DSMB Report for EXAMPLE Trial

April 22, 2017

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```
## Generate test data
set.seed(1)
n ← 500
d ← data.frame(country=sample(c('US', 'Canada', '
      Spain', 'France',
                     'Germany'), n, TRUE),
                   site=sample(1:10, n, TRUE))
d$site   ← paste(substring(d$country, 1, 2), d$site,
      sep='')
d$region ← factor(ifelse(d$country %in% c('US', '
      Canada'),
                               'North America', 'Europe'))

d ← upData(d, edate = as.Date('2005-01-01') +
             round(rgamma(n, 2, .01)) - 600 * (country
                   == 'US'),
             rdate = edate + round(runif(n, 1, 30)),
                   print=FALSE)
d$rdate[runif(nrow(d)) < 0.5] ← NA  # non-randomized
      subjects )

# with(d, table(region, country))

# For US manually compute # randomized per month
us    ← subset(d, country == 'US')
site ← us$site
ed    ← us$edate
rd    ← us$rdate
months ← difftime(as.Date('2007-12-31'), ed, units='
      days') /
  (365.25 / 12)
m ← max(months)
a ← sum(!is.na(rd)) / as.numeric(m)   # .8545774 (
      agrees with chart)
# Compute maximum months elapsed for each site then
      sum over sites
maxpersite ← tapply(months, site, max)
b ← sum(!is.na(rd)) / sum(maxpersite)
## 0.0864429 = 47 / 543.6715 chart: .08645 (rounded)
```

```
## Suppose there are more subjects enrolled and
      randomized than really
## made their way into the dataset
denom ← c(enrolled=nrow(d) * 1.1,
           randomized=sum(!is.na(d$rdate)) + 10)

setgreportOption(gtype=c('pdf', 'interactive')[1], #
      [2] to debug
                 tx.var='treat', denom=denom, texwhere
                      ='')

## Initialize app.tex
file ← sprintf('%s/app.tex', getgreportOption('texdir
      '))
cat('', file=file)
```

1 Notation

Pop-up Tooltips Certain elements of the report, signaled by ↦, have pop-up tooltips behind them. More information will pop up when viewing the report under Acrobat Reader when the mouse hovers over ↦. Clicking on the information in the pop-up will make it "stick", and clicking on the X will make it disappear. For graphics that have pop-up tables you can also click anywhere inside the graph. When the pop-up is a wide table, it will use full-page mode. If the table is tall you may need to scroll vertically. To do that, click on the table when it pops up to make it stick, then scroll, then click again to make it disappear.

Hyperlinks to Tables Some graphics and tables are hyperlinked to tables in the Appendix. For these, clicking anywhere in the graphic or table will move the pdf reader to the supporting table. Clicking on the appendix table will bring you back to the original figure.

Figure Captions Needles represent the fraction of observations used in the current analysis. The first needle (red) shows the fraction of enrolled patients used. If randomization was taken into account, a second needle (green) represents the fraction of randomized subjects included in the analysis. When the analyses consider treatment assignment, two more needles may be added to the display, showing, respectively, the fraction of subjects randomized to treatment A used in the analysis and the fraction of subjects on treatment B who were analyzed. The colors of these last two needles are the colors used for the two treatments throughout the report. The following table shows some examples.

```
# dNeedle uses colors in setgreportOption(tx.col=,
      er.col=)
dNeedle(1,            'lttdemoa')
```

```
dNeedle(c(3,4)/4 ,    'lttdemob')
```

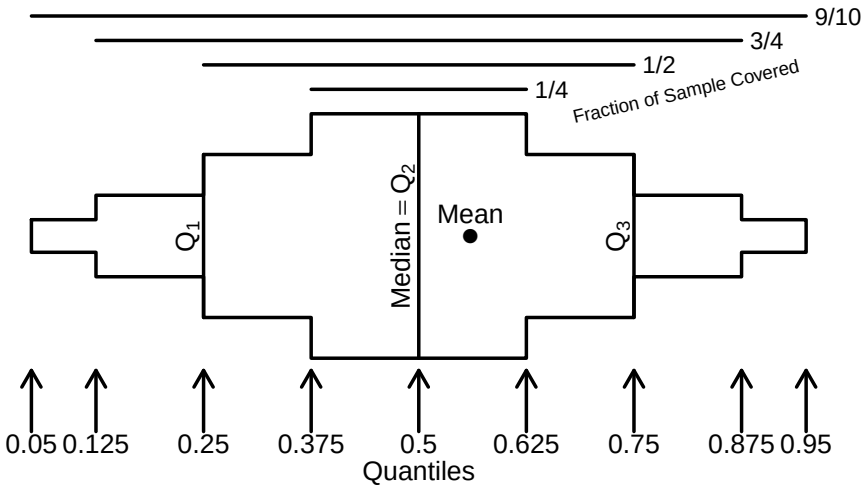
```
dNeedle(c(1,2)/4,     'lttdemoc')
```

```
dNeedle(c(1,2,3,1)/4,'lttdemod')
```

Needles	Interpretation
	All enrolled subjects analyzed, randomization not considered
	Analysis uses $\frac{3}{4}$ of enrolled subjects, and all randomized subjects
	Analysis uses $\frac{1}{4}$ of enrolled subjects, and $\frac{1}{2}$ of randomized subjects
	Same as previous example, and in addition the analysis utilized treatment assignment, analyzing $\frac{3}{4}$ of those randomized to A and $\frac{1}{4}$ of those randomized to B

Extended Box Plots For depicting distributions of continuous variables, many of the following displays use extended box plots, also called box–percentile plots. A prototype, with explanations, is below.

```
bpplt()
```



Dot Charts Dot charts are used to present stratified proportions. In these charts the area of the symbols is proportional to the square root of the denominator. The legend shows representative denominators and their corresponding symbol areas, using denominators that actually occurred in the data and extended from the minimum observed to the maximum observed sample size.

Survival Curves Graphs containing pairs of Kaplan-Meier survival curves show a shaded region centered at the midpoint of the two survival estimates and having a height equal to the half-width of the approximate 0.95 pointwise confidence interval for the difference of the two survival probabilities. Time points at which the two survival estimates do not touch the shaded region denote approximately significantly different survival estimates, without any multiplicity correction.

2 Accrual

```
accrualReport(enroll(edate) + randomize(rdate) ~
              region(region) + country(country) + site
                   (site),
              data=d, hdot=3,
              dateRange=c('2005-01-01', '2007-12-31'),
              targetN=
                data.frame(edate=c(500, 1000), rdate=c
                     (250, 500)),
              targetDate=c('2006-01-01', '2007-12-31')
                   ,
              zoom=c('2005-01-01', '2005-06-30'),
              closeDate='2007-12-31')
```

Table 1: Study Numbers

Number	Category
5	Countries
50	Sites
500	Subjects enrolled
260	Subjects randomized
5.2	Subjects per site
50	Sites randomizing
5.2	Subjects randomized per randomizing site
55.1	Months from first subject randomized (2003-05-29) to 2007-12-31
1873.8	Site-months for sites randomizing
37.5	Average months since a site first randomized
0.14	Subjects randomized per site per month
15	Mean days from enrollment to randomization
15	Median days from enrollment to randomization

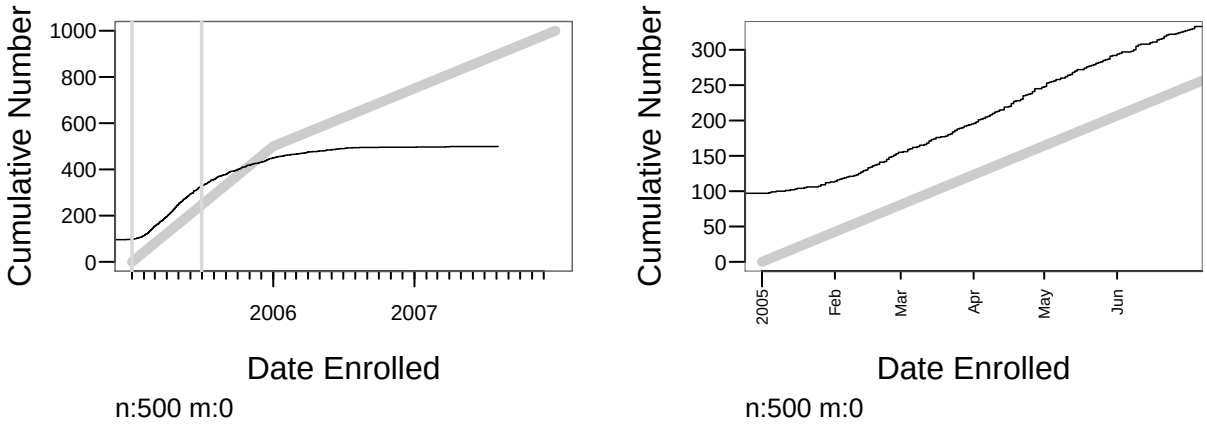


Figure 1: Subjects enrolled over time. The solid back line depicts the cumulative frequency. The thick grayscale line represent targets. The plot is zoomed to show 2005-01-01–2005-06-30 in the right panel. The zoomed interval is depicted with vertical grayscale lines in the left panel ↦

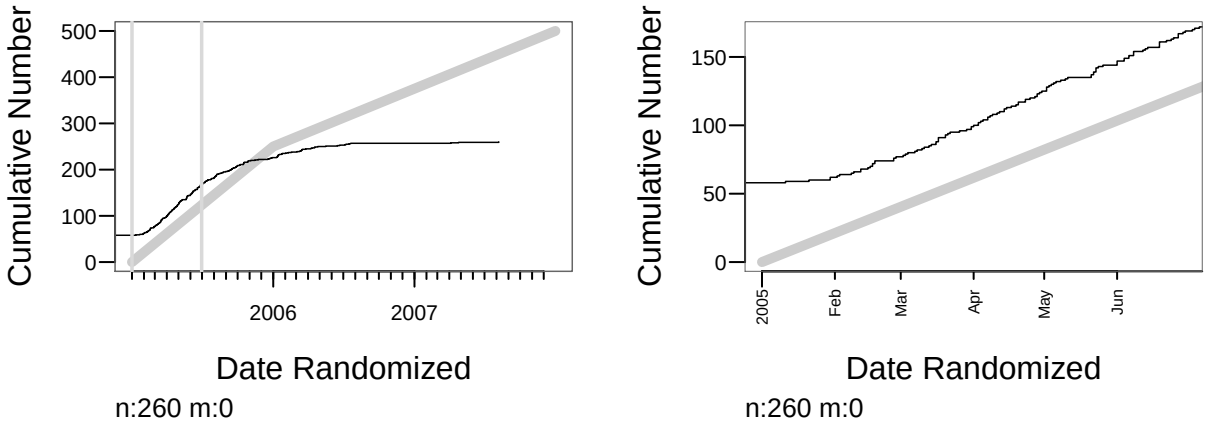


Figure 2: Subjects randomized over time. The solid back line depicts the cumulative frequency. The thick grayscale line represent targets. The plot is zoomed to show 2005-01-01–2005-06-30 in the right panel. The zoomed interval is depicted with vertical grayscale lines in the left panel ↦

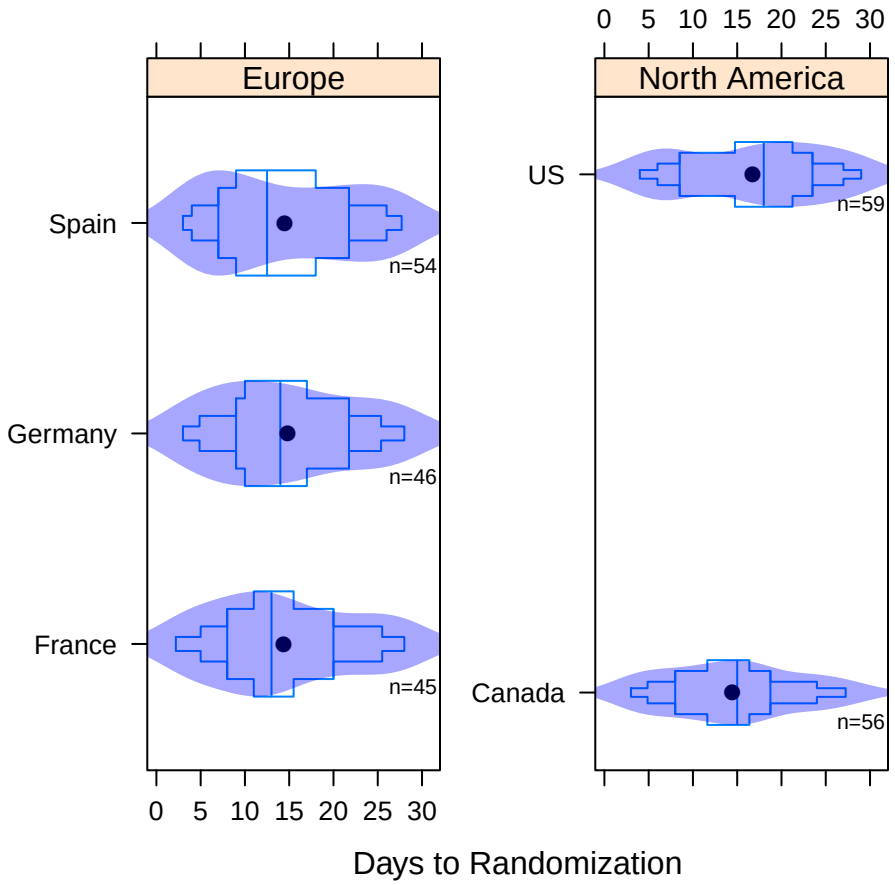


Figure 3: Extended box ↦ plots and violin plots showing the distribution of days from enrollment to randomization (Table 6)

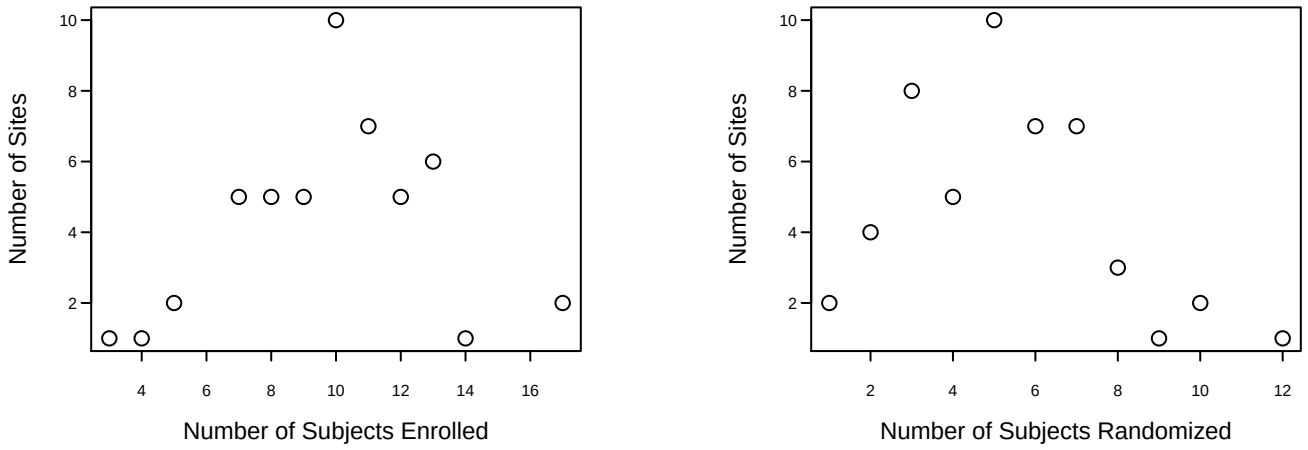


Figure 4: Number of sites having the given number of subjects ↦

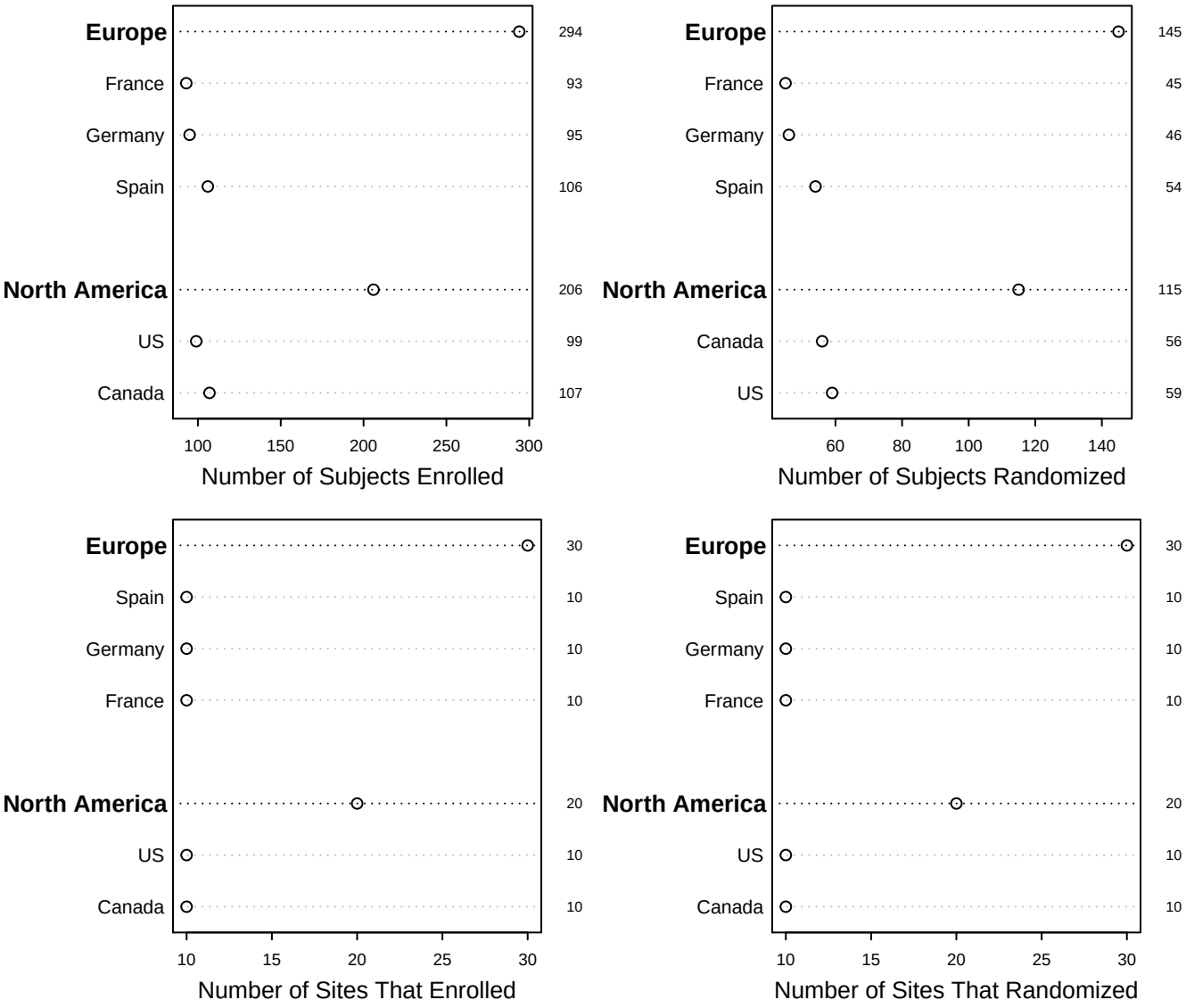


Figure 5: Counts of numbers of subjects and numbers of sites ↦

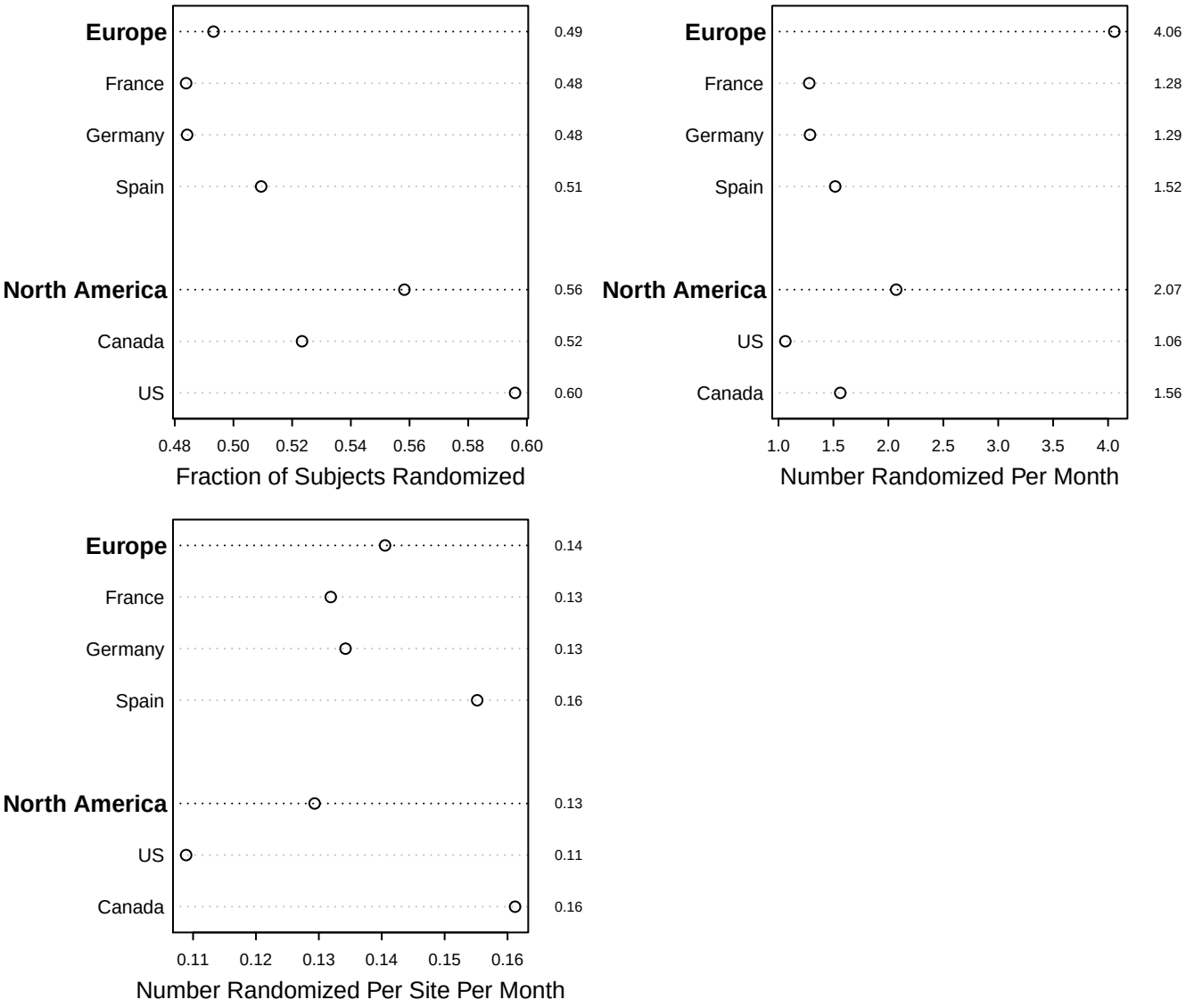


Figure 6: Counts of numbers of subjects and numbers of sites ↦

3 Patient Flow and Exclusions

```
d ← upData(d,
           subjid = 1 : n,
           pend   = rbinom(n, 1, .1),
           e1     = rbinom(n, 1, .02),
           e2     = rbinom(n, 1, .02),
           e3     = rbinom(n, 1, .02),
           e4     = ifelse(runif(n) < 0.25, NA,
                rbinom(n, 1, .10)),
           tested = rbinom(n, 1, .75),
           e5     = ifelse(tested, rbinom(n, 1, .04),
                 NA),
           e6     = rbinom(n, 1, .02),
           e7     = rbinom(n, 1, .02),
           rndz   = rbinom(n, 1, .75),
           labels=c(e1='Prior MI', e2='History of
                Asthma',
             e3='History of Upper GI Bleeding',
             e4='No Significant CAD', e5='Inadequate
                  Renal Function',
             e6='Pneumonia within 6 weeks', e7='Prior
                   cardiac surgery'),
           print=FALSE)

erd ← data.frame(subjid = 1 : 50,
                 loc   = sample(c('gastric', 'lung',
                      'trachea'), 50, TRUE))

# To check warning messages, greportOption denom does
      not match pend, e1-e7
exReport(~ pending(pend) + e1 + e2 + e3 + e4 + e5 + e6
       + e7 +
          randomized(rndz) + id(subjid) + cond(e5, '
               Tested', tested),
          erdata = erd,
          whenapp= c(e4='CCTA done'), data=d, hc=3.75,
               h=4)
```

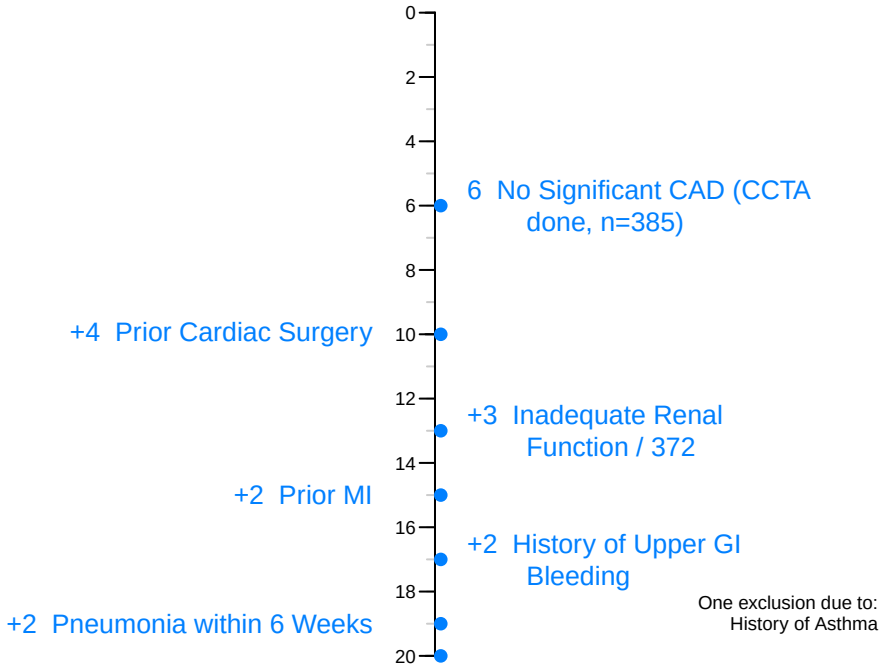


Figure 7: Cumulative number of exclusions (y-axis) and number of additional exclusions after exclusions placed higher, for subjects not actually randomized. Exclusions are sorted by descending number of incremental exclusions. 550 subjects were enrolled, 12 non-excluded subjects are pending randomization, and 20 subjects were excluded. 372 subjects were randomized. **Note**: Number of observations (500) does not equal number officially enrolled (550). **Note**: Number of enrolled (488) minus number excluded (20) does not match official number randomized (270).

Table 2: Exclusions, for subjects not actually randomized. `Incremental Exclusions` are those in addition to exclusions in earlier rows. `Marginal Exclusions` are numbers of subjects excluded for the indicated reason whether or not she was excluded for other reasons. The three `Fractions` are based on incremental exclusions.

Exclusions	Incremental Exclusions	Marginal Exclusions	Fraction of Enrolled	Fraction of Exclusions	Fraction Remaining
No Significant CAD (CCTA done, n=385)	6	6	0.012	0.30	0.988
Prior Cardiac Surgery	4	4	0.008	0.20	0.980
Inadequate Renal Function / 372 $\frac{3}{366}$ =0.008 of Tested	3	3	0.006	0.15	0.973
Prior MI	2	3	0.004	0.10	0.969
History of Upper GI Bleeding	2	2	0.004	0.10	0.965
Pneumonia within 6 Weeks	2	2	0.004	0.10	0.961
History of Asthma	1	1	0.002	0.05	0.959
Total	20		0.041	1.00	0.959

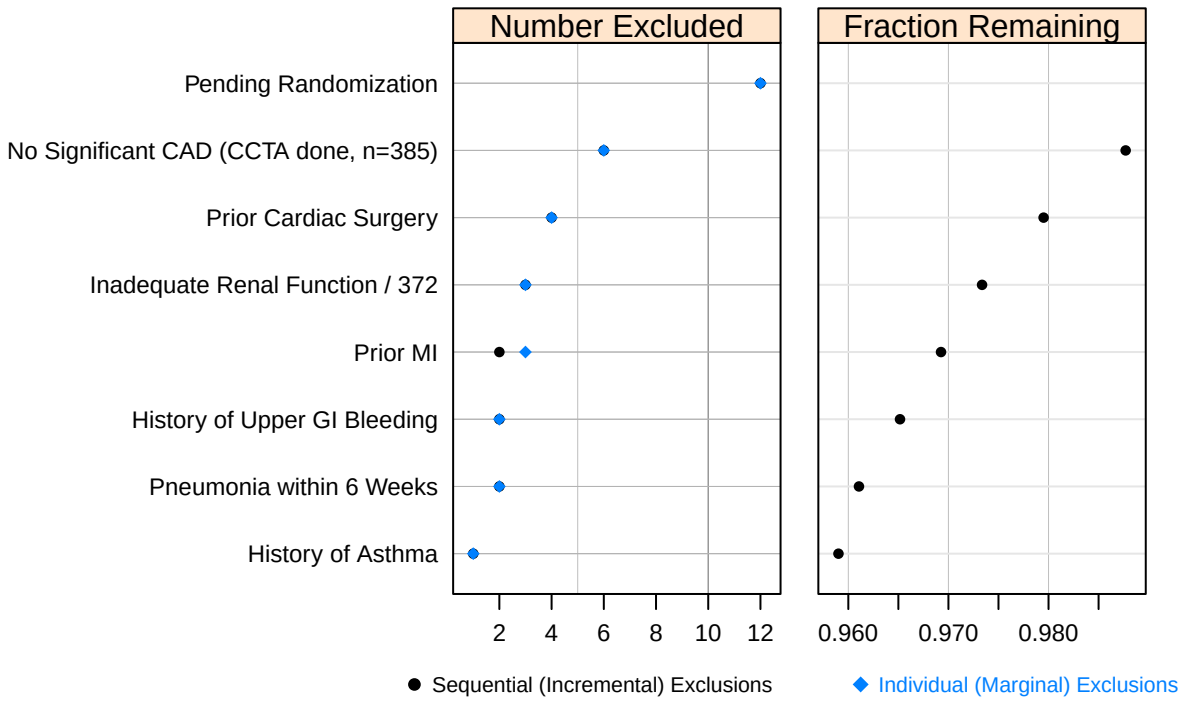


Figure 8: Left panel: Incremental (sequential) and marginal (each exclusion treated separately) exclusions. Right panel: Fraction of subjects remaining after incremental exclusions. The denominator of the fraction is the number of subjects not pending randomization (488). Exclusions are sorted by descending number of incremental exclusions. 550 subjects were enrolled, 12 non-excluded subjects are pending randomization, and 20 subjects were excluded. 372 subjects were randomized. **Note**: Number of observations (500) does not equal number officially enrolled (550). **Note**: Number of enrolled (488) minus number excluded (20) does not match official number randomized (270).

Table 3: Frequency of exclusions for subjects marked as randomized

Exclusion	Frequency
Prior MI	8
History of Asthma	7
History of Upper GI Bleeding	7
No Significant CAD	41
Inadequate Renal Function	15
Pneumonia within 6 Weeks	7
Prior Cardiac Surgery	8
Total Subjects with Any Exclusion	83

```
# Show exclusions in original variable order
exReport(~ pending(pend) + e1 + e2 + e3 + e4 + e5 + e6
       + e7 +
          randomized(rndz) + id(subjid) + cond(e5, '
                Tested', tested),
          erdata=erd,
          whenapp=c(e4='CCTA done'), data=d, hc=3.75, h
                =4,
          sort=FALSE, append=TRUE, subpanel='unsorted',
                 app=FALSE)
```

Table 4: Exclusions, for subjects not actually randomized. `Incremental Exclusions` are those in addition to exclusions in earlier rows. `Marginal Exclusions` are numbers of subjects excluded for the indicated reason whether or not she was excluded for other reasons. The three `Fractions` are based on incremental exclusions.

Exclusions	Incremental Exclusions	Marginal Exclusions	Fraction of Enrolled	Fraction of Exclusions	Fraction Remaining
Prior MI	3	3	0.006	0.15	0.994
History of Asthma	1	1	0.002	0.05	0.992
History of Upper GI Bleeding	2	2	0.004	0.10	0.988
No Significant CAD (CCTA done, n=385)	5	6	0.010	0.25	0.977
Inadequate Renal Function / 372 $\frac{3}{366}$ =0.008 of Tested	3	3	0.006	0.15	0.971
Pneumonia within 6 Weeks	2	2	0.004	0.10	0.967
Prior Cardiac Surgery	4	4	0.008	0.20	0.959
Total	20		0.041	1.00	0.959

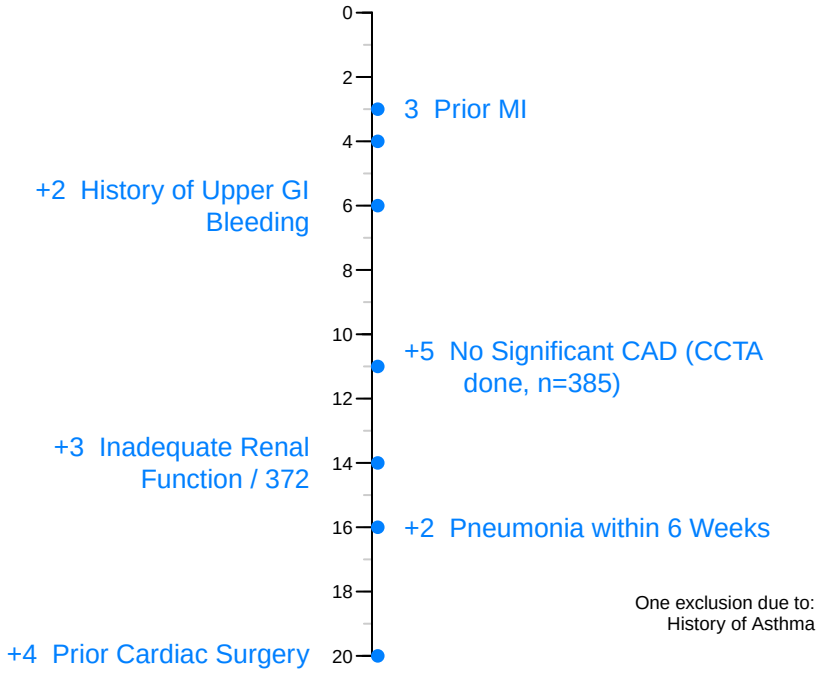


Figure 9: Cumulative number of exclusions (y-axis) and number of additional exclusions after exclusions placed higher, for subjects not actually randomized. Exclusions are in the prespecified order shown in the figure. 550 subjects were enrolled, 12 non-excluded subjects are pending randomization, and 20 subjects were excluded. 372 subjects were randomized. **Note**: Number of observations (500) does not equal number officially enrolled (550). **Note**: Number of enrolled (488) minus number excluded (20) does not match official number randomized (270).

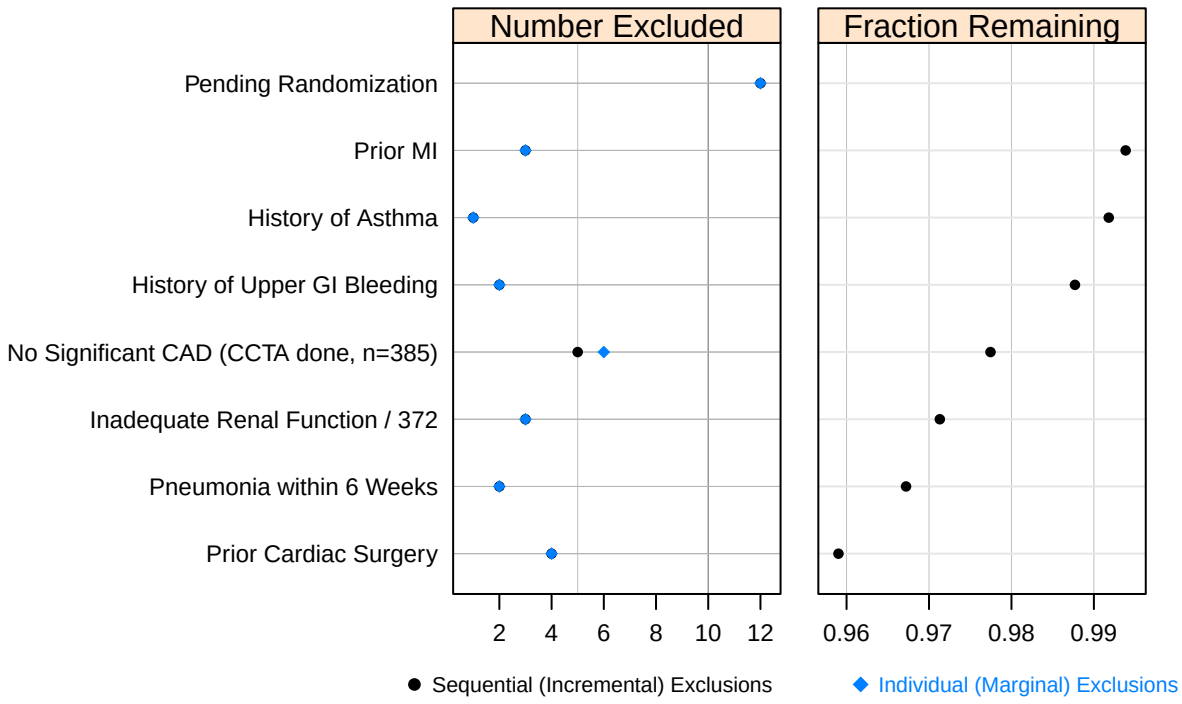


Figure 10: Left panel: Incremental (sequential) and marginal (each exclusion treated separately) exclusions. Right panel: Fraction of subjects remaining after incremental exclusions. The denominator of the fraction is the number of subjects not pending randomization (488). Exclusions are in the prespecified order shown in the figure. 550 subjects were enrolled, 12 non-excluded subjects are pending randomization, and 20 subjects were excluded. 372 subjects were randomized. **Note**: Number of observations (500) does not equal number officially enrolled (550). **Note**: Number of enrolled (488) minus number excluded (20) does not match official number randomized (270).

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Prior Cardiac Surgery	8
Total Subjects with Any Exclusion	83

4 Baseline Variables

```
n ← 100
f ← function(na=FALSE) {
  x ← sample(c('N', 'Y'), n, TRUE)
  if(na) x[runif(100) < .1] ← NA
  x
}
set.seed(1)
d ← data.frame(x1=f(), x2=f(), x3=f(), x4=f(), x5=f()
      , x6=f(),
                x7=f(TRUE),
                age=rnorm(n, 50, 10),
                sbp=rnorm(n, 120, 7),
                dbp=rnorm(n,  80, 6),
                days=sample(1:n, n, TRUE),
                race=sample(c('Asian', 'Black/AA', '
                      White'), n, TRUE),
                sex=sample(c('Female', 'Male'), n,
                      TRUE),
                treat=sample(c('A', 'B'), n, TRUE),
                region=sample(c('North America','
                      Europe'), n, TRUE),
                meda=sample(0:1, n, TRUE), medb=sample
                      (0:1, n, TRUE),
                subjid=1:n)
d$days[1] ← NA
d ← upData(d, labels=c(x1='MI', x2='Stroke', x3='AKI'
      , x4='Migraines',
                 x5='Pregnant', x6='Other event', x7='
                       MD withdrawal',
                 race='Race', sex='Sex', treat='
                       treatment',
                 sbp='Systolic BP', days='Time Since
                       Randomization',
                 meda='Medication A', medb='Medication
                        B'),
            units=c(sbp='mmHg', dbp='mmHg', age='years
                  ', days='days'),
            print=FALSE)
dasna ← subset(d, region=='North America')
# with(dasna, table(race, treat))
den ← c(enrolled=n + 50, randomized=n, table(d$treat)
      )
setgreportOption(denom=den, tx.var='treat')
```

```
dReport(race + sex +
        ynbind(x1, x2, x3, x4, x5, x6, x7, label='
              Exclusions') ~ 1,
        head='Overall frequencies of categorical
              demographic variables and exclusions',
        data=d, w=4, h=4.5)
```

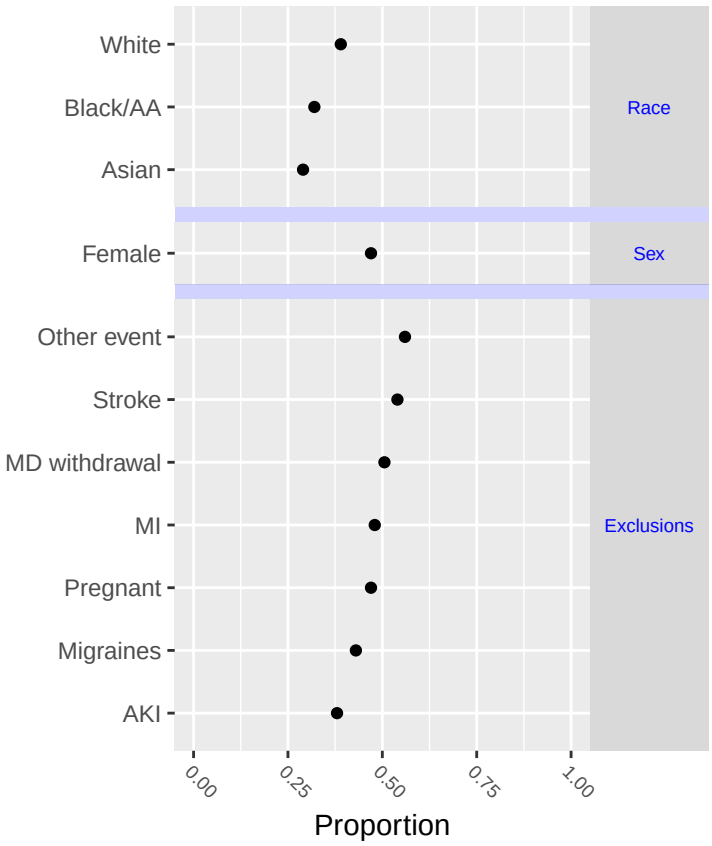

Figure 11: Overall frequencies of categorical demographic variables and exclusions. N=100 (Table 8)

```
dReport(race + sex ~ region, data=addMarginal(d,
     region),
        groups='region', append=TRUE,
        w=4.75, h=3.75, subpanel='demoreg',
        head='Demographics')
```

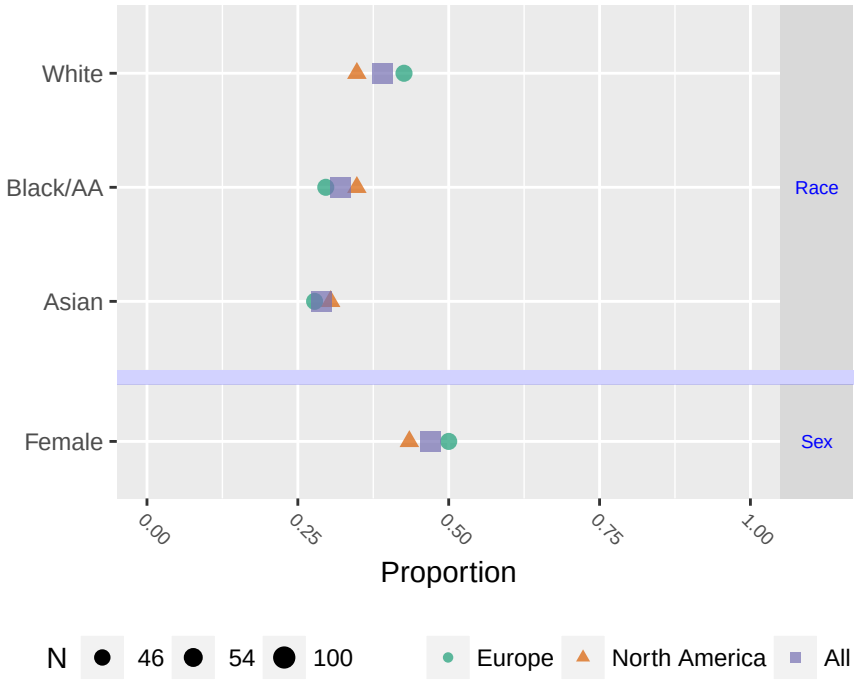

Figure 12: Demographics stratified by region. N=100 (Table 9)

```
## Add a new block of variables that apply only to
      males
dReport(race + sex +
        pBlock(race, subset=sex=='Male', label='Race:
              Males') ~ region,
        data=d, groups='region', append=TRUE,
        w=4.75, h=4, subpanel='demoblock',
        head='Demographics with race for males')
```

```
excl ← with(d, ynbind(x1, x2, x3, x4, x5, x6, x7,
                      label='Exclusions'))
dReport(excl ~ 1, head='Exclusions', append=TRUE,
        w=4, h=2.5, subpanel='excl')
```

```
dReport(race + sex + excl ~ treat + region, groups='
     treat',
```

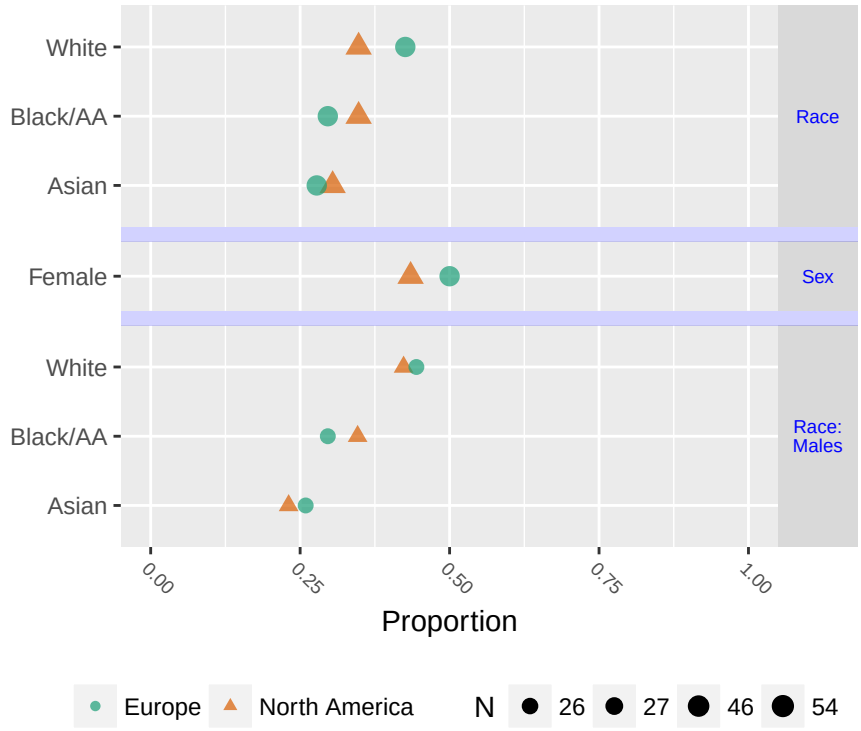

Figure 13: Demographics with race for males stratified by region. N=53 to 100 (Table 10)

```
        head='Categorical demographic variables and
             exclusions',
        data=d, append=TRUE, w=7, h=4.5, subpanel='
             txreg')
```

```
cat('\\clearpage\n')
```

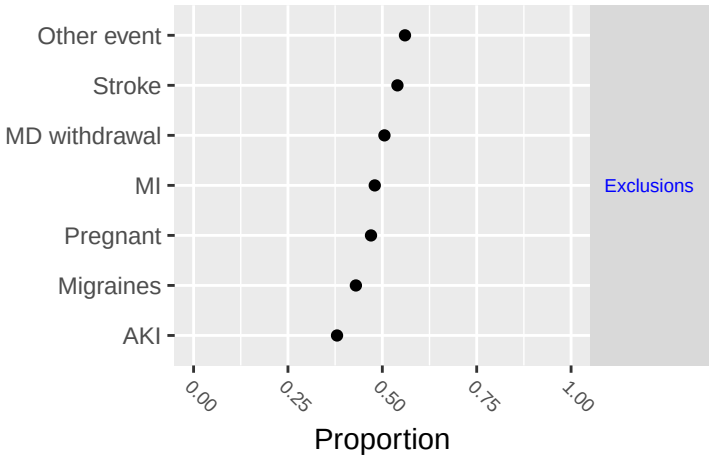

Figure 14: Exclusions. N=100 (Table 11)

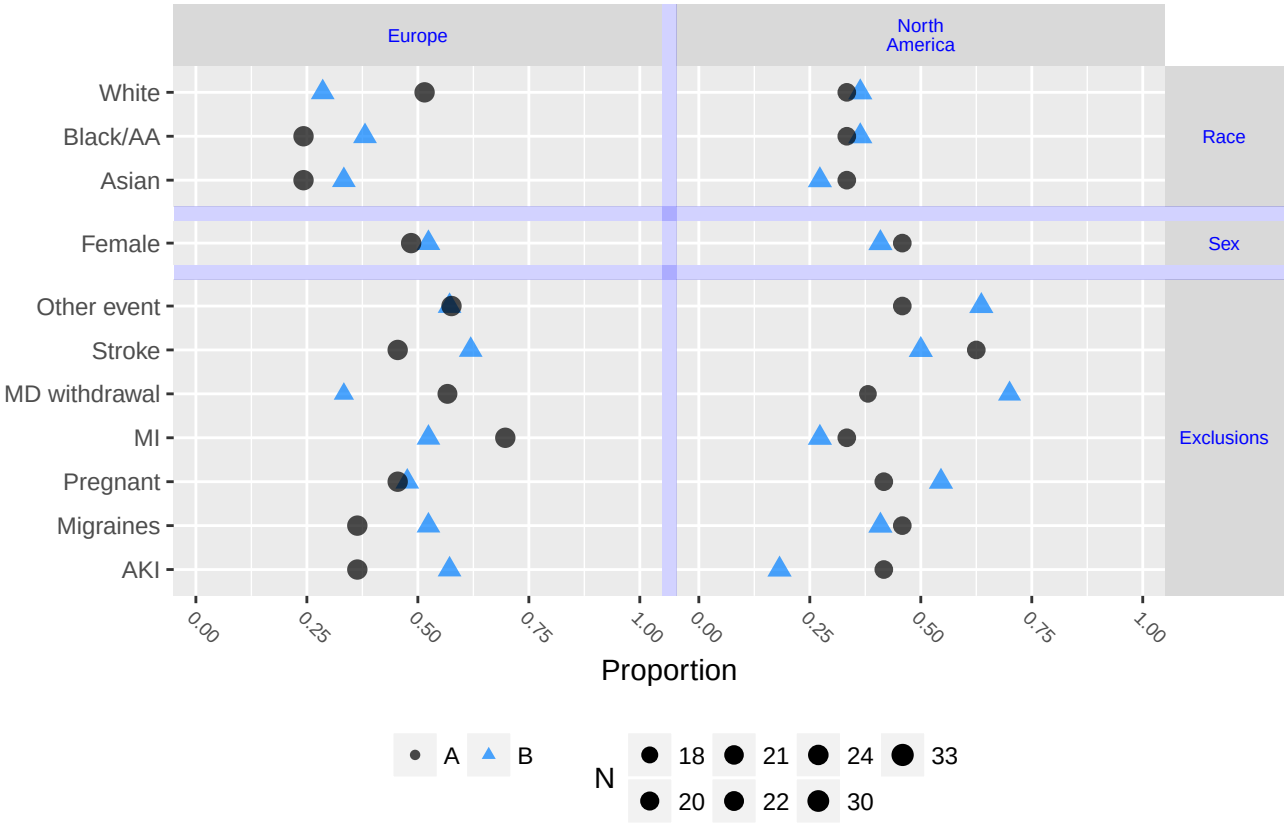

Figure 15: Categorical demographic variables and exclusions stratified by treatment and region. N=100 (Table 12)

```
# Show the same information plus numerators and
      denominators by using
# lattice format

dReport(race + sex + excl ~ treat + region, groups='
     treat',
        head='Categorical demographic variables and
              exclusions',
        data=d, append=TRUE, w=7, h=4.5, subpanel='
              txregl', lattice=TRUE)
```

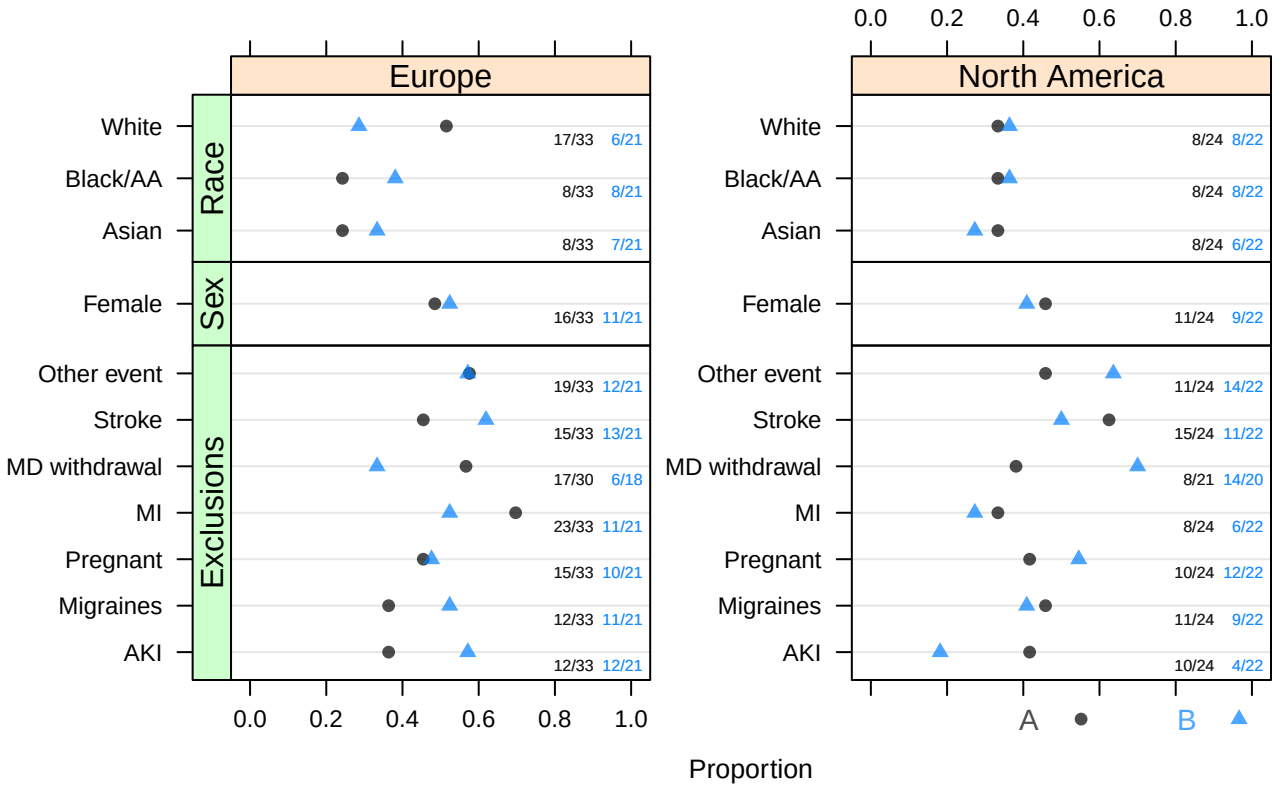

Figure 16: Categorical demographic variables and exclusions stratified by treatment and region. N=100 (Table 13)

```
## Show spike histogram for raw data, 50 bins
```

```
dReport(age + sbp + dbp ~ region,
        data=d, append=TRUE, w=6, h=2,
        sopts=list(datadensity=TRUE,
          scat1d.opts=list(nhistSpike=1,
            col=adjustcolor('red', alpha.f=.5),
            nint=50)),
        head='Baseline continuous variables')
```

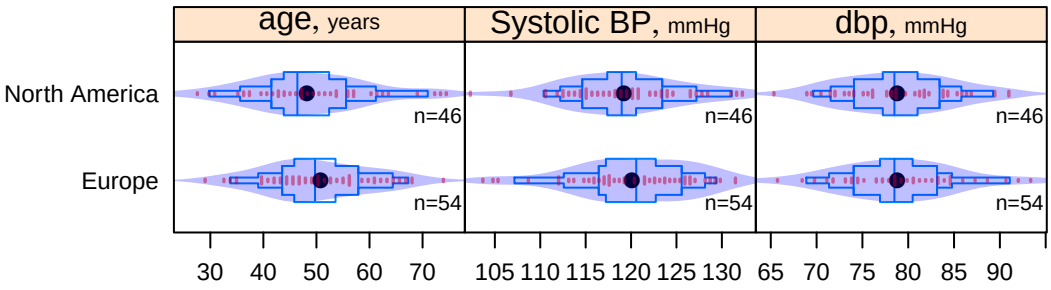

Figure 17: Baseline continuous variables stratified by region. N=100 (Table 14)

```
dReport(age + sbp + dbp ~ treat + region, w=6, h=3.5,
        data=d, append=TRUE, subpanel='txreg',
        sopts=list(cex.strip=.65))
```

```
# Same but show regions combined
dReport(age + sbp + dbp ~ treat + region, w=6, h=4.75,
           data=addMarginal(d, region),
           append=TRUE, subpanel='txregm')
```

```
# Show raw data and smoothed relationship between age
      and sbp,
# stratified.
# Label curves in an empty region, for the first panel
       only
pan ← function(...)
  panel.plsmo(..., type='b', label.curves=max(
        which.packet()) == 1,
              datadensity=TRUE)
dReport(sbp ~ age + treat + region, groups='treat',
     data=d, what='xy',
```

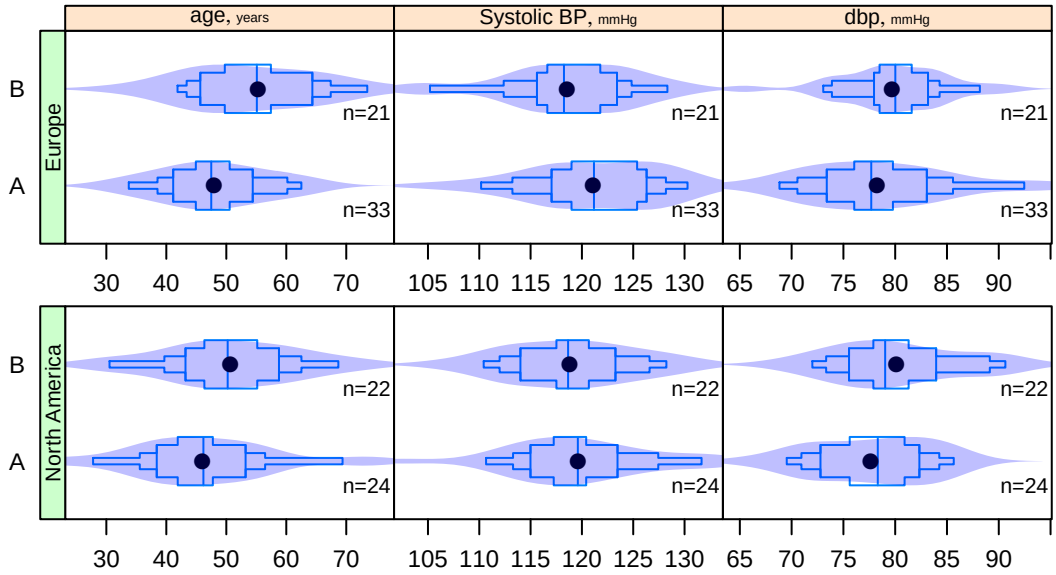

Figure 18: Extended box ↦ and violin plots for age, systolic BP, and dbp stratified by treatment and region. N=100 (Table 15)

```
        popts=list(panel=pan, paneldoesgroups=TRUE,
          scat1d.opts=list(lwd=.7), key=NULL),
        append=TRUE, subpanel='xyplot', h=3, w=6)
```

```
f ← function(x) {
  x ← x[! is.na(x)]
  c(smean.cl.normal(x, na.rm=FALSE), n=length(x))
}

#dReport(sbp ~ treat + region, data=d, groups='treat',
#         fun = f, head='Mean and confidence limits',
#         popts = list(textplot='Mean', digits=1,
#           key=list(space='right')),
#         append=TRUE, subpanel='statstest', h=3, w=5)
dReport(sbp ~ treat + region, data=d,
        fun = f, head='Mean and confidence limits',
        popts = list(textplot='Mean', digits=1),
        append=TRUE, subpanel='stats', h=3, w=5)
```

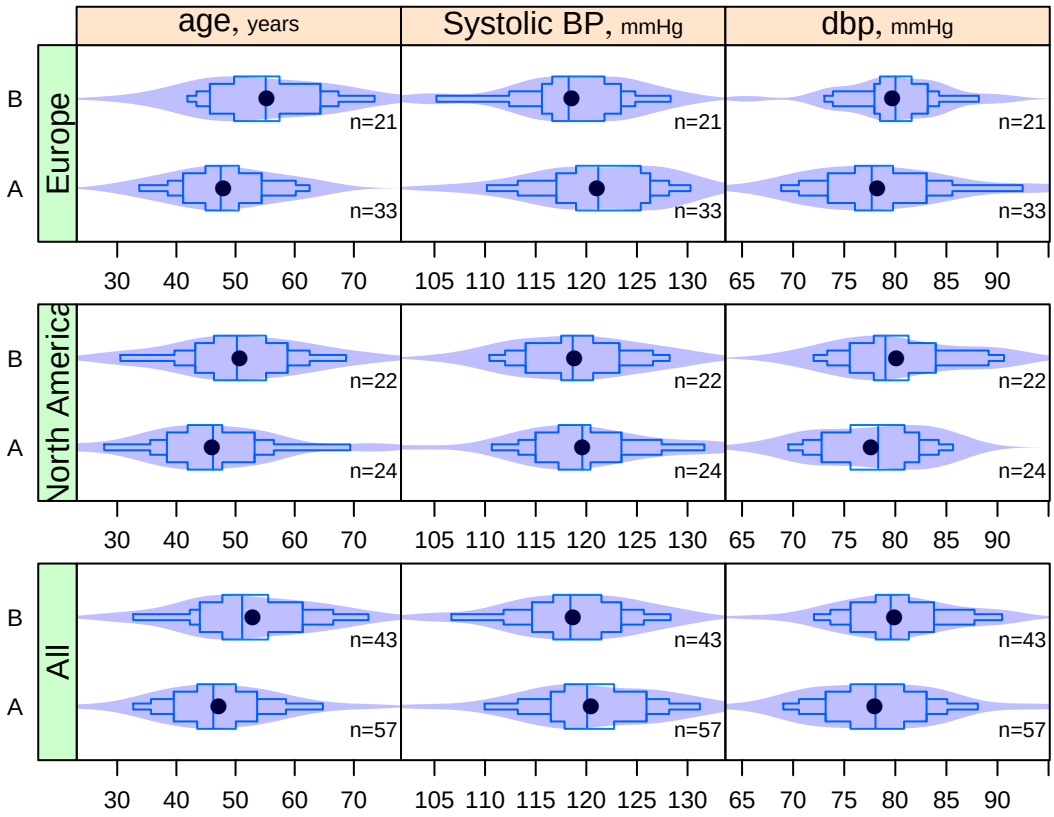

Figure 19: Extended box ↦ and violin plots for age, systolic BP, and dbp stratified by treatment and region. N=100 (Table 16)

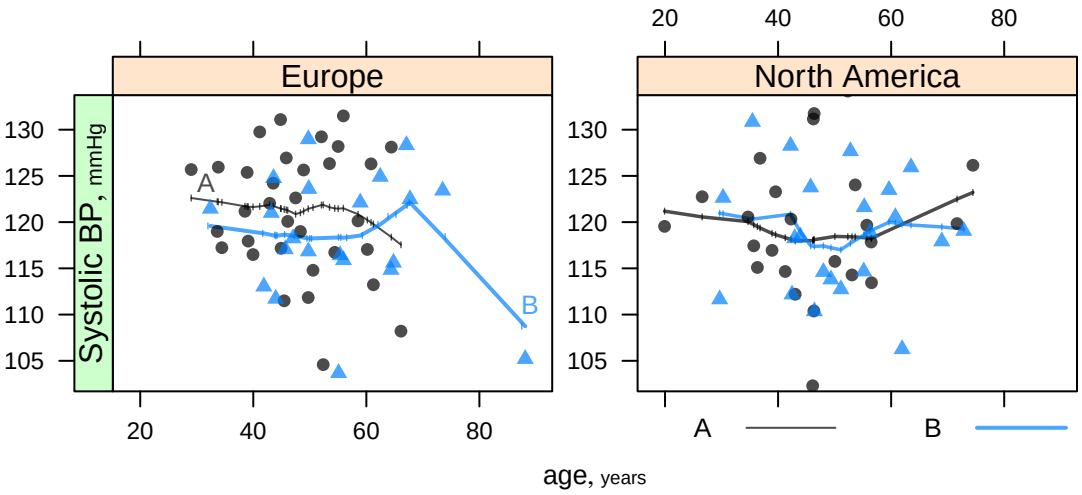

Figure 20: Systolic BP vs. age stratified by treatment and region. N=100

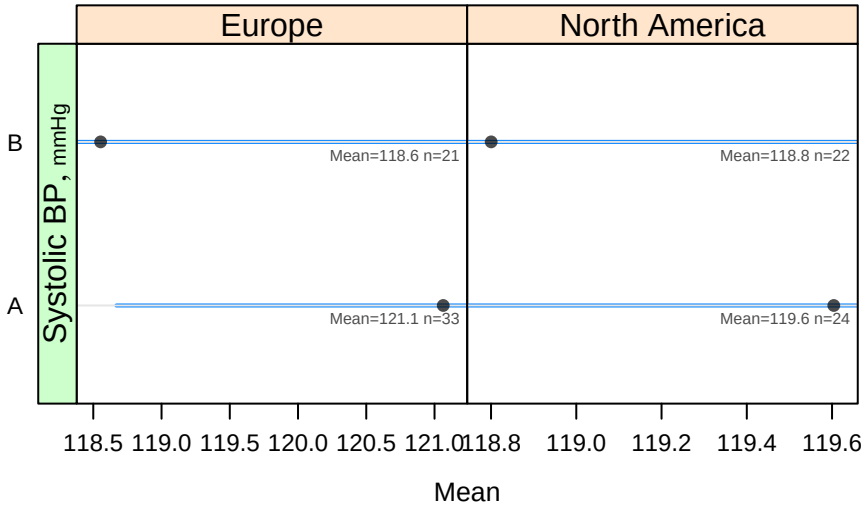

Figure 21: Mean and confidence limits stratified by treatment and region. N=100 (Table 17)

5 Medication Usage Over Time

```
pan ← function(...)
  panel.plsmo(..., type='l', label.curves=max(
        which.packet()) == 1,
              method='intervals', mobs=10)  # normally
                    mobs ≥ 96

# Generalizes xyplot(meda ~ days | region, groups=
      treat,
#                      panel=pan, data=d)
dReport(meda + medb ~ days + treat + region, what='xy'
      ,
        groups='treat', data=d, h=3.75,
        popts=list(panel=pan, paneldoesgroups=TRUE,
          ylab='Proportion Using', xlim=c(0, 130),
          scat1d.opts=list(lwd=.7)),
        head='Medication usage',
        # tail='Tick marks indicate observed
              measurement times.',
        tail='Tick marks indicate mean measurement
              times within intervals.',
        panel='meds')
```

```
# Show number being followed as days since
      randomization gets larger
# make sure nriskReport doesn't get fooled by
      duplicate data
d2 ← rbind(d, d)
nriskReport(days ~ region + id(subjid),
            data=addMarginal(d2, region),
            head='Number of subjects followed for
                  medication usage',
            panel='meds', append=TRUE, h=3, w=4.5)
```

```
# Separate analysis not stratified by region, which
      will also provide
# more detailed graphs.  Make up some new visits to
      have more than 1/subj.
# Make up a new definition of time zero
d2$days[(n + 1) : (2 * n)] ← sample(1 : n, n, TRUE)
nriskReport(days ~ id(subjid), data=d2, time0='PCI',
            panel='medsb', append=TRUE,
            h=3, w=4.5)
```

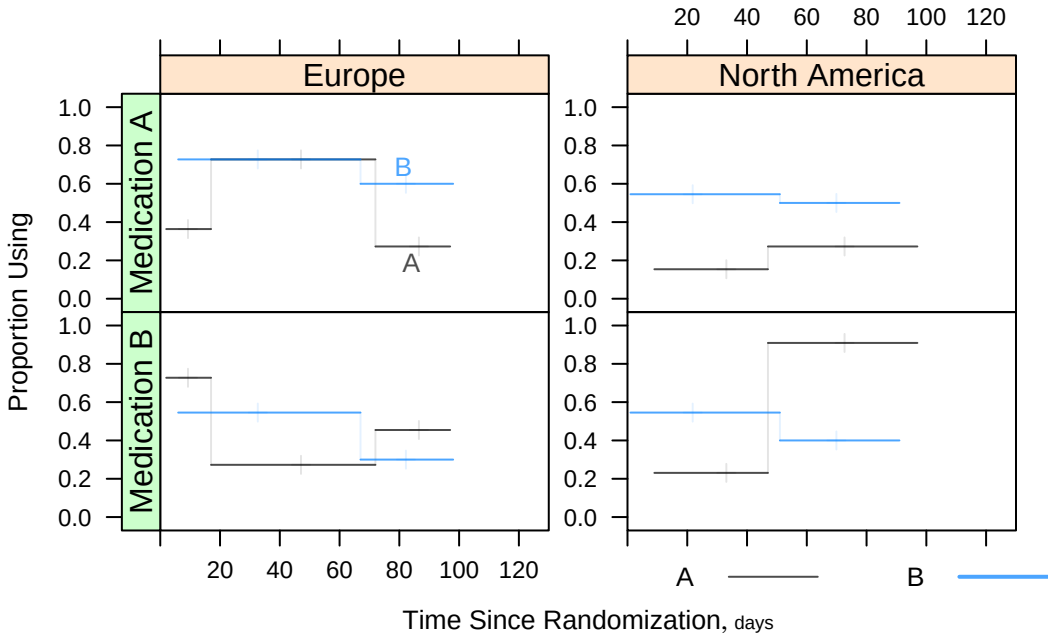

Figure 22: Medication usage stratified by treatment and region. N=100. Tick marks indicate mean measurement times within intervals.

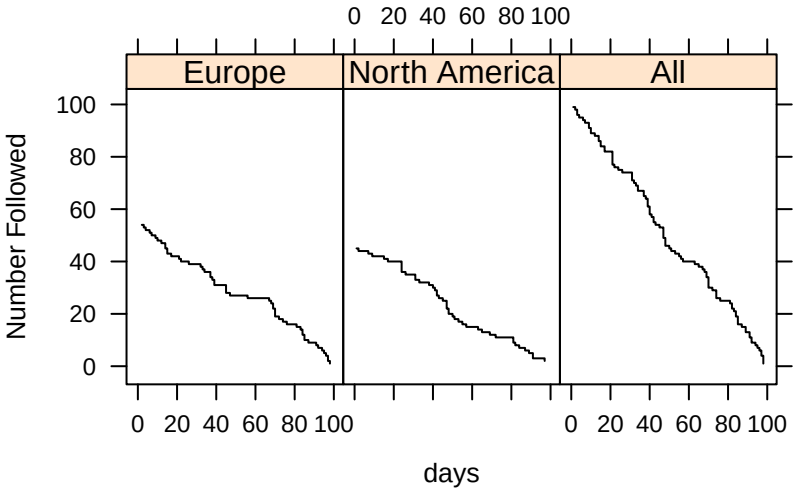

Figure 23: Number of subjects followed for medication usage stratified by Region

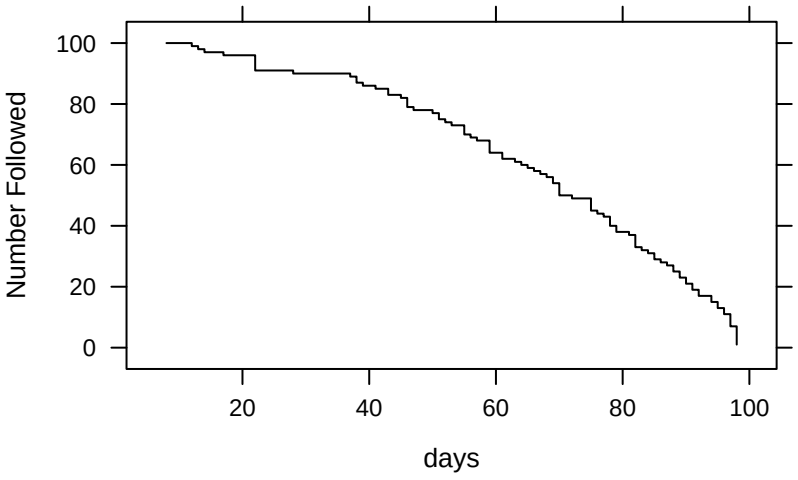

Figure 24: Number of subjects followed at least x days from PCI

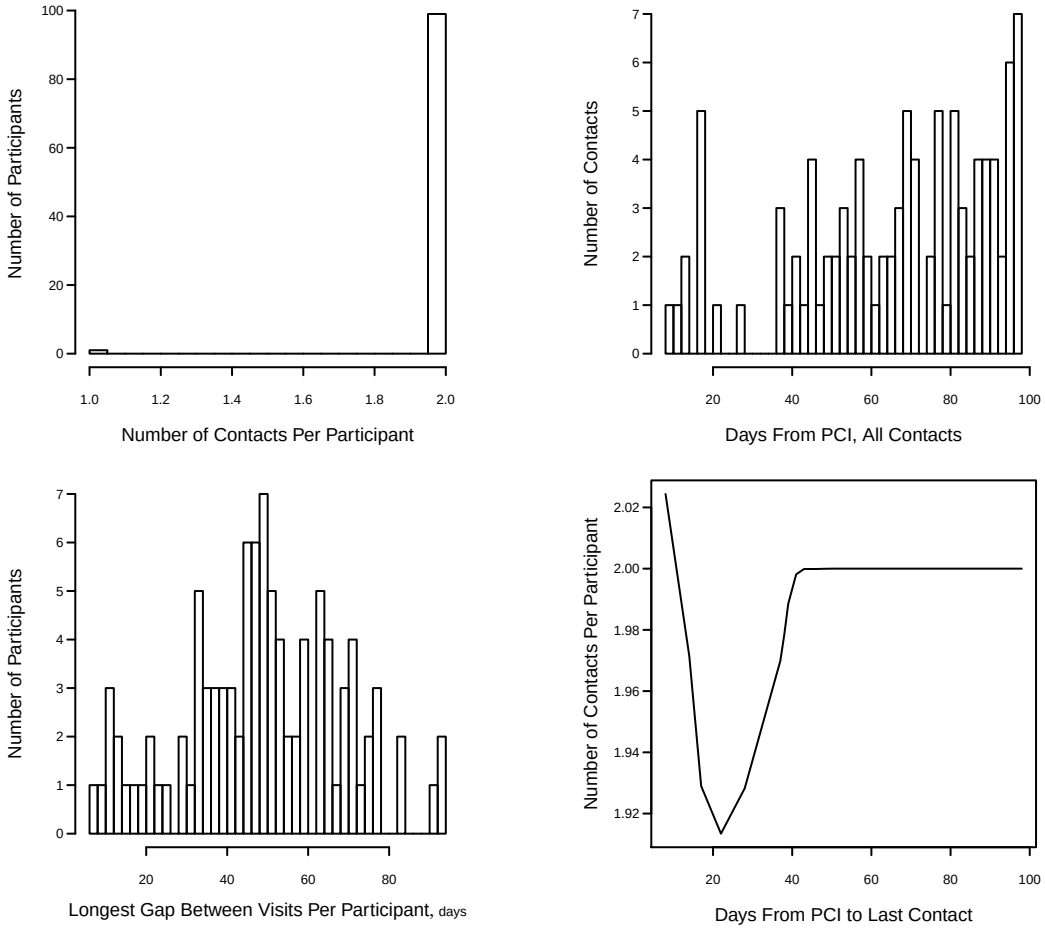

Figure 25: Distributions of follow-up visits, with times in days. Top left panel is a histogram showing the distribution of the number of contacts per participant. Top right panel is a histogram showing the distribution of time from PCI to all contacts. Bottom left panel is a histogram showing the distribution of the longest time gap between visits per participant. Bottom right panel shows the relationship between the time of last contact per subject and the average number of contacts per subject.

6 Time to Hospitalization and Surgery

```
set.seed(1)
n ← 400
dat ← data.frame(t1=runif(n, 2, 5), t2=runif(n, 2, 5)
      ,
                 e1=rbinom(n, 1, .5), e2=rbinom(n, 1,
                       .5),
                 cr1=factor(sample(c('cancer','heart'
                      ,'censor'), n, TRUE),
                           c('censor', 'cancer', '
                                heart')),
                 cr2=factor(sample(c('gastric','
                      diabetic','trauma', 'censor'),
                                n, TRUE),
                           c('censor', 'diabetic', '
                                gastric', 'trauma'))
                                ,
                 treat=sample(c('a','b'), n, TRUE))
dat ← upData(dat,
             labels=c(t1='Time to operation',
                      t2='Time to rehospitalization',
                      e1='Operation', e2='
                           Hospitalization',
                      treat='Treatment'),
             units=c(t1='Year', t2='Year'), print=
                  FALSE)
denom ← c(enrolled=n + 40, randomized=400, a=sum(dat$
      treat=='a'),
           b=sum(dat$treat=='b'))
setgreportOption(denom=denom, tx.var='treat')
survReport(Surv(t1, e1) + Surv(t2, e2) ~ treat, data=
      dat,
           mfrow=c(2,1), w=4.75, h=6, ps=8, what='S')
```

```
# Show estimates combining treatments
survReport(Surv(t1, e1) + Surv(t2, e2) ~ 1, data=dat,
      subpanel='nostrat',
           mfrow=c(2,1), w=4.75, h=6, ps=8, what='S',
                times=3, ylim=c(.1, 1))
```

```
# Same but use multiple figures and use 1 - S(t) scale
survReport(Surv(t1, e1) + Surv(t2, e2) ~ treat, data=
      dat,
           multi=TRUE, subpanel='multi', append=TRUE,
                ps=9, what='1-S',
```

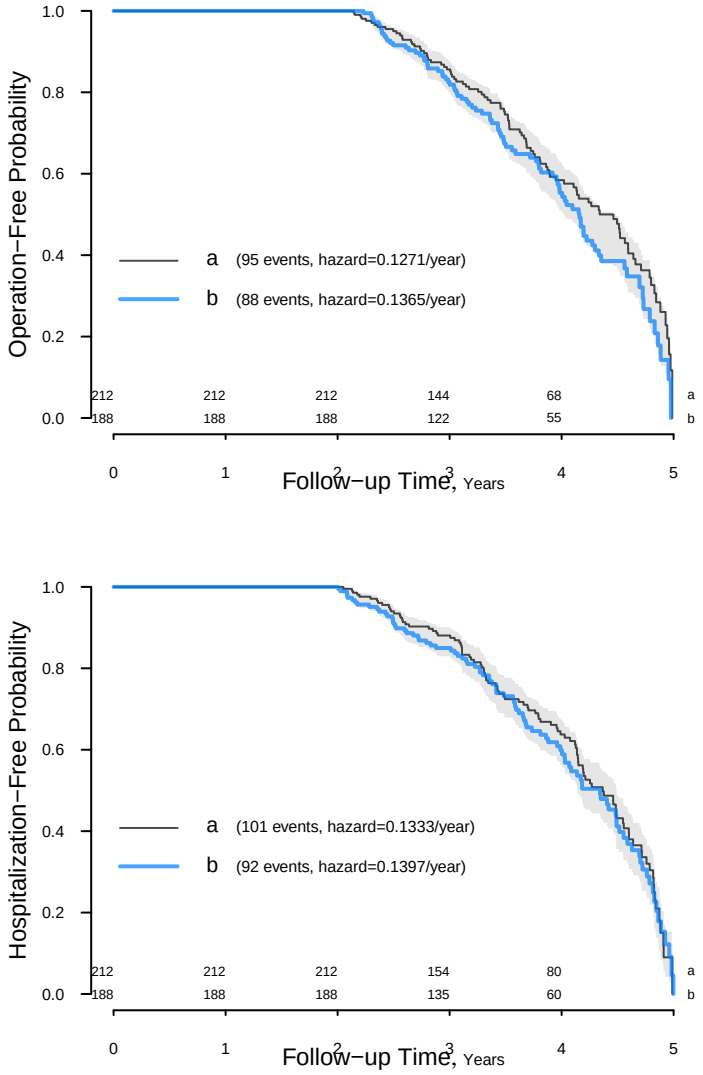

Figure 26: Kaplan-Meier estimates for operation and hospitalization stratified by treatment, along with half-height of 0.95 confidence limits centered at estimate midpoints. N=400.

```
        times=3:4, aehaz=FALSE, y.n.risk=-.02)
```

No empty area large enough for automatic key positioning. Specify keyloc or cex. Width and height of key as computed by key(), in data units: 4.7633276 0.3392002 No empty area large enough for automatic key positioning. Specify

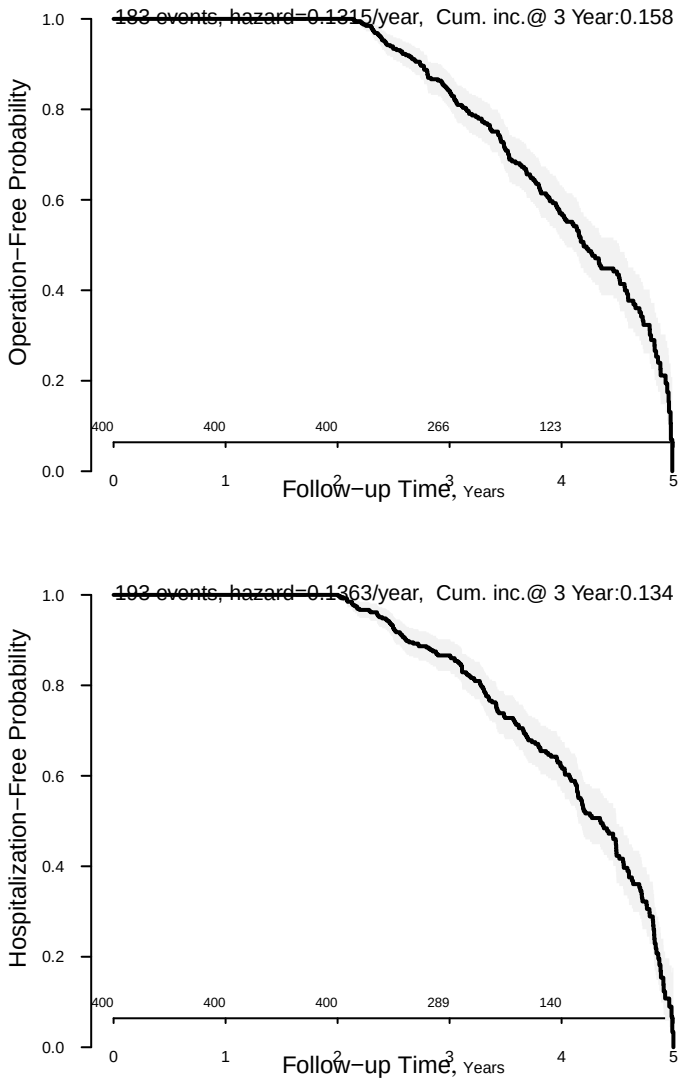

Figure 27: Kaplan-Meier estimates for operation and hospitalization, along with 0.95 confidence bands. N=400.

keyloc or cex. Width and height of key as computed by key(), in data units: 4.8496034 0.3472858

```
survReport(Surv(t1, e1) + Surv(t2, e2) ~ 1, data=dat,
           multi=TRUE, subpanel='multinostrat', append
                =TRUE, ps=9, what='1-S',
           y.n.risk=-.02)
```

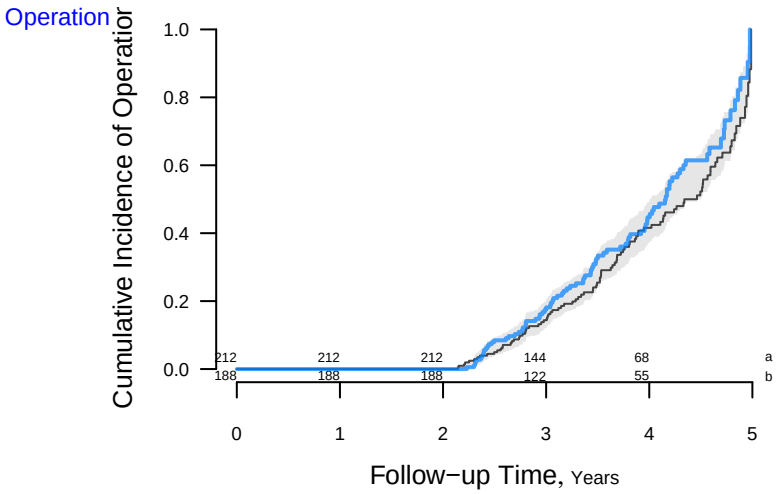

Figure 28: Kaplan-Meier cumulative incidence estimates for operation stratified by treatment, along with half-height of 0.95 confidence limits centered at estimate midpoints. N=400.

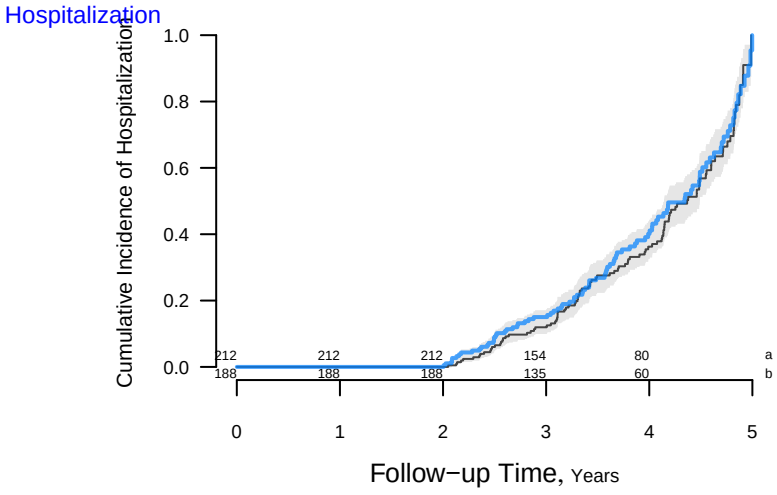

Figure 29: Kaplan-Meier cumulative incidence estimates for hospitalization stratified by treatment, along with half-height of 0.95 confidence limits centered at estimate midpoints. N=400.

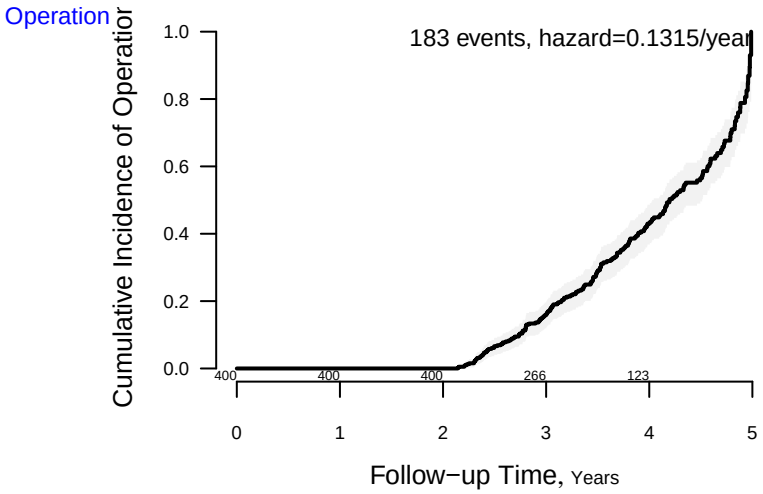

Figure 30: Kaplan-Meier cumulative incidence estimates for operation, along with 0.95 confidence bands. N=400.

```
# Competing risk analysis
if(FALSE) survReport(Surv(t1, cr1) + Surv(t2, cr2) ~
     treat, data=dat,
           cause=list(c('cancer', 'heart'), 'diabetic'
                ),
           subpanel='cr', append=TRUE, w=4.75, h=6, ps
                =8, multi=TRUE)
```

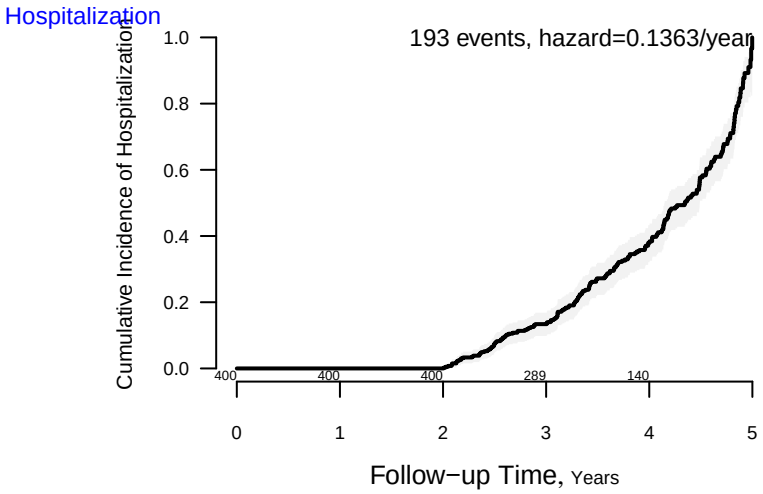

Figure 31: Kaplan-Meier cumulative incidence estimates for hospitalization, along with 0.95 confidence bands. N=400.

7 Adverse Events

For this example, the denominators for the two treatments in the pop-up needles will be incorrect because the dataset did not have subject IDs.

```
# Original source of aeanonym: HH package
# aeanonym <- read.table(hh("datasets/aedotplot.dat"),
      header=TRUE, sep=",")
# Modified to remove denominators from data and to
      generate raw data
# (one record per event per subject)

ae <-
structure(list(RAND = structure(c(1L, 2L, 1L, 2L, 1L,
     2L, 1L,
2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L
     , 2L, 1L,
2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L
     , 2L, 1L,
2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L
     , 2L, 1L,
2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L, 1L, 2L), .Label =
     c("a",
"b"), class = "factor"), PREF = structure(c(12L, 12L,
18L, 18L, 26L, 26L, 33L, 33L, 5L, 5L, 27L, 27L, 6L, 6L
     , 15L,
15L, 22L, 22L, 23L, 23L, 31L, 31L, 17L, 17L, 2L, 2L, 3
     L, 3L,
13L, 13L, 25L, 25L, 28L, 28L, 14L, 14L, 4L, 4L, 8L, 8L
     , 19L,
19L, 21L, 21L, 29L, 29L, 10L, 10L, 20L, 20L, 16L, 16L,
      32L, 32L,
11L, 11L, 1L, 1L, 30L, 30L, 24L, 24L, 9L, 9L, 7L, 7L),
  .Label = tolower(c("ABDOMINAL PAIN",
"ANOREXIA", "ARTHRALGIA", "BACK PAIN", "BRONCHITIS", "
     CHEST PAIN",
"CHRONIC OBSTRUCTIVE AIRWAY", "COUGHING", "DIARRHEA",
     "DIZZINESS",
"DYSPEPSIA", "DYSPNEA", "FATIGUE", "FLATULENCE", "
     GASTROESOPHAGEAL REFLUX",
"HEADACHE", "HEMATURIA", "HYPERKALEMIA", "INFECTION
     VIRAL", "INJURY",
"INSOMNIA", "MELENA", "MYALGIA", "NAUSEA", "PAIN", "
     RASH", "RESPIRATORY DISORDER",
"RHINITIS", "SINUSITIS", "UPPER RESP TRACT INFECTION",
      "URINARY TRACT INFECTION",
```

```
"VOMITING", "WEIGHT DECREASE")), class = "factor"),
      SAE = c(15L,
9L, 4L, 9L, 4L, 9L, 2L, 9L, 8L, 11L, 4L, 11L, 9L, 12L,
       5L, 12L,
7L, 12L, 6L, 12L, 6L, 12L, 2L, 14L, 2L, 15L, 1L, 15L,
      4L, 16L,
4L, 17L, 11L, 17L, 6L, 20L, 10L, 23L, 13L, 26L, 12L,
      26L, 4L,
26L, 13L, 28L, 9L, 29L, 12L, 30L, 14L, 36L, 6L, 37L, 8
      L, 42L,
20L, 61L, 33L, 68L, 10L, 82L, 23L, 90L, 76L, 95L)),
      .Names = c("RAND",
"PREF", "SAE"), class = "data.frame", row.names = c(NA
      ,
-66L))

subs ← rep(1 : nrow(ae), ae$SAE)
ae ← ae[subs, c('RAND', 'PREF')]
names(ae) ← c('treat', 'event')
label(ae$treat) ← 'Treatment'

eReport(event ∼ treat, data=ae, minincidence=.05,
      panel='aevents')
```

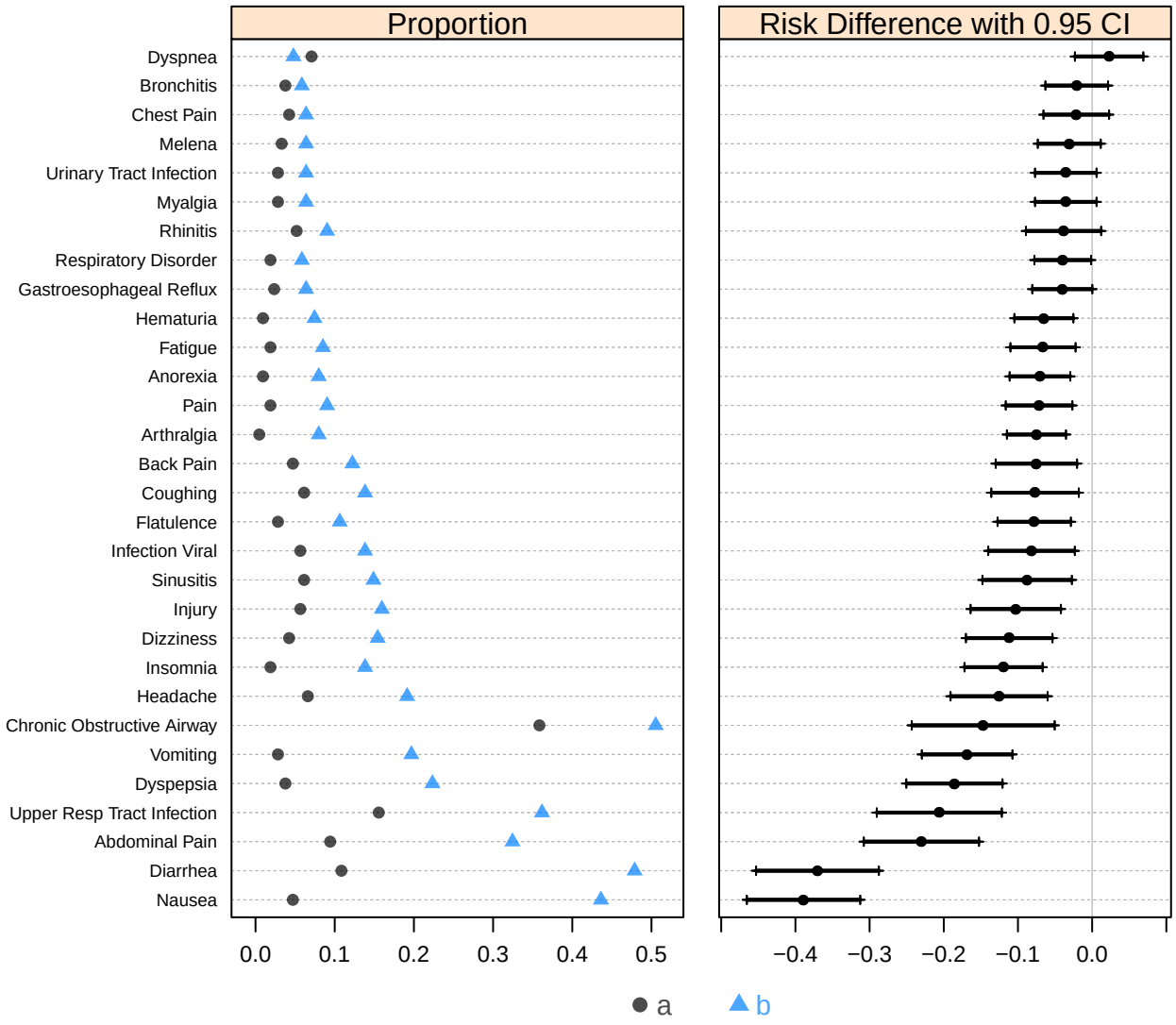

Figure 32: Proportion of adverse events and risk differences by Treatment sorted by risk difference. 3 events with less than 0.05 incidence in at least one group are not shown. (Table 18)

8 Appendix: Supporting Tables

Table 6: Days from enrollment to randomization. *a b c* represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. (Figure 3).

	Europe	North America
	$N = 145$	$N = 115$
Days	8.0 **14.0** 22.0 (14.5 ± 8.4)	8.0 **16.0** 22.0 (15.6 ± 8.0)

Table 7: Subject IDs for randomized subjects with exclusions

←

Prior MI:
90, 130, 212, 253, 277, 324, 445, 451

History of Asthma:
20, 65, 71, 124, 125, 130, 465

History of Upper GI Bleeding:
67, 205, 310, 313, 333, 452, 465

No Significant CAD:
9, 10, 13, 25, 30, 40, 42, 56, 70, 115, 116, 121, 125, 146, 148, 178, 182, 187, 229, 230, 252, 258, 281, 285, 292, 294, 300, 324, 333, 347, 362, 364, 374, 380, 388, 405, 441, 454, 458, 474, 485

Inadequate Renal Function:
27, 40, 49, 73, 91, 157, 186, 197, 229, 237, 245, 295, 298, 325, 487

Pneumonia within 6 Weeks:
32, 169, 233, 238, 316, 450, 476

Prior Cardiac Surgery:
174, 194, 347, 380, 391, 392, 480, 485

subjid	loc
9	gastric
10	gastric
13	trachea
20	lung
25	trachea
27	gastric
30	lung
32	trachea
40	trachea
42	lung
49	gastric

Table 8: (Figure 11).

Race		
	Asian	0.290 $\frac{29}{100}$
	Black/AA	0.320 $\frac{32}{100}$
	White	0.390 $\frac{39}{100}$
Sex		
	Female	0.470 $\frac{47}{100}$
Exclusions		
	AKI	0.380 $\frac{38}{100}$
	Migraines	0.430 $\frac{43}{100}$
	Pregnant	0.470 $\frac{47}{100}$
	MI	0.480 $\frac{48}{100}$
	MD withdrawal	0.506 $\frac{45}{89}$
	Stroke	0.540 $\frac{54}{100}$
	Other event	0.560 $\frac{56}{100}$

Table 9: Proportions for race and sex stratified by region (Figure 12).

		Europe	North America	All
Race				
	Asian	0.278 $\frac{15}{54}$	0.304 $\frac{14}{46}$	0.290 $\frac{29}{100}$
	Black/AA	0.296 $\frac{16}{54}$	0.348 $\frac{16}{46}$	0.320 $\frac{32}{100}$
	White	0.426 $\frac{23}{54}$	0.348 $\frac{16}{46}$	0.390 $\frac{39}{100}$
Sex				
	Female	0.500 $\frac{27}{54}$	0.435 $\frac{20}{46}$	0.470 $\frac{47}{100}$

Table 10: Proportions for race, sex, and race: males stratified by region (Figure 13).

		Europe	North America
Race			
	Asian	0.278 $\frac{15}{54}$	0.304 $\frac{14}{46}$
	Black/AA	0.296 $\frac{16}{54}$	0.348 $\frac{16}{46}$
	White	0.426 $\frac{23}{54}$	0.348 $\frac{16}{46}$
Sex			
	Female	0.500 $\frac{27}{54}$	0.435 $\frac{20}{46}$
Race: Males			
	Asian	0.259 $\frac{7}{27}$	0.231 $\frac{6}{26}$
	Black/AA	0.296 $\frac{8}{27}$	0.346 $\frac{9}{26}$
	White	0.444 $\frac{12}{27}$	0.423 $\frac{11}{26}$

Table 11: (Figure 14).

Exclusions		
	AKI	0.380 $\frac{38}{100}$
	Migraines	0.430 $\frac{43}{100}$
	Pregnant	0.470 $\frac{47}{100}$
	MI	0.480 $\frac{48}{100}$
	MD withdrawal	0.506 $\frac{45}{89}$
	Stroke	0.540 $\frac{54}{100}$
	Other event	0.560 $\frac{56}{100}$

Table 12: Proportions for race, sex, and exclusions stratified by treatment and region (Figure 15).

Europe

		A	B
Race			
	Asian	0.242 $\frac{8}{33}$	0.333 $\frac{7}{21}$
	Black/AA	0.242 $\frac{8}{33}$	0.381 $\frac{8}{21}$
	White	0.515 $\frac{17}{33}$	0.286 $\frac{6}{21}$
Sex			
	Female	0.485 $\frac{16}{33}$	0.524 $\frac{11}{21}$
Exclusions			
	AKI	0.364 $\frac{12}{33}$	0.571 $\frac{12}{21}$
	Migraines	0.364 $\frac{12}{33}$	0.524 $\frac{11}{21}$
	Pregnant	0.455 $\frac{15}{33}$	0.476 $\frac{10}{21}$
	MI	0.697 $\frac{23}{33}$	0.524 $\frac{11}{21}$
	MD withdrawal	0.567 $\frac{17}{30}$	0.333 $\frac{6}{18}$
	Stroke	0.455 $\frac{15}{33}$	0.619 $\frac{13}{21}$
	Other event	0.576 $\frac{19}{33}$	0.571 $\frac{12}{21}$

North America

		A	B
Race			
	Asian	0.333 $\frac{8}{24}$	0.273 $\frac{6}{22}$
	Black/AA	0.333 $\frac{8}{24}$	0.364 $\frac{8}{22}$
	White	0.333 $\frac{8}{24}$	0.364 $\frac{8}{22}$
Sex			
	Female	0.458 $\frac{11}{24}$	0.409 $\frac{9}{22}$
Exclusions			
	AKI	0.417 $\frac{10}{24}$	0.182 $\frac{4}{22}$
	Migraines	0.458 $\frac{11}{24}$	0.409 $\frac{9}{22}$
	Pregnant	0.417 $\frac{10}{24}$	0.545 $\frac{12}{22}$
	MI	0.333 $\frac{8}{24}$	0.273 $\frac{6}{22}$
	MD withdrawal	0.381 $\frac{8}{21}$	0.700 $\frac{14}{20}$
	Stroke	0.625 $\frac{15}{24}$	0.500 $\frac{11}{22}$
	Other event	0.458 $\frac{11}{24}$	0.636 $\frac{14}{22}$

Table 13: Proportions for race, sex, and exclusions stratified by treatment and region (Figure 16).

Europe

		A	B
Race			
	Asian	0.242 $\frac{8}{33}$	0.333 $\frac{7}{21}$
	Black/AA	0.242 $\frac{8}{33}$	0.381 $\frac{8}{21}$
	White	0.515 $\frac{17}{33}$	0.286 $\frac{6}{21}$
Sex			
	Female	0.485 $\frac{16}{33}$	0.524 $\frac{11}{21}$
Exclusions			
	AKI	0.364 $\frac{12}{33}$	0.571 $\frac{12}{21}$
	Migraines	0.364 $\frac{12}{33}$	0.524 $\frac{11}{21}$
	Pregnant	0.455 $\frac{15}{33}$	0.476 $\frac{10}{21}$
	MI	0.697 $\frac{23}{33}$	0.524 $\frac{11}{21}$
	MD withdrawal	0.567 $\frac{17}{30}$	0.333 $\frac{6}{18}$
	Stroke	0.455 $\frac{15}{33}$	0.619 $\frac{13}{21}$
	Other event	0.576 $\frac{19}{33}$	0.571 $\frac{12}{21}$

North America

		A	B
Race			
	Asian	0.333 $\frac{8}{24}$	0.273 $\frac{6}{22}$
	Black/AA	0.333 $\frac{8}{24}$	0.364 $\frac{8}{22}$
	White	0.333 $\frac{8}{24}$	0.364 $\frac{8}{22}$
Sex			
	Female	0.458 $\frac{11}{24}$	0.409 $\frac{9}{22}$
Exclusions			
	AKI	0.417 $\frac{10}{24}$	0.182 $\frac{4}{22}$
	Migraines	0.458 $\frac{11}{24}$	0.409 $\frac{9}{22}$
	Pregnant	0.417 $\frac{10}{24}$	0.545 $\frac{12}{22}$
	MI	0.333 $\frac{8}{24}$	0.273 $\frac{6}{22}$
	MD withdrawal	0.381 $\frac{8}{21}$	0.700 $\frac{14}{20}$
	Stroke	0.625 $\frac{15}{24}$	0.500 $\frac{11}{22}$
	Other event	0.458 $\frac{11}{24}$	0.636 $\frac{14}{22}$

Table 14: Statistics for age, systolic BP, and dbp stratified by region. $_a\ b\ _c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. (Figure 17).

	Europe $N = 54$	North America $N = 46$
age	43.5 **49.7** 57.9 (50.8 ±11.3)	41.5 **46.4** 55.6 (48.2 ±12.1)
Systolic BP mmHg	116.4 **120.6** 125.6 (120.1 ± 6.8)	114.6 **119.0** 123.4 (119.2 ± 6.8)
dbp	74.0 **78.5** 83.1 (78.8 ± 6.8)	74.1 **78.5** 83.4 (78.8 ± 6.1)

Table 15: Statistics for age, systolic BP, and dbp stratified by treatment and region. $_a$ b $_c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. (Figure 18).

Europe

	A	B
	$N = 33$	$N = 21$
age	41.1 **47.5** 54.4 (47.9 ± 9.4)	45.7 **55.1** 64.4 (55.3 ±12.9)
Systolic BP mmHg	117.0 **121.2** 126.3 (121.1 ± 6.8)	115.6 **118.3** 123.4 (118.6 ± 6.7)
dbp	73.4 **77.7** 83.1 (78.2 ± 7.5)	78.0 **80.0** 83.2 (79.7 ± 5.6)

North America

	A	B
	$N = 24$	$N = 22$
age	38.4 **46.2** 53.2 (46.0 ±12.4)	43.2 **50.2** 58.8 (50.7 ±11.5)
Systolic BP mmHg	115.0 **119.6** 123.5 (119.6 ± 7.3)	114.0 **118.7** 123.3 (118.8 ± 6.4)
dbp	72.8 **78.3** 82.3 (77.6 ± 5.9)	75.5 **79.0** 84.0 (80.1 ± 6.3)

Table 16: Statistics for age, systolic BP, and dbp stratified by treatment and region. $_a$ b $_c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. (Figure 19).

Europe

	A	B
	$N = 33$	$N = 21$
age	41.1 **47.5** 54.4 (47.9 ± 9.4)	45.7 **55.1** 64.4 (55.3 ±12.9)
Systolic BP mmHg	117.0 **121.2** 126.3 (121.1 ± 6.8)	115.6 **118.3** 123.4 (118.6 ± 6.7)
dbp	73.4 **77.7** 83.1 (78.2 ± 7.5)	78.0 **80.0** 83.2 (79.7 ± 5.6)

North America

	A	B
	$N = 24$	$N = 22$
age	38.4 **46.2** 53.2 (46.0 ±12.4)	43.2 **50.2** 58.8 (50.7 ±11.5)
Systolic BP mmHg	115.0 **119.6** 123.5 (119.6 ± 7.3)	114.0 **118.7** 123.3 (118.8 ± 6.4)
dbp	72.8 **78.3** 82.3 (77.6 ± 5.9)	75.5 **79.0** 84.0 (80.1 ± 6.3)

All

	A	B
	$N = 57$	$N = 43$
age	39.6 **46.2** 53.6 (47.1 ±10.7)	44.0 **51.1** 61.3 (52.9 ±12.2)
Systolic BP mmHg	116.5 **120.1** 125.9 (120.4 ± 6.9)	114.6 **118.4** 123.4 (118.7 ± 6.5)
dbp	73.2 **78.1** 83.1 (78.0 ± 6.8)	75.6 **79.5** 83.8 (79.9 ± 5.9)

Table 17: Statistics stratified by treatment and region. $_a$ b $_c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. (Figure 21).

Europe

	A	B
	$N = 33$	$N = 21$
Systolic BP mmHg	117.0 **121.2** 126.3 (121.1 ± 6.8)	115.6 **118.3** 123.4 (118.6 ± 6.7)

North America

	A	B
	$N = 24$	$N = 22$
Systolic BP mmHg	115.0 **119.6** 123.5 (119.6 ± 7.3)	114.0 **118.7** 123.3 (118.8 ± 6.4)

Table 18: Proportion of adverse events and risk differences by Treatment (Figure 32).

Event	a	b	Difference	Lower	Upper
Abdominal Pain	0.094	0.324	-0.230	-0.308	-0.152
Anorexia	0.009	0.080	-0.070	-0.111	-0.029
Arthralgia	0.005	0.080	-0.075	-0.115	-0.035
Back Pain	0.047	0.122	-0.075	-0.130	-0.020
Bronchitis	0.038	0.059	-0.021	-0.063	0.021
Chest Pain	0.042	0.064	-0.021	-0.066	0.023
Chronic Obstructive Airway	0.358	0.505	-0.147	-0.243	-0.051
Coughing	0.061	0.138	-0.077	-0.136	-0.018
Diarrhea	0.108	0.479	-0.370	-0.453	-0.287
Dizziness	0.042	0.154	-0.112	-0.170	-0.053
Dyspepsia	0.038	0.223	-0.186	-0.250	-0.121
Dyspnea	0.071	0.048	0.023	-0.023	0.069
Fatigue	0.019	0.085	-0.066	-0.110	-0.022
Flatulence	0.028	0.106	-0.078	-0.127	-0.029
Gastroesophageal Reflux	0.024	0.064	-0.040	-0.081	0.000
Headache	0.066	0.191	-0.125	-0.191	-0.060
Hematuria	0.009	0.074	-0.065	-0.105	-0.025
Infection Viral	0.057	0.138	-0.082	-0.140	-0.023
Injury	0.057	0.160	-0.103	-0.164	-0.042
Insomnia	0.019	0.138	-0.119	-0.172	-0.067
Melena	0.033	0.064	-0.031	-0.073	0.012
Myalgia	0.028	0.064	-0.036	-0.077	0.006
Nausea	0.047	0.436	-0.389	-0.465	-0.313
Pain	0.019	0.090	-0.072	-0.116	-0.027
Respiratory Disorder	0.019	0.059	-0.040	-0.078	-0.001
Rhinitis	0.052	0.090	-0.039	-0.089	0.012
Sinusitis	0.061	0.149	-0.088	-0.148	-0.027
Upper Resp Tract Infection	0.156	0.362	-0.206	-0.290	-0.122
Urinary Tract Infection	0.028	0.064	-0.036	-0.077	0.006
Vomiting	0.028	0.197	-0.169	-0.230	-0.107