Fragility of evidence for anti-fracture efficacy

Nick Tran

2024-05-07

Fragility of evidence for the efficacy of anti-fracture medications

Libraries needed:

```
library(tidyverse)
```

```
## -- Attaching core tidyverse packages ------------------------ tidyverse 2.0.0 --
## v dplyr     1.1.4     v readr     2.1.5
## v forcats   1.0.0     v stringr   1.5.1
## v ggplot2   3.5.1     v tibble    3.2.1
## v lubridate 1.9.3     v tidyr     1.3.1
## v purrr     1.0.2
## -- Conflicts ------------------------------------------ tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
## i Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to become errors
```

```
library(dplyr)
library(fragility)
```

```
## Warning: package 'fragility' was built under R version 4.4.2
```

```
## Registered S3 method overwritten by 'netmeta':
##   method          from
##   subset.pairwise meta
```

```
library(expss)
```

```
## Warning: package 'expss' was built under R version 4.4.2
```

```
## Loading required package: maditr
```

```
## Warning: package 'maditr' was built under R version 4.4.2
```

```
##
## To modify variables or add new variables:
##              let(mtcars, new_var = 42, new_var2 = new_var*hp) %>% head()
##
```

```
##
## Attaching package: 'maditr'
##
## The following objects are masked from 'package:dplyr':
##
##     between, coalesce, first, last
##
## The following object is masked from 'package:purrr':
##
##     transpose
##
## The following object is masked from 'package:readr':
##
##     cols
##
##
## Use 'expss_output_rnotebook()' to display tables inside R Notebooks.
##  To return to the console output, use 'expss_output_default()'.
##
##
## Attaching package: 'expss'
##
## The following objects are masked from 'package:stringr':
##
##     fixed, regex
##
## The following objects are masked from 'package:dplyr':
##
##     compute, contains, na_if, recode, vars, where
##
## The following objects are masked from 'package:purrr':
##
##     keep, modify, modify_if, when
##
## The following objects are masked from 'package:tidyr':
##
##     contains, nest
##
## The following object is masked from 'package:ggplot2':
##
##     vars
```

```
library(ggplot2)
library(gridExtra)
```

```
## Warning: package 'gridExtra' was built under R version 4.4.2
```

```
##
## Attaching package: 'gridExtra'
##
## The following object is masked from 'package:dplyr':
##
##     combine
```

```r
library(grid)
library(table1)
```

```
##
## Attaching package: 'table1'
##
## The following objects are masked from 'package:base':
##
##     units, units<-
```

```r
#library(compareGroups)
library(ggrepel)
```

```
## Warning: package 'ggrepel' was built under R version 4.4.2
```

(1) Data management

Set-up data:

```r
fi = read.csv("C:\\Users\\nickt\\OneDrive\\Documents\\Work Stuff\\Projects\\FI Paper Study\\MOST UP TO D
head(fi)
```

```
##    id study_ext study            author year           st_names journal
## 1 a_1        6b    NA Leder_ACTIVExtend 2020 Leder (2020)_exta1    JCEM
## 2 a_2        1b    NA         Body_VERO 2020     Body (2020)_a1      OI
## 3 a_3        1b    NA         Body_VERO 2020     Body (2020)_a2      OI
## 4 a_4        1b    NA         Body_VERO 2020     Body (2020)_a3      OI
## 5 a_5         1     1      Kendler_VERO 2018  Kendler (2018)_a1  Lancet
## 6 a_6         1    NA      Kendler_VERO 2018  Kendler (2018)_a2  Lancet
##         country blinding    intervention     control women_per timing fi
## 1 International   Double   Abaloparatide Alendronate         1      4  4
## 2 International   Double Teriparatide_20 Risedronate         1      2 NA
## 3 International   Double Teriparatide_20 Risedronate         1      4 NA
## 4 International   Double Teriparatide_20 Risedronate         1      2 NA
## 5 International   Double    Teriparatide Risedronate         1      4 15
## 6 International   Double    Teriparatide Risedronate         1      4 17
##          fq      pval         fx_site outcome   HR lower upper
## 1 0.0035971 0.0092162        Vert_24m       1 0.29  0.10  0.87
## 2        NA        NA         MOF_12m       2 0.38  0.20  0.72
## 3        NA        NA         MOF_24m       2 0.20  0.05  0.86
## 4        NA        NA      ClinFx_12m       2 0.49  0.31  0.78
## 5 0.0142993 0.0002691        Vert_24m       1 0.44  0.29  0.68
## 6 0.0162059 0.0002114 NworsenVert_24m       1 0.46  0.31  0.68
##                                          Notes e_con n_rand_con e_intv
## 1                                                  16        581      3
## 2                                                  24        680     10
## 3                                                  40        680     16
## 4 Did not report clinical fractures @ 24 months    34        680     18
## 5                                                  64        680     28
## 6                                                  69        680     31
##   n_rand_intv      x95_ci p_value pri_endpoint sen_analysis extended
```

```
## 1         558  0.10, 0.87  0.0270            0            1        1
## 2         680  0.20, 0.72  0.0030            0            0        0
## 3         680  0.05, 0.86  0.0310            0            0        0
## 4         690  0.31, 0.78  0.0030            0            0        0
## 5         680 [0.29,0.68]  0.0001            1            0        0
## 6         680 [0.31,0.68]  0.0001            0            0        0
##                           notes
## 1      post-hoc analysis/extended
## 2                VERO (2nd paper)
## 3                VERO (2nd paper)
## 4                VERO (2nd paper)
## 5 6 pt excluded from the analyses
## 6
##                                          st_cohort rep_loss rep_withdr
## 1                   postm osteoporotic women aged 49+        9         62
## 2                    Survival analysis: no loss to FU       NA         NA
## 3                    Survival analysis: no loss to FU       NA         NA
## 4                    Survival analysis: no loss to FU       NA         NA
## 5 postm women aged 45+: <=-1.5, 2+ mod/1+ sev vert fx       12        185
## 6 postm women aged 45+: <=-1.5, 2+ mod/1+ sev vert fx       12        185
##   rep_death rep_compt n_control n_interven
## 1        68      1861       568        544
## 2        NA        NA       680        680
## 3        NA        NA       680        680
## 4        NA        NA       680        680
## 5        20      1013       533        516
## 6        20      1013       533        516
```

```
fi$no_rand = fi$n_rand_con + fi$n_rand_intv
fi$active_sample = fi$n_control + fi$n_interven
fi$n_event = fi$e_con + fi$e_intv

fi$loghr = log(fi$HR)
```

Data management:

(1.1) Fracture sites:

```
fi_final = fi %>%
  mutate(fx_code1 = case_when(fx_site == "Fx_36m" | fx_site == "Fx_70m" | fx_site == "Fx_72m" | fx_site
                              fx_site == "ClinFx_12m" | fx_site == "ClinFx_18m" | fx_site == "ClinFx_24m
                                fx_site == "ClinFx_36m" | fx_site == "ClinFx_72m" | fx_site == "ClinFx_7
                                fx_site == "OtherClinFx_48m" ~ 2,
                              fx_site == "OFx_12m" | fx_site == "OFx_24m" | fx_site == "Ofx_48m" | fx_si
                              fx_site == "MOF_12m" | fx_site == "MOF_18m" | fx_site == "MOF_24m"  ~ 4,
                              fx_site == "Hip_Wrist_Forearm_70m" | fx_site == "Hip_Wrist_Forearm_Vertebra
                              fx_site == "MajorNonVert_12m" | fx_site == "MajorNonVert_24m" | fx_site ==
                                fx_site == "MajorNonVert_60m"  | fx_site == "NonVert_12m" | fx_site == "
                                fx_site == "NonVert_24m" | fx_site == "NonVert_36m" | fx_site == "NonVer
                                fx_site == "NonVert_72m" | fx_site == "NonVertOFx_24m" ~ 6,
                              fx_site == "MajVert_24m" | fx_site == "MNworsenVert_12m" | fx_site == "MNw
                                fx_site == "MultiVert_24m" | fx_site == "MultiVert_36m" | fx_site == "MV
                                fx_site == "MVert_36m" | fx_site == "NmodVert_12m" | fx_site == "NmodVer
                                fx_site == "NworsenVert_12m" | fx_site == "NworsenVert_24m"  | fx_site ==
```

```
                                fx_site == "Vert_18m"  | fx_site == "Vert_24m" | fx_site == "Vert_36m" |
                                fx_site == "Vert_48m" | fx_site == "Vert_48w" | fx_site == "Vert_60m" |
                                fx_site == "Vert_72m" | fx_site == "Vert_72w" ~ 7,
                              fx_site == "ClinVert_12m" | fx_site == "ClinVert_24m" | fx_site == "ClinVert
                                fx_site == "ClinVert_48m" | fx_site == "ClinVert_72m" | fx_site == "ClinV
                              fx_site == "Hip_18m" | fx_site == "Hip_24m" | fx_site == "Hip_36m" | fx_site
                              fx_site == "Forearm_60m" | fx_site == "ForearmWrist_72m" | fx_site == "Wrist
var_lab(fi_final$fx_code1) = "Fracture sites"
val_lab(fi_final$fx_code1) = num_lab("
                                     1 Any_fx
                                     2 Clin_fx
                                     3 OFx
                                     4 MOF
                                     5 Dif_comb
                                     6 NonVert_fx
                                     7 Vert_fx
                                     8 ClinVert_fx
                                     9 Hip
                                     10 Forearm")

fi_final = fi_final %>%
  mutate(fx_code2 = case_when(fx_code1 == "1" | fx_code1 == "2" ~ 1,
                              fx_code1 == "3" | fx_code1 == "4" | fx_code1 == "5" ~ 2,
                              fx_code1 == "6" ~ 3,
                              fx_code1 == "7" ~ 4,
                              fx_code1 == "8" ~ 5,
                              fx_code1 == "9" ~ 6,
                              fx_code1 == "10" ~ 7))
var_lab(fi_final$fx_code2) = "Fracture sites"
val_lab(fi_final$fx_code2) = num_lab("
                                     1 Any
                                     2 Osteoporotic
                                     3 Non-Vertebrae
                                     4 Vertebrae
                                     5 Clinical Vertebrae
                                     6 Hip
                                     7 Forearm")
```

(1.2) Interventions:

```
fi_final = fi_final %>%
  mutate(interv_code1 = case_when(intervention == "Alendronate"  ~ 1.1,
                                  intervention == "Ibandronate daily" | intervention == "Ibandronate int
                                  intervention == "Risendronate" | intervention == "Risedronate_25" | in
                                  intervention == "Minodronate" ~ 1.4,
                                  intervention == "Zoledronate" ~ 1.5,
                                  intervention == "Teriparatide" | intervention == "Teriparatide_20" |
                                    intervention == "Teriparatide_40"  | intervention == "PTH" ~ 2.1,
                                  intervention == "Abaloparatide" ~ 2.2,
                                  intervention == "Romosozumab" ~ 3,
                                  intervention == "Denosumab" ~ 4,
                                  intervention == "Strontium Ranelate" ~ 5,
                                  intervention == "Calcium" | intervention == "Calcium + vit D" | interv
```

```
var_lab(fi_final$interv_code1) = "Interventions"
val_lab(fi_final$interv_code1) = num_lab("
                                    1.1 Alendronate
                                    1.2 Ibandronate
                                    1.3 Risedronate
                                    1.4 Minodronate
                                    1.5 Zoledronate
                                    2.1 Teriparatide
                                    2.2 Abaloparatide
                                    3 Romosozumab
                                    4 Denosumab
                                    5 Strontium_ranelate
                                    6 Calcium_VitD")

fi_final = fi_final %>%
  mutate(interv_code2 = case_when(intervention == "Alendronate" | intervention == "Ibandronate daily" |
                                    intervention == "Ibandronate intermittent" | intervention == "Risen
                                    intervention == "Minodronate" | intervention == "Zoledronate" ~ 1,
                                  intervention == "Teriparatide" | intervention == "Teriparatide_20" |
                                    intervention == "Teriparatide_40" | intervention == "Abaloparatide"
                                  intervention == "Romosozumab" ~ 3,
                                  intervention == "Denosumab" ~ 4,
                                  intervention == "Strontium Ranelate" ~ 5,
                                  intervention == "Calcium" | intervention == "Calcium + vit D" | interv
var_lab(fi_final$interv_code2) = "Interventions"
val_lab(fi_final$interv_code2) = num_lab("
                                    1 Bisphosphonates
                                    2 PTH analog
                                    3 Romosozumab
                                    4 Denosumab
                                    5 Strontium_ranelate
                                    6 Calcium_VitD")
```

(1.3) Journals:

```
fi_final = fi_final %>%
  mutate(journal_code1 = case_when(journal == "NEJM" ~ 1,
                                   journal == "Lancet" ~ 2,
                                   journal == "BMJ" ~ 3,
                                   journal == "JAMA" ~ 4,
                                   journal == "Ann Intern Med" ~ 5,
                                   journal == "JBMR" ~ 6,
                                   journal == "JCEM" | journal == "JECM" ~ 7,
                                   journal == "OI" ~ 8,
                                   journal == "Am J Clin Nutr" | journal == "Arth Rheu" ~ 9))
var_lab(fi_final$journal_code1) = "Journal"
val_lab(fi_final$journal_code1) = num_lab("
                                    1 NEJM
                                    2 Lancet
                                    3 BMJ
                                    4 JAMA
                                    5 Ann Intern Med
                                    6 JBMR
```

```
                                    7 JCEM
                                    8 OI
                                    9 Other")

fi_final = fi_final %>%
  mutate(journal_code2 = case_when(journal == "NEJM" ~ 1,
                                   journal == "Lancet" ~ 2,
                                   journal == "BMJ" ~ 3,
                                   journal == "JAMA" ~ 4,
                                   journal == "Ann Intern Med" ~ 5,
                                   journal == "JBMR" ~ 6,
                                   journal == "JCEM" | journal == "JECM" ~ 7,
                                   journal == "OI" | journal == "Am J Clin Nutr" | journal == "Arth Rheu
var_lab(fi_final$journal_code2) = "Journal"
val_lab(fi_final$journal_code2) = num_lab("
                                    1 NEJM
                                    2 Lancet
                                    3 BMJ
                                    4 JAMA
                                    5 Ann Intern Med
                                    6 JBMR
                                    7 JCEM
                                    8 Other")
```

(1.4) Other variables:

```
var_lab(fi_final$outcome) = "Types of fracture outcome"
val_lab(fi_final$outcome) = num_lab("
                                    1 Binary
                                    2 Time-to-event")

var_lab(fi_final$timing) = "Timing of outcome assessed"
val_lab(fi_final$timing) = num_lab("
                                    1 0-6m
                                    2 >6-12m
                                    3 >12-18m
                                    4 >18-24m
                                    5 >24-36m
                                    6 >36-48m
                                    7 >48-60m
                                    8 >60-72m
                                    9 >72m")

fi_final = fi_final %>%
  mutate(sex = case_when(women_per == 0 ~ "Men",
                         women_per == 1 ~ "Women",
                         women_per > 0 & women_per < 1 ~ "Both"))
var_lab(fi_final$sex) = "Sex"

fi_final = fi_final %>%
  mutate(placebo = case_when(control == "Placebo" ~ "Placebo",
                             control == "Alendronate" | control == "Risedronate" ~ "Active"))
var_lab(fi_final$placebo) = "Placebo"
```

(2) Calculate Fragility index (FI) and Fragility quotient (FQ)

```
fi_screen = frag.studies(e_con, n_control, e_intv, n_interven, data = fi_final, methods = "RR")
fi_screen
```

```
## The input dataset contains 149 studies
## Significance level = 0.05
## Null hypothesis: RR = 1
## p-value (two-sided) is based on:
##   relative risk
##
## Fragility index (FI) and fragility quotient (FQ):
## Based on relative risk,
##   141 studies yield significance with
##     median FI = 9, range 1-171, IQR 4-19 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%;
##   8 studies yield non-significance with
##     median FI = 1, range 1-6, IQR 1-4 and
##     median FQ = 0.1%, range 0.0%-1.0%, IQR 0.0%-0.1%;
##   overall, among all studies,
##     median FI = 8, range 1-171, IQR 3-18 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%
```

```
fi_final$Pval_screen = fi_screen$pval
```

Only analyses with statistically significant results from logistic regression/Fisher exact test (binary outcome) are included

```
fi_sig = subset(fi_final, Pval_screen<= 0.05)
fi_only_sig = frag.studies(e_con, n_control, e_intv, n_interven, data = fi_sig, methods = "RR")
fi_only_sig
```

```
## The input dataset contains 141 studies
## Significance level = 0.05
## Null hypothesis: RR = 1
## p-value (two-sided) is based on:
##   relative risk
##
## Fragility index (FI) and fragility quotient (FQ):
## Based on relative risk,
##   141 studies yield significance with
##     median FI = 9, range 1-171, IQR 4-19 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%;
##   0 study yields non-significance
##   overall, among all studies,
##     median FI = 9, range 1-171, IQR 4-19 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%
```

```
fi_sig$FI_final = fi_only_sig$FI
fi_sig$FQ_final = fi_only_sig$FQ
fi_sig$Pval_final = fi_only_sig$pval
```

(3) PRIMARY ANALYSIS: All analyses with statistically significant results from logistic regression

n= 141 analyses from all 27 RCT (27 original studies [with 6 extended phase] + 1 extended phases which original study found no significant result)

(3.1) Table 1: Characteristics of the trials included in the primary analysis (n= 27)

```
fi_sig_st = subset(fi_sig, study >= 1)

table1(~ as.factor(interv_code2) + as.factor(journal_code2) + as.factor(placebo) + sex + no_rand, data =
```

	Overall
	(N=27)
as.factor(interv__code2)	
Bisphosphonates	12 (44.4%)
PTH analog	5 (18.5%)
Romosozumab	2 (7.4%)
Denosumab	2 (7.4%)
Strontium_ranelate	2 (7.4%)
Calcium_VitD	4 (14.8%)
as.factor(journal__code2)	
NEJM	12 (44.4%)
Lancet	2 (7.4%)
BMJ	1 (3.7%)
JAMA	3 (11.1%)
Ann Intern Med	1 (3.7%)
JBMR	1 (3.7%)
JCEM	2 (7.4%)
Other	5 (18.5%)
as.factor(placebo)	
Active	3 (11.1%)
Placebo	24 (88.9%)
Sex	
Both	5 (18.5%)
Men	2 (7.4%)
Women	20 (74.1%)
no__rand	
Median [Q1, Q3]	1910 [1280, 2980]

(3.1) Table 1: Characteristics of the analyses included in the primary analysis (n= 141)

```
fi_sig$missing_fi[fi_sig$rep_loss > fi_sig$FI_final] = 1
fi_sig$missing_fi[fi_sig$rep_loss <= fi_sig$FI_final] = 0
is.na(fi_sig$rep_loss)
```

```
##   [1] FALSE  TRUE  TRUE  TRUE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
```

```
##  [13] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [25] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [37] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [49] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE  TRUE
##  [61]  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE FALSE
##  [73] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [85] FALSE FALSE FALSE FALSE FALSE FALSE FALSE  TRUE  TRUE  TRUE  TRUE  TRUE
##  [97]  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE FALSE  TRUE  TRUE
## [109]  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE FALSE FALSE FALSE FALSE FALSE
## [121] FALSE FALSE FALSE  TRUE  TRUE  TRUE  TRUE FALSE FALSE FALSE FALSE FALSE
## [133] FALSE FALSE FALSE FALSE FALSE  TRUE  TRUE  TRUE  TRUE
```

```
fi_sig$missing_fi[fi_sig$rep_loss == NA] = NA
fi_sig$fi4[fi_sig$FI_final>4] = "FI > 4"
  fi_sig$fi4[fi_sig$FI_final<=4] = "FI <= 4"

table1(~ as.factor(fx_code2) + as.factor(interv_code2) + as.factor(journal_code2) + as.factor(placebo) +
```

	Overall
	(N=141)
as.factor(fx_code2)	
Any	18 (12.8%)
Osteoporotic	10 (7.1%)
Non-Vertebrae	19 (13.5%)
Vertebrae	68 (48.2%)
Clinical Vertebrae	14 (9.9%)
Hip	9 (6.4%)
Forearm	3 (2.1%)
as.factor(interv_code2)	
Bisphosphonates	48 (34.0%)
PTH analog	30 (21.3%)
Romosozumab	28 (19.9%)
Denosumab	9 (6.4%)
Strontium_ranelate	12 (8.5%)
Calcium_VitD	14 (9.9%)
as.factor(journal_code2)	
NEJM	79 (56.0%)
Lancet	9 (6.4%)
BMJ	5 (3.5%)
JAMA	10 (7.1%)
Ann Intern Med	1 (0.7%)
JBMR	6 (4.3%)
JCEM	12 (8.5%)
Other	19 (13.5%)
as.factor(placebo)	
Active	29 (20.6%)
Placebo	112 (79.4%)
Sex	
Both	15 (10.6%)
Men	10 (7.1%)
Women	116 (82.3%)
no_rand	
Mean (SD)	2870 (2300)
Median [Q1, Q3]	1960 [1220, 4090]
Median [min, max]	1960 [450, 7870]
HR	
Mean (SD)	0.487 (0.185)
Median [Q1, Q3]	0.510 [0.350, 0.640]
Median [min, max]	0.510 [0.0600, 0.810]
loghr	
Mean (SD)	-0.820 (0.497)
Median [Q1, Q3]	-0.673 [-1.05, -0.446]
Median [min, max]	-0.673 [-2.81, -0.211]
active_sample	
Mean (SD)	2510 (2080)
Median [Q1, Q3]	1770 [1060, 3610]
Median [min, max]	1770 [339, 7810]
n_event	
Mean (SD)	155 (157)
Median [Q1, Q3]	86.0 [52.0, 210]
Median [min, max]	86.0 [10.0, 764]
FI_final	
Mean (SD)	16.8 (24.0)
Median [Q1, Q3]	9.00 [4.00, 19.0]

(3.2) Table 2: Fragility of evidence for anti-fracture efficacy

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(int
```

(3.2.1) Table 2 - Intervention

	Bisphosphonates	PTH analog	Romosozu
	(N=48)	(N=30)	(N=28)
no_rand			
Median [Q1, Q3]	1960 [1200, 2030]	1100 [1090, 1360]	4090 [4090
active_sample			
Median [Q1, Q3]	1800 [742, 1970]	892 [841, 1240]	4040 [3640
n_event			
Median [Q1, Q3]	72.5 [58.8, 141]	44.0 [34.0, 59.0]	173 [106, 2
FI_final			
Median [Q1, Q3]	8.50 [4.00, 14.0]	6.50 [3.00, 12.5]	19.5 [7.00,
FQ_final			
Median [Q1, Q3]	0.00535 [0.00272, 0.00859]	0.00741 [0.00325, 0.0137]	0.00354 [0
as.factor(missing_fi)			
0	5 (10.4%)	2 (6.7%)	2 (7.1%)
1	34 (70.8%)	9 (30.0%)	26 (92.9%
Missing	9 (18.8%)	19 (63.3%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(fx_
```

(3.2.2) Table 2 - Fracture sites

	Any	Osteoporotic	Non-Vert
	(N=18)	(N=10)	(N=19)
no_rand			
Median [Q1, Q3]	2010 [1390, 4090]	3390 [1730, 4090]	3270 [136
active_sample			
Median [Q1, Q3]	1890 [1140, 3690]	3110 [1510, 3940]	2380 [125
n_event			
Median [Q1, Q3]	210 [76.0, 401]	163 [67.3, 320]	168 [71.0
FI_final			
Median [Q1, Q3]	9.00 [5.00, 20.3]	12.0 [6.00, 29.0]	5.00 [2.00
FQ_final			
Median [Q1, Q3]	0.00731 [0.00235, 0.0115]	0.00686 [0.00227, 0.00750]	0.00315 [
as.factor(missing_fi)			
0	1 (5.6%)	2 (20.0%)	1 (5.3%)
1	11 (61.1%)	6 (60.0%)	13 (68.4%
Missing	6 (33.3%)	2 (20.0%)	5 (26.3%

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(ti
```

(3.2.3) Table 2 - Timing of fracture assessment:

	>6-12m	>12-18m
	(N=26)	(N=18)
no_rand		
Median [Q1, Q3]	1650 [1360, 4090]	1650 [578, 3270]
active_sample		
Median [Q1, Q3]	1390 [1190, 3910]	1340 [451, 1770]
n_event		
Median [Q1, Q3]	65.5 [52.3, 137]	53.0 [34.5, 142]
FI_final		
Median [Q1, Q3]	5.00 [3.00, 9.75]	7.50 [4.00, 11.0]
FQ_final		
Median [Q1, Q3]	0.00240 [0.00149, 0.00489]	0.00660 [0.00358,
as.factor(missing_fi)		
0	1 (3.8%)	0 (0%)
1	20 (76.9%)	12 (66.7%)
Missing	5 (19.2%)	6 (33.3%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(jou
```

(3.2.4) Table 2 - Journal:

	NEJM	Lancet	BMJ
	(N=79)	(N=9)	(N=5)
no_rand			
Median [Q1, Q3]	3270 [1560, 7180]	1360 [1360, 2030]	2300 [1770, 230
active_sample			
Median [Q1, Q3]	2790 [1350, 6240]	1160 [1050, 2030]	2300 [1770, 230
n_event			
Median [Q1, Q3]	117 [54.5, 248]	91.0 [63.0, 100]	315 [262, 475]
FI_final			
Median [Q1, Q3]	12.0 [4.50, 26.0]	11.0 [4.00, 15.0]	16.0 [11.0, 22.0
FQ_final			
Median [Q1, Q3]	0.00393 [0.00226, 0.00831]	0.00691 [0.00259, 0.0143]	0.00695 [0.0062
as.factor(missing_fi)			
0	7 (8.9%)	2 (22.2%)	0 (0%)
1	51 (64.6%)	7 (77.8%)	1 (20.0%)
Missing	21 (26.6%)	0 (0%)	4 (80.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | sex, data = 
```

(3.2.5) Table 2 - Sex:

	Both	Men	Women
	(N=15)	(N=10)	(N=116)
no_rand			
Median [Q1, Q3]	578 [564, 665]	1200 [1200, 1470]	2000 [1630, 4090]
active_sample			
Median [Q1, Q3]	451 [426, 659]	1130 [1130, 1350]	1950 [1280, 3870]
n_event			
Median [Q1, Q3]	39.0 [32.5, 58.5]	26.0 [21.5, 34.3]	107 [65.8, 251]
FI_final			
Median [Q1, Q3]	4.00 [2.50, 7.00]	3.00 [1.25, 4.00]	11.0 [5.00, 23.0]
FQ_final			
Median [Q1, Q3]	0.00840 [0.00454, 0.0132]	0.00216 [0.00115, 0.00296]	0.00538 [0.00244, 0.
as.factor(missing_fi)			
0	0 (0%)	0 (0%)	10 (8.6%)
1	7 (46.7%)	10 (100%)	68 (58.6%)
Missing	8 (53.3%)	0 (0%)	38 (32.8%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | placebo, data
```

(3.2.6) Table 2 - Placebo:

	Active	Placebo	Overall
	(N=29)	(N=112)	(N=141)
no_rand			
Median [Q1, Q3]	4090 [1360, 4090]	1940 [1170, 3270]	1960 [1220, 40
active_sample			
Median [Q1, Q3]	3320 [1280, 3660]	1720 [882, 2710]	1770 [1060, 36
n_event			
Median [Q1, Q3]	107 [53.0, 255]	82.5 [50.3, 194]	86.0 [52.0, 210
FI_final			
Median [Q1, Q3]	10.0 [5.00, 18.0]	8.50 [4.00, 19.3]	9.00 [4.00, 19.0
FQ_final			
Median [Q1, Q3]	0.00440 [0.00221, 0.00908]	0.00516 [0.00244, 0.0106]	0.00514 [0.002
as.factor(missing_fi)			
0	4 (13.8%)	6 (5.4%)	10 (7.1%)
1	22 (75.9%)	63 (56.3%)	85 (60.3%)
Missing	3 (10.3%)	43 (38.4%)	46 (32.6%)

(3.3) Table 3: Fragility of evidence for anti-fracture efficacy in the subgroup analyses

(3.3.1) Table 3.1- Fracture as the predefined primary endpoint: Data-set

```
fx_prim = subset(fi_sig, pri_endpoint == 1)
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi), data = fx_pri
```

(3.3.1.1) Table 3.1 - Overall:

	Overall
	(N=33)
no_rand	
Median [Q1, Q3]	1960 [1200, 4090]
active_sample	
Median [Q1, Q3]	1700 [1050, 3640]
n_event	
Median [Q1, Q3]	112 [60.0, 223]
FI_final	
Median [Q1, Q3]	14.0 [11.0, 33.0]
FQ_final	
Median [Q1, Q3]	0.0107 [0.00532, 0.0206]
as.factor(missing_fi)	
0	3 (9.1%)
1	20 (60.6%)
Missing	10 (30.3%)

Additional analyses for discussion

```
fi_sig$fx_primary[fi_sig$pri_endpoint == 1] = "Primary endpoint"
fi_sig$fx_primary[fi_sig$pri_endpoint == 0] = "Secondary endpoint"
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | fx_primary ,
```

	Primary endpoint	Secondary endpoint	Overall
	(N=33)	(N=108)	(N=141)
no_rand			
Median [Q1, Q3]	1960 [1200, 4090]	1940 [1330, 4090]	1960 [1220, 4090]
active_sample			
Median [Q1, Q3]	1700 [1050, 3640]	1770 [1110, 3570]	1770 [1060, 3610]
n_event			
Median [Q1, Q3]	112 [60.0, 223]	76.0 [50.3, 205]	86.0 [52.0, 210]
FI_final			
Median [Q1, Q3]	14.0 [11.0, 33.0]	7.00 [3.00, 17.0]	9.00 [4.00, 19.0]
FQ_final			
Median [Q1, Q3]	0.0107 [0.00532, 0.0206]	0.00417 [0.00218, 0.00749]	0.00514 [0.00239, 0.0104]
as.factor(missing_fi)			
0	3 (9.1%)	7 (6.5%)	10 (7.1%)
1	20 (60.6%)	65 (60.2%)	85 (60.3%)
Missing	10 (30.3%)	36 (33.3%)	46 (32.6%)

```
# Check whether the difference between two groups was statistically significant
#fi_sig$missing_fi = factor(fi_sig$missing_fi)
#createTable(compareGroups(fx_primary ~ no_rand + active_sample + n_event + FI_final + FQ_final + missi
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(fx
```

(3.3.1.2) Table 3.1 - Fracture sites:

	Any	Osteoporotic	Vertebra
	(N=2)	(N=1)	(N=26)
no_rand			
Median [Q1, Q3]	3110 [2620, 3600]	2000 [2000, 2000]	1650 [11
active_sample			
Median [Q1, Q3]	2060 [1270, 2850]	1950 [1950, 1950]	1440 [93
n_event			
Median [Q1, Q3]	348 [289, 406]	312 [312, 312]	103 [51.0
FI_final			
Median [Q1, Q3]	16.5 [11.8, 21.3]	33.0 [33.0, 33.0]	15.0 [11.
FQ_final			
Median [Q1, Q3]	0.0109 [0.00901, 0.0127]	0.0169 [0.0169, 0.0169]	0.0129 [0
as.factor(missing_fi)			
0	0 (0%)	1 (100%)	2 (7.7%)
1	2 (100%)	0 (0%)	14 (53.8%
Missing	0 (0%)	0 (0%)	10 (38.5%

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(in
```

(3.3.1.3) Table 3.1 - Interventions:

	Bisphosphonates	PTH analog	Romos
	(N=14)	(N=8)	(N=5)
no_rand			
Median [Q1, Q3]	1960 [1200, 2100]	1230 [958, 1640]	4090 [4
active_sample			
Median [Q1, Q3]	1660 [782, 1950]	971 [774, 1410]	4090 [3
n_event			
Median [Q1, Q3]	131 [103, 206]	54.0 [39.8, 83.8]	221 [10
FI_final			
Median [Q1, Q3]	13.0 [8.00, 18.8]	13.0 [11.0, 17.0]	40.0 [2
FQ_final			
Median [Q1, Q3]	0.00933 [0.00566, 0.0195]	0.0200 [0.00889, 0.0265]	0.0071
as.factor(missing_fi)			
0	1 (7.1%)	1 (12.5%)	1 (20.0
1	10 (71.4%)	3 (37.5%)	4 (80.0
Missing	3 (21.4%)	4 (50.0%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(ti
```

(3.3.1.4) Table 3.1 - Timing of fracture assessment:

	>6-12m	>12-18m
	(N=1)	(N=8)
no_rand		
Median [Q1, Q3]	7180 [7180, 7180]	2090 [1370, 3
active_sample		
Median [Q1, Q3]	6640 [6640, 6640]	1560 [1160, 1
n_event		
Median [Q1, Q3]	75.0 [75.0, 75.0]	53.0 [39.8, 89
FI_final		
Median [Q1, Q3]	24.0 [24.0, 24.0]	9.50 [6.00, 11
FQ_final		
Median [Q1, Q3]	0.00361 [0.00361, 0.00361]	0.00591 [0.00
as.factor(missing_fi)		
0	0 (0%)	0 (0%)
1	1 (100%)	6 (75.0%)
Missing	0 (0%)	2 (25.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(jou
```

(3.3.1.5) Table 3.1 - Journal:

	NEJM	Lancet	JAMA
	(N=19)	(N=2)	(N=4)
no_rand			
Median [Q1, Q3]	3270 [1650, 5640]	1690 [1530, 1860]	1640 [1640, 234
active_sample			
Median [Q1, Q3]	2380 [1280, 4880]	1500 [1270, 1720]	1410 [1390, 210
n_event			
Median [Q1, Q3]	190 [84.5, 341]	158 [125, 190]	78.5 [35.5, 129]
FI_final			
Median [Q1, Q3]	25.0 [7.50, 43.5]	27.5 [21.3, 33.8]	12.0 [11.0, 13.0
FQ_final			
Median [Q1, Q3]	0.0115 [0.00349, 0.0223]	0.0174 [0.0159, 0.0190]	0.00785 [0.0065
as.factor(missing_fi)			
0	2 (10.5%)	1 (50.0%)	0 (0%)
1	12 (63.2%)	1 (50.0%)	3 (75.0%)
Missing	5 (26.3%)	0 (0%)	1 (25.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | sex, data =
```

(3.3.1.6) Table 3.1 - Sex:

	Both	Men	Women
	(N=4)	(N=2)	(N=27)
no_rand			
Median [Q1, Q3]	622 [571, 1030]	1200 [1200, 1200]	2030 [1640, 4090]
active_sample			
Median [Q1, Q3]	465 [445, 524]	1090 [1070, 1110]	1950 [1410, 3880]
n_event			
Median [Q1, Q3]	44.5 [40.5, 93.8]	33.0 [31.0, 35.0]	140 [89.0, 268]
FI_final			
Median [Q1, Q3]	9.00 [7.00, 11.5]	3.50 [2.25, 4.75]	20.0 [12.5, 40.0]
FQ_final			
Median [Q1, Q3]	0.0202 [0.0136, 0.0266]	0.00313 [0.00204, 0.00423]	0.00928 [0.00506,
as.factor(missing_fi)			
0	0 (0%)	0 (0%)	3 (11.1%)
1	2 (50.0%)	2 (100%)	16 (59.3%)
Missing	2 (50.0%)	0 (0%)	8 (29.6%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | placebo, data
```

(3.3.1.7) Table 3.1 - Placebo:

	Active	Placebo	Overall
	(N=6)	(N=27)	(N=33)
no_rand			
Median [Q1, Q3]	2870 [1640, 4090]	1960 [1150, 3270]	1960 [1200, 4
active_sample			
Median [Q1, Q3]	2540 [1410, 3660]	1700 [887, 2580]	1700 [1050, 3
n_event			
Median [Q1, Q3]	157 [50.0, 333]	112 [67.5, 207]	112 [60.0, 223
FI_final			
Median [Q1, Q3]	20.5 [13.5, 38.0]	13.0 [7.50, 29.0]	14.0 [11.0, 33.
FQ_final			
Median [Q1, Q3]	0.0104 [0.00810, 0.0136]	0.0107 [0.00386, 0.0258]	0.0107 [0.0053
as.factor(missing_fi)			
0	2 (33.3%)	1 (3.7%)	3 (9.1%)
1	4 (66.7%)	16 (59.3%)	20 (60.6%)
Missing	0 (0%)	10 (37.0%)	10 (30.3%)

(3.3.2) Table 3.2 - Analyses with highly significant results (p< 0.001) Data-set

```
p_sig = subset(fi_sig, Pval_screen<=0.001)
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi), data = p_sig,
```

(3.3.2.1) Table 3.2 - Overall:

	Overall
	(N=45)
no_rand	
Median [Q1, Q3]	2420 [1640, 7180]
active_sample	
Median [Q1, Q3]	2380 [1270, 6530]
n_event	
Median [Q1, Q3]	128 [82.0, 330]
FI_final	
Median [Q1, Q3]	26.0 [18.0, 42.0]
FQ_final	
Median [Q1, Q3]	0.0131 [0.00670, 0.0193]
as.factor(missing_fi)	
0	6 (13.3%)
1	24 (53.3%)
Missing	15 (33.3%)

Additional analysis for discussion:

```
# Comparison of different P values:
fi_sig$p_sig1[fi_sig$p_value<=0.001] = "Highly significant"
  fi_sig$p_sig1[fi_sig$p_value>0.001] = "Significant"
fi_sig$p_sig2[fi_sig$Pval_screen<=0.001] = "Highly significant"
  fi_sig$p_sig2[fi_sig$Pval_screen>0.001] = "Significant"

table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | p_sig2 , data
```

	Highly significant	Significant	Overall
	(N=45)	(N=96)	(N=141)
no_rand			
Mean (SD)	3860 (2780)	2410 (1880)	2870 (2300)
Median [Q1, Q3]	2420 [1640, 7180]	1770 [1200, 3270]	1960 [1220, 4090]
Median [min, max]	2420 [549, 7870]	1770 [450, 7870]	1960 [450, 7870]
active_sample			
Mean (SD)	3430 (2520)	2080 (1680)	2510 (2080)
Median [Q1, Q3]	2380 [1270, 6530]	1530 [890, 2450]	1770 [1060, 3610]
Median [min, max]	2380 [426, 7810]	1530 [339, 6670]	1770 [339, 7810]
n_event			
Mean (SD)	220 (190)	125 (128)	155 (157)
Median [Q1, Q3]	128 [82.0, 330]	69.5 [39.0, 150]	86.0 [52.0, 210]
Median [min, max]	128 [34.0, 764]	69.5 [10.0, 563]	86.0 [10.0, 764]
FI_final			
Mean (SD)	37.9 (33.0)	6.84 (5.54)	16.8 (24.0)
Median [Q1, Q3]	26.0 [18.0, 42.0]	5.00 [2.75, 10.0]	9.00 [4.00, 19.0]
Median [min, max]	26.0 [9.00, 171]	5.00 [1.00, 26.0]	9.00 [1.00, 171]
FQ_final			
Mean (SD)	0.0163 (0.0154)	0.00458 (0.00397)	0.00831 (0.0107)
Median [Q1, Q3]	0.0131 [0.00670, 0.0193]	0.00328 [0.00184, 0.00633]	0.00514 [0.00239, 0.0104]
Median [min, max]	0.0131 [0.00230, 0.0966]	0.00328 [0.000151, 0.0203]	0.00514 [0.000151, 0.0966]
as.factor(missing_fi)			
0	6 (13.3%)	4 (4.2%)	10 (7.1%)
1	24 (53.3%)	61 (63.5%)	85 (60.3%)
Missing	15 (33.3%)	31 (32.3%)	46 (32.6%)

```
#createTable(compareGroups(p_sig2 ~ no_rand + active_sample + n_event + FI_final + FQ_final + missing_f
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(fx
```

(3.3.2.2) Table 3.2 - Fracture sites:

	Any	Osteoporotic	Non-
	(N=2)	(N=5)	(N=4
no_rand			
Median [Q1, Q3]	7460 [7320, 7600]	4090 [2000, 4090]	7180
active_sample			
Median [Q1, Q3]	6620 [6580, 6660]	3530 [1950, 3840]	6590
n_event			
Median [Q1, Q3]	505 [376, 635]	323 [312, 355]	290 [
FI_final			
Median [Q1, Q3]	62.5 [49.3, 75.8]	30.0 [26.0, 33.0]	24.0
FQ_final			
Median [Q1, Q3]	0.00949 [0.00743, 0.0115]	0.00754 [0.00736, 0.0169]	0.005
as.factor(missing_fi)			
0	0 (0%)	2 (40.0%)	0 (0%
1	2 (100%)	3 (60.0%)	4 (10
Missing	0 (0%)	0 (0%)	0 (0%

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(in
```

(3.3.2.3) Table 3.2 - Interventions:

	Bisphosphonates	PTH analog	Romosoz
	(N=10)	(N=11)	(N=13)
no_rand			
Median [Q1, Q3]	4880 [1970, 7740]	1100 [1090, 1500]	7180 [409
active_sample			
Median [Q1, Q3]	3810 [1950, 6240]	892 [882, 1160]	6640 [384
n_event			
Median [Q1, Q3]	167 [101, 380]	48.0 [42.5, 84.5]	225 [106,
FI_final			
Median [Q1, Q3]	39.0 [23.3, 42.8]	15.0 [12.0, 19.5]	36.0 [26.0
FQ_final			
Median [Q1, Q3]	0.0109 [0.00694, 0.0197]	0.0193 [0.0118, 0.0258]	0.00601 [
as.factor(missing_fi)			
0	1 (10.0%)	2 (18.2%)	2 (15.4%
1	8 (80.0%)	3 (27.3%)	11 (84.6%
Missing	1 (10.0%)	6 (54.5%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(ti
```

(3.3.2.4) Table 3.2 - Timing of fracture assessment:

	>6-12m	>12-18m
	(N=5)	(N=6)
no_rand		
Median [Q1, Q3]	4090 [1650, 7180]	1640 [843, 16
active_sample		
Median [Q1, Q3]	3980 [1390, 6640]	1330 [655, 14
n_event		
Median [Q1, Q3]	76.0 [75.0, 128]	42.5 [37.3, 47
FI_final		
Median [Q1, Q3]	24.0 [19.0, 27.0]	12.0 [11.0, 13
FQ_final		
Median [Q1, Q3]	0.00754 [0.00391, 0.00828]	0.00990 [0.00
as.factor(missing_fi)		
0	1 (20.0%)	0 (0%)
1	3 (60.0%)	4 (66.7%)
Missing	1 (20.0%)	2 (33.3%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(jou
```

(3.3.2.5) Table 3.2 - Journal:

	NEJM	Lancet	JAMA
	(N=31)	(N=3)	(N=4)
no_rand			
Median [Q1, Q3]	4090 [1820, 7460]	1360 [1360, 1690]	1640 [1640, 165
active_sample			
Median [Q1, Q3]	4090 [1700, 6650]	1050 [1050, 1500]	1370 [1310, 141
n_event			
Median [Q1, Q3]	221 [94.5, 353]	100 [96.0, 162]	40.0 [35.5, 47.5
FI_final			
Median [Q1, Q3]	36.0 [23.5, 44.0]	17.0 [16.0, 28.5]	11.0 [10.5, 11.5
FQ_final			
Median [Q1, Q3]	0.0115 [0.00594, 0.0187]	0.0162 [0.0153, 0.0184]	0.00799 [0.0075
as.factor(missing_fi)			
0	3 (9.7%)	2 (66.7%)	0 (0%)
1	17 (54.8%)	1 (33.3%)	4 (100%)
Missing	11 (35.5%)	0 (0%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | sex, data = p
```

(3.3.2.6) Table 3.2 - Sex:

	Both	Women	Overall
	(N=2)	(N=43)	(N=45)
no_rand			
Median [Q1, Q3]	564 [556, 571]	3270 [1650, 7180]	2420 [1640, 7180]
active_sample			
Median [Q1, Q3]	439 [432, 445]	2420 [1360, 6540]	2380 [1270, 6530]
n_event			
Median [Q1, Q3]	44.5 [42.8, 46.3]	168 [84.5, 331]	128 [82.0, 330]
FI_final			
Median [Q1, Q3]	12.0 [11.5, 12.5]	27.0 [19.5, 42.5]	26.0 [18.0, 42.0]
FQ_final			
Median [Q1, Q3]	0.0273 [0.0266, 0.0281]	0.0125 [0.00664, 0.0188]	0.0131 [0.00670, 0.0
as.factor(missing_fi)			
0	0 (0%)	6 (14.0%)	6 (13.3%)
1	0 (0%)	24 (55.8%)	24 (53.3%)
Missing	2 (100%)	13 (30.2%)	15 (33.3%)

(3.3.2.7) Table 3.2 - Placebo:

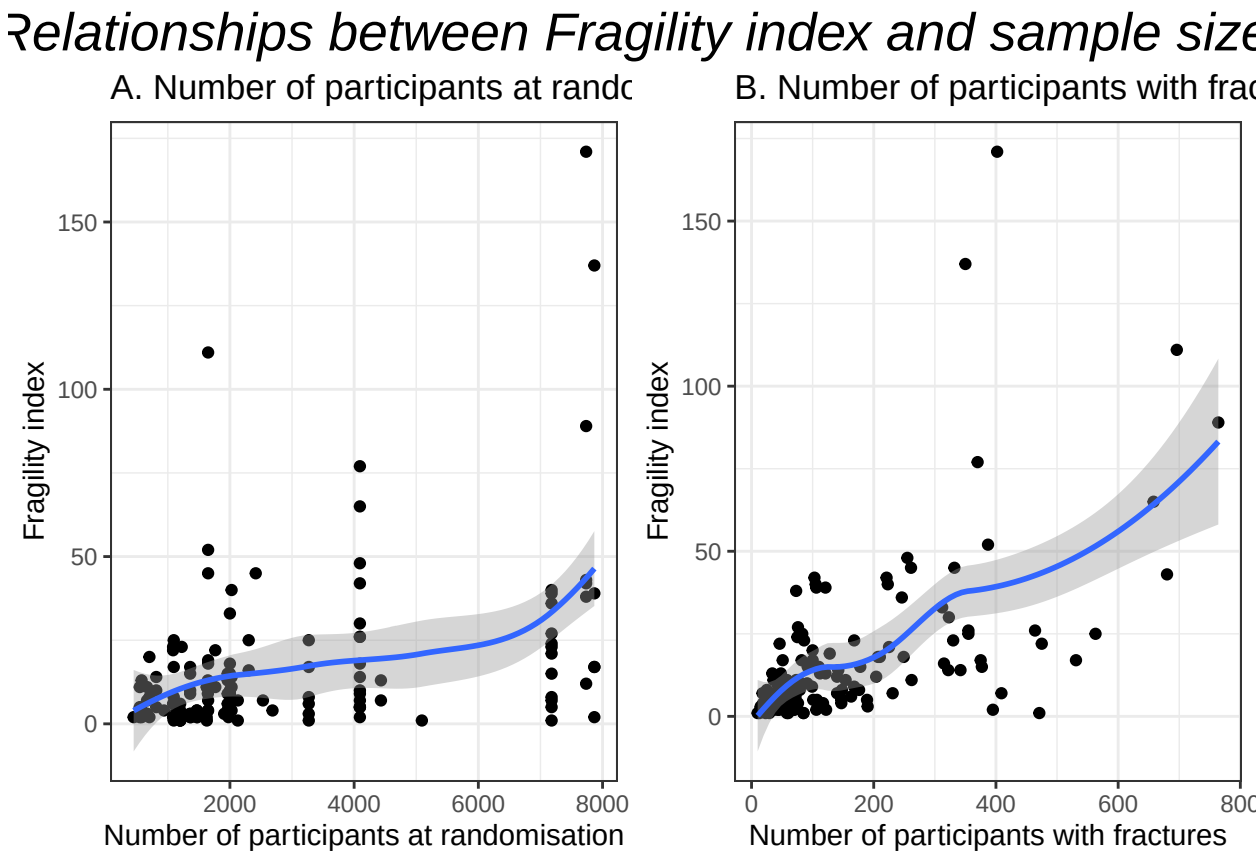
```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | placebo, data
```

	Active	Placebo	Overall
	(N=11)	(N=34)	(N=45)
no_rand			
Median [Q1, Q3]	4090 [1640, 4090]	2220 [1630, 7180]	2420 [1640, 7180]
active_sample			
Median [Q1, Q3]	3530 [1330, 3750]	2160 [1250, 6640]	2380 [1270, 6530]
n_event			
Median [Q1, Q3]	221 [68.0, 339]	125 [82.3, 326]	128 [82.0, 330]
FI_final			
Median [Q1, Q3]	26.0 [14.0, 45.0]	26.0 [20.3, 41.5]	26.0 [18.0, 42.0]
FQ_final			
Median [Q1, Q3]	0.0115 [0.00762, 0.0153]	0.0137 [0.00614, 0.0255]	0.0131 [0.00670, 0.0193]
as.factor(missing_fi)			
0	4 (36.4%)	2 (5.9%)	6 (13.3%)
1	7 (63.6%)	17 (50.0%)	24 (53.3%)
Missing	0 (0%)	15 (44.1%)	15 (33.3%)

(3.4) Figure 3: Correlation between sample size and FI

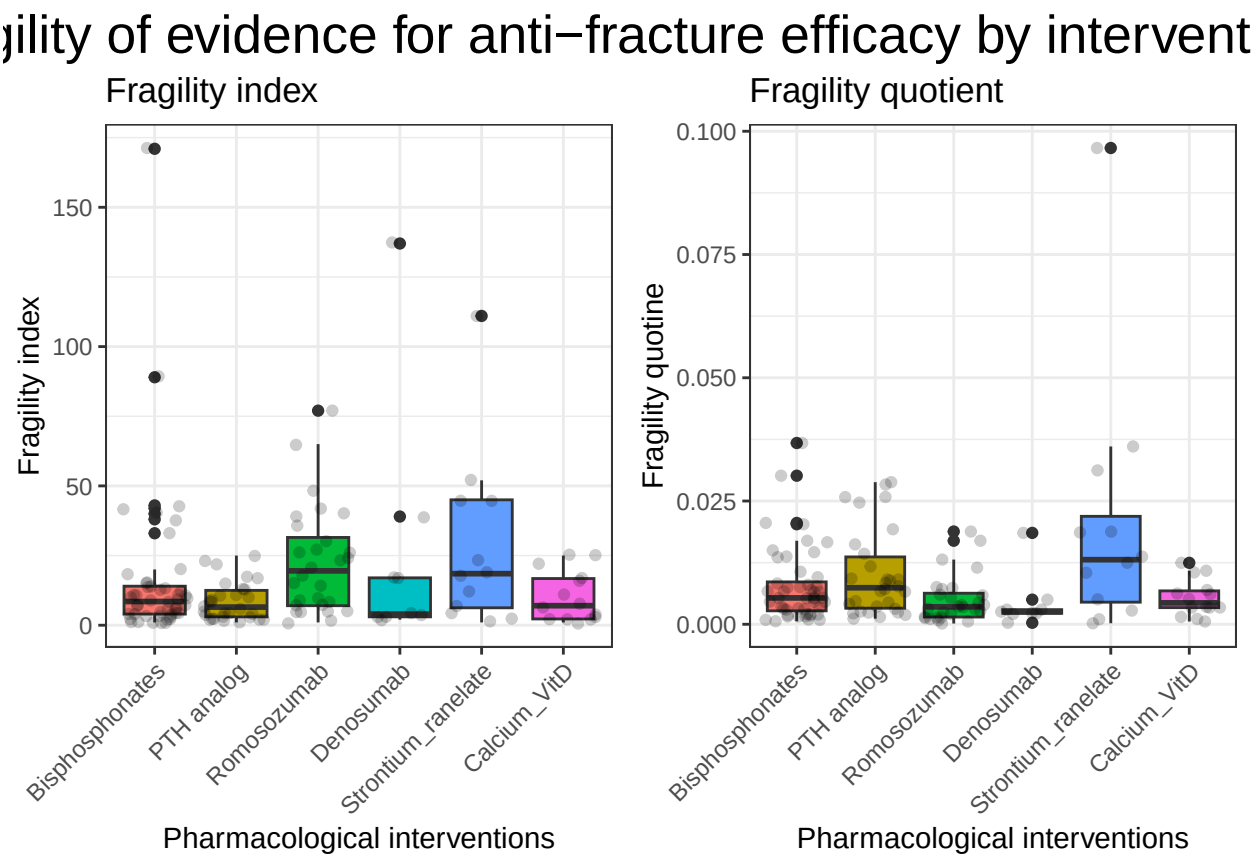
```
p = ggplot(data = fi_sig, aes(x = no_rand, y = FI_final))
p1 = p + geom_point() + geom_smooth() + labs(title = "A. Number of participants at randomisation", x = "

p = ggplot(data = fi_sig, aes(x = n_event, y = FI_final))
p2 = p + geom_point() + geom_smooth() + labs(title = "B. Number of participants with fractures", x = "Nu

grid.arrange(p1, p2, nrow = 1, top = textGrob("Relationships between Fragility index and sample size", g
```

```
## `geom_smooth()` using method = 'loess' and formula = 'y ~ x'
## `geom_smooth()` using method = 'loess' and formula = 'y ~ x'
```



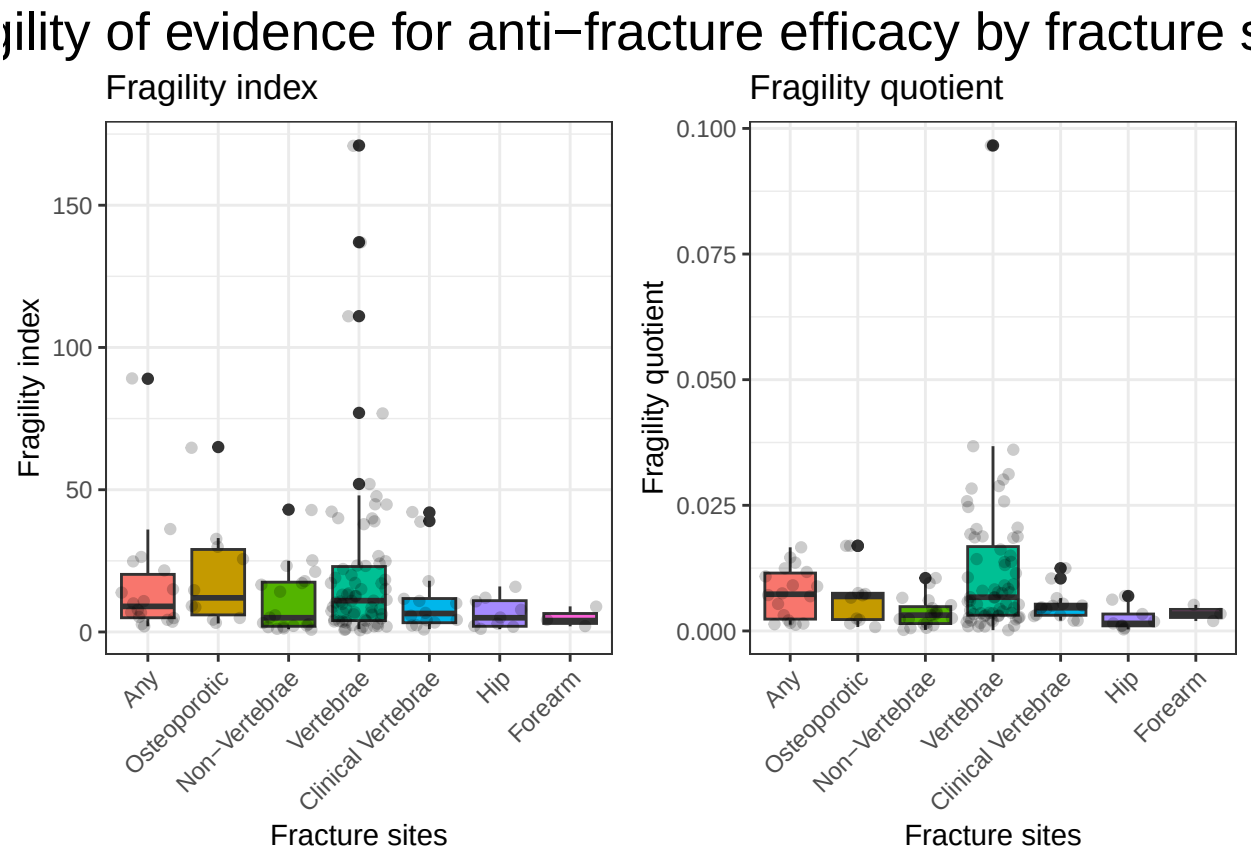
(3.5) Figure 4: Fragility of evidence for anti-fracture efficacy by pharmacological interventions

```
p1 = ggplot(data = fi_sig, aes(y = FI_final, x = as.factor(interv_code2), fill = as.factor(interv_code2)
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "Fragility index", x = "Pharmacological interventions", y = "Fragility index") + theme(a
p2 = ggplot(data = fi_sig, aes(y = FQ_final, x = as.factor(interv_code2), fill = as.factor(interv_code2)
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "Fragility quotient", x = "Pharmacological interventions", y = "Fragility quotine") + the

grid.arrange(p1, p2, nrow = 1, top = textGrob("Fragility of evidence for anti-fracture efficacy by inte
```



(3.6) Figure 5: Fragility of evidence for anti-fracture efficacy by fracture sites

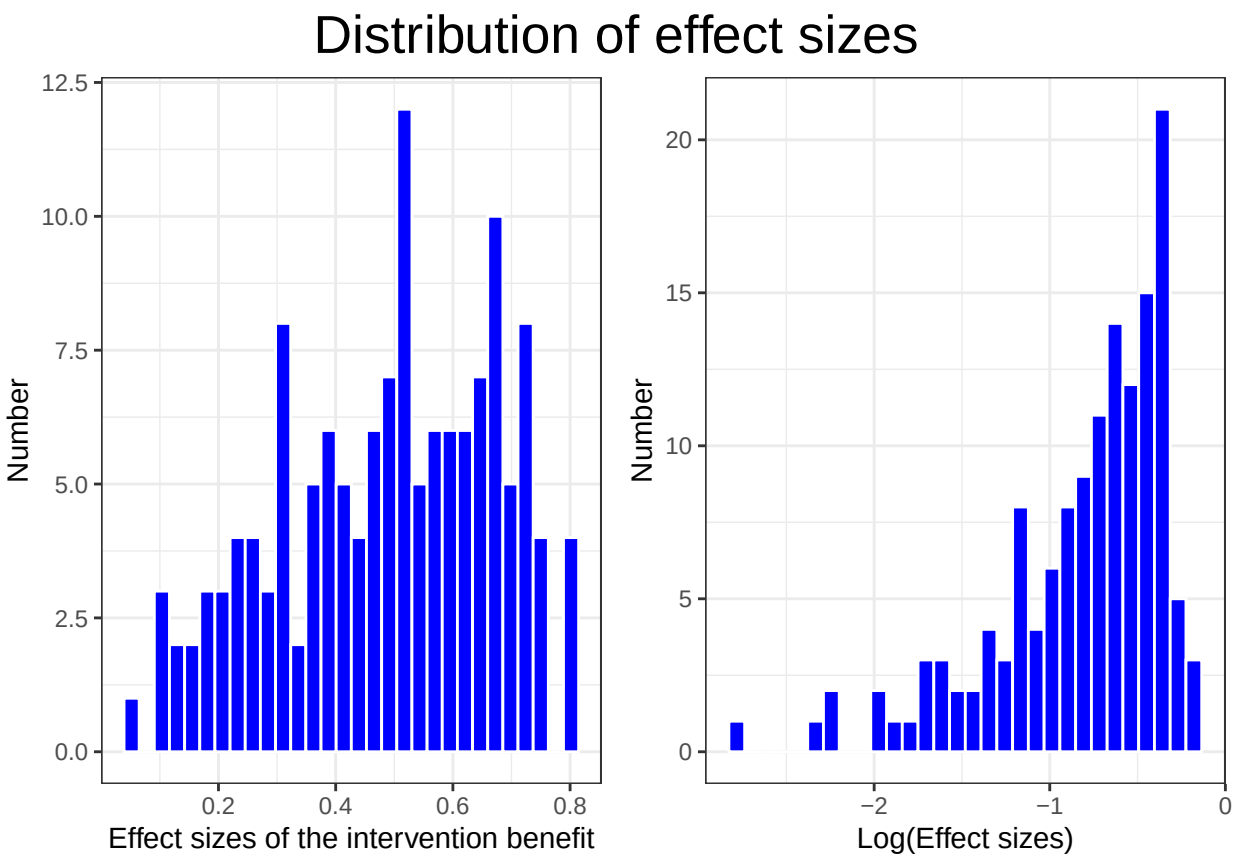
```
p1 = ggplot(data = fi_sig, aes(y = FI_final, x = as.factor(fx_code2), fill = as.factor(fx_code2))) + ge
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "Fragility index", x = "Fracture sites", y = "Fragility index") + theme(axis.text.x = el
p2 = ggplot(data = fi_sig, aes(y = FQ_final, x = as.factor(fx_code2), fill = as.factor(fx_code2))) + ge
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "Fragility quotient", x = "Fracture sites", y = "Fragility quotient") + theme(axis.text.

grid.arrange(p1, p2, nrow = 1, top = textGrob("Fragility of evidence for anti-fracture efficacy by frac
```



(3.7) Figure S1: Distribution of effect sizes for intervetion benefits

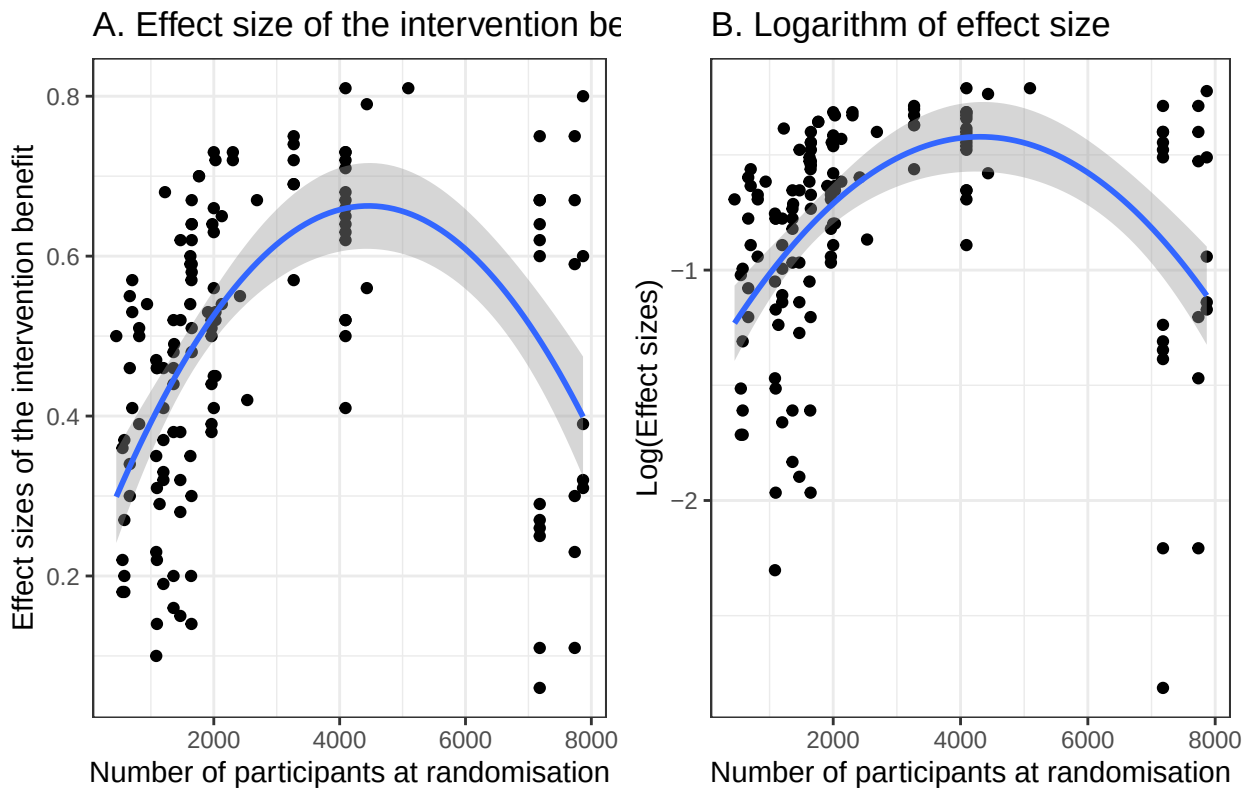
```
p = ggplot(data = fi_sig, aes(x = HR))
p1 = p + geom_histogram(color = "white", fill = "blue") + labs(x = "Effect sizes of the intervention be

p = ggplot(data = fi_sig, aes(x = loghr))
p2 = p + geom_histogram(color = "white", fill = "blue") + labs(x = "Log(Effect sizes)", y = "Number") +

grid.arrange(p1, p2, nrow = 1, top = textGrob("Distribution of effect sizes", gp = gpar(fontsize = 20,
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```



(3.8) Figure S2: Correlation between effect sizes for the intervention benefits and sample size

```
p = ggplot(data = fi_sig, aes(x = no_rand, y = HR))
p.1 = p + geom_point() + geom_smooth(method = "lm", formula = y ~ x + I(x^2)) + labs(title = "A. Effect

p = ggplot(data = fi_sig, aes(x = no_rand, y = loghr))
p.2 = p + geom_point() + geom_smooth(method = "lm", formula = y ~ x + I(x^2)) + labs(title = "B. Logari

grid.arrange(p.1, p.2, nrow = 1, top = textGrob("Correlation between effect size and sample size", gp =
```



(4) PREDEFINED SENSITIVITY ANALYSIS: including only results of the original studies

Set-up data

```
ori_st = subset(fi_sig, sen_analysis == 0)
ori_st_st = subset(ori_st, study == 1)
```

(4.1) Baseline characteristics

```
table1(~ as.factor(interv_code2) + as.factor(journal_code1) + as.factor(placebo) + sex + no_rand, data =
```

(4.1.1) By studies

	Overall
	(N=26)
as.factor(interv__code2)	
Bisphosphonates	12 (46.2%)
PTH analog	5 (19.2%)
Romosozumab	2 (7.7%)
Denosumab	2 (7.7%)
Strontium_ranelate	2 (7.7%)
Calcium_VitD	3 (11.5%)
as.factor(journal__code1)	
NEJM	12 (46.2%)
Lancet	2 (7.7%)
BMJ	1 (3.8%)
JAMA	3 (11.5%)
Ann Intern Med	1 (3.8%)
JBMR	1 (3.8%)
JCEM	2 (7.7%)
OI	4 (15.4%)
as.factor(placebo)	
Active	3 (11.5%)
Placebo	23 (88.5%)
Sex	
Both	5 (19.2%)
Men	2 (7.7%)
Women	19 (73.1%)
no__rand	
Median [Q1, Q3]	1940 [1240, 3120]

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi), data = ori_st
```

(4.1.2) By analyses

	Overall
	(N=124)
no__rand	
Median [Q1, Q3]	1960 [1360, 4090]
active__sample	
Median [Q1, Q3]	1770 [1050, 3660]
n__event	
Median [Q1, Q3]	82.5 [52.8, 181]
FI__final	
Median [Q1, Q3]	9.00 [4.00, 18.3]
FQ__final	
Median [Q1, Q3]	0.00510 [0.00234, 0.00907]
as.factor(missing__fi)	
0	8 (6.5%)
1	76 (61.3%)
Missing	40 (32.3%)

Additional analyses for discussion:

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(se
```

	0	1	Overall
	(N=124)	(N=17)	(N=141)
no_rand			
Mean (SD)	2970 (2400)	2110 (1220)	2870 (2300)
Median [Q1, Q3]	1960 [1360, 4090]	1650 [1200, 3270]	1960 [1220, 4090]
Median [min, max]	1960 [450, 7870]	1650 [549, 4090]	1960 [450, 7870]
active_sample			
Mean (SD)	2600 (2160)	1880 (1140)	2510 (2080)
Median [Q1, Q3]	1770 [1050, 3660]	1440 [1110, 2420]	1770 [1060, 3610]
Median [min, max]	1770 [339, 7810]	1440 [426, 4090]	1770 [339, 7810]
n_event			
Mean (SD)	151 (160)	186 (133)	155 (157)
Median [Q1, Q3]	82.5 [52.8, 181]	190 [41.0, 330]	86.0 [52.0, 210]
Median [min, max]	82.5 [10.0, 764]	190 [19.0, 375]	86.0 [10.0, 764]
FI_final			
Mean (SD)	16.6 (24.5)	18.1 (20.5)	16.8 (24.0)
Median [Q1, Q3]	9.00 [4.00, 18.3]	11.0 [4.00, 23.0]	9.00 [4.00, 19.0]
Median [min, max]	9.00 [1.00, 171]	11.0 [1.00, 77.0]	9.00 [1.00, 171]
FQ_final			
Mean (SD)	0.00803 (0.0109)	0.0104 (0.00932)	0.00831 (0.0107)
Median [Q1, Q3]	0.00510 [0.00234, 0.00907]	0.00609 [0.00337, 0.0186]	0.00514 [0.00239, 0.0104]
Median [min, max]	0.00510 [0.000151, 0.0966]	0.00609 [0.000946, 0.0312]	0.00514 [0.000151, 0.0966]
as.factor(missing_fi)			
0	8 (6.5%)	2 (11.8%)	10 (7.1%)
1	76 (61.3%)	9 (52.9%)	85 (60.3%)
Missing	40 (32.3%)	6 (35.3%)	46 (32.6%)

```
fi_sig$sensitive[fi_sig$sen_analysis == 1] = "Sensitivity/Posthoc"
  fi_sig$sensitive[fi_sig$sen_analysis == 0] = "Original"
#createTable(compareGroups(sensitive ~ no_rand + active_sample + n_event + FI_final + FQ_final + missin
```

(4.2) Table S2: Fragility of evidence for anti-fracture efficacy - Predefined sesnitivity analyses excluding the extended phases of trials

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(fx
```

(4.2.1) Table S2 - Fracture sites:

	Any	Osteoporotic	Non-V
	(N=17)	(N=10)	(N=17
no_rand			
Median [Q1, Q3]	2030 [1470, 4090]	3390 [1730, 4090]	3270 [1
active_sample			
Median [Q1, Q3]	2010 [1280, 3700]	3110 [1510, 3940]	1910 [8
n_event			
Median [Q1, Q3]	231 [76.0, 409]	163 [67.3, 320]	163 [57
FI_final			
Median [Q1, Q3]	10.0 [5.00, 22.0]	12.0 [6.00, 29.0]	3.00 [2
FQ_final			
Median [Q1, Q3]	0.00714 [0.00209, 0.0109]	0.00686 [0.00227, 0.00750]	0.0025
as.factor(missing_fi)			
0	1 (5.9%)	2 (20.0%)	1 (5.9%
1	11 (64.7%)	6 (60.0%)	11 (64.
Missing	5 (29.4%)	2 (20.0%)	5 (29.4

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(in
```

(4.2.2) Table S2 - Interventions:

	Bisphosphonates	PTH analog	Romos
	(N=47)	(N=26)	(N=26
no_rand			
Median [Q1, Q3]	1960 [1200, 2030]	1230 [1090, 1360]	4090 [4
active_sample			
Median [Q1, Q3]	1860 [725, 1980]	971 [880, 1270]	3910 [3
n_event			
Median [Q1, Q3]	73.0 [59.5, 141]	47.0 [34.3, 72.0]	168 [10
FI_final			
Median [Q1, Q3]	9.00 [4.00, 14.0]	7.50 [3.00, 13.0]	18.0 [7
FQ_final			
Median [Q1, Q3]	0.00537 [0.00301, 0.00891]	0.00741 [0.00273, 0.0130]	0.0033
as.factor(missing_fi)			
0	5 (10.6%)	2 (7.7%)	1 (3.8%
1	33 (70.2%)	8 (30.8%)	25 (96.
Missing	9 (19.1%)	16 (61.5%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(ti
```

(4.2.3) Table S2 - Timing of fracture assessment:

	>6-12m	>12-18m
	(N=25)	(N=11)
no_rand		
Median [Q1, Q3]	1650 [1360, 4090]	1650 [641, 2090]
active_sample		
Median [Q1, Q3]	1390 [1160, 3700]	1280 [517, 1560]
n_event		
Median [Q1, Q3]	65.0 [52.0, 128]	48.0 [35.0, 68.0]
FI_final		
Median [Q1, Q3]	5.00 [3.00, 9.00]	7.00 [4.00, 10.0]
FQ_final		
Median [Q1, Q3]	0.00222 [0.00147, 0.00505]	0.00711 [0.00376
as.factor(missing_fi)		
0	1 (4.0%)	0 (0%)
1	19 (76.0%)	8 (72.7%)
Missing	5 (20.0%)	3 (27.3%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(jou
```

(4.2.4) Table S2 - Journal:

	NEJM	Lancet	BMJ
	(N=69)	(N=9)	(N=5)
no_rand			
Median [Q1, Q3]	4090 [1470, 7180]	1360 [1360, 2030]	2300 [1770, 2
active_sample			
Median [Q1, Q3]	3400 [1350, 6430]	1160 [1050, 2030]	2300 [1770, 2
n_event			
Median [Q1, Q3]	103 [48.0, 231]	91.0 [63.0, 100]	315 [262, 475
FI_final			
Median [Q1, Q3]	10.0 [5.00, 26.0]	11.0 [4.00, 15.0]	16.0 [11.0, 22
FQ_final			
Median [Q1, Q3]	0.00391 [0.00222, 0.00748]	0.00691 [0.00259, 0.0143]	0.00695 [0.00
as.factor(missing_fi)			
0	6 (8.7%)	2 (22.2%)	0 (0%)
1	45 (65.2%)	7 (77.8%)	1 (20.0%)
Missing	18 (26.1%)	0 (0%)	4 (80.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | sex, data = d
```

(4.2.5) Table S2 - Sex:

	Both	Men	Women
	(N=12)	(N=9)	(N=103)
no_rand			
Median [Q1, Q3]	665 [578, 1030]	1200 [1200, 1470]	2000 [1550, 4260]
active_sample			
Median [Q1, Q3]	478 [451, 661]	1130 [1130, 1350]	1950 [1270, 4060]
n_event			
Median [Q1, Q3]	43.5 [34.8, 64.0]	23.0 [21.0, 36.0]	100 [63.5, 224]
FI_final			
Median [Q1, Q3]	4.00 [2.75, 7.00]	3.00 [2.00, 4.00]	11.0 [5.00, 22.5]
FQ_final			
Median [Q1, Q3]	0.00677 [0.00451, 0.0116]	0.00222 [0.00177, 0.00296]	0.00537 [0.00237,
as.factor(missing_fi)			
0	0 (0%)	0 (0%)	8 (7.8%)
1	7 (58.3%)	9 (100%)	60 (58.3%)
Missing	5 (41.7%)	0 (0%)	35 (34.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | placebo, data
```

(4.2.6) Table S2 - Placebo:

	Active	Placebo	Overall
	(N=26)	(N=98)	(N=124)
no_rand			
Median [Q1, Q3]	4090 [1360, 4090]	1960 [1120, 4430]	1960 [1360,
active_sample			
Median [Q1, Q3]	3280 [1300, 3640]	1750 [882, 4360]	1770 [1050,
n_event			
Median [Q1, Q3]	104 [53.8, 247]	76.0 [52.3, 161]	82.5 [52.8, 1
FI_final			
Median [Q1, Q3]	9.50 [5.00, 16.5]	8.50 [4.00, 18.8]	9.00 [4.00, 1
FQ_final			
Median [Q1, Q3]	0.00528 [0.00210, 0.00874]	0.00510 [0.00240, 0.00902]	0.00510 [0.0
as.factor(missing_fi)			
0	3 (11.5%)	5 (5.1%)	8 (6.5%)
1	20 (76.9%)	56 (57.1%)	76 (61.3%)
Missing	3 (11.5%)	37 (37.8%)	40 (32.3%)

(4.3) Table S3: Fragility of evidence for anti-fracture efficacy in subgroup analyses- Predefined sensitivity analyses excluding the extended phases of the trial

(4.3.1) Fracture as the predefined primary endpoint Data-set

```
fx_prim2 = subset(ori_st, pri_endpoint == 1)
```

(4.3.1.1) Table S3.1 - Overall

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi), data = fx_pri
```

	Overall
	(N=27)
no_rand	
Median [Q1, Q3]	1960 [1280, 4090]
active_sample	
Median [Q1, Q3]	1700 [971, 3650]
n_event	
Median [Q1, Q3]	110 [67.5, 222]
FI_final	
Median [Q1, Q3]	15.0 [11.5, 29.5]
FQ_final	
Median [Q1, Q3]	0.0107 [0.00634, 0.0204]
as.factor(missing_fi)	
0	2 (7.4%)
1	17 (63.0%)
Missing	8 (29.6%)

Additional analysis for discussion

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | fx_primary ,
```

	Primary endpoint	Secondary endpoint	Overall
	(N=27)	(N=97)	(N=124)
no_rand			
Mean (SD)	2970 (2440)	2980 (2400)	2970 (2400)
Median [Q1, Q3]	1960 [1280, 4090]	1960 [1360, 4090]	1960 [1360, 4090]
Median [min, max]	1960 [578, 7870]	1960 [450, 7870]	1960 [450, 7870]
active_sample			
Mean (SD)	2520 (2190)	2620 (2170)	2600 (2160)
Median [Q1, Q3]	1700 [971, 3650]	1770 [1100, 3660]	1770 [1050, 3660]
Median [min, max]	1700 [451, 7390]	1770 [339, 7810]	1770 [339, 7810]
n_event			
Mean (SD)	156 (125)	149 (169)	151 (160)
Median [Q1, Q3]	110 [67.5, 222]	73.0 [51.0, 168]	82.5 [52.8, 181]
Median [min, max]	110 [34.0, 464]	73.0 [10.0, 764]	82.5 [10.0, 764]
FI_final			
Mean (SD)	29.3 (38.4)	13.0 (17.6)	16.6 (24.5)
Median [Q1, Q3]	15.0 [11.5, 29.5]	7.00 [3.00, 16.0]	9.00 [4.00, 18.3]
Median [min, max]	15.0 [1.00, 171]	7.00 [1.00, 111]	9.00 [1.00, 171]
FQ_final			
Mean (SD)	0.0142 (0.0107)	0.00630 (0.0104)	0.00803 (0.0109)
Median [Q1, Q3]	0.0107 [0.00634, 0.0204]	0.00355 [0.00206, 0.00711]	0.00510 [0.00234, 0.00907]
Median [min, max]	0.0107 [0.000567, 0.0368]	0.00355 [0.000151, 0.0966]	0.00510 [0.000151, 0.0966]
as.factor(missing_fi)			
0	2 (7.4%)	6 (6.2%)	8 (6.5%)
1	17 (63.0%)	59 (60.8%)	76 (61.3%)
Missing	8 (29.6%)	32 (33.0%)	40 (32.3%)

```
#createTable(compareGroups(fx_primary ~ no_rand + active_sample + n_event + FI_final + FQ_final + missi
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(fx_
```

(4.3.1.2) Table S3.1 - Fracture sites:

	Any	Osteoporotic	Vertebr
	(N=2)	(N=1)	(N=22)
no_rand			
Median [Q1, Q3]	3110 [2620, 3600]	2000 [2000, 2000]	1650 [1
active_sample			
Median [Q1, Q3]	2060 [1270, 2850]	1950 [1950, 1950]	1440 [9
n_event			
Median [Q1, Q3]	348 [289, 406]	312 [312, 312]	103 [63
FI_final			
Median [Q1, Q3]	16.5 [11.8, 21.3]	33.0 [33.0, 33.0]	15.0 [13
FQ_final			
Median [Q1, Q3]	0.0109 [0.00901, 0.0127]	0.0169 [0.0169, 0.0169]	0.0111
as.factor(missing_fi)			
0	0 (0%)	1 (100%)	1 (4.5%
1	2 (100%)	0 (0%)	13 (59.
Missing	0 (0%)	0 (0%)	8 (36.4

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(in
```

(4.3.1.3) Table S3.1 - Interventions:

	Bisphosphonates	PTH analog	Romos
	(N=13)	(N=7)	(N=4)
no_rand			
Median [Q1, Q3]	1960 [1200, 2130]	1360 [1090, 1640]	5640 [
active_sample			
Median [Q1, Q3]	1950 [690, 1950]	1050 [887, 1410]	5150 [
n_event			
Median [Q1, Q3]	140 [110, 223]	60.0 [42.0, 84.5]	163 [9
FI_final			
Median [Q1, Q3]	13.0 [11.0, 20.0]	13.0 [12.0, 19.0]	33.0 [2
FQ_final			
Median [Q1, Q3]	0.0107 [0.00666, 0.0203]	0.0143 [0.00849, 0.0271]	0.0065
as.factor(missing_fi)			
0	1 (7.7%)	1 (14.3%)	0 (0%
1	9 (69.2%)	3 (42.9%)	4 (100
Missing	3 (23.1%)	3 (42.9%)	0 (0%

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(ti
```

(4.3.1.4) Table S3.1 - Timing of fracture assessment:

	>6-12m	>12-18m
	(N=1)	(N=5)
no_rand		
Median [Q1, Q3]	7180 [7180, 7180]	1650 [1640,
active_sample		
Median [Q1, Q3]	6640 [6640, 6640]	1430 [1400,
n_event		
Median [Q1, Q3]	75.0 [75.0, 75.0]	48.0 [36.0, 5
FI_final		
Median [Q1, Q3]	24.0 [24.0, 24.0]	11.0 [7.00, 1
FQ_final		
Median [Q1, Q3]	0.00361 [0.00361, 0.00361]	0.00770 [0.0
as.factor(missing_fi)		
0	0 (0%)	0 (0%)
1	1 (100%)	4 (80.0%)
Missing	0 (0%)	1 (20.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(jou
```

(4.3.1.5) Table S3.1 - Journal:

	NEJM	Lancet	JAMA
	(N=14)	(N=2)	(N=4)
no_rand			
Median [Q1, Q3]	3680 [1740, 7180]	1690 [1530, 1860]	1640 [1640, 23
active_sample			
Median [Q1, Q3]	2800 [1210, 6250]	1500 [1270, 1720]	1410 [1390, 21
n_event			
Median [Q1, Q3]	181 [83.8, 341]	158 [125, 190]	78.5 [35.5, 129
FI_final			
Median [Q1, Q3]	25.5 [14.8, 41.5]	27.5 [21.3, 33.8]	12.0 [11.0, 13.
FQ_final			
Median [Q1, Q3]	0.0130 [0.00550, 0.0240]	0.0174 [0.0159, 0.0190]	0.00785 [0.006
as.factor(missing_fi)			
0	1 (7.1%)	1 (50.0%)	0 (0%)
1	9 (64.3%)	1 (50.0%)	3 (75.0%)
Missing	4 (28.6%)	0 (0%)	1 (25.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | sex, data =
```

(4.3.1.6) Table S3.1 - Sex:

	Both	Men	Women
	(N=3)	(N=1)	(N=23)
no_rand			
Median [Q1, Q3]	665 [622, 1400]	1200 [1200, 1200]	2000 [1630, 4260
active_sample			
Median [Q1, Q3]	479 [465, 568]	1130 [1130, 1130]	1950 [1390, 3900
n_event			
Median [Q1, Q3]	48.0 [43.5, 140]	37.0 [37.0, 37.0]	112 [84.5, 222]
FI_final			
Median [Q1, Q3]	7.00 [7.00, 10.0]	6.00 [6.00, 6.00]	20.0 [13.0, 36.5]
FQ_final			
Median [Q1, Q3]	0.0146 [0.0126, 0.0217]	0.00532 [0.00532, 0.00532]	0.00928 [0.00634
as.factor(missing_fi)			
0	0 (0%)	0 (0%)	2 (8.7%)
1	2 (66.7%)	1 (100%)	14 (60.9%)
Missing	1 (33.3%)	0 (0%)	7 (30.4%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | placebo, data
```

(4.3.1.7) Table S3.1 - Placebo:

	Active	Placebo	Overall
	(N=5)	(N=22)	(N=27)
no_rand			
Median [Q1, Q3]	1650 [1640, 4090]	1980 [1120, 4140]	1960 [1280,
active_sample			
Median [Q1, Q3]	1430 [1400, 3640]	1730 [885, 3590]	1700 [971, 3
n_event			
Median [Q1, Q3]	92.0 [36.0, 221]	111 [77.0, 206]	110 [67.5, 2
FI_final			
Median [Q1, Q3]	15.0 [13.0, 26.0]	14.5 [11.3, 31.0]	15.0 [11.5, 1
FQ_final			
Median [Q1, Q3]	0.00928 [0.00770, 0.0115]	0.0126 [0.00550, 0.0245]	0.0107 [0.00
as.factor(missing_fi)			
0	1 (20.0%)	1 (4.5%)	2 (7.4%)
1	4 (80.0%)	13 (59.1%)	17 (63.0%)
Missing	0 (0%)	8 (36.4%)	8 (29.6%)

(4.3.2) Analyses with P< 0.001 Data-set

```
p_sig2 = subset(ori_st, Pval_screen<=0.001)
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi), data = p_sig2
```

(4.3.2.1) Table S3.2 - Overall:

	Overall
	(N=38)
no_rand	
Median [Q1, Q3]	4090 [1640, 7180]
active_sample	
Median [Q1, Q3]	3600 [1280, 6620]
n_event	
Median [Q1, Q3]	108 [77.5, 298]
FI_final	
Median [Q1, Q3]	26.5 [17.5, 41.5]
FQ_final	
Median [Q1, Q3]	0.0104 [0.00655, 0.0191]
as.factor(missing_fi)	
0	4 (10.5%)
1	22 (57.9%)
Missing	12 (31.6%)

Additional analysis for discussion:

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | p_sig2 , data
```

	Highly significant	Significant	Overall
	(N=38)	(N=86)	(N=124)
no_rand			
Mean (SD)	4180 (2870)	2440 (1940)	2970 (2400)
Median [Q1, Q3]	4090 [1640, 7180]	1770 [1200, 3120]	1960 [1360, 4090]
Median [min, max]	4090 [578, 7870]	1770 [450, 7870]	1960 [450, 7870]
active_sample			
Mean (SD)	3710 (2610)	2110 (1740)	2600 (2160)
Median [Q1, Q3]	3600 [1280, 6620]	1530 [885, 2300]	1770 [1050, 3660]
Median [min, max]	3600 [451, 7810]	1530 [339, 6670]	1770 [339, 7810]
n_event			
Mean (SD)	211 (201)	124 (131)	151 (160)
Median [Q1, Q3]	108 [77.5, 298]	69.0 [44.0, 147]	82.5 [52.8, 181]
Median [min, max]	108 [34.0, 764]	69.0 [10.0, 563]	82.5 [10.0, 764]
FI_final			
Mean (SD)	38.5 (34.8)	6.90 (5.51)	16.6 (24.5)
Median [Q1, Q3]	26.5 [17.5, 41.5]	5.00 [3.00, 10.0]	9.00 [4.00, 18.3]
Median [min, max]	26.5 [9.00, 171]	5.00 [1.00, 26.0]	9.00 [1.00, 171]
FQ_final			
Mean (SD)	0.0157 (0.0165)	0.00465 (0.00406)	0.00803 (0.0109)
Median [Q1, Q3]	0.0104 [0.00655, 0.0191]	0.00318 [0.00187, 0.00665]	0.00510 [0.00234, 0.00907]
Median [min, max]	0.0104 [0.00230, 0.0966]	0.00318 [0.000151, 0.0203]	0.00510 [0.000151, 0.0966]
as.factor(missing_fi)			
0	4 (10.5%)	4 (4.7%)	8 (6.5%)
1	22 (57.9%)	54 (62.8%)	76 (61.3%)
Missing	12 (31.6%)	28 (32.6%)	40 (32.3%)

```
#createTable(compareGroups(p_sig2 ~ no_rand + active_sample + n_event + FI_final + FQ_final + missing_f
```

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(fx
```

(4.3.2.2) Table S3.2 - Fracture sites:

	Any	Osteoporotic	Non
	(N=2)	(N=5)	(N=
no_rand			
Median [Q1, Q3]	7460 [7320, 7600]	4090 [2000, 4090]	718
active_sample			
Median [Q1, Q3]	6620 [6580, 6660]	3530 [1950, 3840]	665
n_event			
Median [Q1, Q3]	505 [376, 635]	323 [312, 355]	225
FI_final			
Median [Q1, Q3]	62.5 [49.3, 75.8]	30.0 [26.0, 33.0]	23.0
FQ_final			
Median [Q1, Q3]	0.00949 [0.00743, 0.0115]	0.00754 [0.00736, 0.0169]	0.00
as.factor(missing_fi)			
0	0 (0%)	2 (40.0%)	0 (0
1	2 (100%)	3 (60.0%)	3 (1
Missing	0 (0%)	0 (0%)	0 (0

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(in
```

(4.3.2.3) Table S3.2 - Interventions:

	Bisphosphonates	PTH analog	Romosc
	(N=10)	(N=10)	(N=12)
no_rand			
Median [Q1, Q3]	4880 [1970, 7740]	1230 [1090, 1570]	7180 [4
active_sample			
Median [Q1, Q3]	3810 [1950, 6240]	971 [885, 1210]	6640 [3
n_event			
Median [Q1, Q3]	167 [101, 380]	49.5 [44.5, 85.3]	223 [10
FI_final			
Median [Q1, Q3]	39.0 [23.3, 42.8]	16.0 [13.0, 20.8]	33.0 [25
FQ_final			
Median [Q1, Q3]	0.0109 [0.00694, 0.0197]	0.0177 [0.0105, 0.0255]	0.00594
as.factor(missing_fi)			
0	1 (10.0%)	2 (20.0%)	1 (8.3%
1	8 (80.0%)	3 (30.0%)	11 (91.7
Missing	1 (10.0%)	5 (50.0%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(tim
```

(4.3.2.4) Table S3.2 - Timing of fracture assessment:

	>6-12m	>12-18m
	(N=5)	(N=4)
no_rand		
Median [Q1, Q3]	4090 [1650, 7180]	1640 [1370,
active_sample		
Median [Q1, Q3]	3980 [1390, 6640]	1330 [1060,
n_event		
Median [Q1, Q3]	76.0 [75.0, 128]	40.0 [35.5, 4
FI_final		
Median [Q1, Q3]	24.0 [19.0, 27.0]	12.0 [10.5, 1
FQ_final		
Median [Q1, Q3]	0.00754 [0.00391, 0.00828]	0.00849 [0.0
as.factor(missing_fi)		
0	1 (20.0%)	0 (0%)
1	3 (60.0%)	3 (75.0%)
Missing	1 (20.0%)	1 (25.0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(jou
```

(4.3.2.5) Table S3.2 - Journal:

	NEJM	Lancet	JAMA
	(N=27)	(N=3)	(N=4)
no_rand			
Median [Q1, Q3]	7180 [3050, 7740]	1360 [1360, 1690]	1640 [1640, 1
active_sample			
Median [Q1, Q3]	5680 [2740, 6650]	1050 [1050, 1500]	1370 [1310, 1
n_event			
Median [Q1, Q3]	168 [84.5, 337]	100 [96.0, 162]	40.0 [35.5, 47
FI_final			
Median [Q1, Q3]	36.0 [23.5, 42.5]	17.0 [16.0, 28.5]	11.0 [10.5, 11
FQ_final			
Median [Q1, Q3]	0.00754 [0.00562, 0.0177]	0.0162 [0.0153, 0.0184]	0.00799 [0.00
as.factor(missing_fi)			
0	2 (7.4%)	2 (66.7%)	0 (0%)
1	16 (59.3%)	1 (33.3%)	4 (100%)
Missing	9 (33.3%)	0 (0%)	0 (0%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | sex, data = p
```

(4.3.2.6) Table S3.2 - Sex:

	Both	Women	Overall
	(N=1)	(N=37)	(N=38)
no_rand			
Median [Q1, Q3]	578 [578, 578]	4090 [1650, 7180]	4090 [1640, 7180]
active_sample			
Median [Q1, Q3]	451 [451, 451]	3660 [1330, 6640]	3600 [1280, 6620]
n_event			
Median [Q1, Q3]	48.0 [48.0, 48.0]	110 [82.0, 312]	108 [77.5, 298]
FI_final			
Median [Q1, Q3]	13.0 [13.0, 13.0]	27.0 [19.0, 42.0]	26.5 [17.5, 41.5]
FQ_final			
Median [Q1, Q3]	0.0288 [0.0288, 0.0288]	0.00928 [0.00653, 0.0185]	0.0104 [0.00655, 0
as.factor(missing_fi)			
0	0 (0%)	4 (10.8%)	4 (10.5%)
1	0 (0%)	22 (59.5%)	22 (57.9%)
Missing	1 (100%)	11 (29.7%)	12 (31.6%)

```
table1(~ no_rand + active_sample + n_event + FI_final + FQ_final + as.factor(missing_fi) | placebo, data
```

(4.3.2.7) Table S3.2 - Placebo:

	Active	Placebo	Overall
	(N=10)	(N=28)	(N=38)
no_rand			
Median [Q1, Q3]	2870 [1640, 4090]	7180 [1640, 7740]	4090 [1640, 7
active_sample			
Median [Q1, Q3]	2480 [1300, 3660]	5680 [1280, 6650]	3600 [1280, 6
n_event			
Median [Q1, Q3]	161 [56.0, 306]	108 [80.5, 263]	108 [77.5, 29
FI_final			
Median [Q1, Q3]	21.5 [13.5, 39.0]	30.0 [20.8, 40.5]	26.5 [17.5, 4
FQ_final			
Median [Q1, Q3]	0.0104 [0.00758, 0.0140]	0.0109 [0.00574, 0.0249]	0.0104 [0.000
as.factor(missing_fi)			
0	3 (30.0%)	1 (3.6%)	4 (10.5%)
1	7 (70.0%)	15 (53.6%)	22 (57.9%)
Missing	0 (0%)	12 (42.9%)	12 (31.6%)