Making the complex obvious

Use graphics! - consider R

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Introduction

”Nocturne of Chopin; it’s so beautiful music. But few people will appreciate the music if I just show them the notes. Most of us need to listen to the music to understand how beautiful it is. But often that’s how we present statistics; we just show the notes, we don’t play the music.”

Hans Rosling: Founder of gapminder. OECD World Forum in Istanbul, June 2007

Understanding your data with graphics

1. Some key technical elements
   - Build a graph in layers
   - Control the positioning of objects
   - Use a plotting matrix for complex graphs
   - Think! What is it that you want to display?

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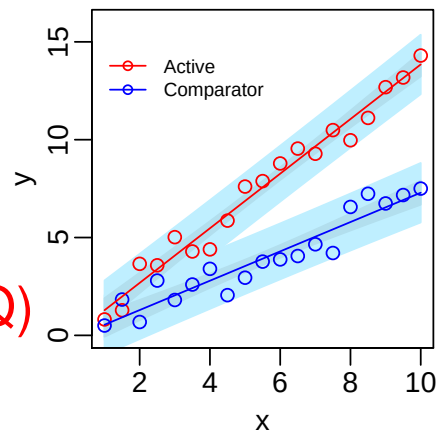
2. Some real world pharma examples
   - Example 1: Change from BL
   - Example 2: Planning a study
   - Example 3: Overview of safety
   - Example 4: Interactions & Outliers (HAQ)



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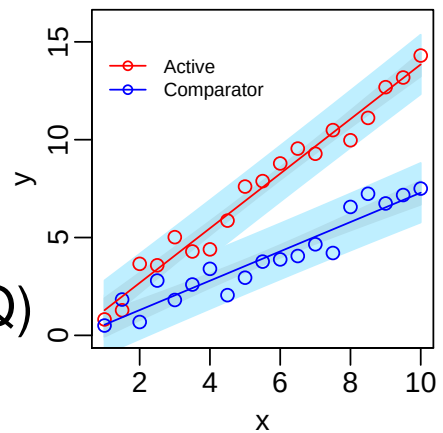
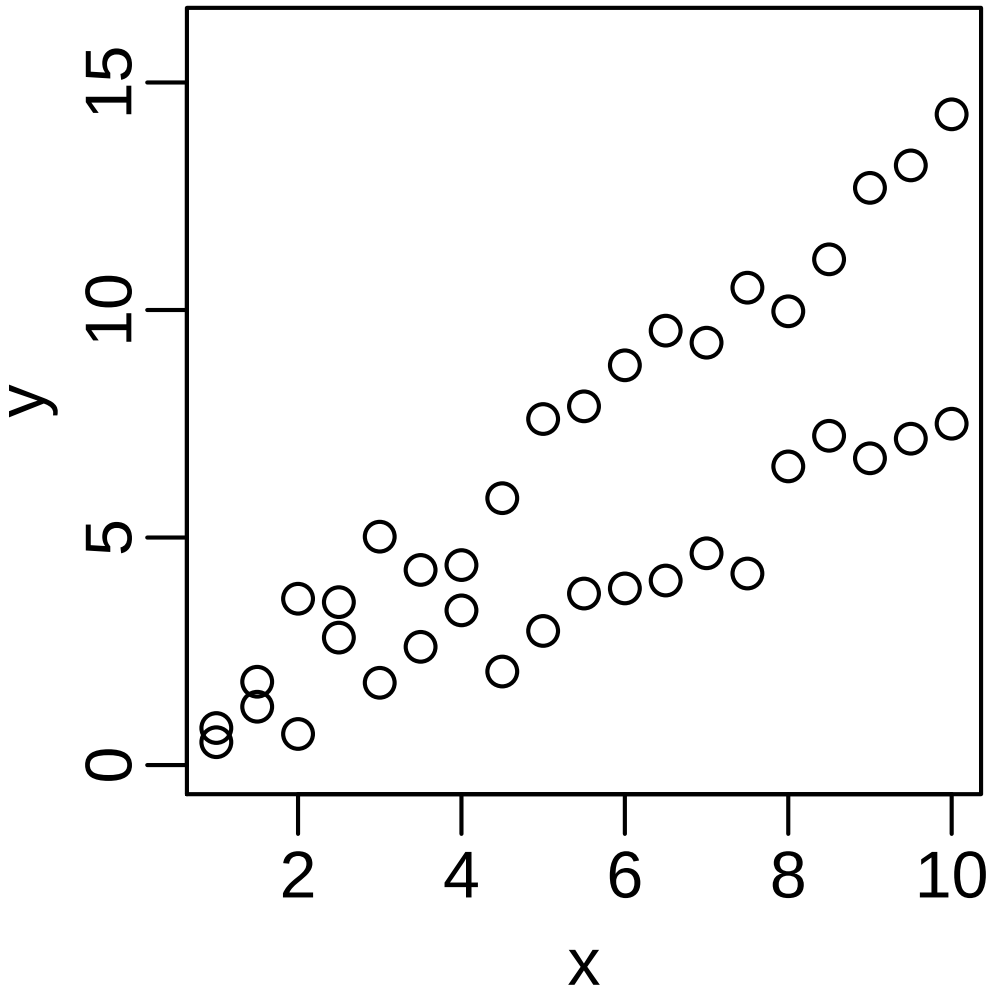


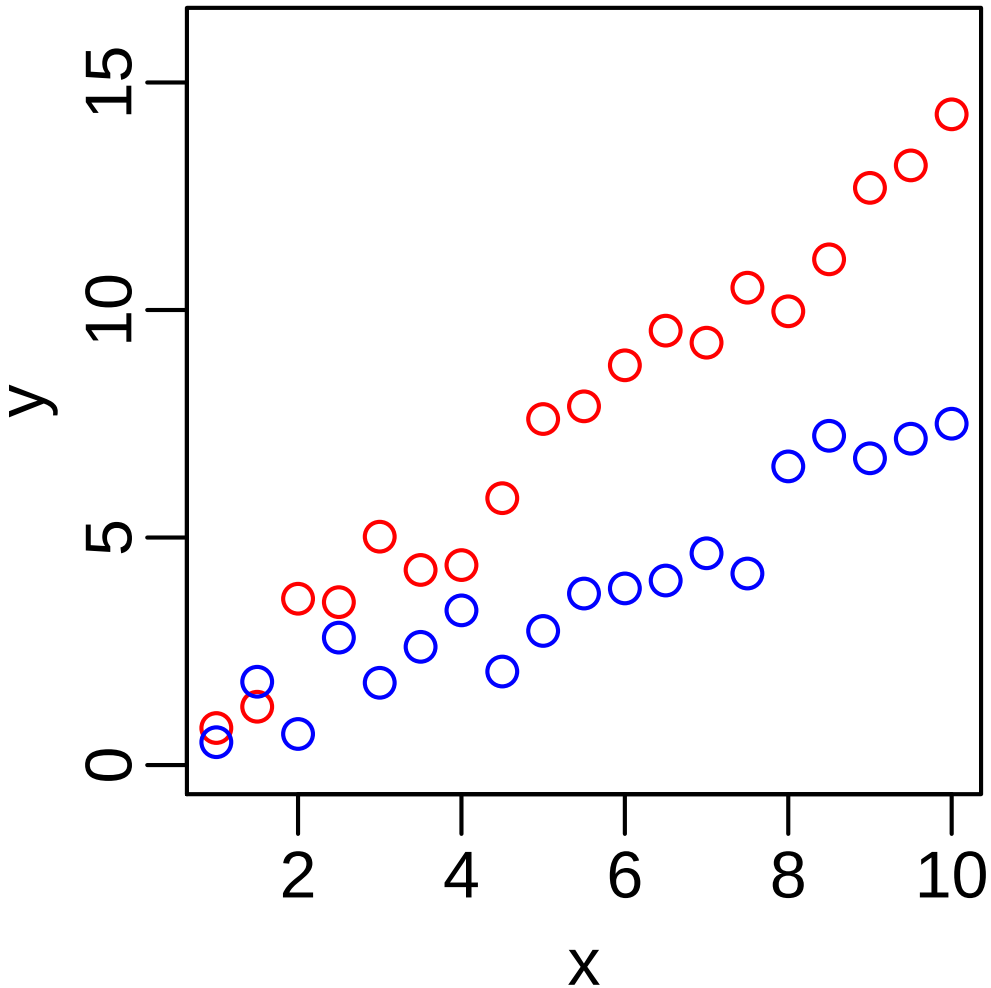
Note:

- Examples are real, data is not.

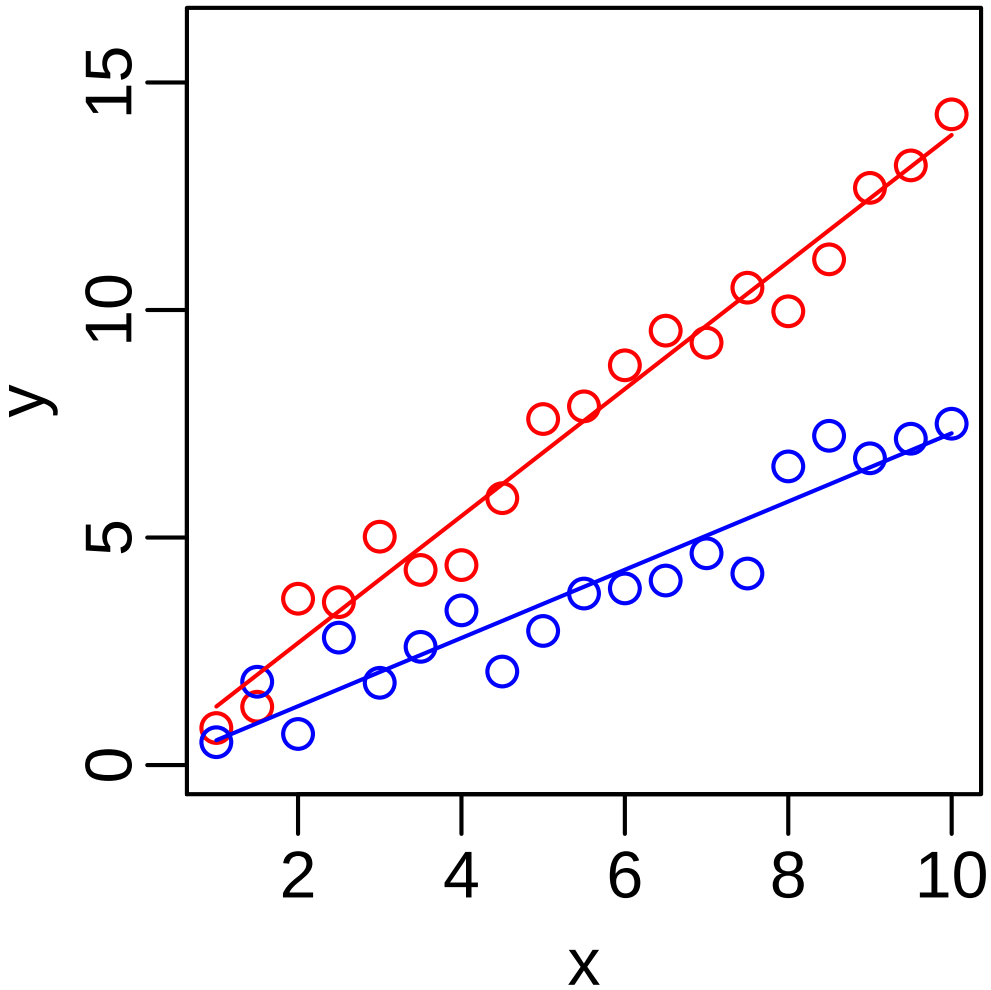
Step 1: Response vs Predictor



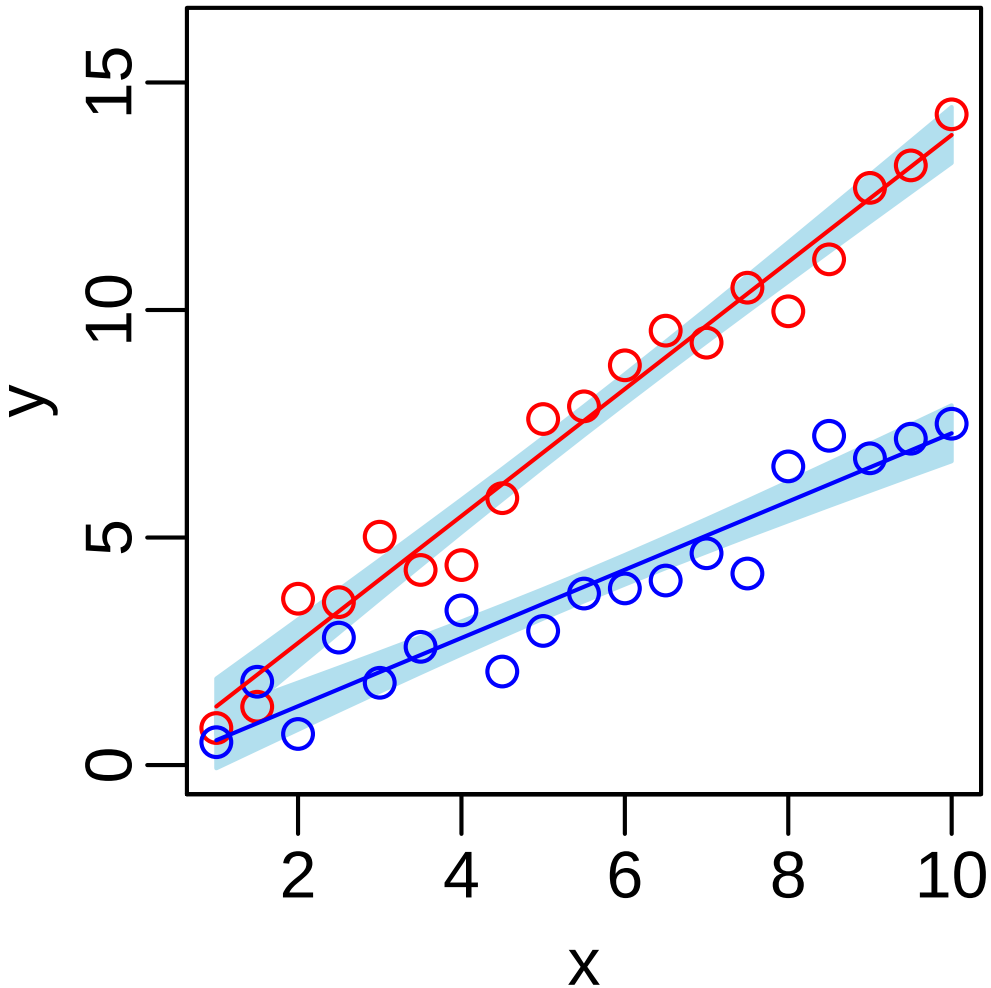
Step 2: Response vs Predictor: add colors



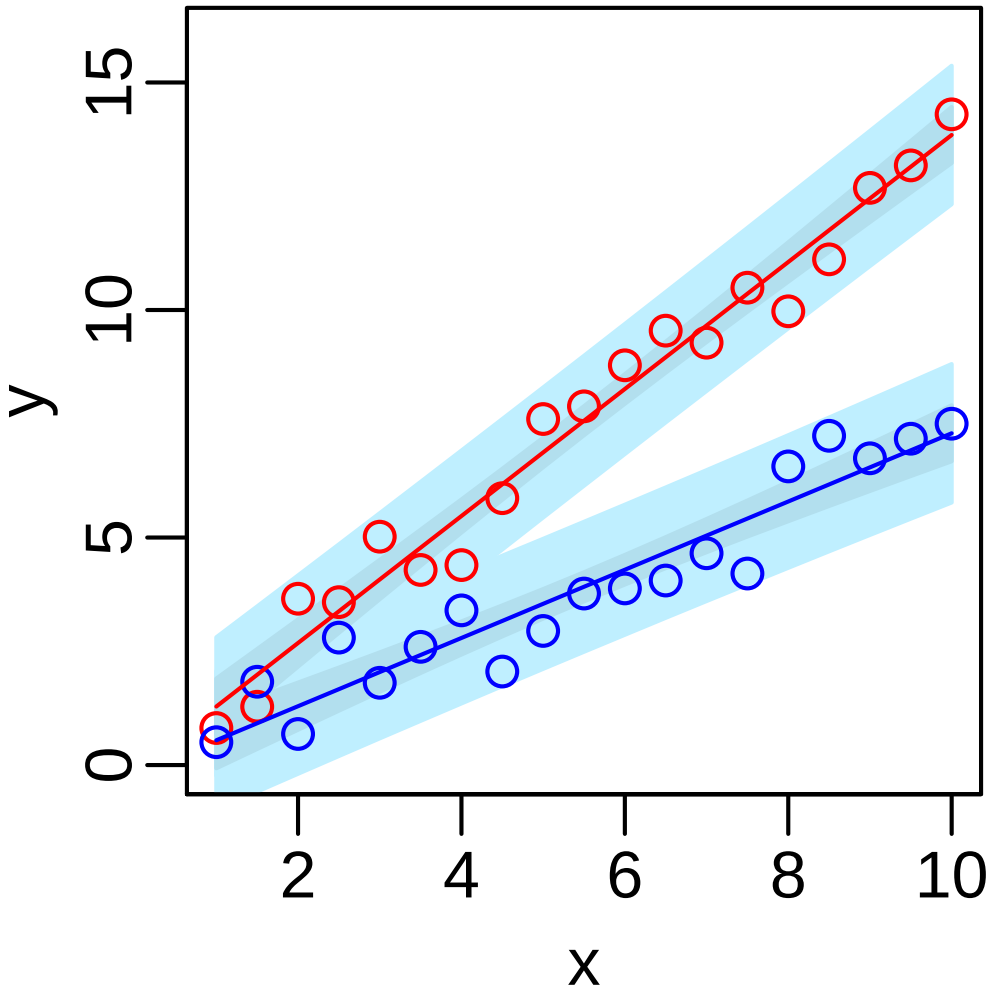
Step 3: Response vs Predictor: add a model fit



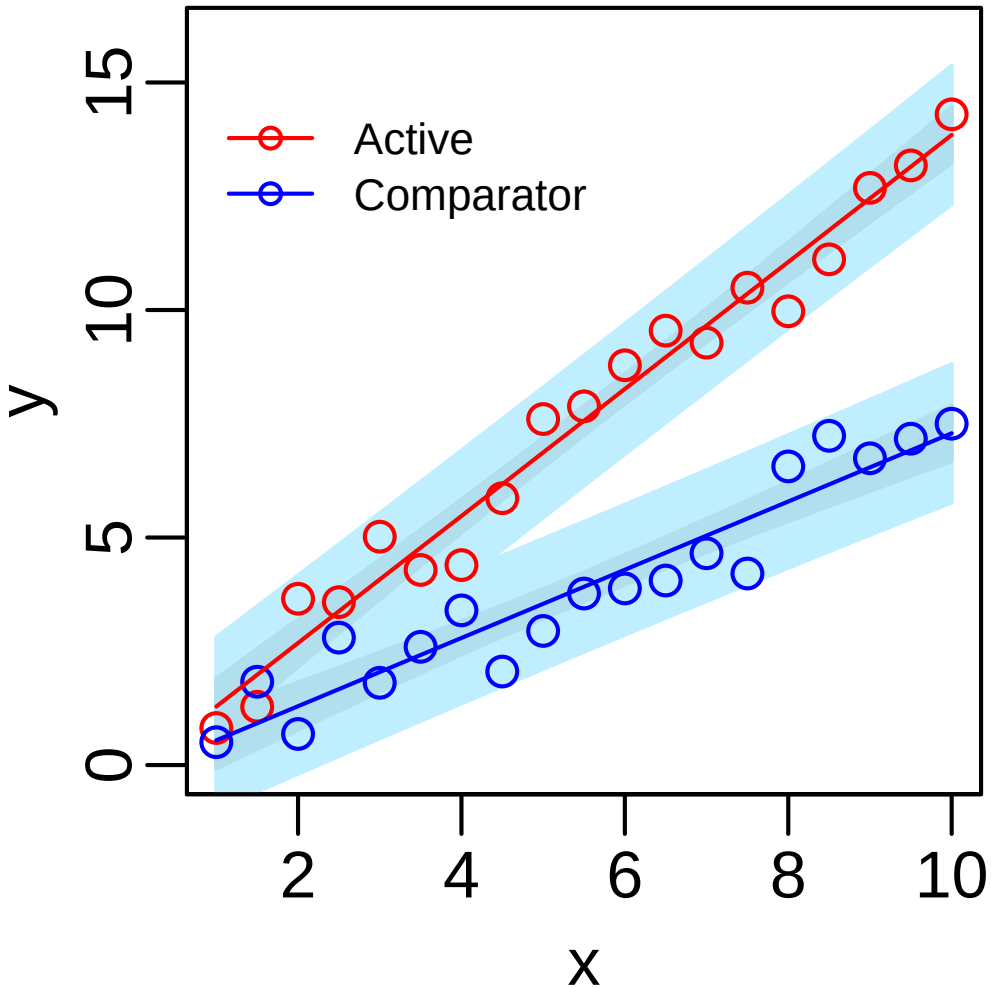
Step 4: Response vs Predictor: add confidence limits



Step 5: Response vs Predictor: add prediction limits

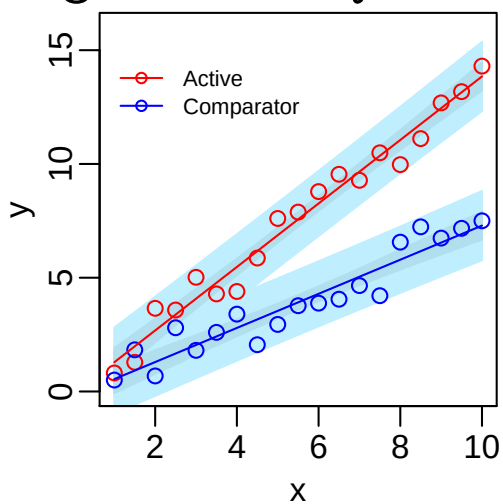


Step 6: Response vs Predictor: add a legend

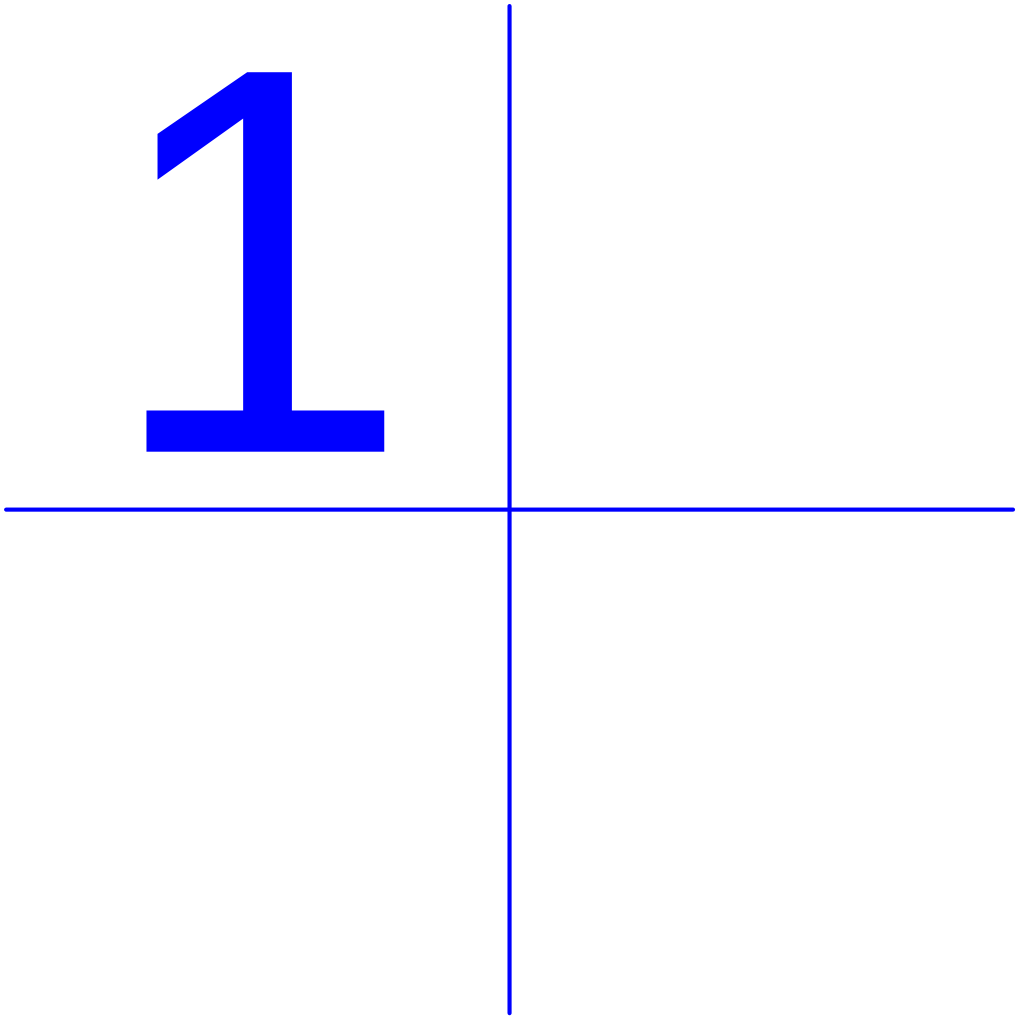


Layer plot

```
plot(....)
polygon(x=poly.x, y=poly.y, col="lightblue1")
points(y x, col="red"))
abline(....)
legend(x=1, y=15, legend=c(Comparator", Active"))
```



Plotting matrix



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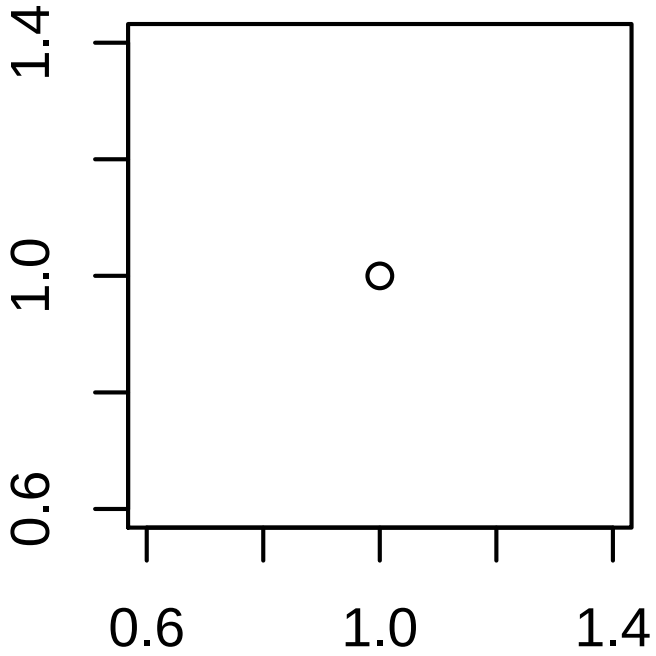

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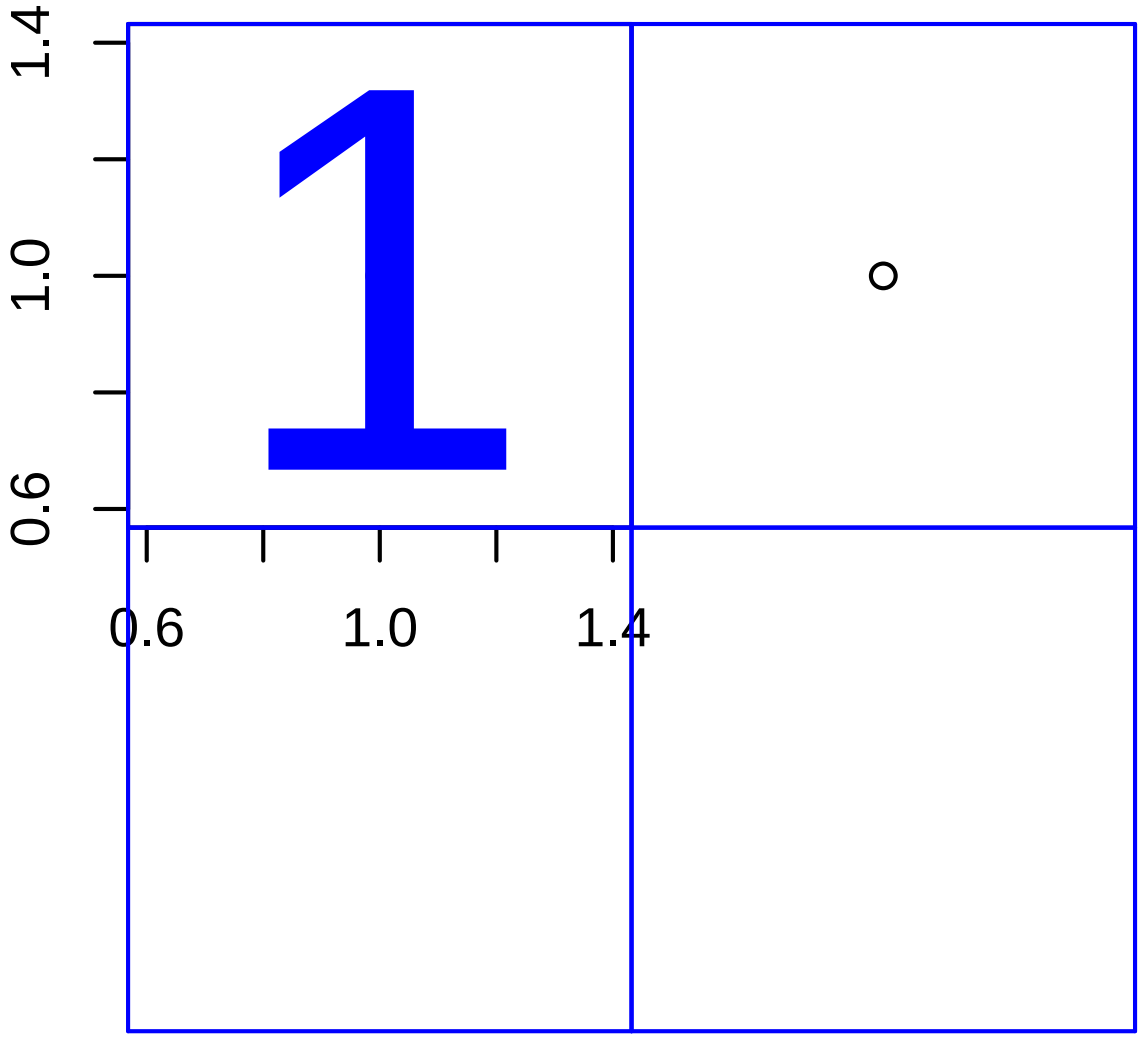
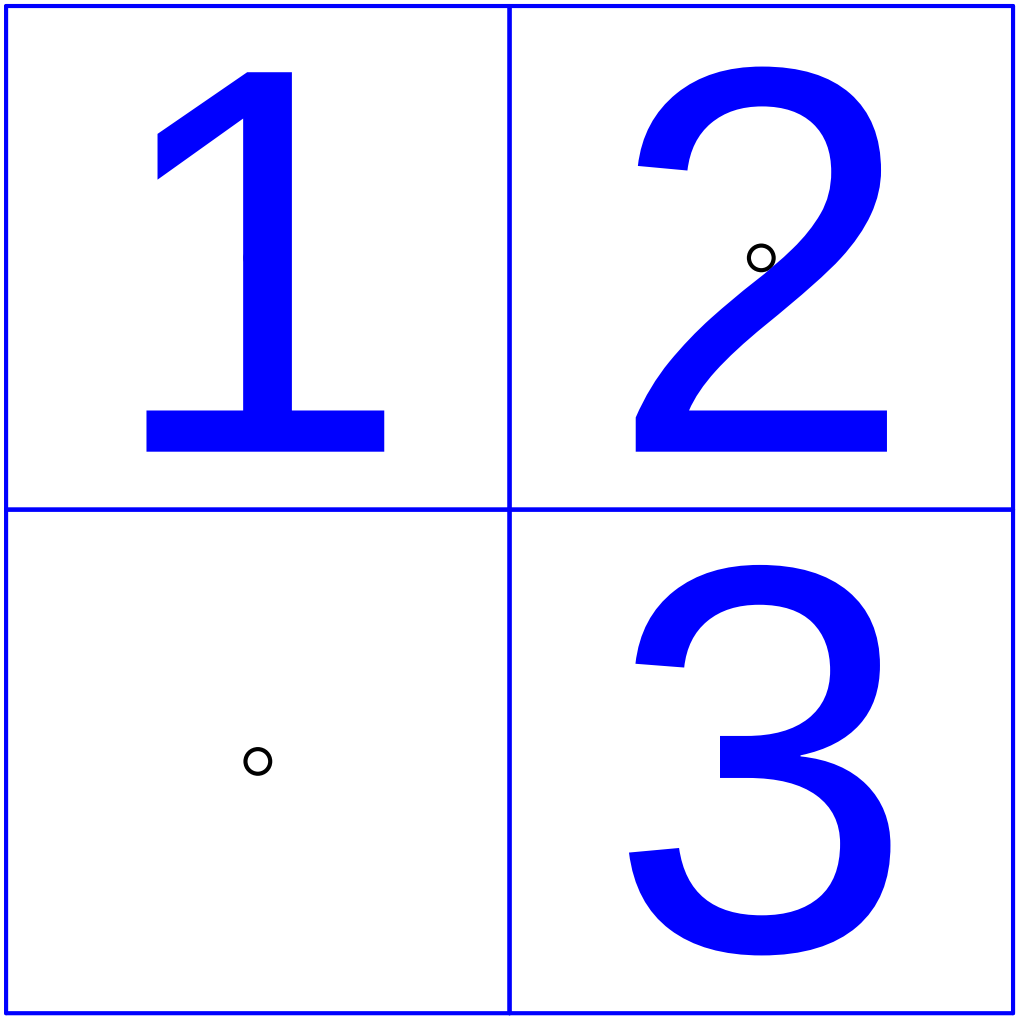
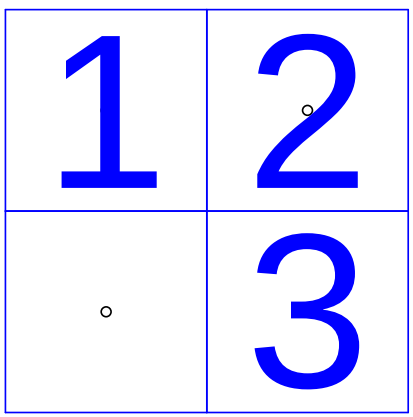


Plotting matrix



Plotting matrix

```
mat <- matrix(c(1,2,4,3), nrow=2, ncol=2, byrow=TRUE)
nf <- layout(mat)
plot(x=1, y=1)
plot(x=1, y=1)
plot(x=1, y=1)
plot(x=1, y=1)
```



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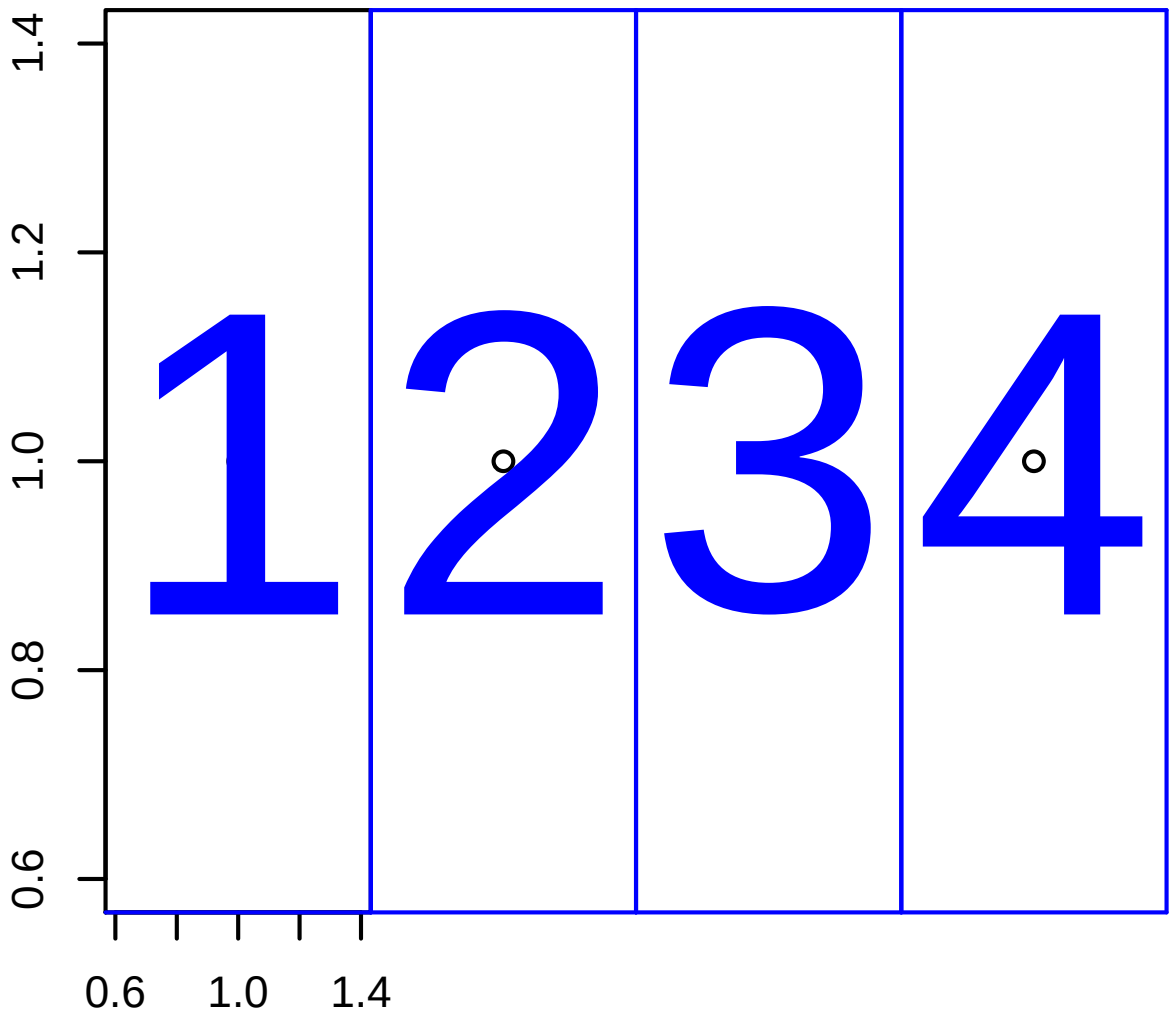

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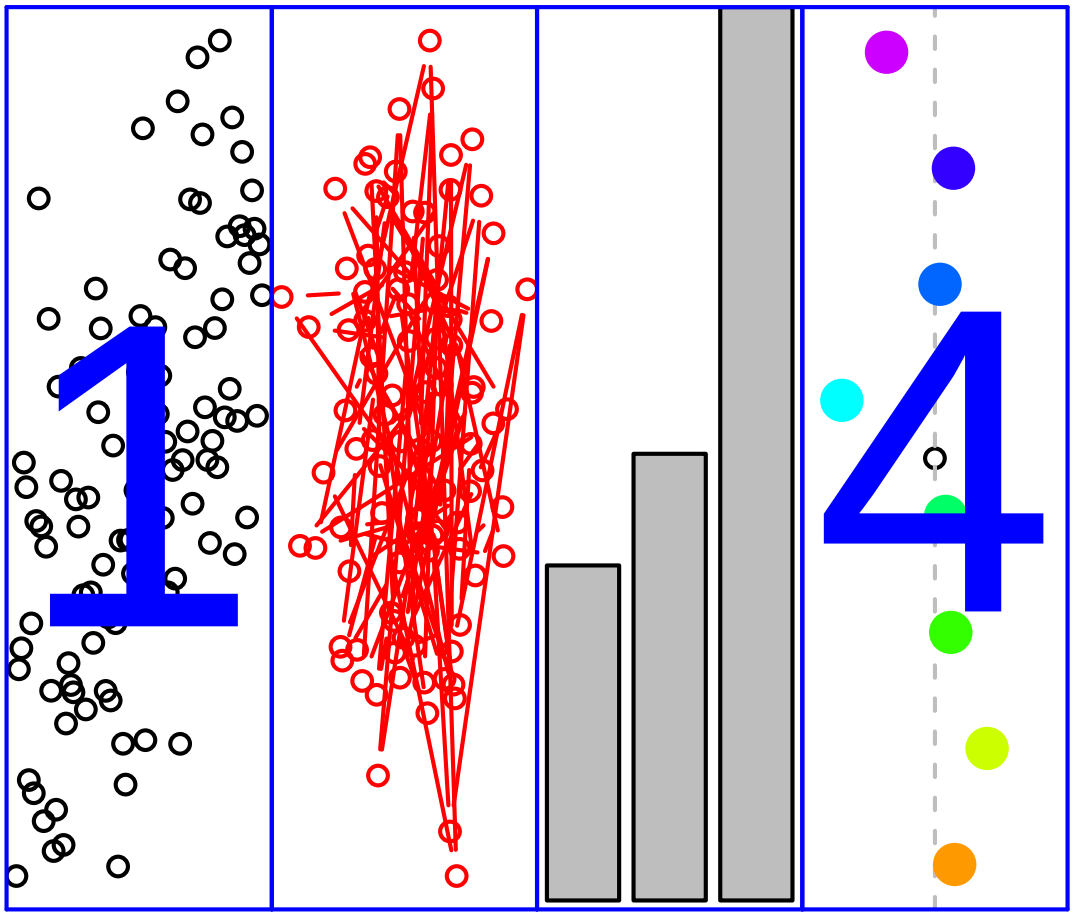
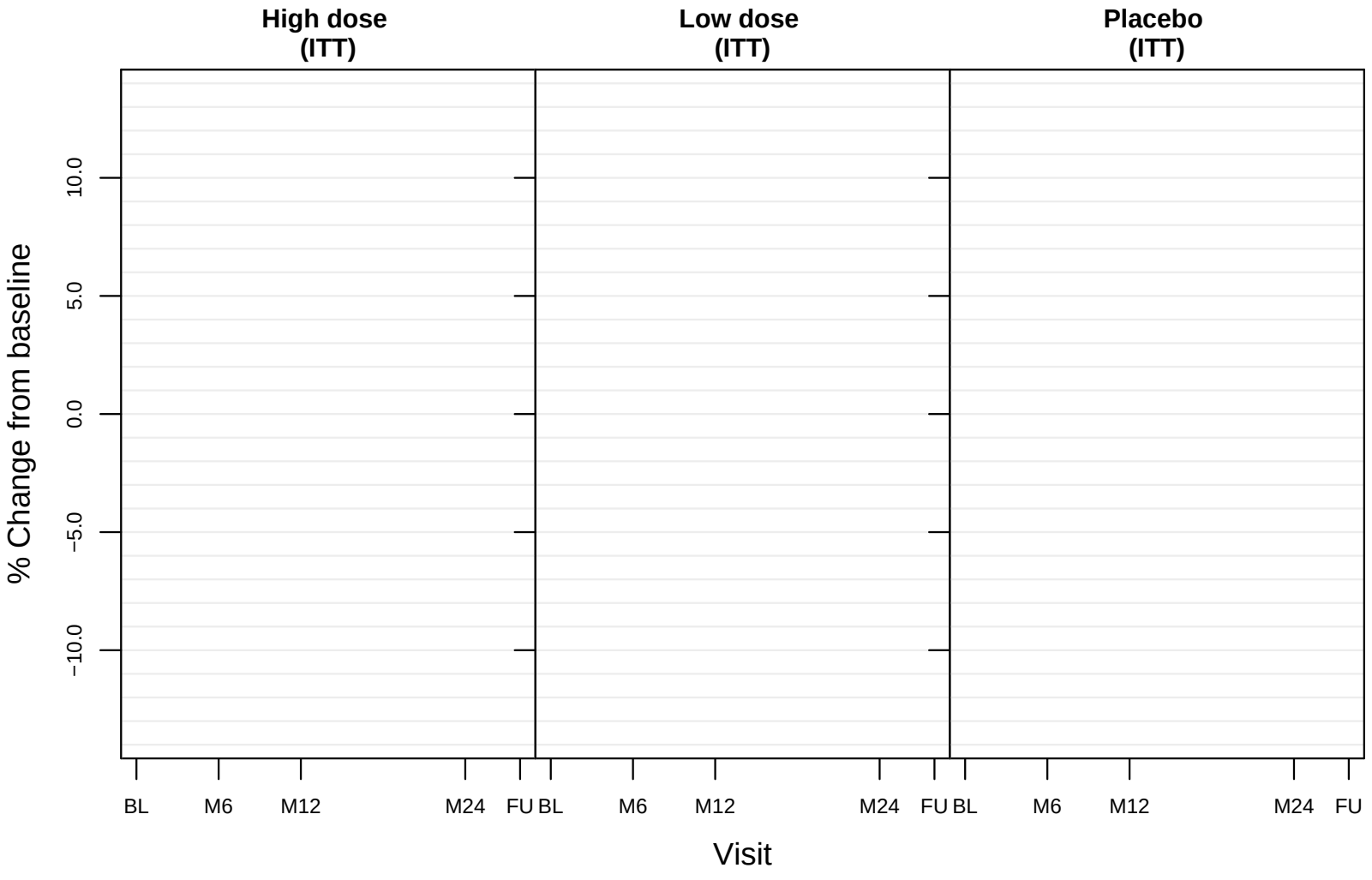
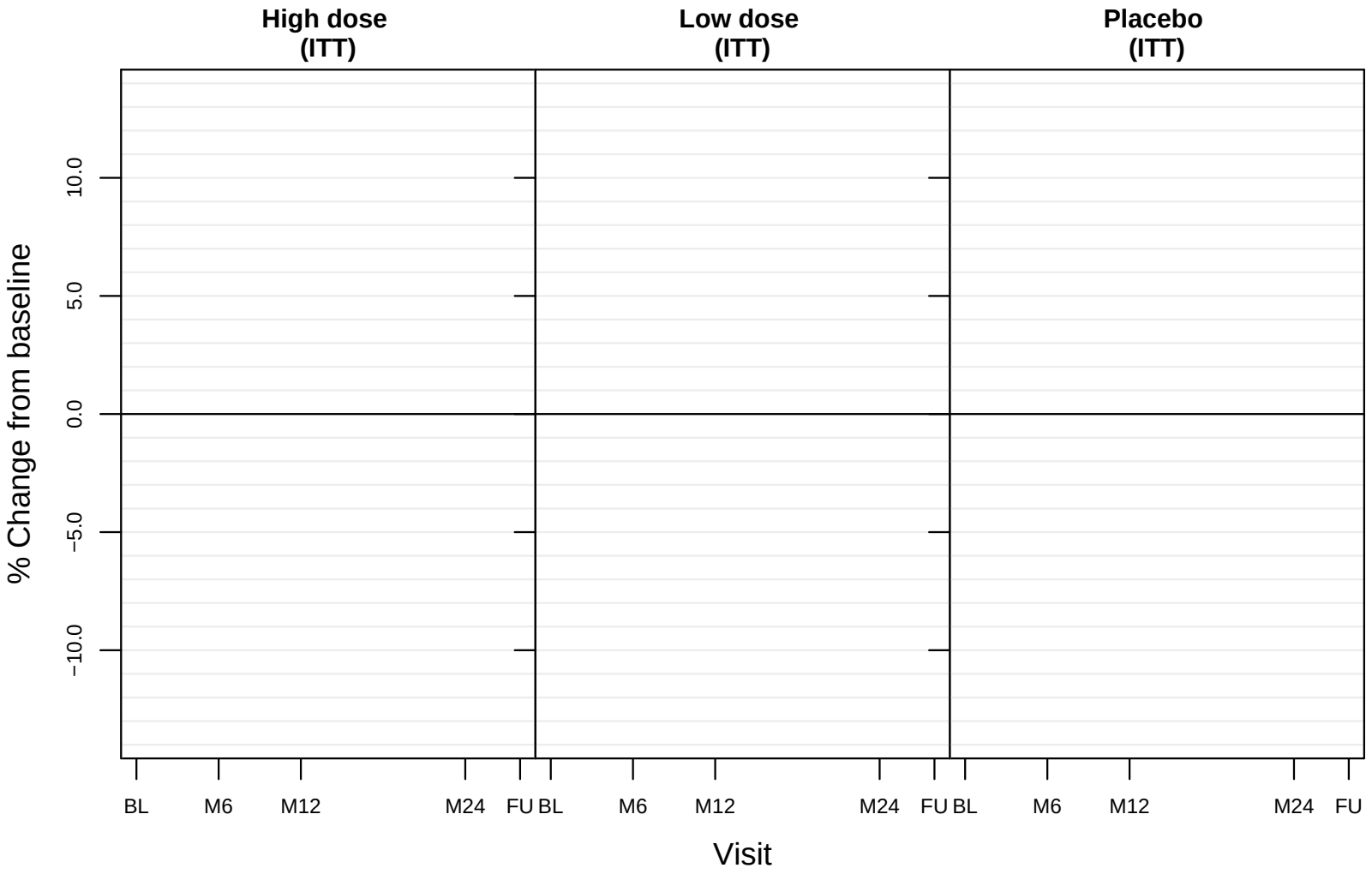


Some real-world pharma examples

Change from baseline over time

- Illustrate the individual change from baseline, by treatment


High dose
(ITT)
Low dose
(ITT)
Placebo
(ITT)
% Change from baseline
10.0
5.0
0.0
−5.0
−10.0
BL
M6
M12
M24
FU
Visit


High dose
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10.0
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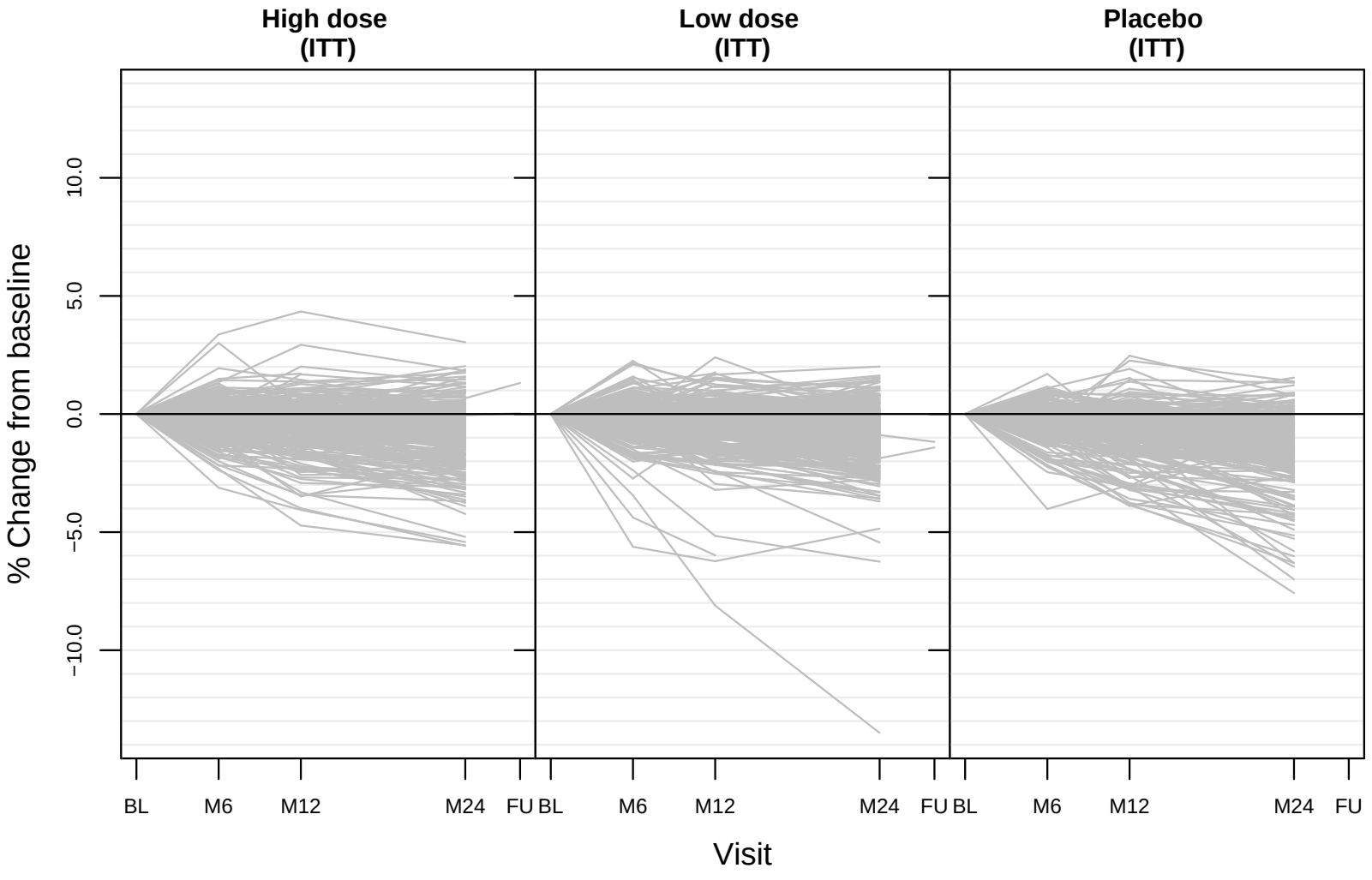
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Should there be an interim analysis?

Imagine: today=June 2012

- Health authorities require a final study report in November 2015.
- Recruitment has just started, but is very slow. June 2012: 0.07 patients per center and months.

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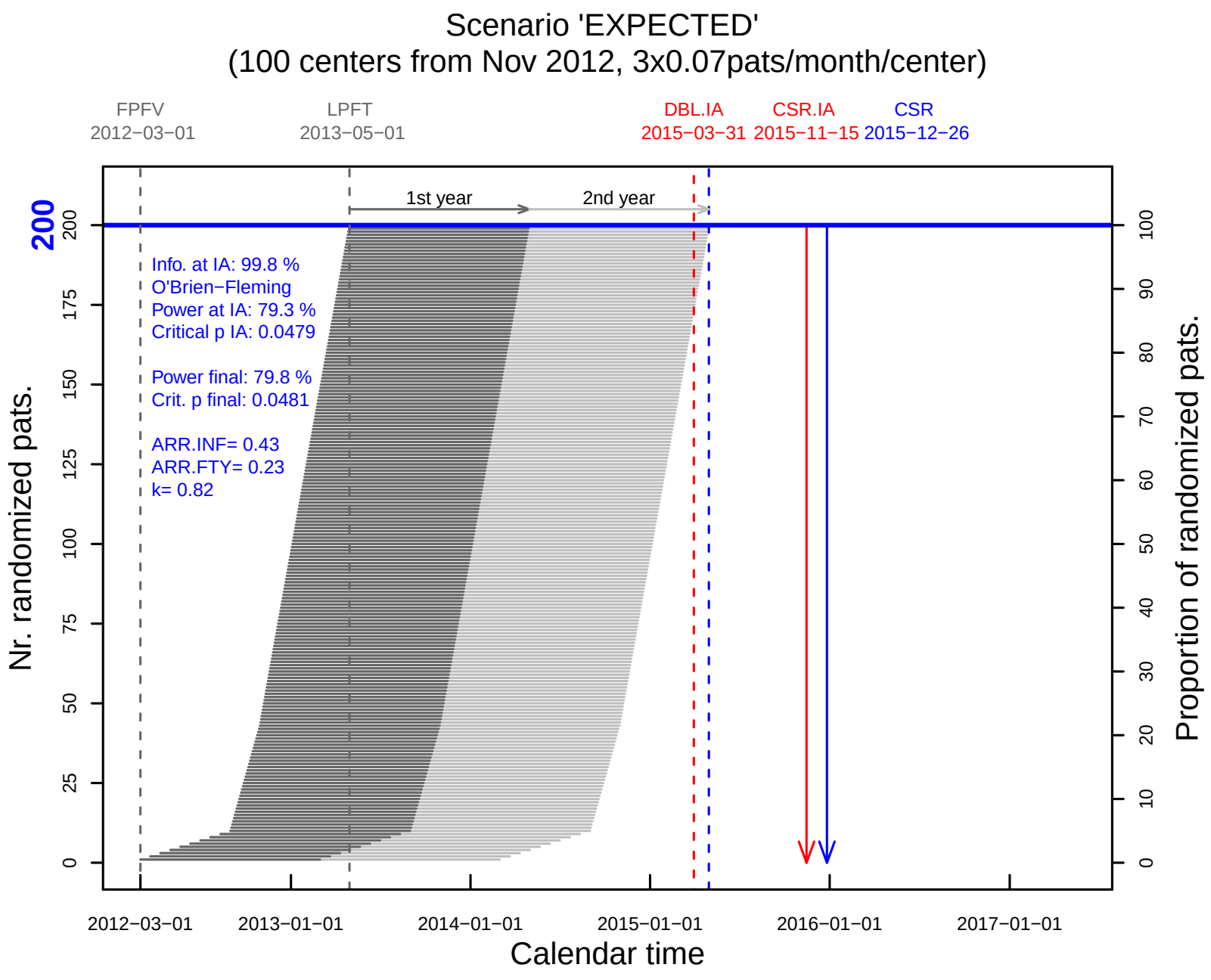
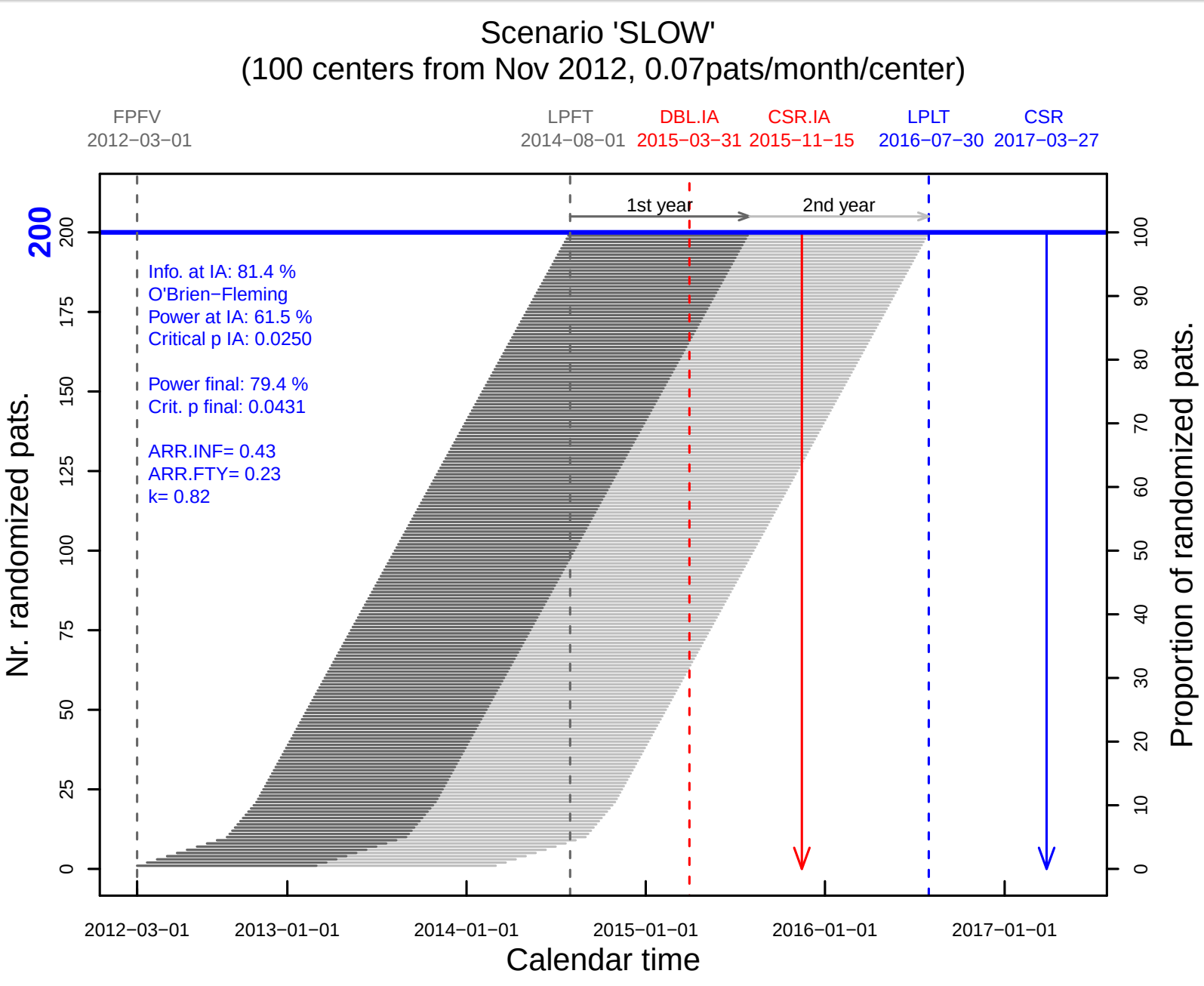
Imagine: today=June 2012

- Health authorities require a final study report in November 2015.
- Recruitment has just started, but is very slow. June 2012: 0.07 patients per center and months.
- If recruitment doesn't accelerate soon, it will become unlikely that the final report could be submitted in November 2015.
- Should there be an interim analysis?


Scenario 'EXPECTED'
(100 centers from Nov 2012, 3x0.07pats/month/center)
FPFV
2012−03−01
LPFT
2013−05−01
DBL.IA
2015−03−31
CSR.IA
2015−11−15
CSR
2015−12−26
1st year
2nd year
200
Info. at IA: 99.8 %
O'Brien−Fleming
Power at IA: 79.3 %
Critical p IA: 0.0479
Power final: 79.8 %
Crit. p final: 0.0481
ARR.INF= 0.43
ARR.FTY= 0.23
k= 0.82
Nr. randomized pats.
Proportion of randomized pats.
0
25
50
75
100
125
150
175
200
0
10
20
30
40
50
60
70
80
90
100
2012−03−01
2013−01−01
2014−01−01
2015−01−01
2016−01−01
2017−01−01
Calendar time


Scenario 'SLOW'
(100 centers from Nov 2012, 0.07pats/month/center)
FPFV
2012−03−01
LPFT
2014−08−01
DBL.IA
2015−03−31
CSR.IA
2015−11−15
LPLT
2016−07−30
CSR
2017−03−27
1st year
2nd year
200
Info. at IA: 81.4 %
O'Brien−Fleming
Power at IA: 61.5 %
Critical p IA: 0.0250
Power final: 79.4 %
Crit. p final: 0.0431
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ARR.FTY= 0.23
k= 0.82
Nr. randomized pats.
Proportion of randomized pats.
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75
100
125
150
175
200
0
10
20
30
40
50
60
70
80
90
100
2012−03−01
2013−01−01
2014−01−01
2015−01−01
2016−01−01
2017−01−01
Calendar time

Overview of safety

Provide a graphical overview of adverse events

1. At different hierarchical MedDRA levels
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   - Risks & PTs, etc.

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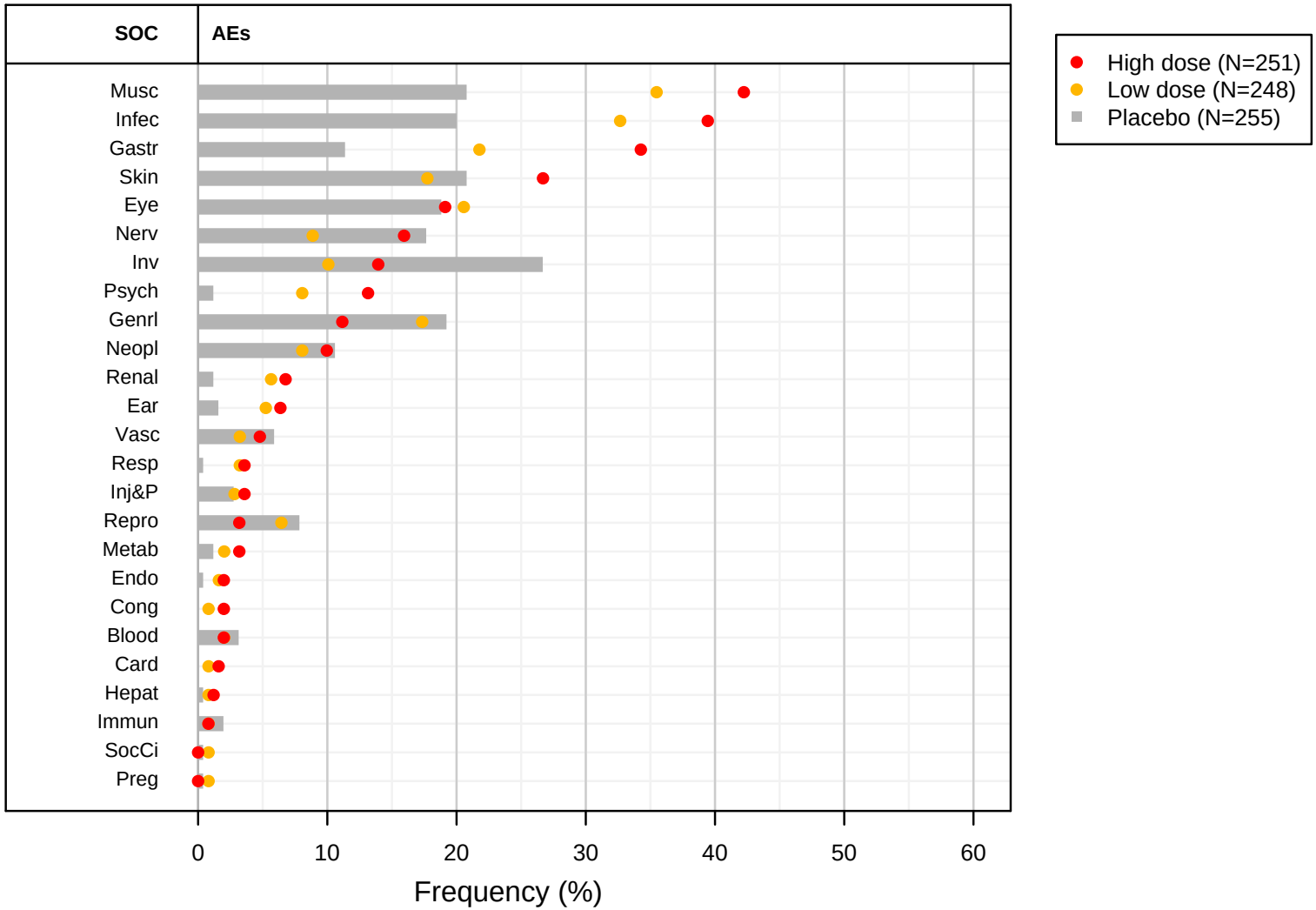
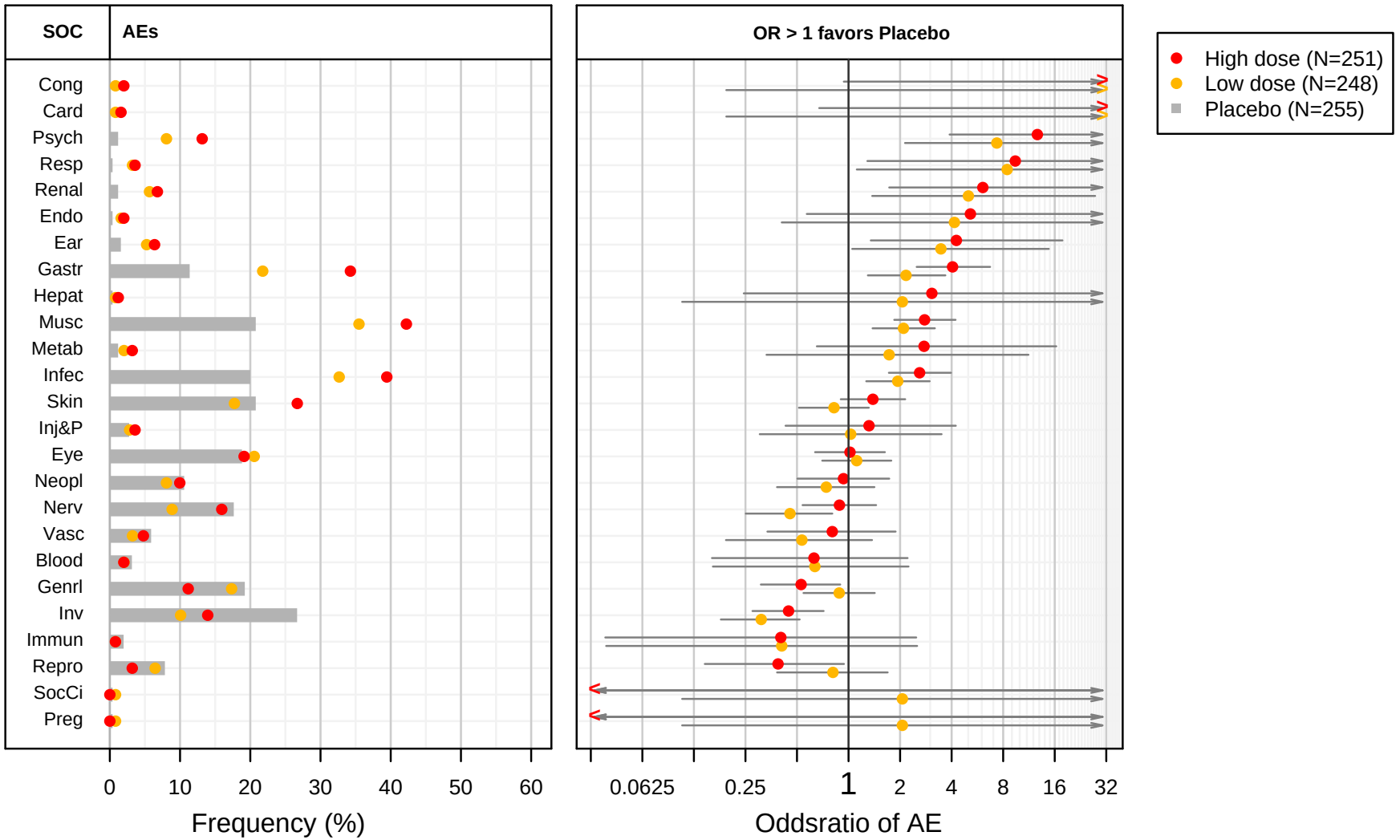
4. Seriousness of events
5. If possible, all on one page

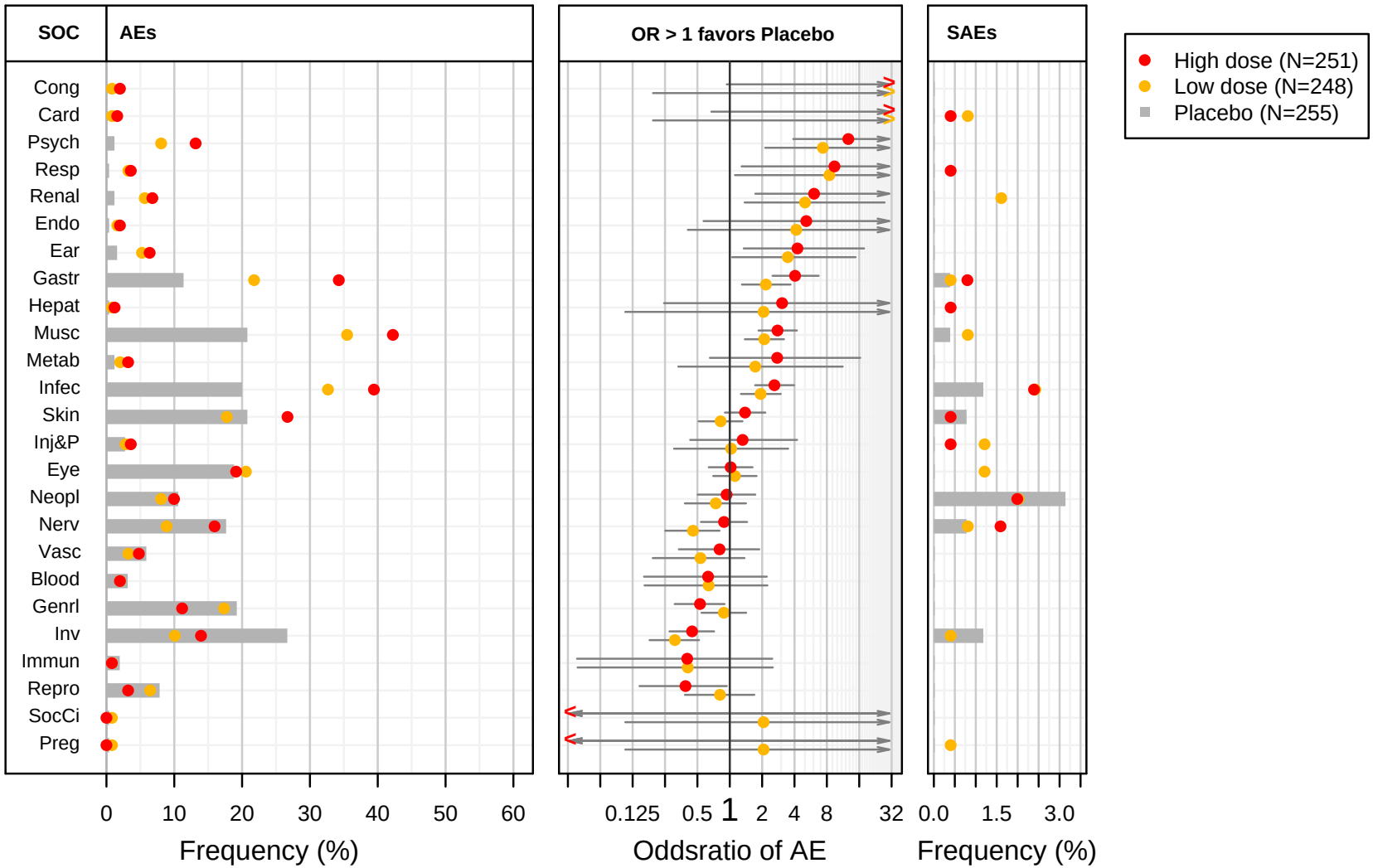
CDAH159A2301: SOC safety profile as compared to Placebo sorted by frequency of AEs in the High dose group



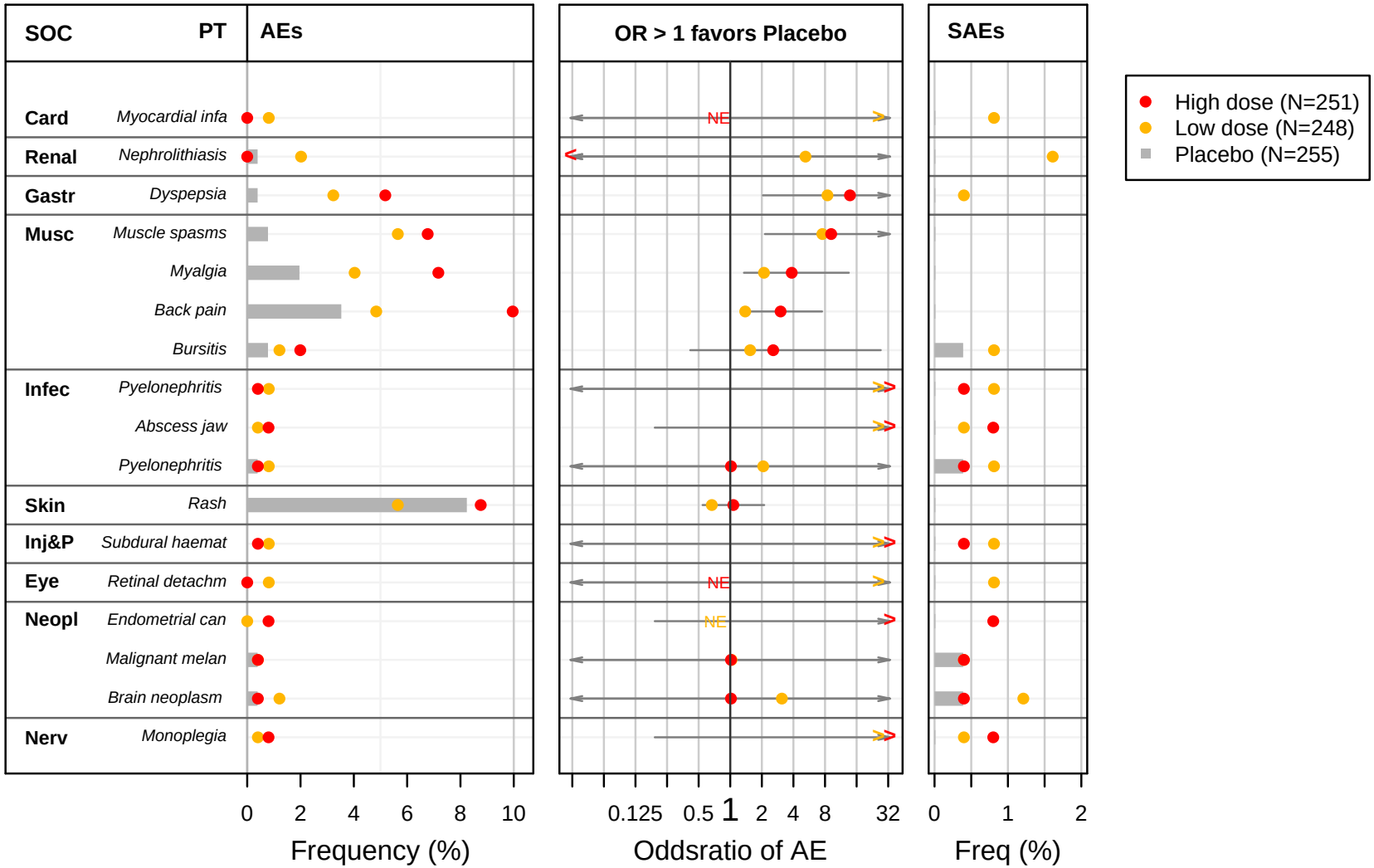
CDAH159A2301: SOC safety profile as compared to Placebo sorted by oddsratio in the High dose group



CDAH159A2301: SOC safety profile as compared to Placebo sorted by oddsratio in the High dose group



CDAH159A2301 : Selected* adverse events as compared to Placebo (grey bars) sorted by oddsratio (OR) of SOC and OR of PT within SOC in the High dose group



* Selected adverse events (AEs) are those which occur with at least 2 SAEs on active treatment, and those which have PT.OR>1 and frequency on high dose >5%

Example: Interactions and outliers

Health Authority Question (efficacy):

You have shown a significant treatment benefit (overall), but there is also a significant treatment x covariate interaction.

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1. Describe the interaction
2. Identify outliers
3. Describe the influence of outliers on your results

Statistical output from a negative binomial model (Deviance table)

	Df	Deviance	Resid. Df	Resid. Dev	P($>|\chi|$)
NULL			1092	1873.7	-
treat	2	803.29	1090	1070.5	$<$0.0001
co	1	0.80	1089	1069.7	0.37
treat:co	1	8.95	1088	1060.7	0.0027

Results show:

- A significant treatment (main) effect
- But also a significant treatment x covariate interaction?

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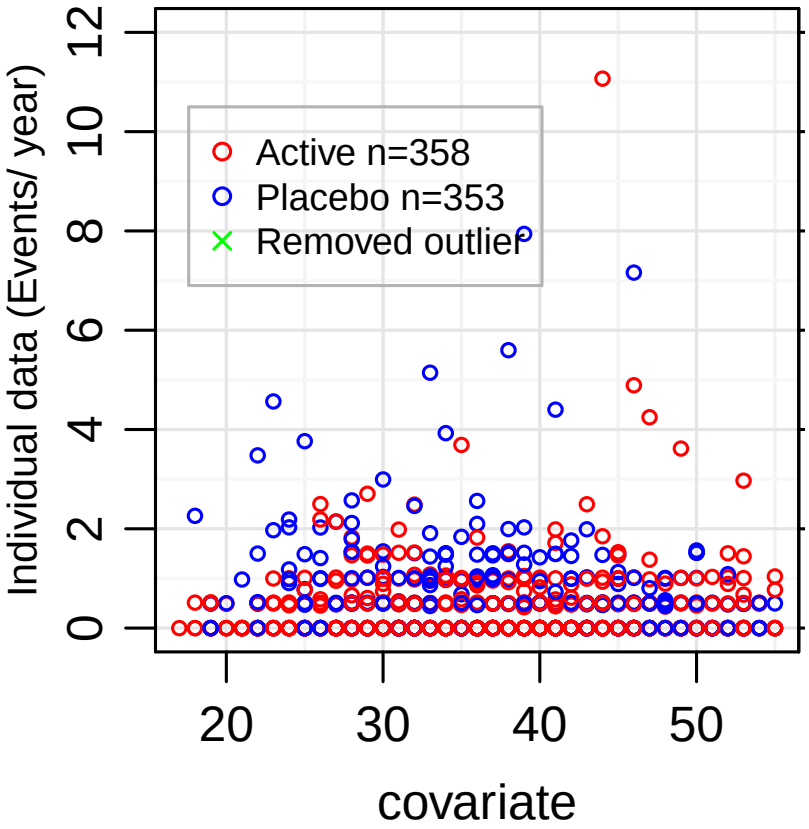
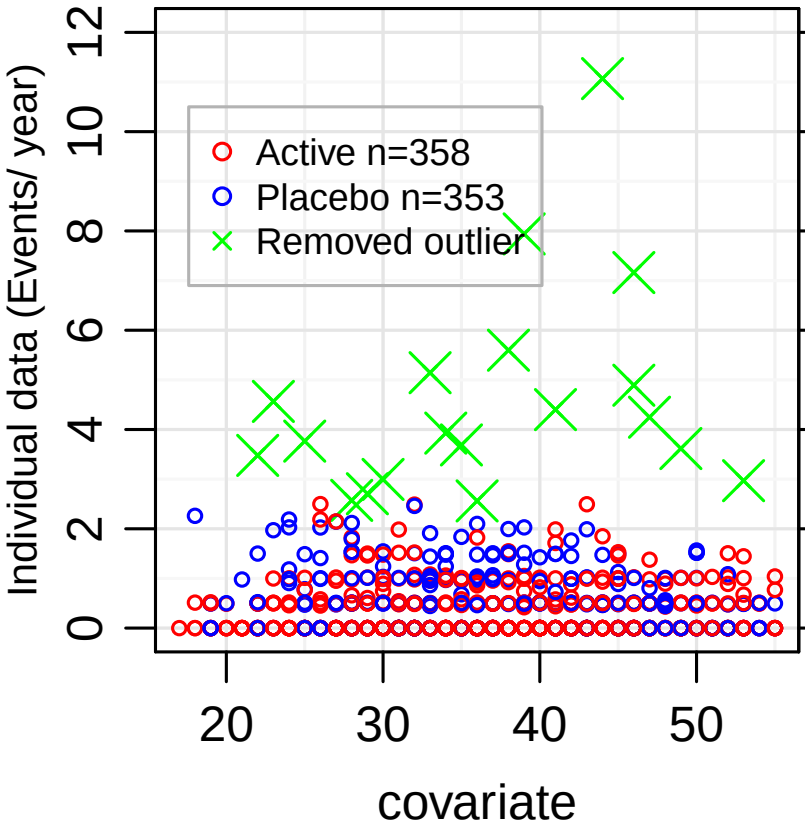
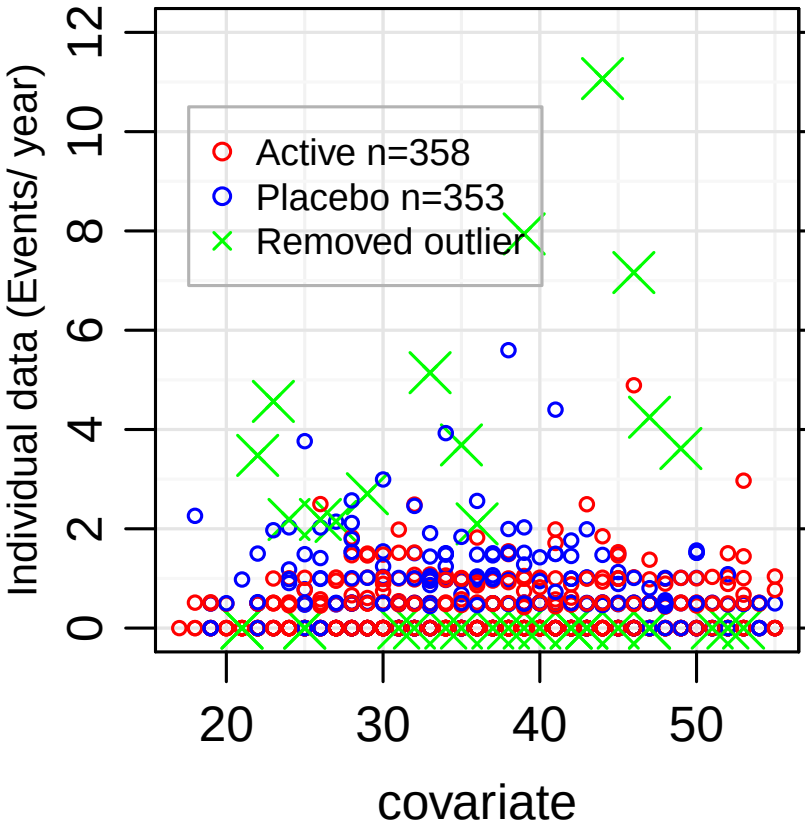


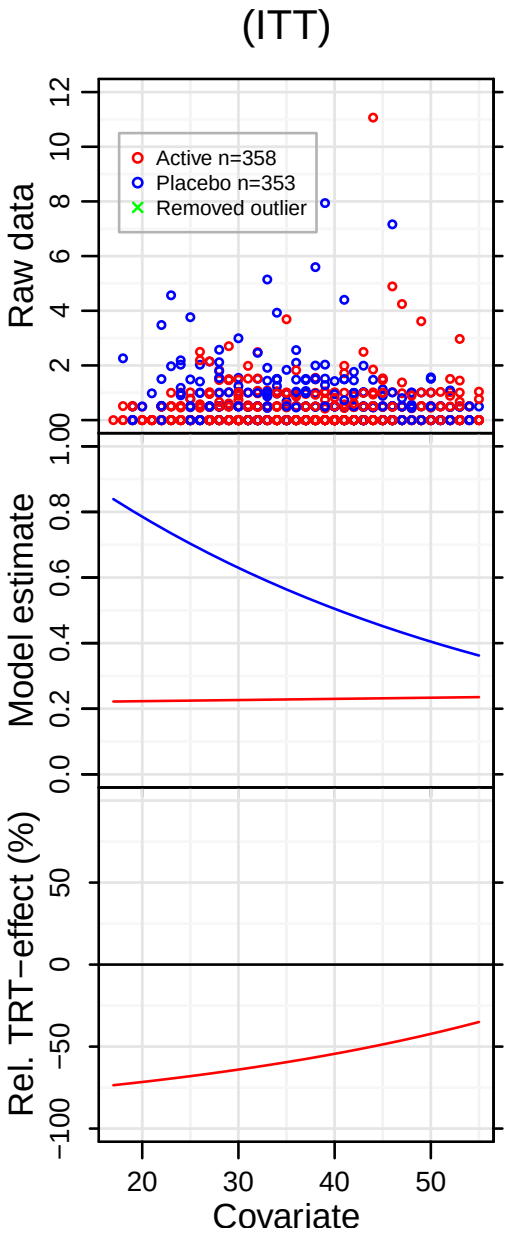
Events/ year:
Usually patients have 0, 1, 2 events per year.

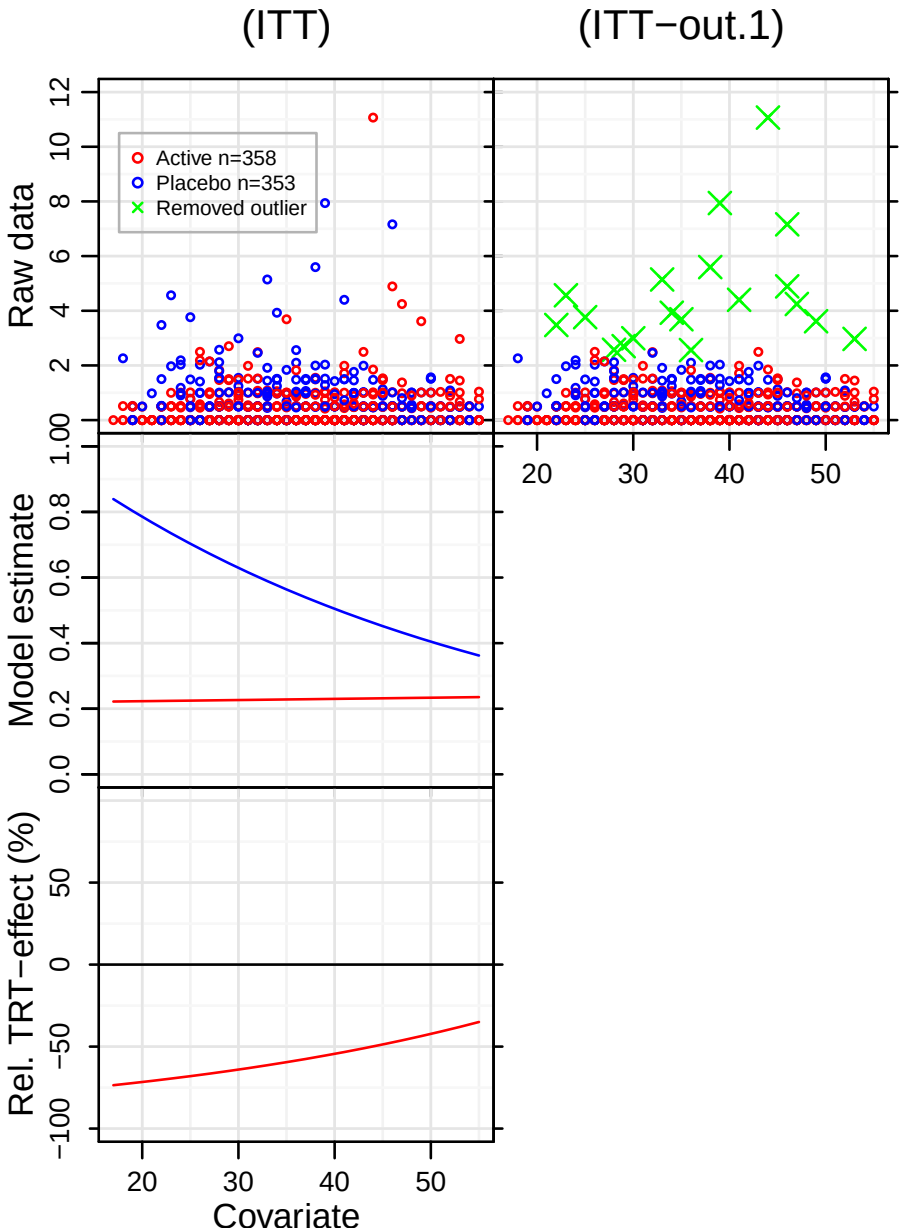


Outlier definition 1:
Patients with individual values for events/time-at-risk$>$2.5



Outlier definition 2:
Patients who were in the study for less than 180 days (i.e. early drop-outs)


(ITT)
Raw data
Active n=358
Placebo n=353
Removed outlier
Model estimate
Rel. TRT−effect (%)
Covariate


(ITT)
(ITT−out.1)
Raw data
Active n=358
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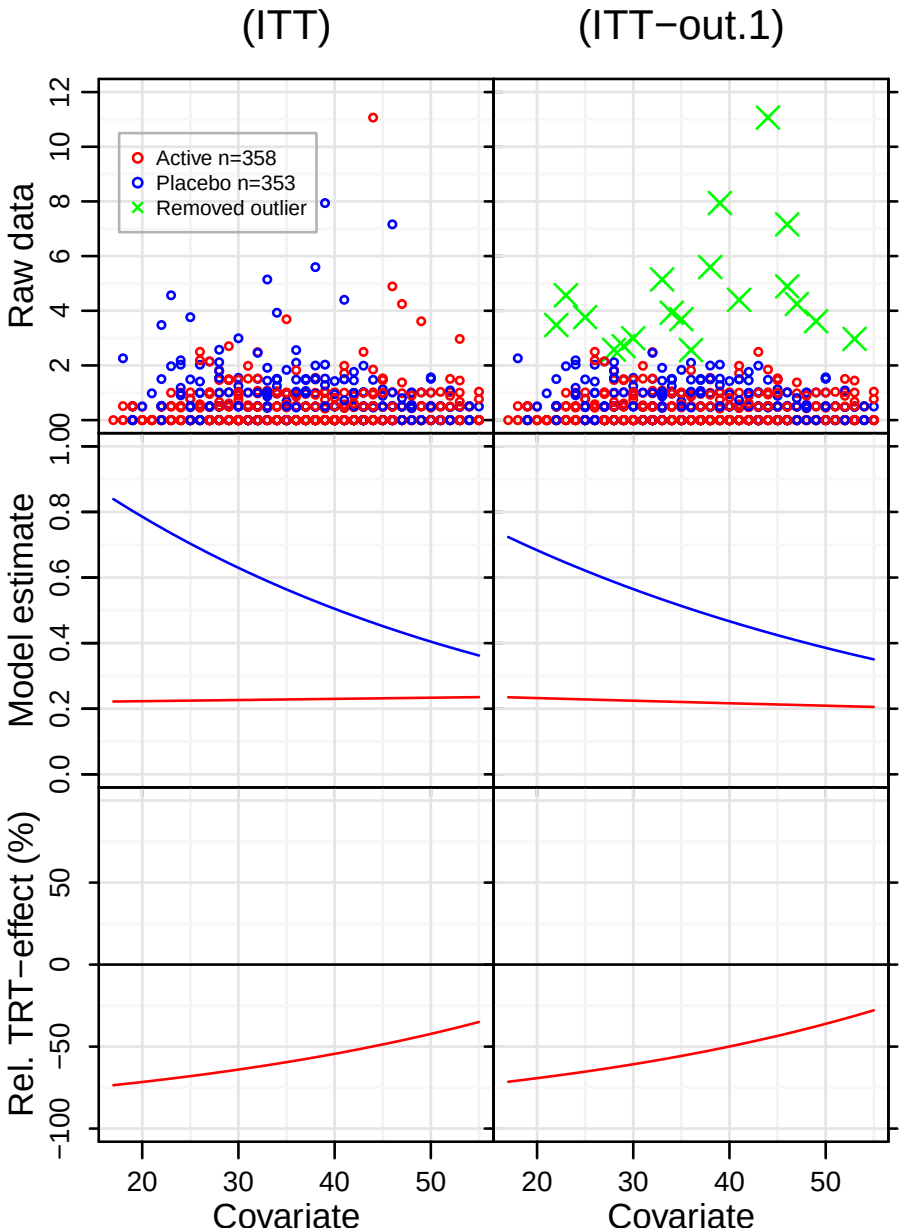
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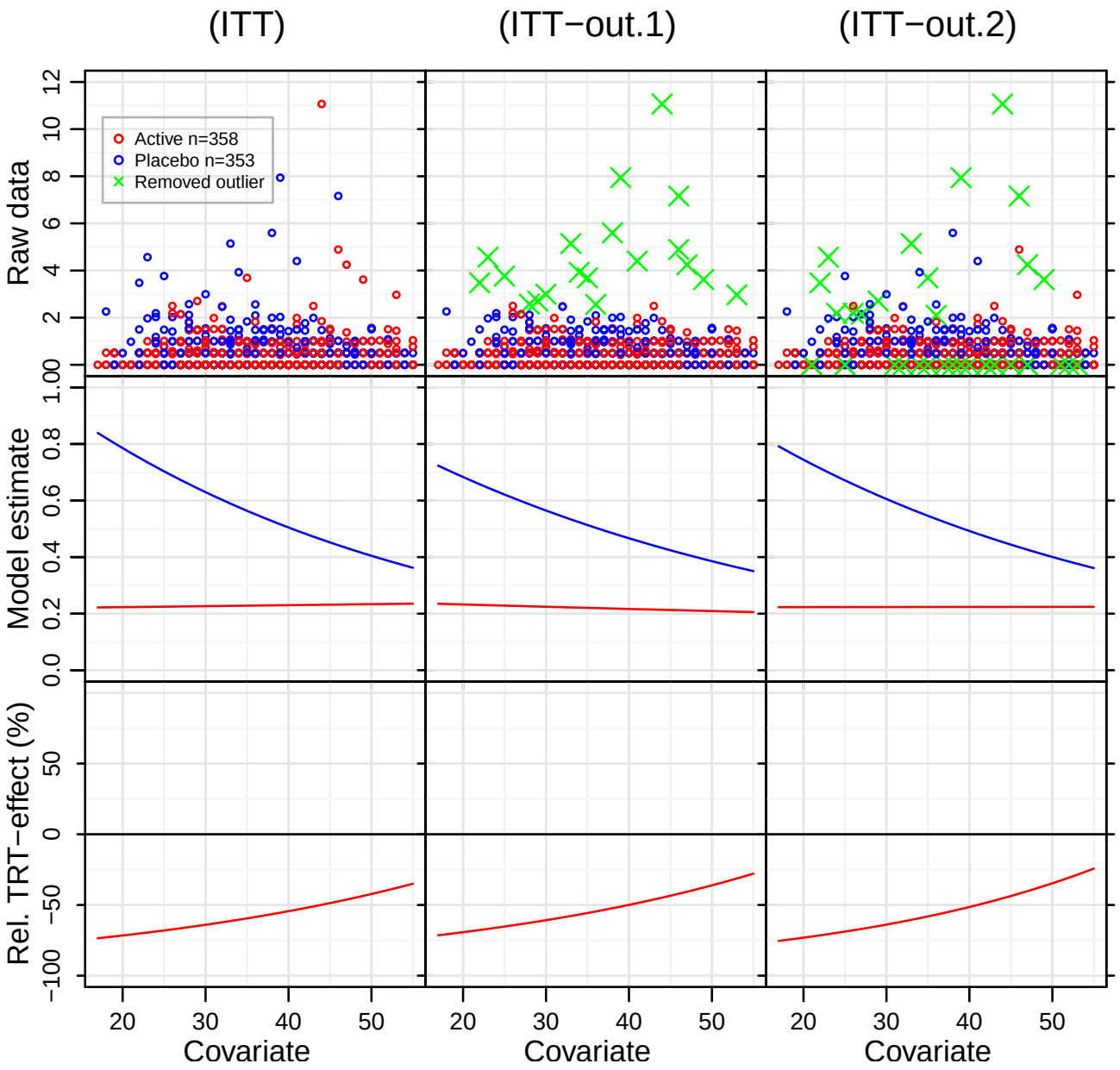
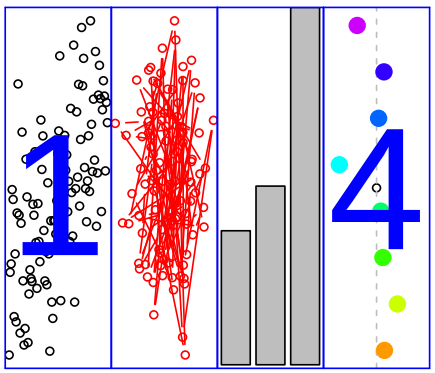
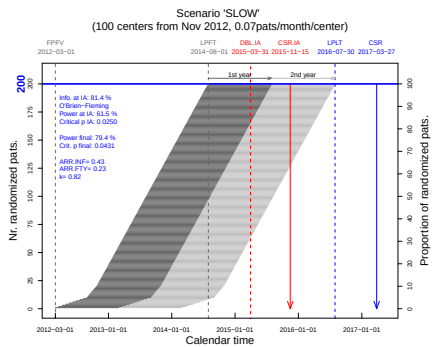
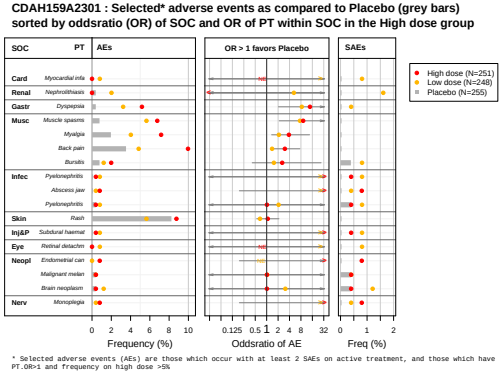
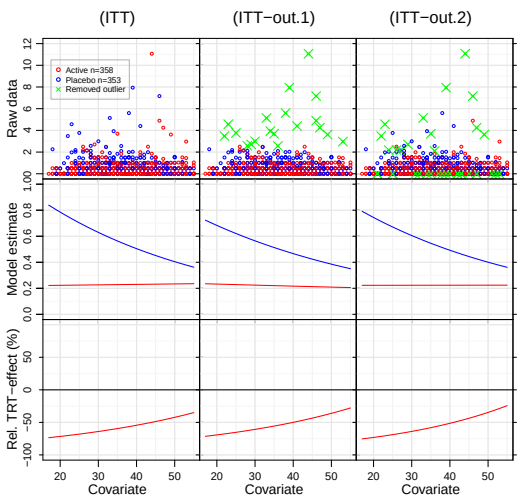

(ITT)
(ITT−out.1)
(ITT−out.2)
Raw data
Active n=358
Placebo n=353
Removed outlier
Model estimate
Rel. TRT−effect (%)
Covariate
Covariate
Covariate

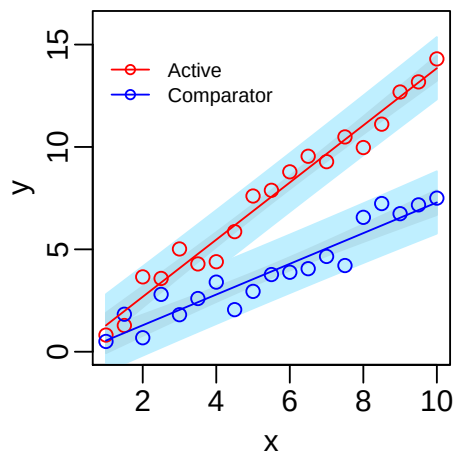
Thank you very much for your attention!











On R in general:

- For R-beginners: `An introduction to R` (Venables, Smith, et al.)
  Google (free download) from the R-website
- A comprehensive book: `The R Book` (Crawley), *Wiley*
  Highly recommended

Specifically for Graphics in R:

- On 'Grammar of Graphics': `ggplot2, elegant graphics for data analysis` (Wickham), *Springer*
- On Lattice: `Multivariate Data Visualization with R` (Deepayan), *Springer*