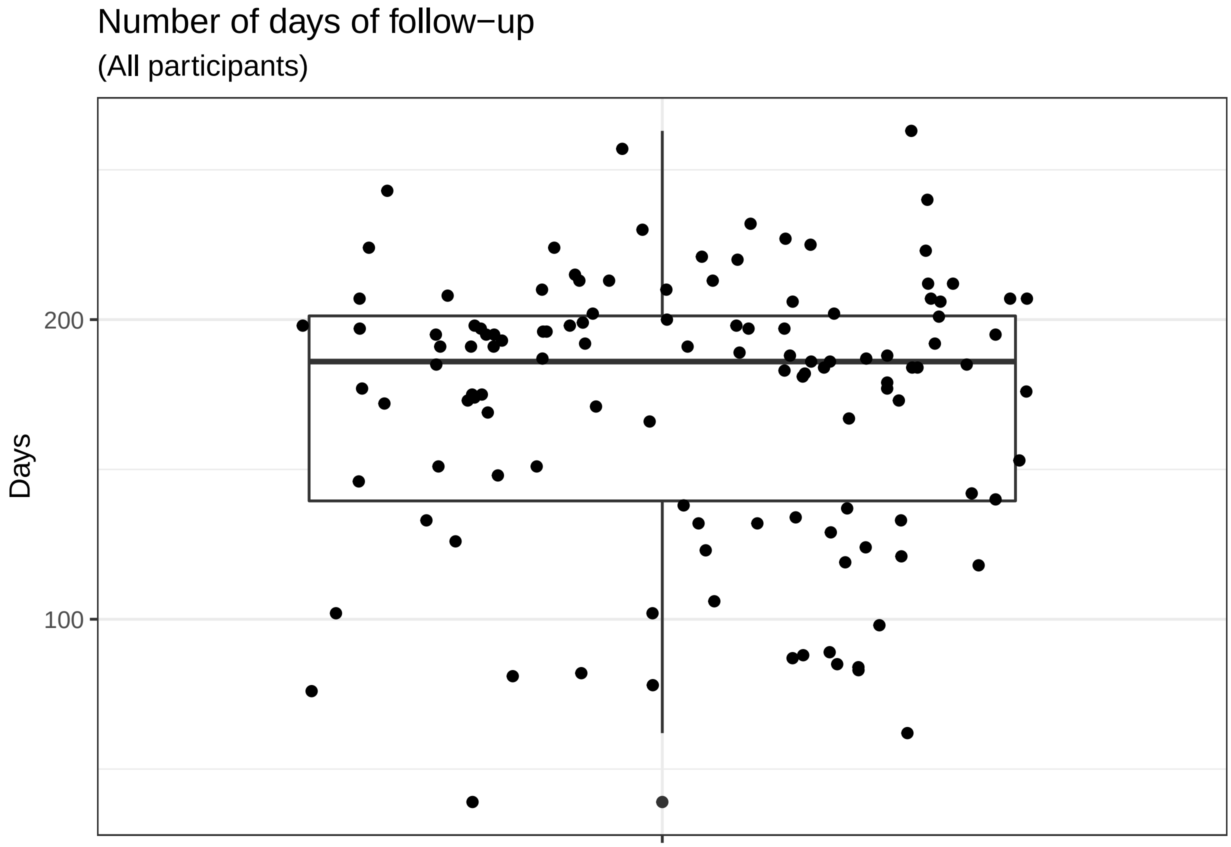
```
# Summary table
data_v2 %>%
    summarise(n = n(),
              Median.days = median(max_duration),
              Q25 = quantile(max_duration, 0.25),
              Q75 = quantile(max_duration, 0.75),
              min = min(max_duration),
              max = max(max_duration))
```

```
## # A tibble: 1 x 6
##       n Median.days   Q25   Q75   min   max
##   <int>       <dbl> <dbl> <dbl> <dbl> <dbl>
## 1   120         186  140.  201.    39   263
```

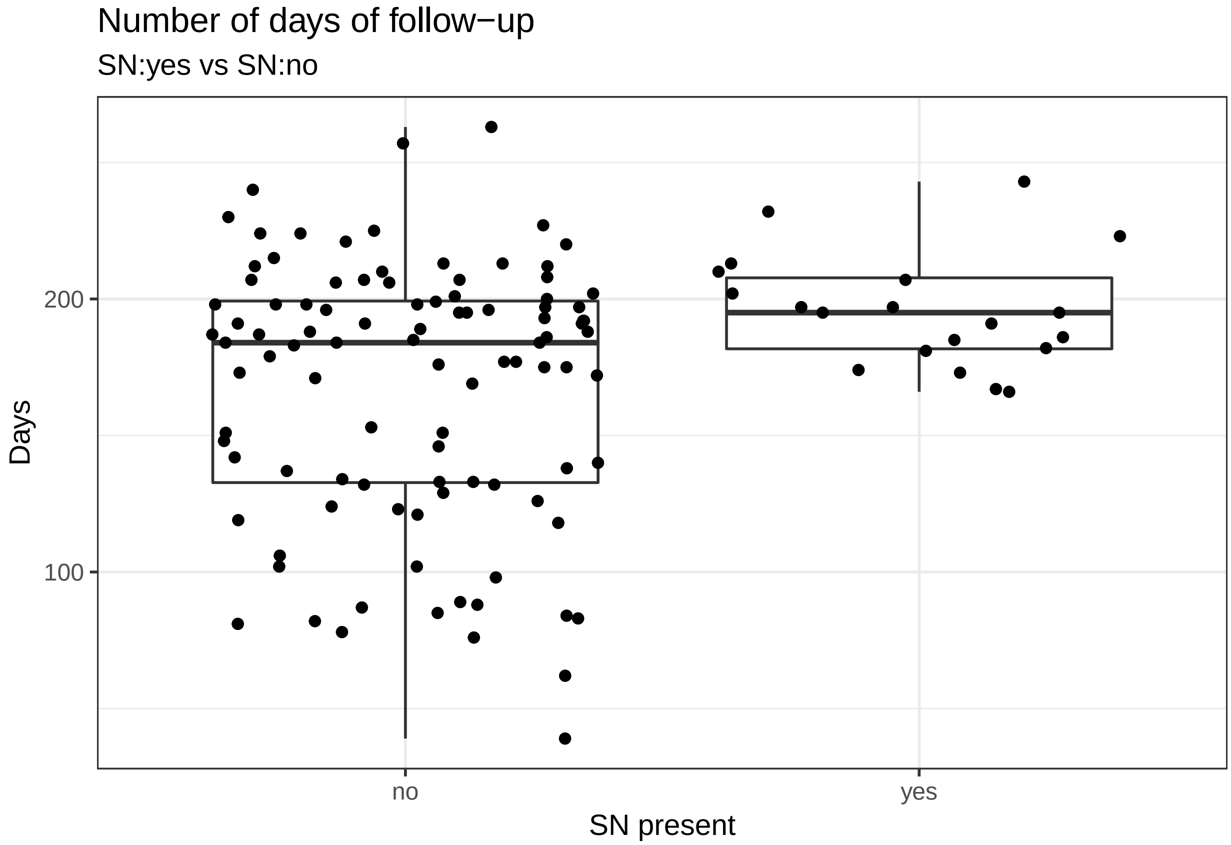
```
# Summary table (conditioned on sn)
data_v2 %>%
    group_by(sn) %>%
    summarise(n = n(),
              Median.days = median(max_duration),
              Q25 = quantile(max_duration, 0.25),
              Q75 = quantile(max_duration, 0.75),
              min = min(max_duration),
              max = max(max_duration))
```

```
## # A tibble: 2 x 7
##   sn        n Median.days   Q25   Q75   min   max
##   <fct> <int>       <dbl> <dbl> <dbl> <dbl> <dbl>
## 1 no      100         184  133.  199.    39   263
## 2 yes      20         195  182.  208.   166   243
```

```
# Plots
data_v2 %>%
    ggplot(data = .) +
    aes(y = max_duration,
        x = 'All patients') +
    geom_boxplot() +
    geom_jitter(height = 0) +
    labs(title = 'Number of days of follow-up',
         subtitle = '(All participants)',
         y = 'Days') +
    theme(axis.title.x = element_blank(),
          axis.text.x = element_blank())
```



```
## Conditional on SN
data_v2 %>%
    ggplot(data = .) +
    aes(y = max_duration,
        x = sn) +
    geom_boxplot() +
    geom_jitter(height = 0) +
    labs(title = 'Number of days of follow-up',
         subtitle = 'SN:yes vs SN:no',
         y = 'Days',
         x = 'SN present')
```



```
# Stats
normal_test(max_duration ~ factor(sn),
            data = data_v2,
            distribution = approximate(B = 10000))
```

```
##
##  Approximative Two-Sample van der Waerden (Normal Quantile) Test
##
## data:  max_duration by factor(sn) (no, yes)
## Z = -2.103, p-value = 0.0342
## alternative hypothesis: true mu is not equal to 0
```

Time between successive clinic visits

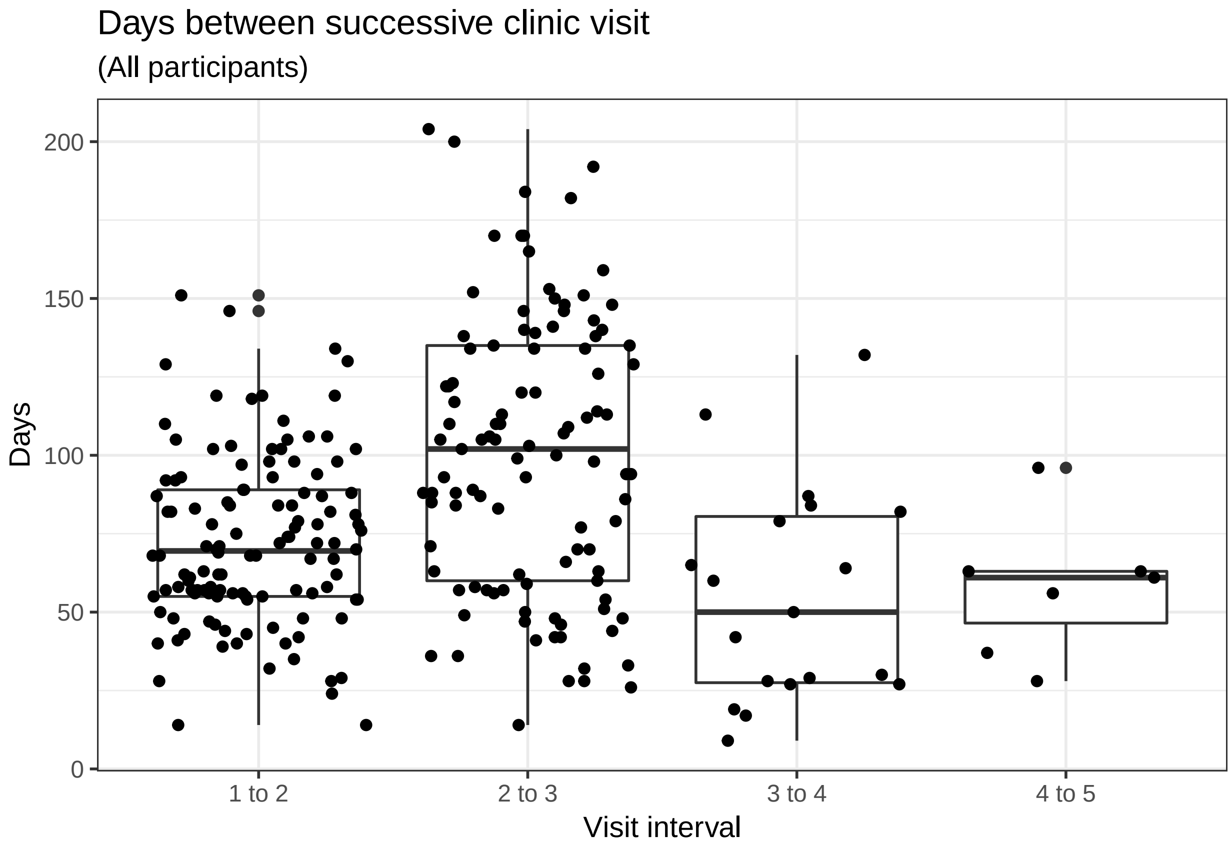
```
# Summary table
data_v1 %>%
    filter(visit_number != 1) %>%
    group_by(visit_number) %>%
    summarise(n = n(),
              Mean.days = mean(visit_break),
              Median.days = median(visit_break),
              SD = sd(visit_break),
              Q25 = quantile(visit_break, 0.25),
              Q75 = quantile(visit_break, 0.75),
              min = min(visit_break),
              max = max(visit_break))
```

```
## # A tibble: 4 x 9
##   visit_number     n Mean.days Median.days    SD   Q25   Q75   min   max
##          <int> <int>     <dbl>       <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
## 1            2   120      72.4        69.5  27.1  55    89       14   151
## 2            3   105     100.        102     44.4  60   135       14   204
## 3            4    19      54.9        50     34.4  27.5  80.5      9   132
## 4            5     7      57.7        61     21.8  46.5  63       28    96
```

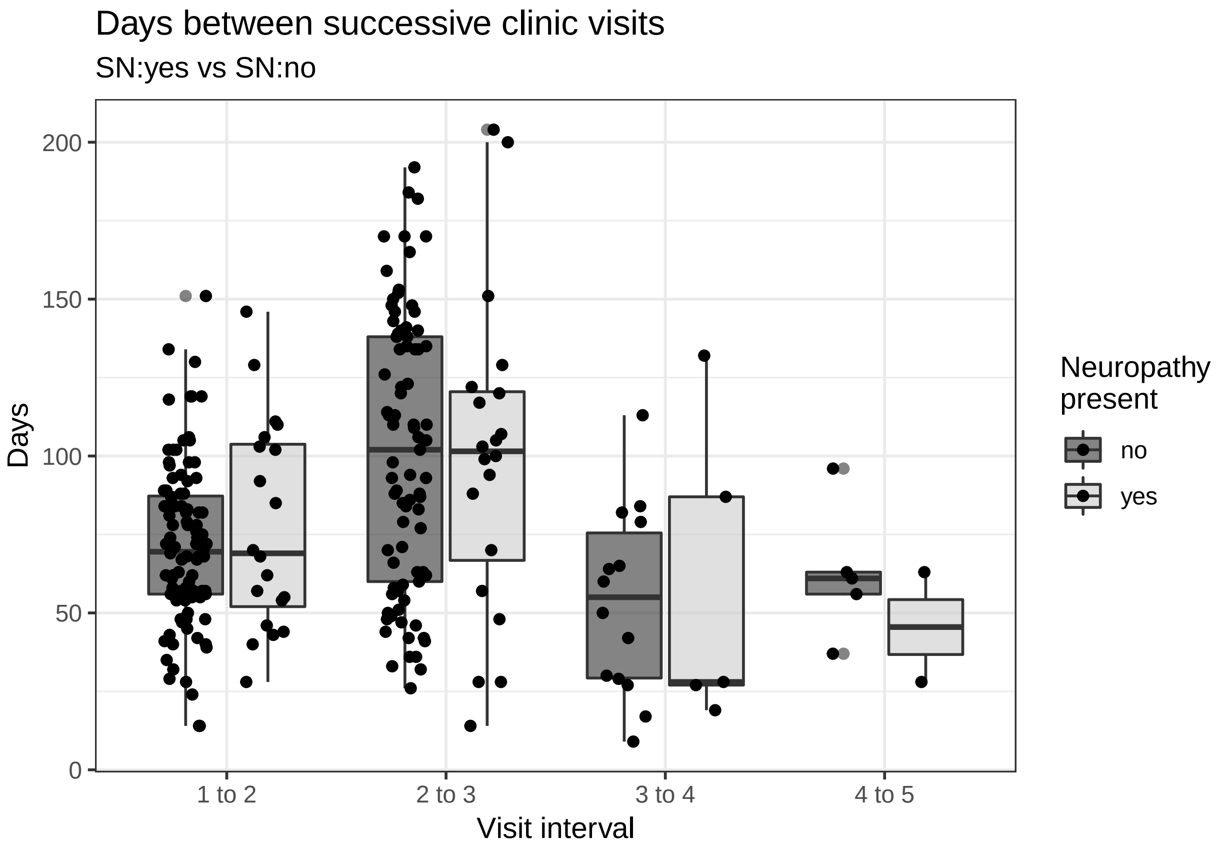
```
# Summary table (conditioned on sn)
data_v1 %>%
    filter(visit_number != 1) %>%
    group_by(visit_number, sn) %>%
    summarise(n = n(),
              Mean.days = mean(visit_break),
              Median.days = median(visit_break),
              SD = sd(visit_break),
              Q25 = quantile(visit_break, 0.25),
              Q75 = quantile(visit_break, 0.75),
              min = min(visit_break),
              max = max(visit_break))
```

```
## # A tibble: 8 x 10
## # Groups:   visit_number [4]
##   visit_number sn        n Mean.days Median.days    SD   Q25   Q75   min
##          <int> <fct> <int>     <dbl>       <dbl> <dbl> <dbl> <dbl> <dbl>
## 1            2 no      100      71.4        69.5  25.8  56    87.2     14
## 2            2 yes      20      77.6        69    33.1  52   104.      28
## 3            3 no       85     100.        102     43.1  60    138       26
## 4            3 yes      20      99.2       102.    50.7  66.8 120.      14
## 5            4 no       14      53.6        55     29.8  29.2  75.5      9
## 6            4 yes       5      58.6        28     49.2  27    87       19
## 7            5 no        5      62.6        61     21.3  56    63       37
## 8            5 yes       2      45.5        45.5  24.7  36.8  54.2     28
## # ... with 1 more variable: max <dbl>
```

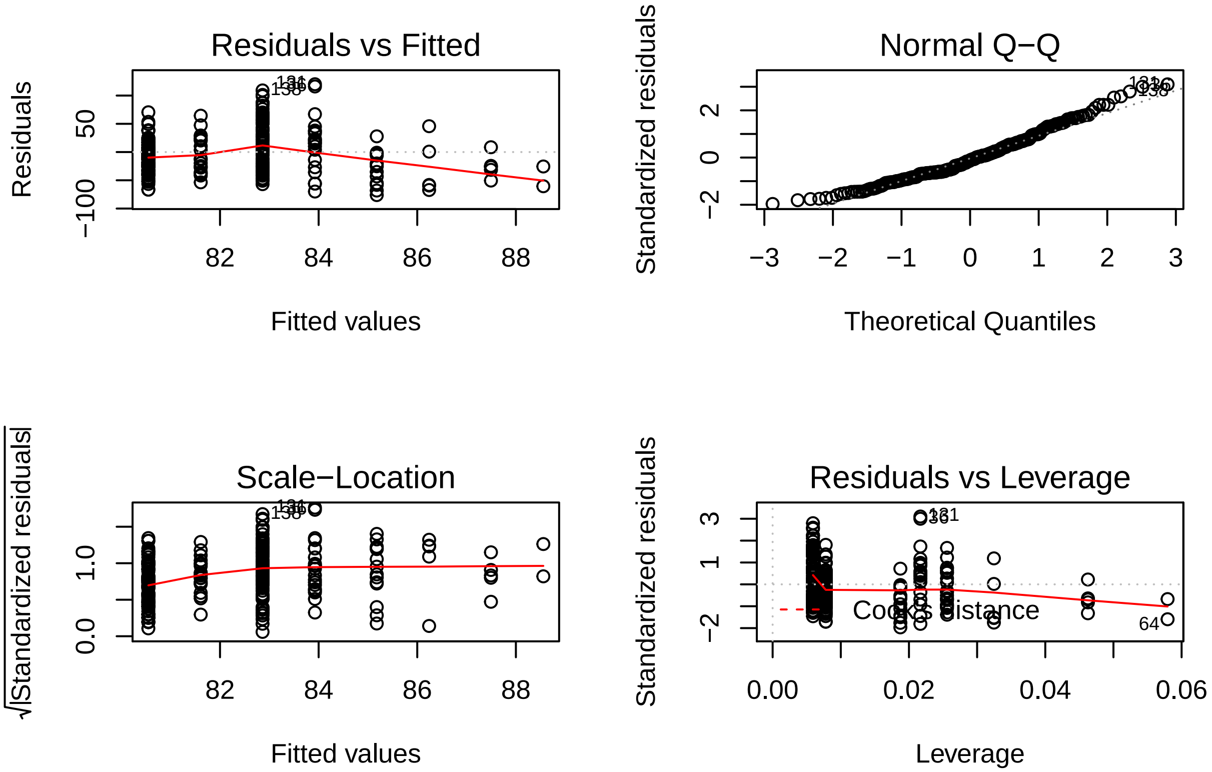
```
# Plots
data_v1 %>%
    filter(visit_number != 1) %>%
    ggplot(data = .) +
    aes(y = visit_break,
        x = factor(visit_number)) +
    geom_boxplot() +
    geom_jitter(height = 0) +
    scale_x_discrete(labels = c('1 to 2', '2 to 3',
                                '3 to 4', '4 to 5')) +
    labs(title = 'Days between successive clinic visit ',
         subtitle = '(All participants)',
         y = 'Days',
         x = 'Visit interval')
```



```
## Conditional on SN
data_v1 %>%
    filter(visit_number != 1) %>%
    ggplot(data = .) +
    aes(y = visit_break,
        x = factor(visit_number),
        fill = sn) +
    geom_boxplot(alpha = 0.6) +
    geom_point(position = position_jitterdodge(jitter.height = 0)) +
    scale_x_discrete(labels = c('1 to 2', '2 to 3',
                                '3 to 4', '4 to 5')) +
    scale_fill_grey(name = 'Neuropathy\npresent') +
    labs(title = 'Days between successive clinic visits',
         subtitle = 'SN:yes vs SN:no',
         y = 'Days',
         x = 'Visit interval')
```



```
# Stats
## Generate data
data_lmer <- data_v1 %>%
    filter(visit_number != 1) %>%
    select(ID, visit_number, visit_break, sn)

## Generate model (ID included as random effects)
mod <- lm(visit_break ~ sn + visit_number,
            data = data_lmer)

## Analysis of Deviance Table (Type II Wald F tests with Kenward-Roger df)
Anova(mod = mod,
      type = 'II',
      test.statistic = 'F')

## Anova Table (Type II tests)
##
## Response: visit_break
##               Sum Sq  Df F value Pr(>F)
## sn                43   1  0.0280 0.8673
## visit_number     730   1  0.4767 0.4906
## Residuals     379751 248

## Basic diagnostics
par(mfrow = c(2, 2))
plot(mod)
```



```r
par(mfrow = c(1, 1))
```

Session information

```r
sessionInfo()
```

```
## R version 3.5.2 (2018-12-20)
## Platform: x86_64-apple-darwin15.6.0 (64-bit)
## Running under: macOS Mojave 10.14.3
## 
## Matrix products: default
## BLAS: /Library/Frameworks/R.framework/Versions/3.5/Resources/lib/libRblas.0.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/3.5/Resources/lib/libRlapack.dylib
## 
## locale:
## [1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
## 
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base     
## 
## other attached packages:
##  [1] car_3.0-2       carData_3.0-2   lmerTest_3.1-0  lme4_1.1-20    
##  [5] Matrix_1.2-15   coin_1.2-2      survival_2.43-3 patchwork_0.0.1
##  [9] forcats_0.4.0   stringr_1.4.0   dplyr_0.8.0.1   purrr_0.3.1    
## [13] readr_1.3.1     tidyr_0.8.3     tibble_2.0.1    ggplot2_3.1.0  
## [17] tidyverse_1.2.1 magrittr_1.5   
## 
```

```
## loaded via a namespace (and not attached):
##  [1] httr_1.4.0        jsonlite_1.6      splines_3.5.2
##  [4] modelr_0.1.4      assertthat_0.2.0  stats4_3.5.2
##  [7] cellranger_1.1.0  yaml_2.2.0        numDeriv_2016.8-1
## [10] pillar_1.3.1      backports_1.1.3   lattice_0.20-38
## [13] glue_1.3.0        digest_0.6.18     rvest_0.3.2
## [16] minqa_1.2.4       colorspace_1.4-0  sandwich_2.5-0
## [19] htmltools_0.3.6   plyr_1.8.4        pkgconfig_2.0.2
## [22] broom_0.5.1       haven_2.1.0       mvtnorm_1.0-9
## [25] scales_1.0.0      openxlsx_4.1.0    rio_0.5.16
## [28] generics_0.0.2    ellipsis_0.1.0    TH.data_1.0-10
## [31] withr_2.1.2.9000  lazyeval_0.2.1    cli_1.0.1
## [34] crayon_1.3.4      readxl_1.3.0      evaluate_0.13
## [37] fansi_0.4.0       nlme_3.1-137      MASS_7.3-51.1
## [40] xml2_1.2.0        foreign_0.8-71    tools_3.5.2
## [43] data.table_1.12.0 hms_0.4.2         multcomp_1.4-8
## [46] munsell_0.5.0     zip_2.0.0         compiler_3.5.2
## [49] rlang_0.3.1       grid_3.5.2        nloptr_1.2.1
## [52] rstudioapi_0.9.0  labeling_0.3      rmarkdown_1.11
## [55] gtable_0.2.0      codetools_0.2-16  abind_1.4-5
## [58] curl_3.3          R6_2.4.0          zoo_1.8-4
## [61] lubridate_1.7.4   knitr_1.21        utf8_1.1.4
## [64] modeltools_0.2-22 stringi_1.3.1     Rcpp_1.0.0
## [67] tidyselect_0.2.5  xfun_0.5
```