

Supplement 4

Analysis of the primary outcome

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The primary outcome was the reduction in pain severity score (PSS) between week 0 (BL) and week 48 (Wk48). The PSS is a composite measure of the mean of: pain at the assessment, and worst, least, and average pain in the last week.

The baseline observation carried forward (BOCF) analysis used data from week 0 to interpolate missing week 48 data. Some participants did not arrive for their week 0 appointment and therefore did not have data at baseline. These missing data were interpolated using the week 0 study site average PSS. No heed was paid to whether data were available at intermediate time points between week 0 and week 48.

The per protocol (PP) analysis included all individuals with complete data (i.e., no interpolation required).

Statistical significance was assessed using a permutation test that tested the independence of the therapeutic relationship only group (T, control) and the P groups (positive-living programme and therapeutic relationship). The conditional null distribution of the test statistic was calculated using Monte Carlo resampling ($n = 100000$).

Dosage was calculated as the number of assessments attended, on average) by participants in each group, and the number of intervention sessions attended by participants in group P and the change in NRS. *Note that the latter analysis excludes site U1 because the data were inadvertently destroyed.*

Import and sort data

```
# Get BPI data
## BPI
bpi <- read_rds('data-cleaned/bpi.rds') %>%
  select(ID, contains('Pain'))

## Demographics
```

```

demo <- read_rds('data-cleaned/demographics.rds') %>%
  select(ID, Study_site, Group)

## Dosage
dosage <- read_rds('data-cleaned/dosage.rds')

## Join BPI and demographics
data <- demo %>%
  left_join(bpi)

## Add dosage data
data %<>% left_join(dosage)

## Primary outcome
primary <- data %>%
  select(-contains('present'))

```

Quick look

```
glimpse(primary)
```

```

## Observations: 160
## Variables: 28
## $ ID <chr> "J1", "J3", "J4", "J5", "J6", "J7", "J9", "J...
## $ Study_site <chr> "U1", "U1", "U1", "U1", "U1", "U1", "U1", "U...
## $ Group <chr> "P", "T", "P", "P", "P", "T", "T", "T", "P",...
## $ Worst_pain.BL <int> 8, 9, 5, 7, 7, 8, 10, 10, 9, 0, 10, NA, 9, 8...
## $ Worst_pain.Wk4 <int> NA, NA, 3, NA, NA, 8, 8, 9, 8, NA, NA, NA, 8...
## $ Worst_pain.Wk8 <int> NA, NA, 0, NA, NA, NA, 8, 9, 10, 4, NA, NA, ...
## $ Worst_pain.Wk12 <int> NA, NA, 3, NA, NA, NA, 7, 9, 10, 7, 10, NA, ...
## $ Worst_pain.Wk24 <int> NA, NA, 6, NA, NA, NA, 7, 9, NA, 6, NA, NA, ...
## $ Worst_pain.Wk48 <int> NA, NA, 6, NA, NA, NA, 7, 8, NA, 8, NA, NA, ...
## $ Least_pain.BL <int> 4, 1, 1, 10, 2, 3, 3, 5, 3, 0, 3, NA, 3, 3, ...
## $ Least_pain.Wk4 <int> NA, NA, 1, NA, NA, 3, 5, 4, 2, NA, NA, NA, 3...
## $ Least_pain.Wk8 <int> NA, NA, 0, NA, NA, NA, 3, 4, 5, 1, NA, NA, 4...
## $ Least_pain.Wk12 <int> NA, NA, 1, NA, NA, NA, 3, 6, 5, 4, 5, NA, NA...
## $ Least_pain.Wk24 <int> NA, NA, 2, NA, NA, NA, 3, 5, NA, 2, NA, NA, ...
## $ Least_pain.Wk48 <int> NA, NA, 2, NA, NA, NA, 3, 5, NA, 2, NA, NA, ...
## $ Average_pain.BL <int> 4, 4, 3, 5, 4, 6, 6, 7, 6, 0, 6, NA, 6, 6, 5...
## $ Average_pain.Wk4 <int> NA, NA, 1, NA, NA, 5, 5, 6, 5, NA, NA, NA, 5...
## $ Average_pain.Wk8 <int> NA, NA, 0, NA, NA, NA, 5, 7, 8, 2, NA, NA, 6...
## $ Average_pain.Wk12 <int> NA, NA, 2, NA, NA, NA, 4, 7, 7, 6, 8, NA, NA...
## $ Average_pain.Wk24 <int> NA, NA, 4, NA, NA, NA, 5, 7, NA, 4, NA, NA, ...
## $ Average_pain.Wk48 <int> NA, NA, 4, NA, NA, NA, 5, 7, NA, 5, NA, NA, ...
## $ Pain_now.BL <int> 6, 4, 0, 5, 2, 9, 0, 0, 9, 0, 3, NA, 0, 8, 6...
## $ Pain_now.Wk4 <int> NA, NA, 0, NA, NA, 8, 8, 4, 6, NA, NA, NA, 0...
## $ Pain_now.Wk8 <int> NA, NA, 0, NA, NA, NA, 3, 5, 10, 1, NA, NA, ...
## $ Pain_now.Wk12 <int> NA, NA, 2, NA, NA, NA, 8, 5, 10, 3, 8, NA, N...
## $ Pain_now.Wk24 <int> NA, NA, 2, NA, NA, NA, 3, 8, NA, 3, NA, NA, ...
## $ Pain_now.Wk48 <int> NA, NA, 4, NA, NA, NA, 3, 2, NA, 5, NA, NA, ...
## $ dosage <dbl> NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, ...

```

BOCF data processing and analysis

```
# Calculate Pain Severity Score (PSS) for weeks 0 (BL) and 48 (Wk48)
BOCF <- primary %>%
  gather(key = 'Time',
         value = 'NRS',
         - ID, -Study_site, -Group) %>%
  separate(col = Time,
           into = c('Pain', 'Period'),
           sep = '\\\\.') %>%
  group_by(ID, Study_site, Group, Period) %>%
  nest() %>%
  mutate(PPS = map(.x = data,
                   ~ summarise(.x, Mean = mean(NRS, na.rm = TRUE)))) %>%
  select(-data) %>%
  unnest() %>%
  filter(Period %in% c('BL', 'Wk48')) %>%
  mutate(Mean = ifelse(is.nan(Mean),
                      yes = NA,
                      no = Mean))

# Missing baseline data
BOCF[is.na(BOCF$Mean) & BOCF$Period == 'BL', ]

## # A tibble: 16 x 5
##   ID      Study_site Group Period  Mean
##   <chr> <chr>      <chr> <chr> <dbl>
## 1 J18    U1          T     BL    NA
## 2 J29    U1          T     BL    NA
## 3 J59    U1          T     BL    NA
## 4 J67    U1          T     BL    NA
## 5 M1     R1          T     BL    NA
## 6 M8     R1          T     BL    NA
## 7 M9     R1          T     BL    NA
## 8 M12    R1          T     BL    NA
## 9 M20    R1          P     BL    NA
## 10 M21   R1          P     BL    NA
## 11 M23   R1          P     BL    NA
## 12 M25   R1          P     BL    NA
## 13 M29   R1          P     BL    NA
## 14 M38   R1          P     BL    NA
## 15 M41   R1          P     BL    NA
## 16 M45   R1          T     BL    NA

# Number of participants with missing baselines
nrow(BOCF[is.na(BOCF$Mean) & BOCF$Period == 'BL', ])

## [1] 16

# Calculate baseline mean for study sites R1 and U1 (sites with missing data)
R1 <- mean(BOCF$Mean[!is.na(BOCF$Mean) &
                  BOCF$Study_site == 'R1' &
```

```

      BOCF$Period == 'BL'])

U1 <- mean(BOCF$Mean[!is.na(BOCF$Mean) &
      BOCF$Study_site == 'U1' &
      BOCF$Period == 'BL'])

# Substitute missing baselines with Study_site means
BOCF %<>%
  mutate(Mean = ifelse(is.na(Mean) & Study_site == 'R1',
    yes = R1,
    no = Mean),
    Mean = ifelse(is.na(Mean) & Study_site == 'U1',
    yes = U1,
    no = Mean))

# Spread data
BOCF_wide <- BOCF %>%
  spread(key = Period,
    value = Mean)

# Number of participants
BOCF_wide %>%
  summarise(Count = n())

## # A tibble: 1 x 1
##   Count
##   <int>
## 1    160

# Number with missing data at week 48
BOCF_wide %>%
  filter(is.na(Wk48)) %>%
  summarise(Count = n())

## # A tibble: 1 x 1
##   Count
##   <int>
## 1     35

# Number with missing data at week 48 (by intervention)
BOCF_wide %>%
  filter(is.na(Wk48)) %>%
  group_by(Group) %>%
  summarise(Count = n())

## # A tibble: 2 x 2
##   Group Count
##   <chr> <int>
## 1 P      20
## 2 T      15

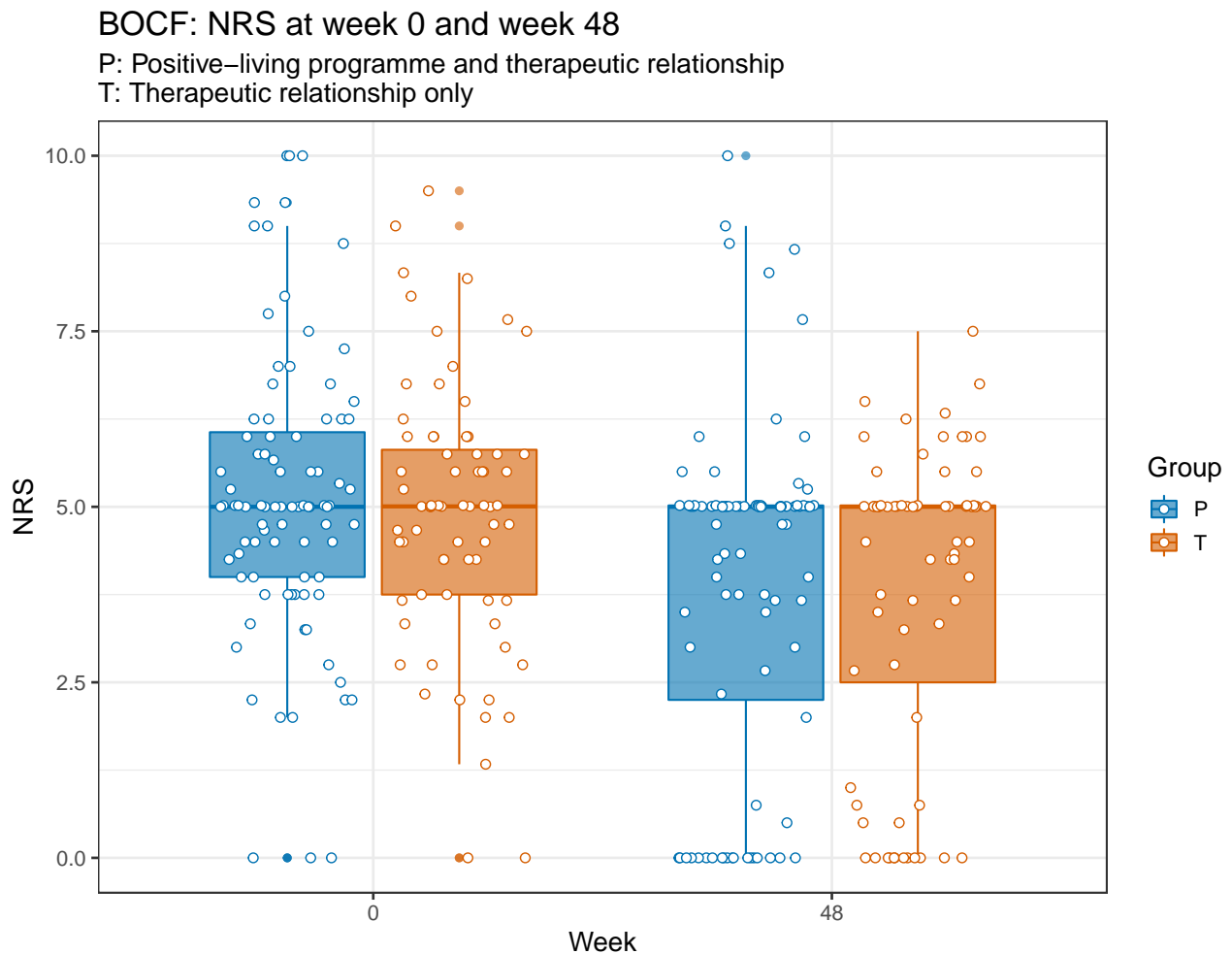
# Create BOCF dataframe
BOCF_wide %<>%
  mutate(Wk48 = ifelse(is.na(Wk48),
    yes = BL,
    no = Wk48))

```

```

# Plot of BOCF NRS data at weeks 0 and 48 (by intervention)
BOCF_wide %>%
  gather(key = Period,
         value = NRS,
         BL, Wk48) %>%
  ggplot(data = .) +
  aes(x = Period,
      y = NRS,
      colour = Group,
      fill = Group) +
  geom_boxplot(alpha = 0.6) +
  geom_point(position = position_jitterdodge(jitter.height = 0,
                                             jitter.width = 0.3),
             shape = 21,
             fill = '#FFFFFF',
             size = 2) +
  labs(title = 'BOCF: NRS at week 0 and week 48',
       subtitle = 'P: Positive-living programme and therapeutic relationship\nT: Therapeutic relationship only',
       x = 'Week') +
  scale_fill_manual(values = pal) +
  scale_colour_manual(values = pal) +
  scale_x_discrete(labels = c(0, 48))

```



```

# Calculate change from baseline to Wk48
BOCF_wide %<>%
  mutate(Delta = Wk48 - BL)

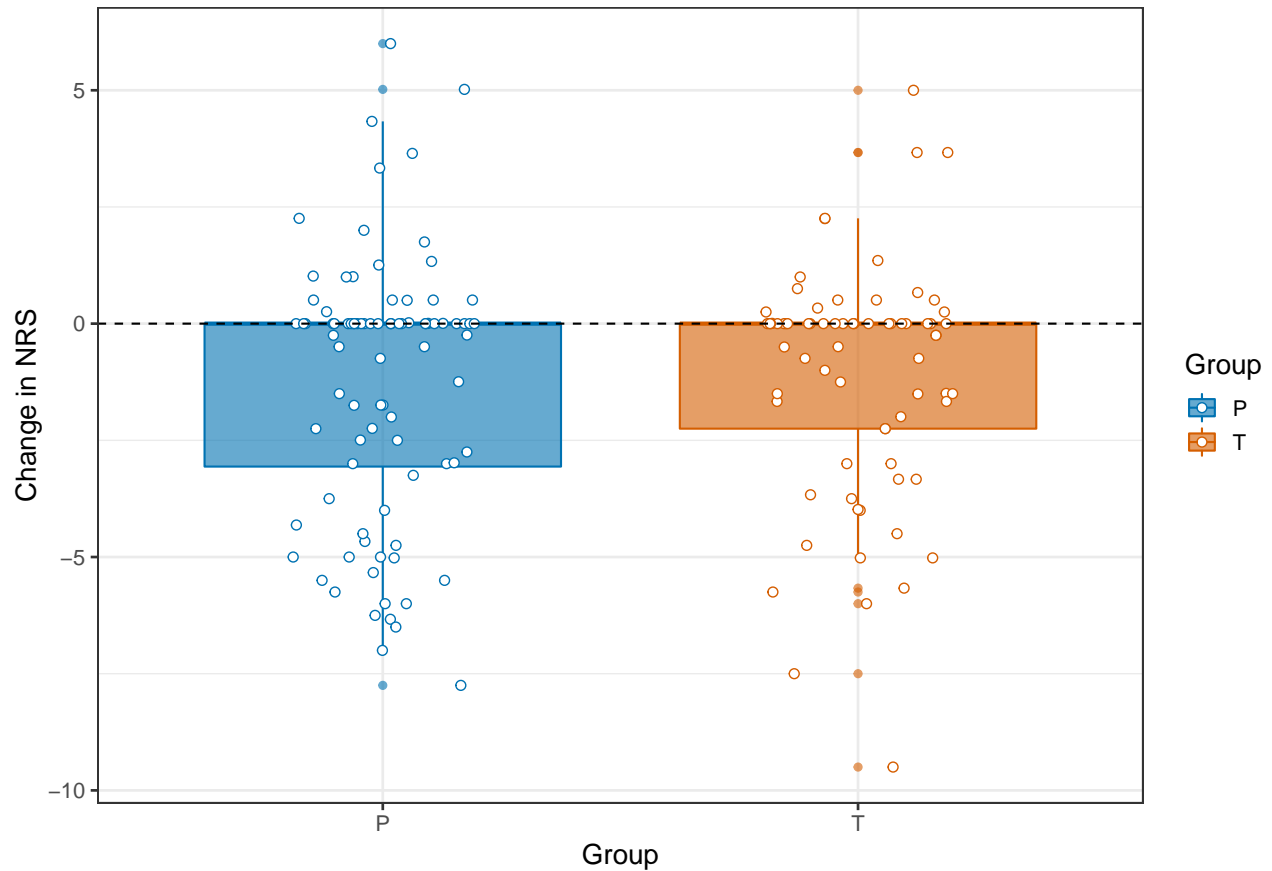
# Compare the P and T groups
## Plot of BOCF change in NRS between week 0 and 48 (by intervention)
ggplot(data = BOCF_wide) +
  aes(x = Group,
      y = Delta,
      fill = Group,
      colour = Group) +
  geom_boxplot(alpha = 0.6) +
  geom_point(position = position_jitterdodge(jitter.height = 0,
                                             jitter.width = 0.4),
             shape = 21,
             size = 2,
             fill = '#FFFFFF') +
  geom_hline(yintercept = 0,
             linetype = 2) +
  labs(title = 'BOCF: Change in NRS from week 0 to week 48',
       subtitle = 'P: Positive-living programme and therapeutic relationship\nT: Therapeutic relationship',
       y = 'Change in NRS') +
  scale_fill_manual(values = pal) +
  scale_colour_manual(values = pal)

```

BOCF: Change in NRS from week 0 to week 48

P: Positive-living programme and therapeutic relationship

T: Therapeutic relationship only



Slope plot of individual responses

BOCF_wide %>%

```
mutate(Change = ifelse(Delta < 0,
                        yes = 'Decreased',
                        no = 'Increased')) %>%
```

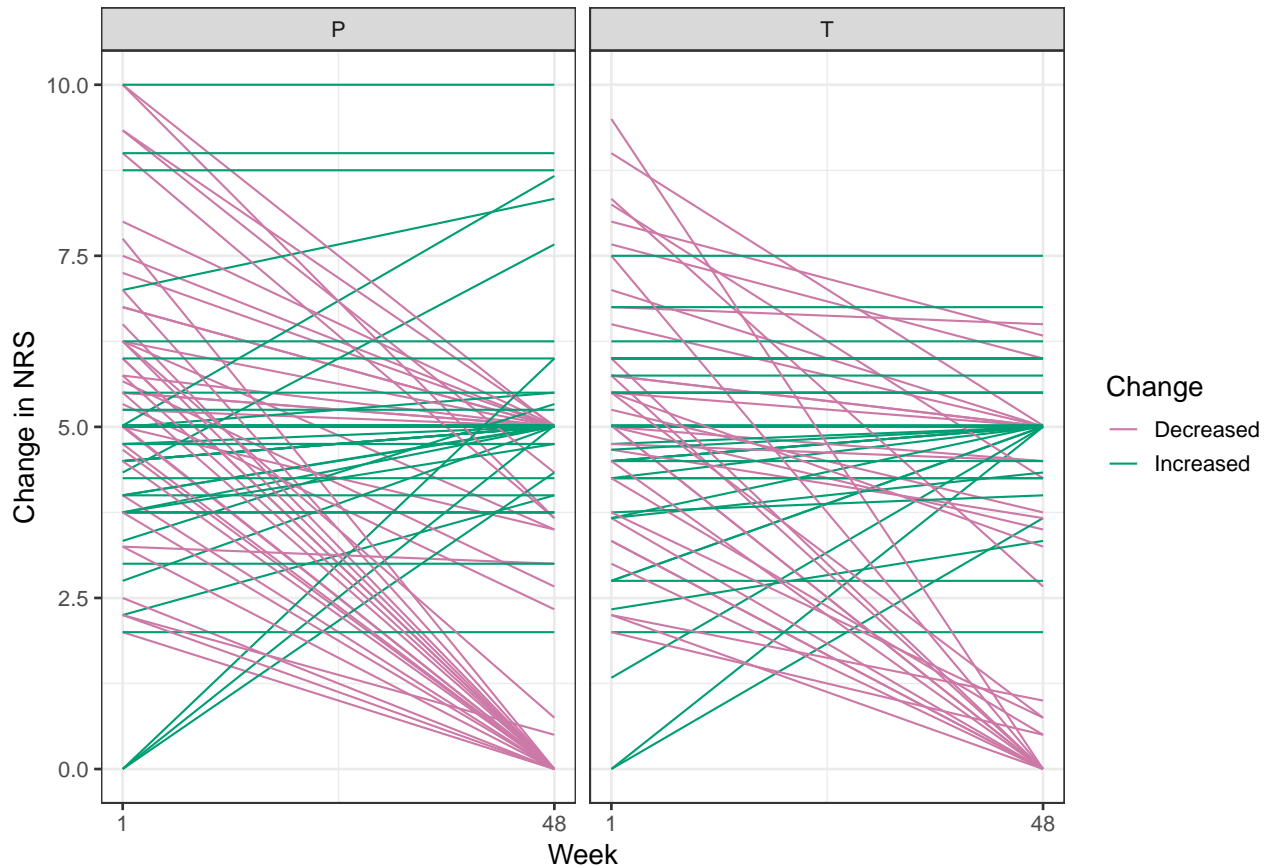
```
ggplot(data = .) +
  aes(colour = Change) +
  geom_segment(aes(x = 1, xend = 2,
                  y = BL, yend = Wk48)) +
  scale_x_continuous(breaks = c(1, 2),
                    labels = c(1, 48)) +
  scale_colour_manual(values = pal2) +
```

```
labs(title = "BOCF: Individuals' changes in NRS from week 0 to week 48",
     subtitle = 'P: Positive-living programme and therapeutic relationship\nT: Therapeutic relationship only',
     x = 'Week',
     y = 'Change in NRS') +
  facet_wrap(~ Group)
```

BOCF: Individuals' changes in NRS from week 0 to week 48

P: Positive-living programme and therapeutic relationship

T: Therapeutic relationship only



```
## Statistical test
independence_test(Delta ~ factor(Group),
  data = BOCF_wide,
  distribution = approximate(nresample = 100000))

##
## Approximative General Independence Test
##
## data: Delta by factor(Group) (P, T)
## Z = -0.4306, p-value = 0.6695
## alternative hypothesis: two.sided
```

Per protocol data processing and analysis

```
# Calculate Pain Severity Score (PSS) for weeks 0 (BL) and 48 (Wk48)
PP_wide <- primary %>%
  gather(key = 'Time',
    value = 'NRS',
    - ID, -Study_site, -Group) %>%
  separate(col = Time,
```



```

        into = c('Pain', 'Period'),
        sep = '\\\\.') %>%
group_by(ID, Study_site, Group, Period) %>%
nest() %>%
mutate(PPS = map(.x = data,
                  ~ summarise(.x, Mean = mean(NRS, na.rm = TRUE)))) %>%
select(-data) %>%
unnest() %>%
mutate(Mean = ifelse(is.nan(Mean),
                     yes = NA,
                     no = Mean)) %>%
mutate(Period = case_when(
  Period == 'BL' ~ 'T00',
  Period == 'Wk4' ~ 'T04',
  Period == 'Wk8' ~ 'T08',
  Period == 'Wk12' ~ 'T12',
  Period == 'Wk24' ~ 'T24',
  Period == 'Wk48' ~ 'T48'
)) %>%
spread(key = Period,
       value = Mean) %>%
select(-`<NA>`)

# PP cohort
PP_wide %>%
  filter(complete.cases())

# Number of participants with complete data
PP_wide %>%
  summarise(Count = n())

## # A tibble: 1 x 1
##   Count
##   <int>
## 1     32

# Number of participants with complete data (by intervention)
PP_wide %>%
  group_by(Group) %>%
  summarise(Count = n())

## # A tibble: 2 x 2
##   Group Count
##   <chr> <int>
## 1 P      19
## 2 T      13

# Plot of BOCF NRS data at weeks 0 and 48 (by intervention)
PP_wide %>%
  gather(key = Period,
        value = NRS,
        -ID, -Study_site, -Group) %>%
  ggplot(data = .) +
  aes(x = Period,
      y = NRS,
      colour = Group,

```

```

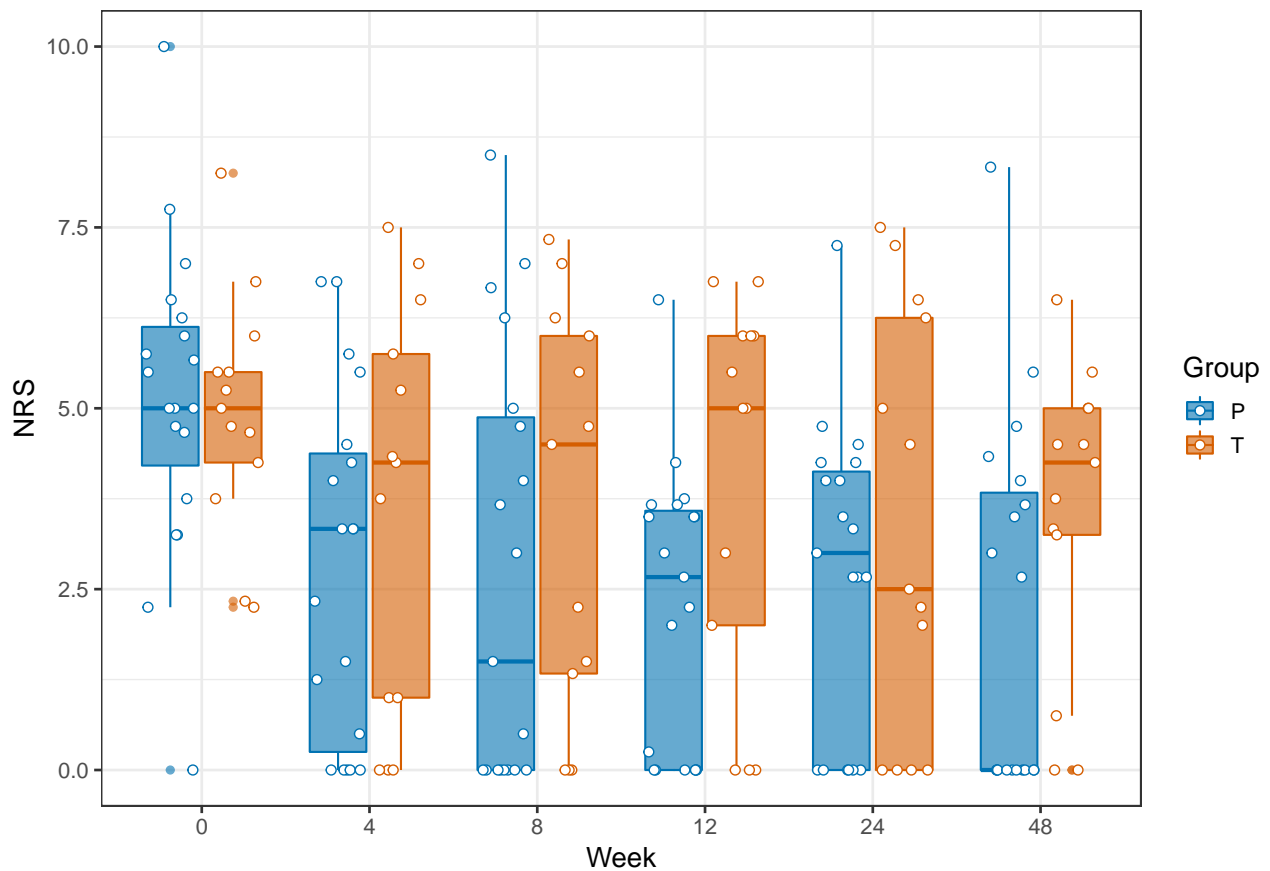
    fill = Group) +
  geom_boxplot(alpha = 0.6) +
  geom_point(position = position_jitterdodge(jitter.height = 0,
                                             jitter.width = 0.3),
            shape = 21,
            fill = '#FFFFFF',
            size = 2) +
  labs(title = 'PP: NRS at weeks 0 through to 48',
       subtitle = 'P: Positive-living programme and therapeutic relationship\nT: Therapeutic relationship only',
       x = 'Week') +
  scale_fill_manual(values = pal) +
  scale_colour_manual(values = pal) +
  scale_x_discrete(labels = c(0, 4, 8, 12, 24, 48))

```

PP: NRS at weeks 0 through to 48

P: Positive-living programme and therapeutic relationship

T: Therapeutic relationship only



```
# Calculate change from baseline to Wk48
```

```
PP_wide %<>%
```

```
  mutate(Delta = T48 - T00)
```

```
# Compare the P and T groups
```

```
## Plot of BOCF change in NRS between week 0 and 48 (by intervention)
```

```
ggplot(data = PP_wide) +
```

```
  aes(x = Group,
```

```
      y = Delta,
```

```

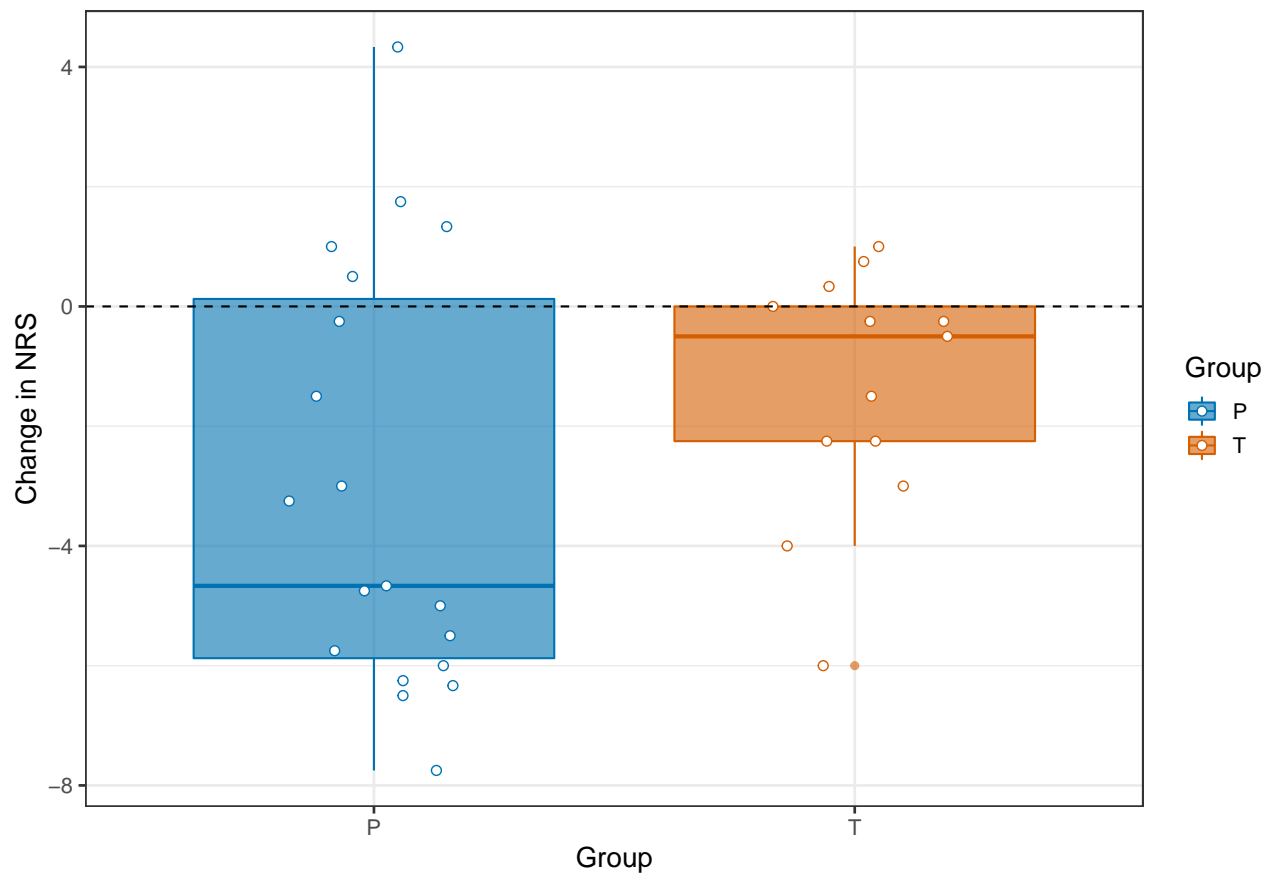
    fill = Group,
    colour = Group) +
  geom_boxplot(alpha = 0.6) +
  geom_point(position = position_jitterdodge(jitter.height = 0,
                                             jitter.width = 0.4),
             shape = 21,
             size = 2,
             fill = '#FFFFFF') +
  geom_hline(yintercept = 0,
             linetype = 2) +
  labs(title = 'PP: Change in NRS from week 0 to week 48',
       subtitle = 'P: Positive-living programme and therapeutic relationship\nT: Therapeutic relationship only',
       y = 'Change in NRS') +
  scale_fill_manual(values = pal) +
  scale_colour_manual(values = pal)

```

PP: Change in NRS from week 0 to week 48

P: Positive-living programme and therapeutic relationship

T: Therapeutic relationship only



```

# Slope plot of individual responses
PP_wide %>%
  mutate(Change = ifelse(Delta < 0,
                          yes = 'Decreased',
                          no = 'Increased')) %>%
  ggplot(data = .) +
  aes(colour = Change) +

```

```

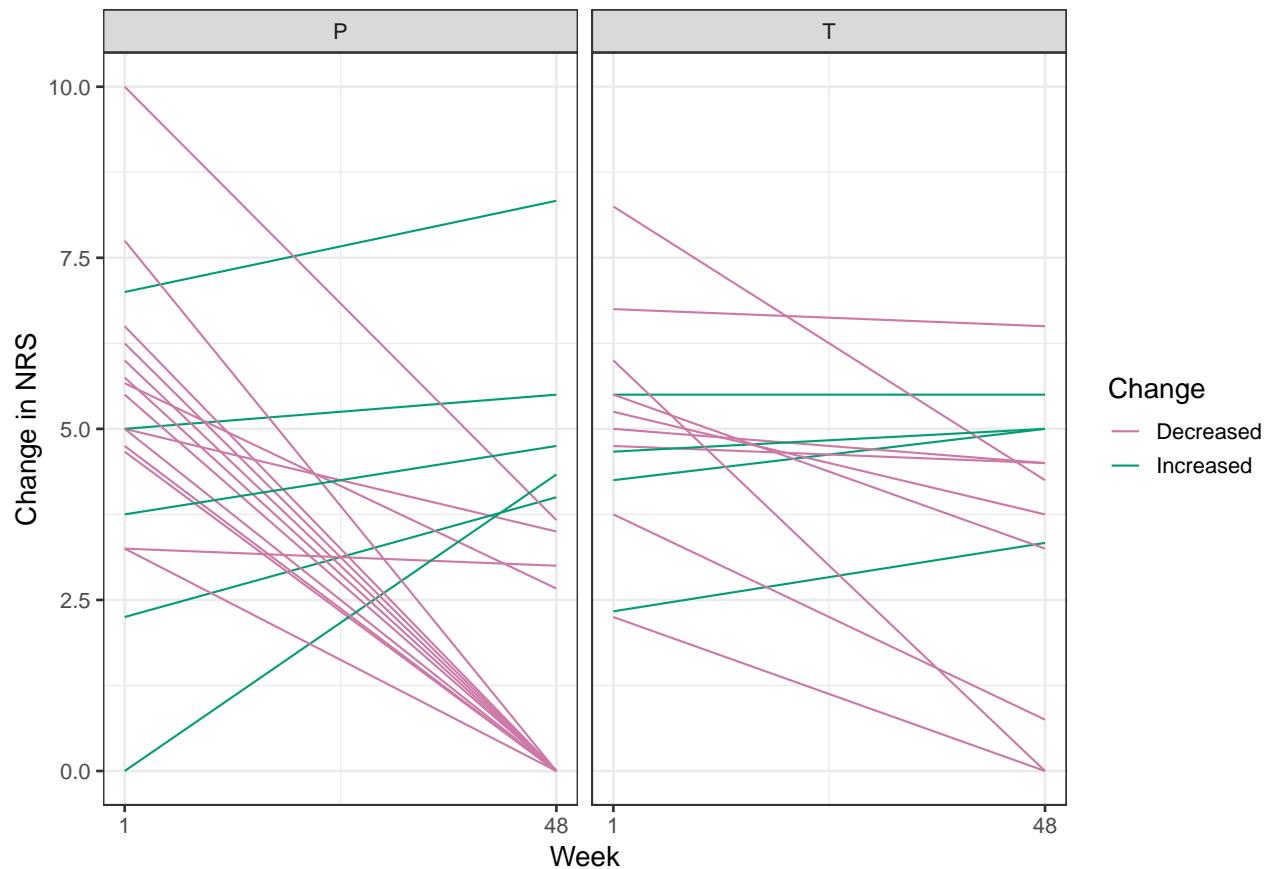
geom_segment(aes(x = 1, xend = 2,
                 y = T00, yend = T48)) +
scale_x_continuous(breaks = c(1, 2),
                  labels = c(1, 48)) +
scale_colour_manual(values = pal2) +
labs(title = "PP: Individuals' changes in NRS from week 0 to week 48",
     subtitle = 'P: Positive-living programme and therapeutic relationship\nT: Therapeutic relationship only',
     x = 'Week',
     y = 'Change in NRS') +
facet_wrap(~ Group)

```

PP: Individuals' changes in NRS from week 0 to week 48

P: Positive-living programme and therapeutic relationship

T: Therapeutic relationship only



```

## Statistical test
independence_test(Delta ~ factor(Group),
                 data = PP_wide,
                 distribution = approximate(nresample = 100000))

##
## Approximative General Independence Test
##
## data: Delta by factor(Group) (P, T)
## Z = -1.4904, p-value = 0.1387
## alternative hypothesis: two.sided

```

Treatment dose

Number of assessments attended on average

```
dose <- primary %>%
  gather(key = 'Time',
         value = 'NRS',
         - ID, -Study_site, -Group) %>%
  separate(col = Time,
         into = c('Pain', 'Period'),
         sep = '\\\\.') %>%
  group_by(ID, Study_site, Group, Period) %>%
  nest() %>%
  mutate(PPS = map(.x = data,
                  ~ summarise(.x, Mean = mean(NRS, na.rm = TRUE)))) %>%
  select(-data) %>%
  unnest() %>%
  mutate(Mean = ifelse(is.nan(Mean),
                      yes = NA,
                      no = Mean)) %>%
  mutate(Period = case_when(
    Period == 'BL' ~ 'T00',
    Period == 'Wk4' ~ 'T04',
    Period == 'Wk8' ~ 'T08',
    Period == 'Wk12' ~ 'T12',
    Period == 'Wk24' ~ 'T24',
    Period == 'Wk48' ~ 'T48'
  ))

# Calculate dose per individual
dose_b <- dose %>%
  mutate(Mean = ifelse(is.na(Mean),
                      yes = 0,
                      no = 1)) %>%
  group_by(Group, Study_site, ID) %>%
  summarise(Count = sum(Mean))

# Calculate summary stat for dose
dose_b %>%
  ungroup() %>%
  summarise(Median = median(Count),
            q25 = quantile(Count, probs = 0.25),
            a75 = quantile(Count, probs = 0.75),
            min = min(Count),
            max = max(Count))

## # A tibble: 1 x 5
##   Median q25 a75 min max
##   <dbl> <dbl> <dbl> <dbl> <dbl>
## 1     5     3     6     0     7

# Calculate summary stat for dose (by intervention)
dose_b %>%
  group_by(Group) %>%
```

```

  summarise(Median = median(Count),
            q25 = quantile(Count, probs = 0.25),
            a75 = quantile(Count, probs = 0.75),
            min = min(Count),
            max = max(Count))

## # A tibble: 2 x 6
##   Group Median   q25   a75   min   max
##   <chr>   <dbl> <dbl> <dbl> <dbl> <dbl>
## 1 P         5     3     6     1     7
## 2 T         4     2     5     0     6

```

Relationship between treatment session attendance (Group P) and outcome

Excludes site U1 (data missing).

```

# Spread dose data
dose %<>%
  spread(key = Period,
         value = Mean)

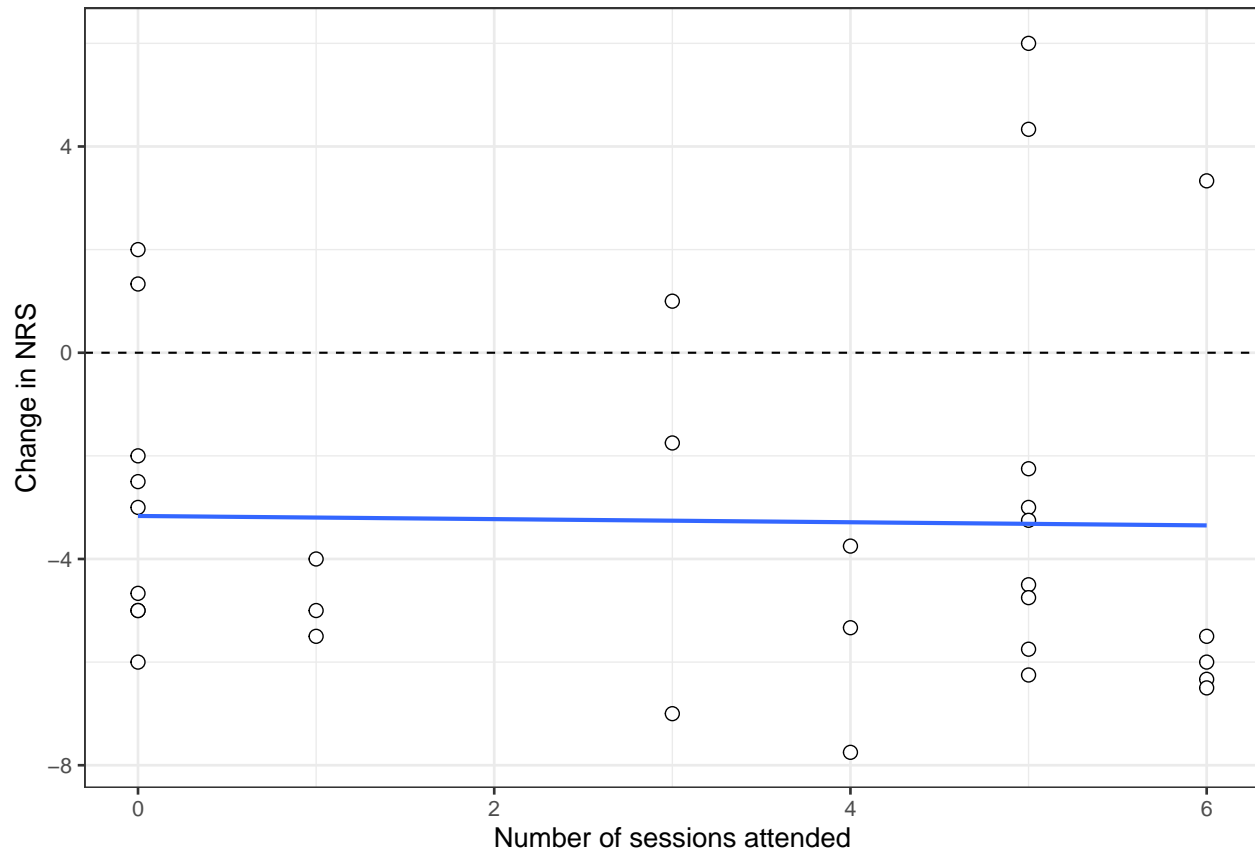
# Calculate change from baseline to Wk48, PL group only
dose %<>%
  mutate(Delta = T48 - T00) %>%
  left_join(dosage) %>%
  filter(Group == 'P') %>%
  filter(Delta != 'NA') %>%
  filter(dosage != 'NA') # filters out 5 participants all from J site

# Plot of P group's change in NRS between week 0 and 48
# (by PL session attendance)
ggplot(data = dose) +
  aes(x = dosage,
      y = Delta) +
  geom_point(shape = 21,
            fill = '#FFFFFF',
            size = 3) +
  geom_hline(yintercept = 0,
            linetype = 2) +
  geom_smooth(method = 'lm',
            se = FALSE) +
  labs(title = 'Change in NRS from week 0 to week 48\nby number of sessions attended',
       subtitle = 'Positive-living group only',
       y = 'Change in NRS',
       x = 'Number of sessions attended')

```

Change in NRS from week 0 to week 48 by number of sessions attended

Positive-living group only



Session information

```
## R version 3.6.0 (2019-04-26)
## Platform: x86_64-apple-darwin15.6.0 (64-bit)
## Running under: macOS Mojave 10.14.4
##
## Matrix products: default
## BLAS:   /Library/Frameworks/R.framework/Versions/3.6/Resources/lib/libRblas.0.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/3.6/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] coin_1.3-0      survival_2.44-1.1 forcats_0.4.0
## [4] stringr_1.4.0    dplyr_0.8.0.1      purrr_0.3.2
## [7] readr_1.3.1      tidyr_0.8.3        tibble_2.1.1
```

```

## [10] ggplot2_3.1.1      tidyverse_1.2.1    magrittr_1.5
##
## loaded via a namespace (and not attached):
## [1] Rcpp_1.0.1          lubridate_1.7.4     mvtnorm_1.0-10
## [4] lattice_0.20-38     zoo_1.8-5           assertthat_0.2.1
## [7] digest_0.6.18       utf8_1.1.4          R6_2.4.0
## [10] cellranger_1.1.0    plyr_1.8.4          backports_1.1.4
## [13] stats4_3.6.0        evaluate_0.13        httr_1.4.0
## [16] pillar_1.3.1        rlang_0.3.4          lazyeval_0.2.2
## [19] multcomp_1.4-10     readxl_1.3.1         rstudioapi_0.10
## [22] Matrix_1.2-17       rmarkdown_1.12       labeling_0.3
## [25] splines_3.6.0       munsell_0.5.0        broom_0.5.2
## [28] compiler_3.6.0      modelr_0.1.4         xfun_0.6
## [31] pkgconfig_2.0.2     libcoin_1.0-4        htmltools_0.3.6
## [34] tidyselect_0.2.5    codetools_0.2-16     matrixStats_0.54.0
## [37] fansi_0.4.0         crayon_1.3.4         withr_2.1.2.9000
## [40] MASS_7.3-51.4       grid_3.6.0           nlme_3.1-139
## [43] jsonlite_1.6         gtable_0.3.0         scales_1.0.0
## [46] cli_1.1.0           stringi_1.4.3         xml2_1.2.0
## [49] generics_0.0.2      sandwich_2.5-1       TH.data_1.0-10
## [52] tools_3.6.0         glue_1.3.1           hms_0.4.2
## [55] parallel_3.6.0      yaml_2.2.0           colorspace_1.4-1
## [58] rvest_0.3.3         knitr_1.22           haven_2.1.0
## [61] modeltools_0.2-22

```