

Graphical Analyses of Clinical Trial Safety Data

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Overview

- Current situation of clinical trial safety analyses
- Examples of statistical graphs used in safety analyses environment
- Summary

Clinical Trial Safety Analysis

- Safety assessment is crucial in drug development
- As part of risk management, safety data should be continuously monitored
- Current practice and available tools are not up to standard
- Recognize the need to develop new tools for reviewing, presenting and analyzing clinical trial safety data

Reviewing Safety Data

The image shows a large, multi-column table of safety data, likely a hazard assessment or risk matrix. The table is organized into several vertical columns, each containing text and numerical data. The data is presented in a grid-like format with horizontal lines separating rows. Several rows are highlighted in red, and some text within the table is highlighted in yellow. The table appears to be a detailed record of safety information, possibly related to a specific project or process. The table is spread across multiple pages, with the visible portion showing several columns of data. The text is small and dense, typical of a technical or regulatory document. The overall layout is structured and systematic, designed for easy review and comparison of data points across different categories.

Safety Outputs



Building Blocks in Safety Analysis

- Standards for clinical trial data (CDISC)
 - Clinical Data Interchange Standards Consortium
- Approaches to coding of adverse events and MedDRA search strategies for use in clinical trial event counting and analysis
- Software tools for data access, exploration, analysis
- Modern statistical metrics to characterize event rates, risk and risk factors
- Some visual graphs and displays to facilitate understanding

Graphical Analyses

- A graph is worth 10000 words
- Statistical graphics are useful tools for exploring data, aiding inference and communicating results
 - Display large data coherently
 - Maximize the ability to detect unusual features
 - Facilitate communication with: regulators, investigators, collaborators, upper management, DMC, etc.

Application

- Examples of statistical graphs used to better visualize different types of clinical trial safety data and facilitate safety signal detection.
- Graphics tool-box in development
- Some questions to answer
 - Which AEs are elevated in treatment vs. placebo?
 - Any special patterns of AE onset?
 - What is the trend of treatment effects on safety outcomes over time?
 - Which patients have abrupt changes in lab tests? Is there temporal causality of drug intake?

Clinical Safety Data

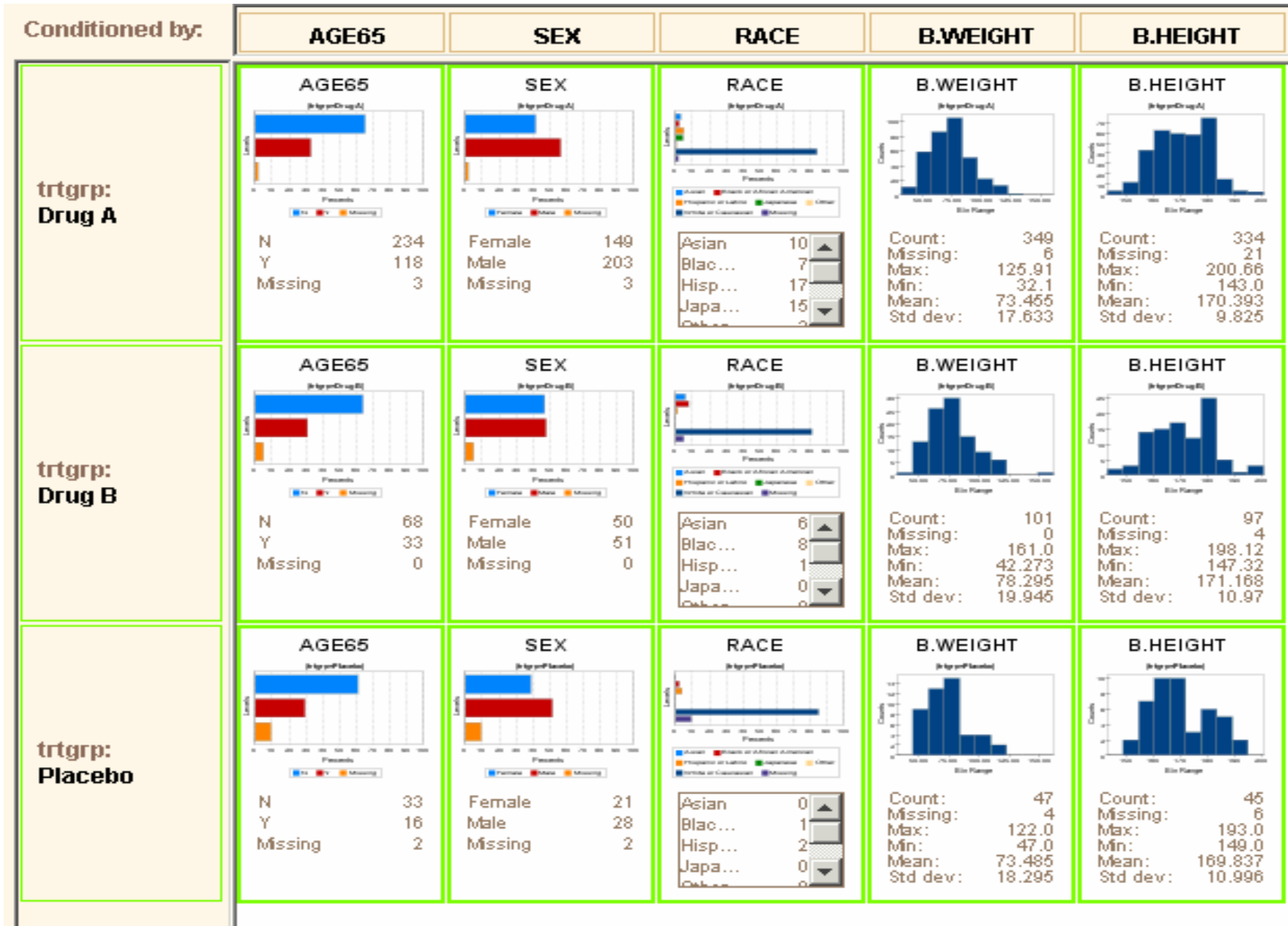
- Data types:
 - Adverse Event Data
 - Lab Data
 - Other Data: demographic, exposure, vital signs, conMed, etc.
- Level of details:
 - Group level information display
 - Individual level information display

Demographic data
Drug exposure

**Table 2.1. Baseline Demographics
(Subjects Exposed to Study Drug)**

	Study XXXX		
	Placebo (N=165)	Drug A (N=164)	Total (N=329)
Sex - n(%)			
Female	65 (39.4)	64 (39.0)	129 (39.2)
Male	100 (60.6)	100 (61.0)	200 (60.8)
Race - n(%)			
Caucasian	136 (82)	135 (82)	271 (82)
African American	6 (4)	8 (5)	14 (4)
Hispanic	13 (8)	10 (6)	23 (7)
Asian	6 (4)	7 (4)	13 (4)
Japanese	2 (1)	2 (1)	4 (1)
American Indian	0 (0)	1 (1)	1 (0)
Native Hawaiian	0 (0)	0 (0)	0 (0)
Other	2 (1)	1 (1)	3 (1)

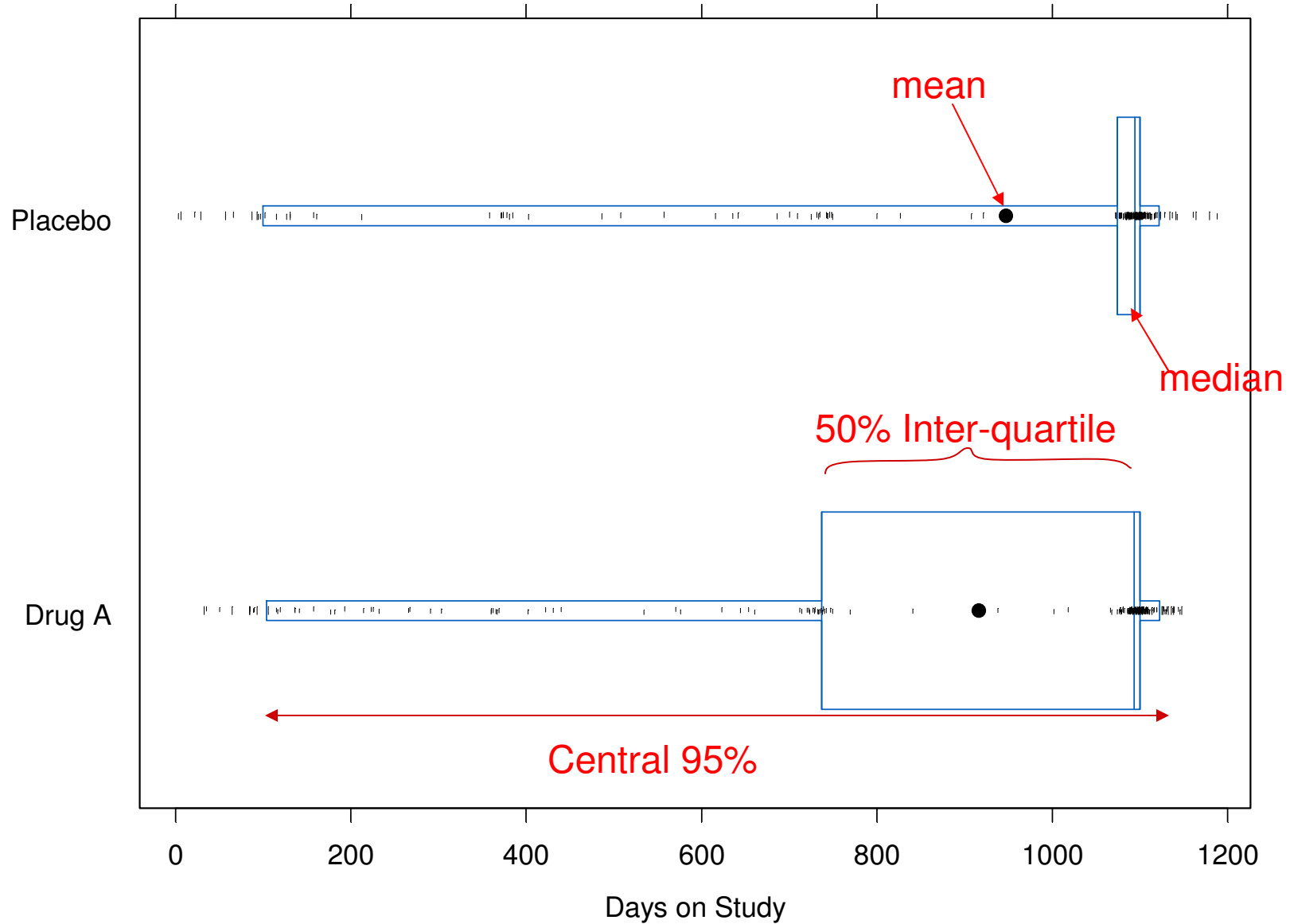
Baseline Demographics



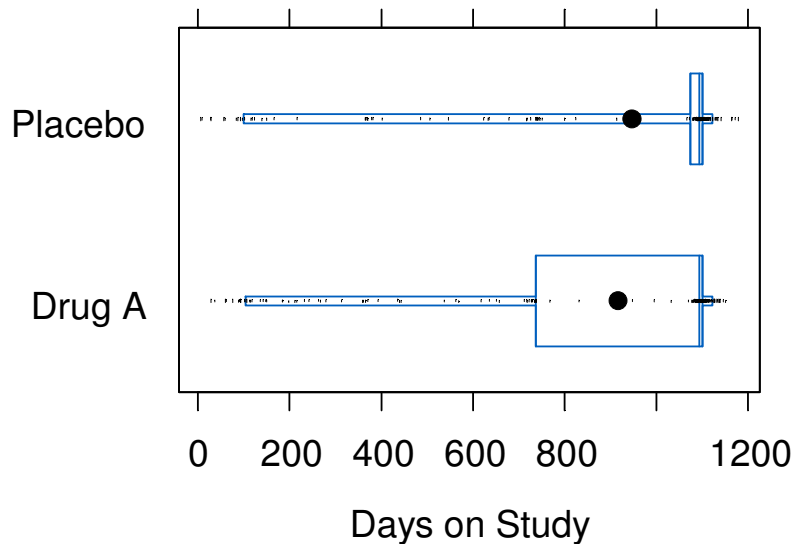
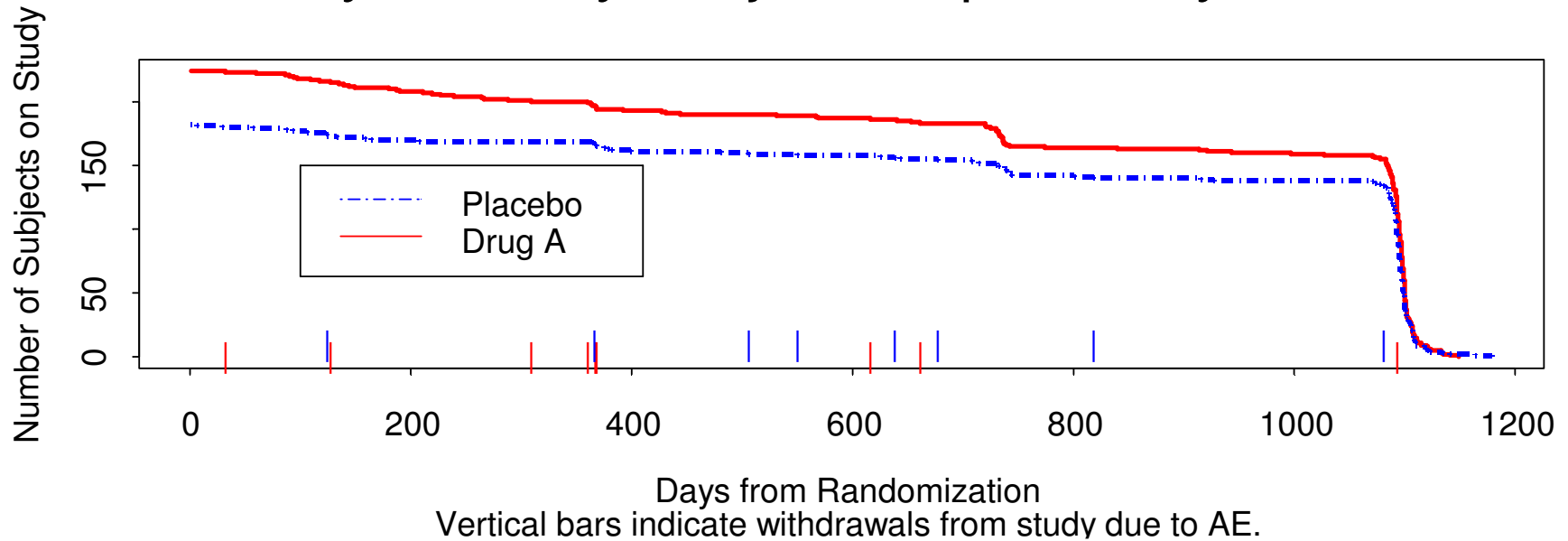
**Table 1.1 Summary of Subject-year Follow-up
(Subjects Exposed to Study Drug)
(Study XXXX)**

	Study XXXX		
	Placebo (N=184)	Drug A (N=224)	Total (N=406)
Subjects Exposed to Study Drug (Subject-years)			
N	182	224	406
Total	471.98	561.93	1033.91
Duration Exposed to Study Drug (Days)			
n	182	224	406
Mean	947.2	916.3	930.14
SD	302.01	321.81	313.09
Median	1094.0	1094.0	1094.0
Q1, Q3	1074.0, 1100.0	737.0, 1100.0	823.5, 1100.0
Min, Max	6.0, 1179.0	32.0, 1149.0	6.0, 1179.0

Summary of Safety Subjects Exposure by Treatment



Summary of Safety Subjects Exposure by Treatment



	Placebo	Drug A
n	:182	:224
Min.	: 6.0	: 32.0
1st Qu.	:1074.0	: 737.0
Median	:1094.0	:1094.0
Mean	: 947.2	: 916.3
3rd Qu.	:1100.0	:1100.0
Max.	:1179.0	:1149.0

Adverse events data

Table 2. Subject Incidence of All Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency

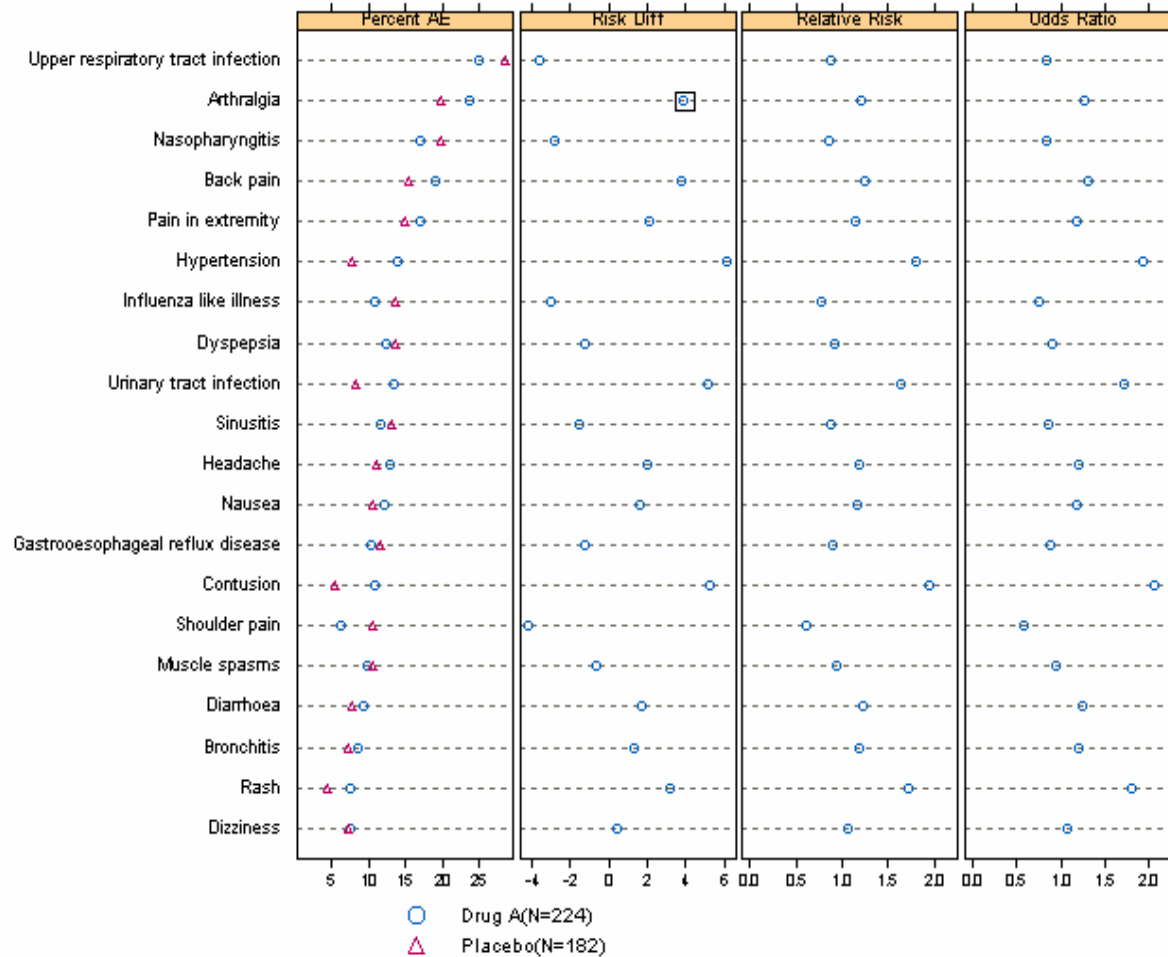
(Subjects Exposed to Study Drug)

PREFERRED TERM	Placebo (N = 184) n (%)	Drug A (N = 224) n (%)
Number of Subjects Reporting Any Adverse Events	146 (79.3)	195 (87.0)
CONSTIPATION	43 (23.4)	59 (26.3)
ASTHENIA	32 (17.4)	39 (17.4)
BACK PAIN	27 (14.7)	37 (16.5)
BONE PAIN	23 (12.5)	34 (15.1)
FATIGUE	22 (12.0)	29 (12.9)
HYPOCALCAEMIA	5 (2.7)	16 (7.1)
INSOMNIA	22 (12.0)	10 (4.5)
DIZZINESS	5 (2.7)	0 (0)

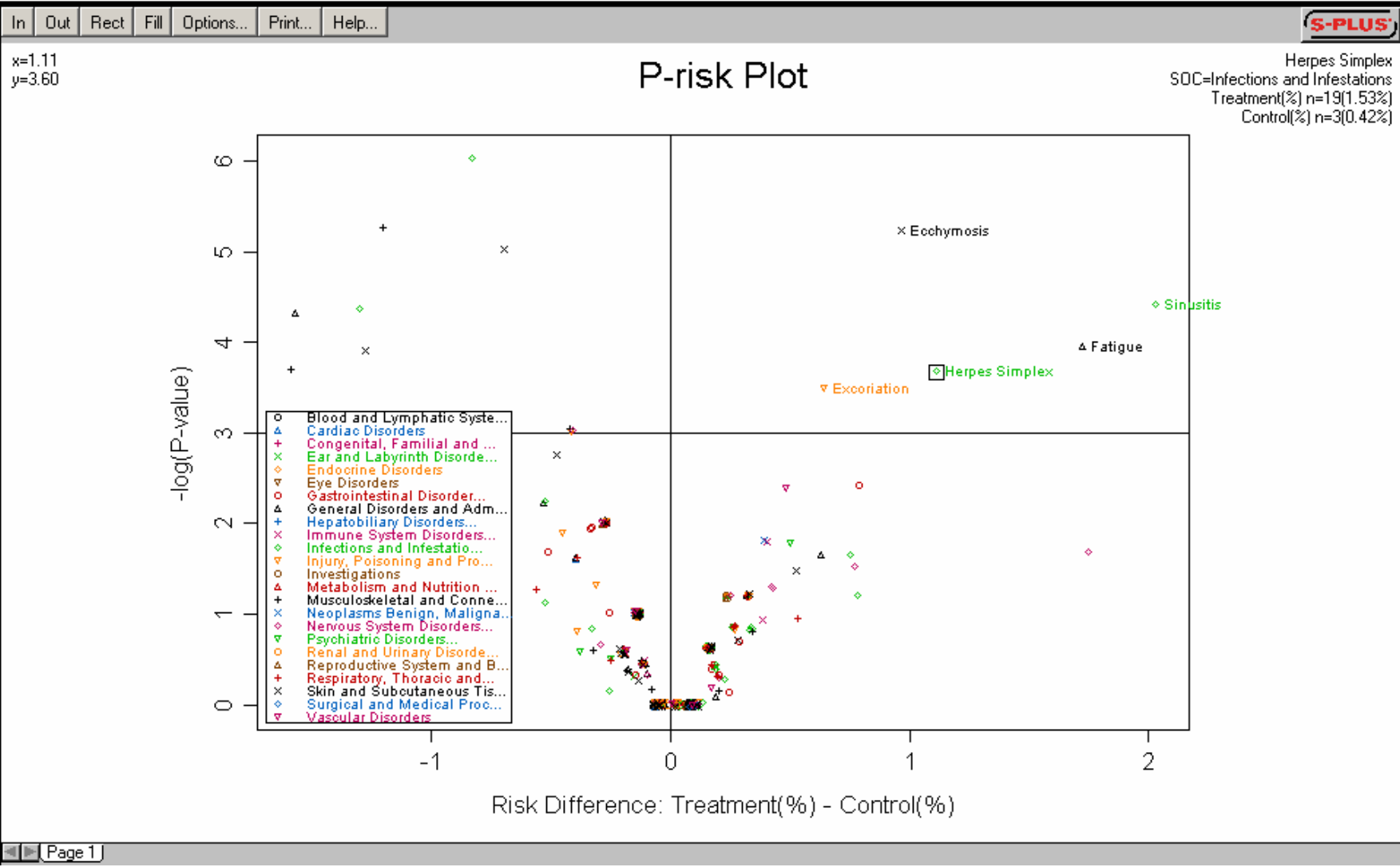
x=3.67
y=18.75

3.88

Adverse Events $\geq 5\%$ by Preferred Term in Descending Order of Frequency

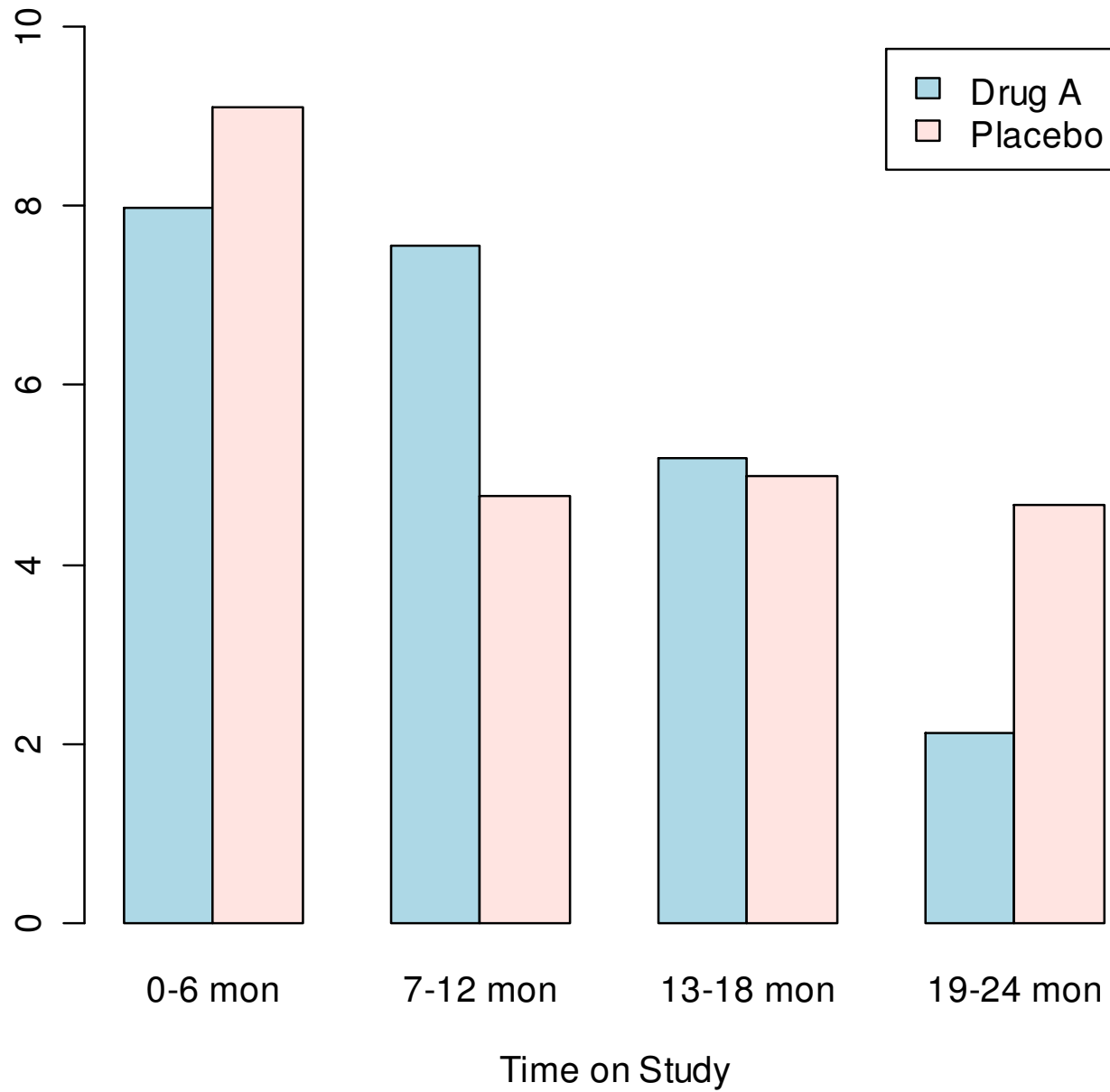


- AE dot plot by descending order of frequency
- AE dot plot by descending order of risk difference

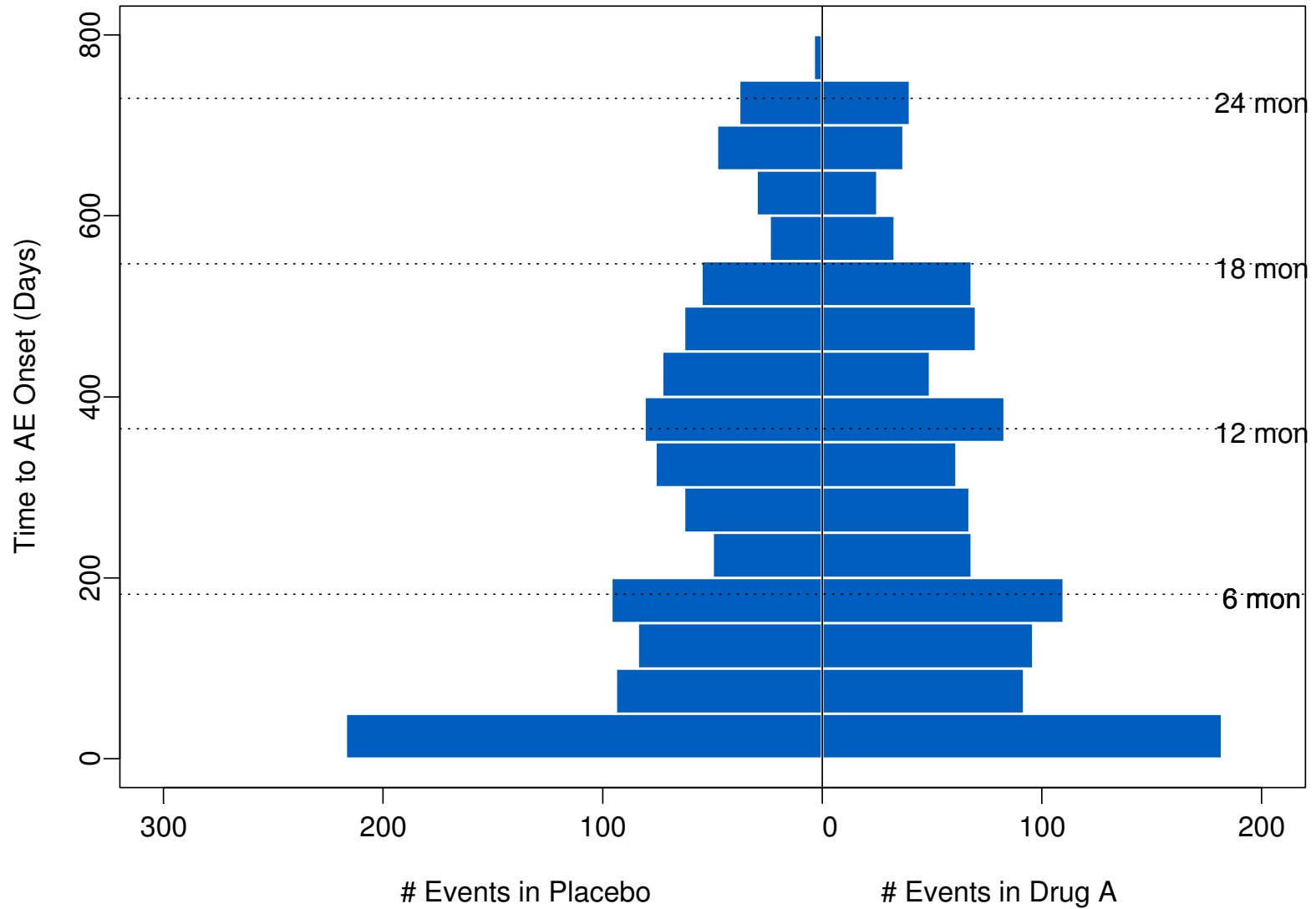


• [P-risk plot](#)

Serious Adverse Events Incidences (%)

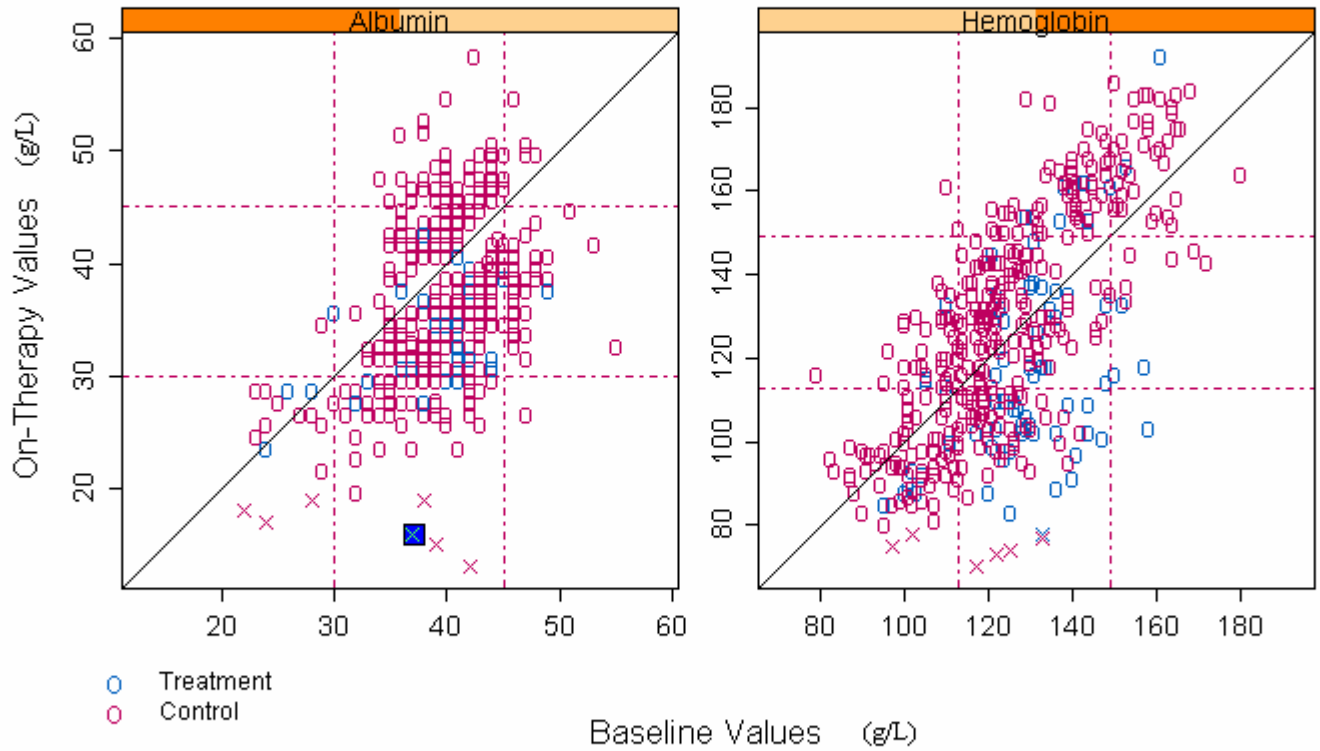


Distribution of Days on Study to AE Onset for Subjects with AE



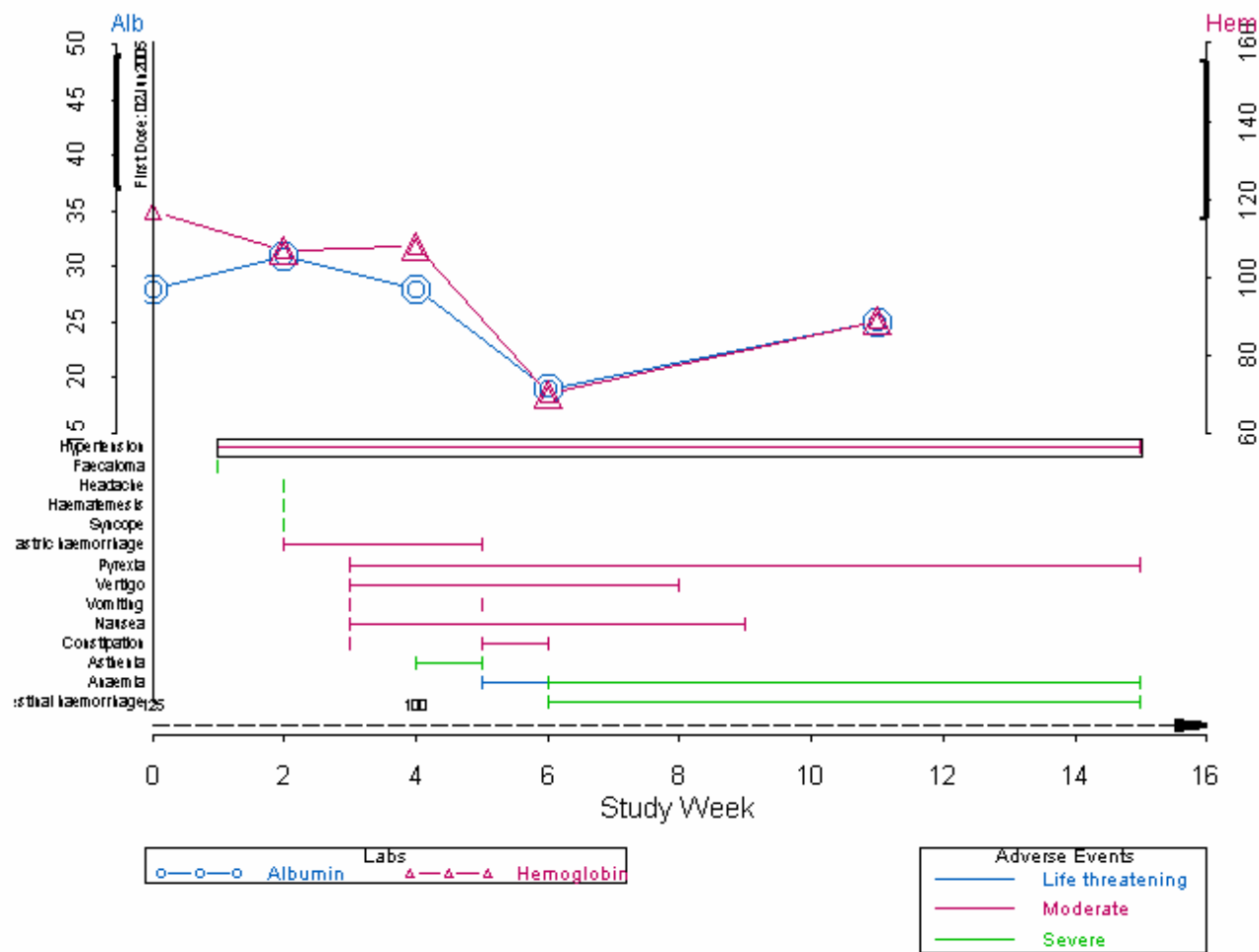
Lab test data

Lab Shift Plots

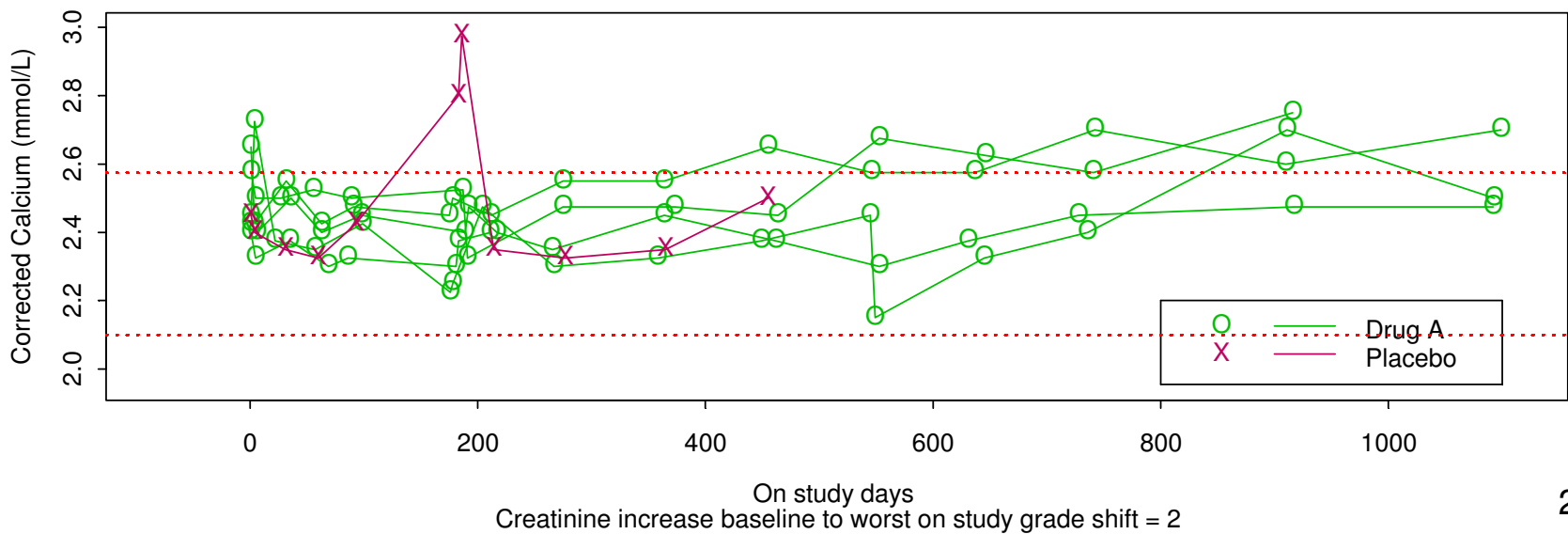
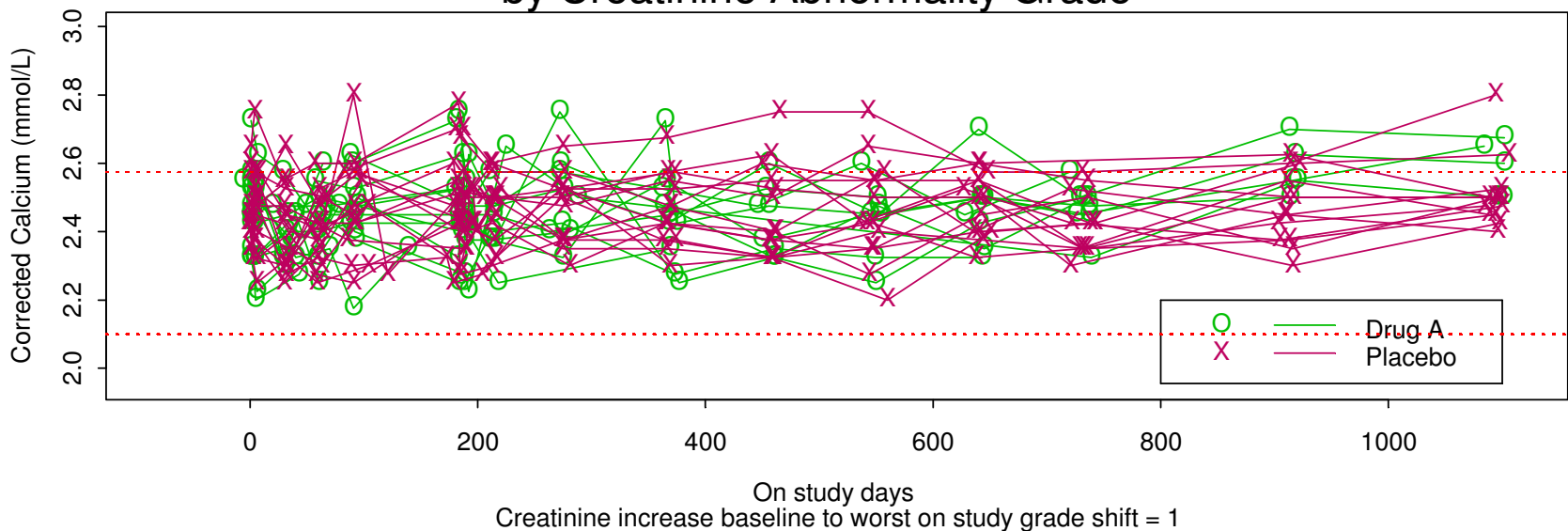


Subject Profile

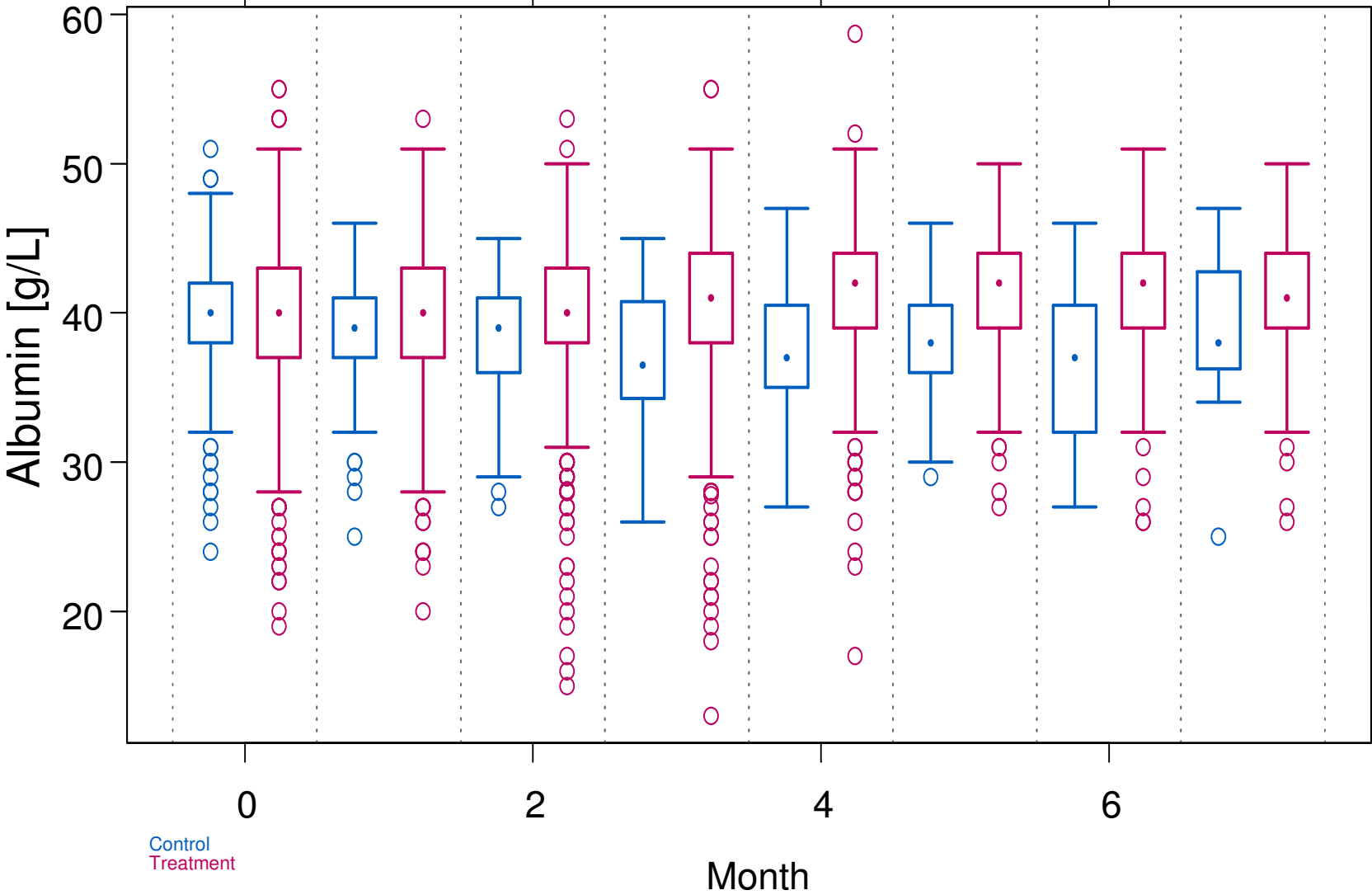
ae=Hypertension
 startTime=06/06/2005
 stopTime=09/17/2005
 severity=Moderate



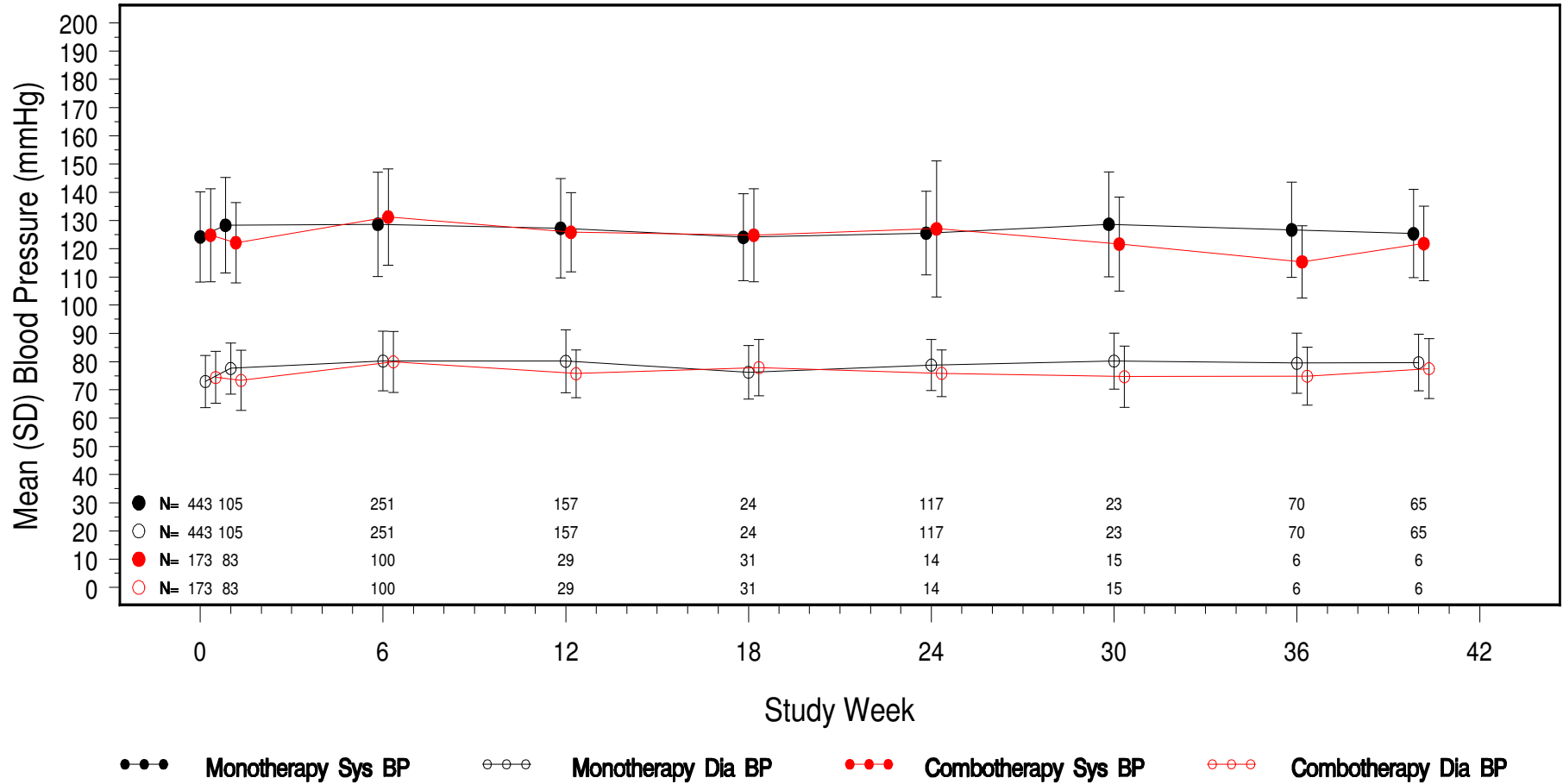
Change of Albumin Corrected Calcium over Time by Creatinine Abnormality Grade



BOX PLOT



**Figure 7.1. Mean (SD) Blood Pressure Subgrouped by Therapy Over Visit Weeks
Safety Analysis Set**



Patient Profile

- Simultaneous display of large amount of relevant information of a subject
- Efficiently establish safety profile of a subject
- Easier to see drug effect, drug/drug interaction, connections between lab test and adverse events, etc.

Patient Profile

Study: 20001 Subject: 1001 Age/Sex: 68/F
 Race: Hispanic Country: USA
 Arm: Treatment

Basic info: demog,
 treatment, visit time,
 dosing

Study day	1	85	183	267	374	449	583	644	752	920	1095	1284
Dosing	14	14	14	14	14	14	14	14	60	60	60	60
Body Temp	36.8	36.5	36.8	36.9	36.4	36.5	36.7	36.3	36	35.7	36.8	36.2
WBC (10 ³ /uL)	7.97	7.95	7.95	7.95	7.95	7.95	7.95	7.95	7.95	7.95	7.95	7.95
LYM (%)	25.1	28.3	24.5	19.1	19.1	22.4	20.3	20.8	18.1	18.1	18.1	25.4
MONO (%)	6.9	7.6	5.2	6.1	6.1	5.7	7.3	8	7.7	7.7	7.7	9.4
BASO (%)	0.6	0.7	1	0.3	0.3	0.4	0.8	0.5	0.9	0.9	0.9	0.8
EOS (%)	2.4	4.1	2.4	1.1	1.1	0.4	4.3	0.5	7.6	7.6	7.6	2.7
BANDS (%)	0	0	0	0	0	0	0	0	0	0	0	0
HGB (g/dL)	15	15	15	15	15	15	15	15	15	15	15	15
PLT (10 ³ /uL)	186	26	26	26	26	26	26	26	26	26	26	26
K (mEq/L)	3.74	4	4	4	4	4	4	4	4	4	4	4
CL (mEq/L)	36.98	36.98	36.98	36.98	36.98	36.98	36.98	36.98	36.98	36.98	36.98	36.98
BICARB (mEq/L)	27.3	27	27	27	27	27	27	27	27	27	27	27
BUN (mg/dL)	6	7	7	7	7	7	7	7	7	7	7	7
GLUCOSE (mg/dL)	84.82	8	8	8	8	8	8	8	8	8	8	8
CA_CR (mg/dL)	0.99	5	5	5	5	5	5	5	5	5	5	5
MG (mEq/L)	1.8	1	1	1	1	1	1	1	1	1	1	1
PHOS (mg/dL)	3.42	3	3	3	3	3	3	3	3	3	3	3
SGPT (U/L)	37.31	21	21	21	21	21	21	21	21	21	21	21
SGOT (U/L)	42.30	2	2	2	2	2	2	2	2	2	2	2
ALP (U/L)	85.80	7	7	7	7	7	7	7	7	7	7	7
BILI_TL (mg/dL)	0.40	0	0	0	0	0	0	0	0	0	0	0
ALB (g/dL)	4.54	4	4	4	4	4	4	4	4	4	4	4
PRO_TL (g/dL)	7.57	7	7	7	7	7	7	7	7	7	7	7

Lab values

Bladder cancer (ARISg) ▲
 Cellulitis (ARISg) ▲
 Arteriosclerosis ①
 Bladder cancer ▲
 Bladder spasm ①
 Cellulitis ▲
 Dysuria ①
 Endometrial disorder ①
 Hepatic cyst ①
 Nausea ①
 Rash ①
 Rheumatoid arthritis ②
 Thermal burn ②③
 Urinary tract infection ④

serious
 AE/SAEs
 non-serious

Concomitant medications

ongoing
 resolved

Patient Profile Legend

- Different symbols/colors to distinguish severity, seriousness
- Arrow to indicate whether AE/conMed resolved

Lab Values

	grade = 0		grade = 3
	grade = 1		grade = 4, 5
	grade = 2		w/t CTCAE3.0 grade

CTDB AE/SAE Records

① Mild, Nonserious	▲ Mild, Serious
② Moderate, Nonserious	▲ Moderate, Serious
③ Severe, Nonserious	▲ Severe, Serious
▲ Life-threatening, Serious	▲ Fatal, Serious
→ Not-resolved	— Resolved

Summary

- Graphics are powerful in concisely and efficiently conveying multiple pieces of safety information
- Graphics are useful for efficacy analysis as well
- Graphs are not cure-all, should be used in combination with other statistical analyses methods and display formats
- There is a need for standardized statistical graphical language across industry and regulatory
 - SOPs on validation of graphic outputs are needed
- New tools and processes will facilitate signal detection and clinical trial safety management
- Still much to be done in this area

Reference

- Ohad Amit, Understanding Patients Safety Through Use of Statistical Graphics.
- William Blackwell, Tools for Data Mining and Signal Detection, DIA 19th Annual EuroMeeting
- Simon Day, Signal Detection from Clinical Trial Databases
- Trevor Gibbs, Pharmacovigilance and Risk Management. DIA 19th Euro meeting talk
- Michael O'Connell, Graphic analysis and reporting of safety data, 42th DIA annual meeting talk
- Robert T. O'Neill, Signal Detection in Clinical Trials Some perspectives on New tools and Processes - A Critical Path Update, 19th Annual DIA Eurometing

Acknowledgement

- Rachel Flodin
- Springer Li
- Ying Tian
- Bob Treder
- Jenny Yuan



Back-up Slides

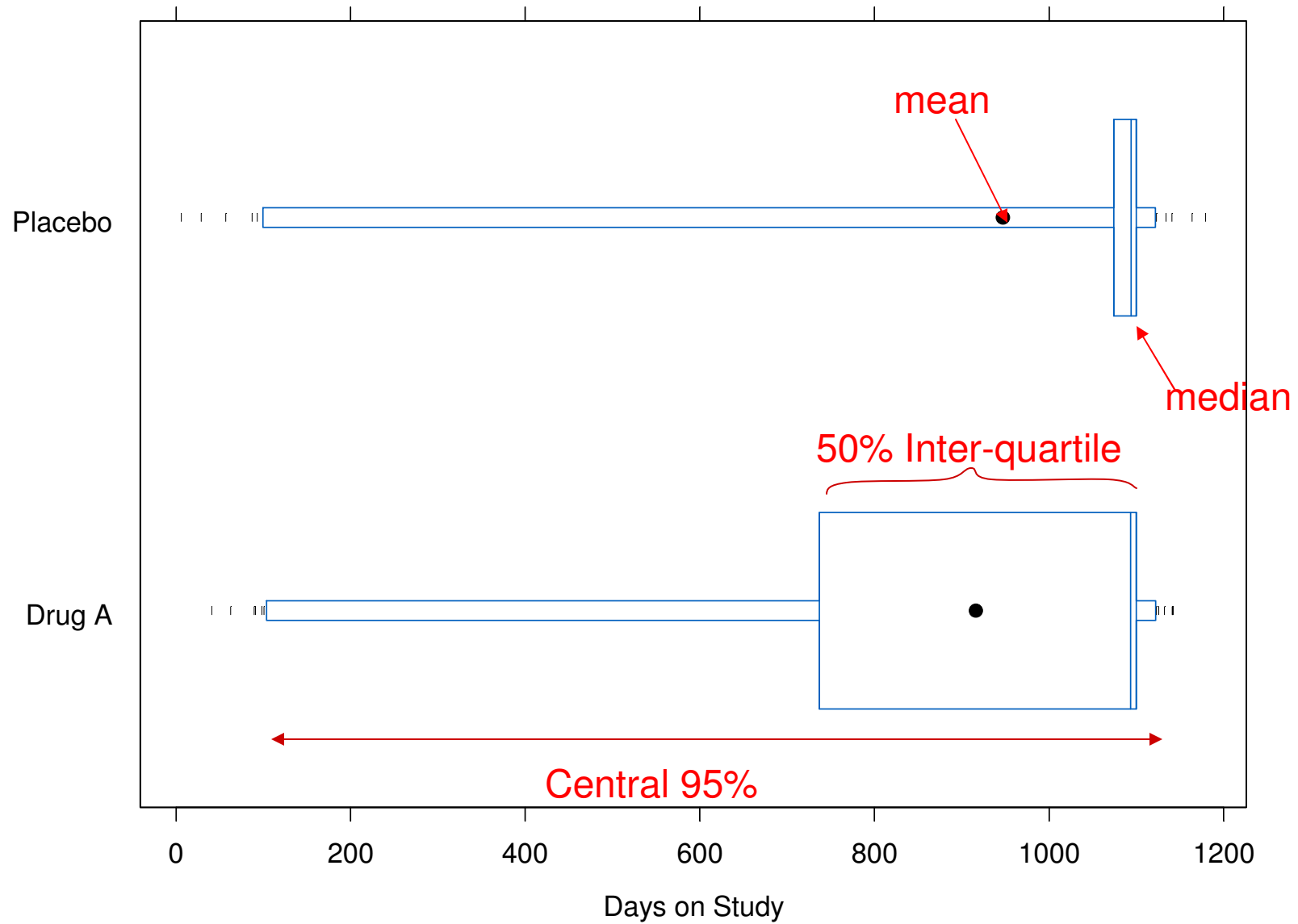
Clinical Trial Safety Analysis

- Safety data are often collected concomitantly in clinical trials - lack of proactive planning
- Safety analyses are usually descriptive in nature - lack of power
- Safety data and analysis results often reported in form of tables and listings – not easy to review and interpret

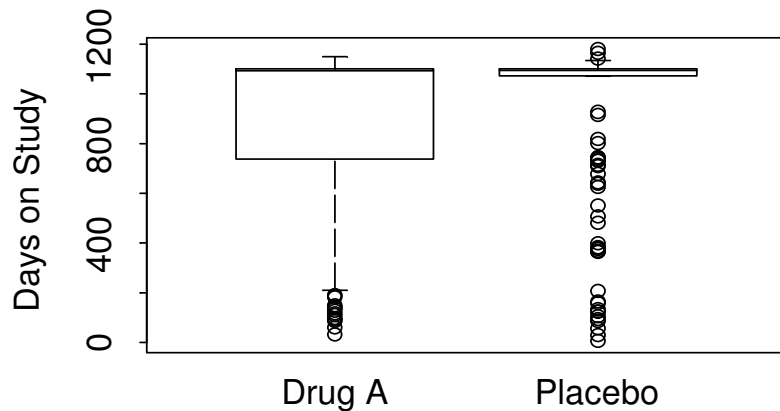
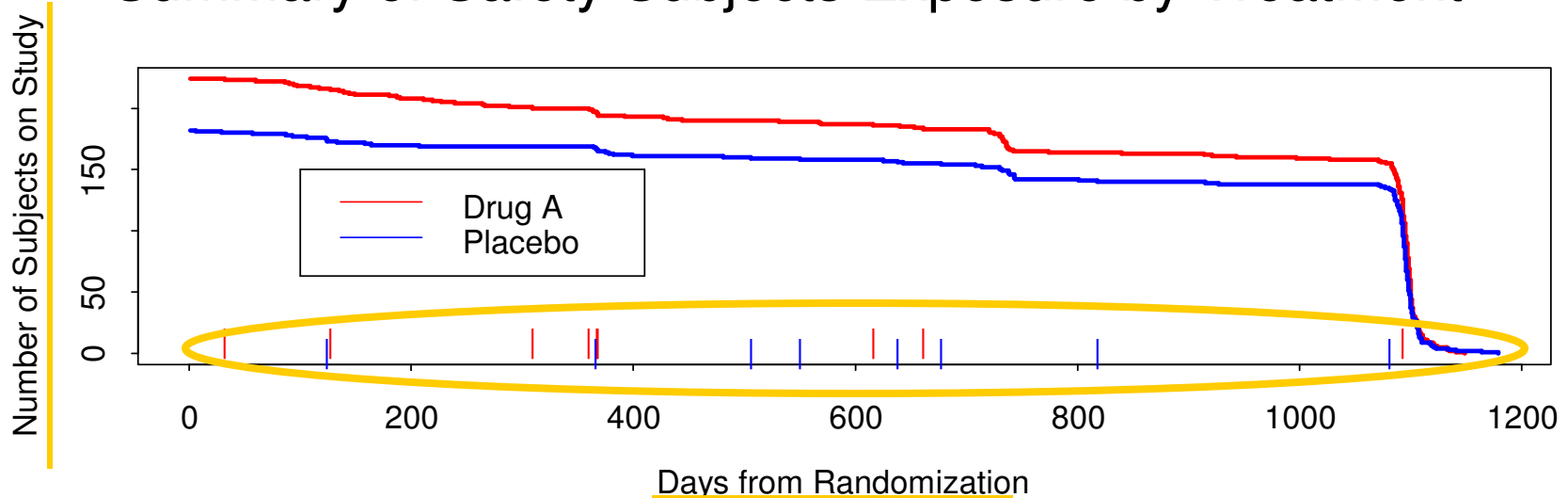
How to Lie With Statistics

- Huff's timeless 1954 classic, *How to Lie With Statistics*. A beginning playbook might read as follows.
- Omit sample size, confidence, and any greeks ("The blindfolded leading the blind.")
- Sample high, but use a flawed methodology to drive action from biased conclusions ("Measure with a micrometer, mark with a crayon, cut with an axe.")
- Sample low, or at least sub-sample until the means tell an insightful story ("Throw it against the wall and see what sticks. Okay, throw it again.")

Summary of Safety Subjects Exposure by Treatment

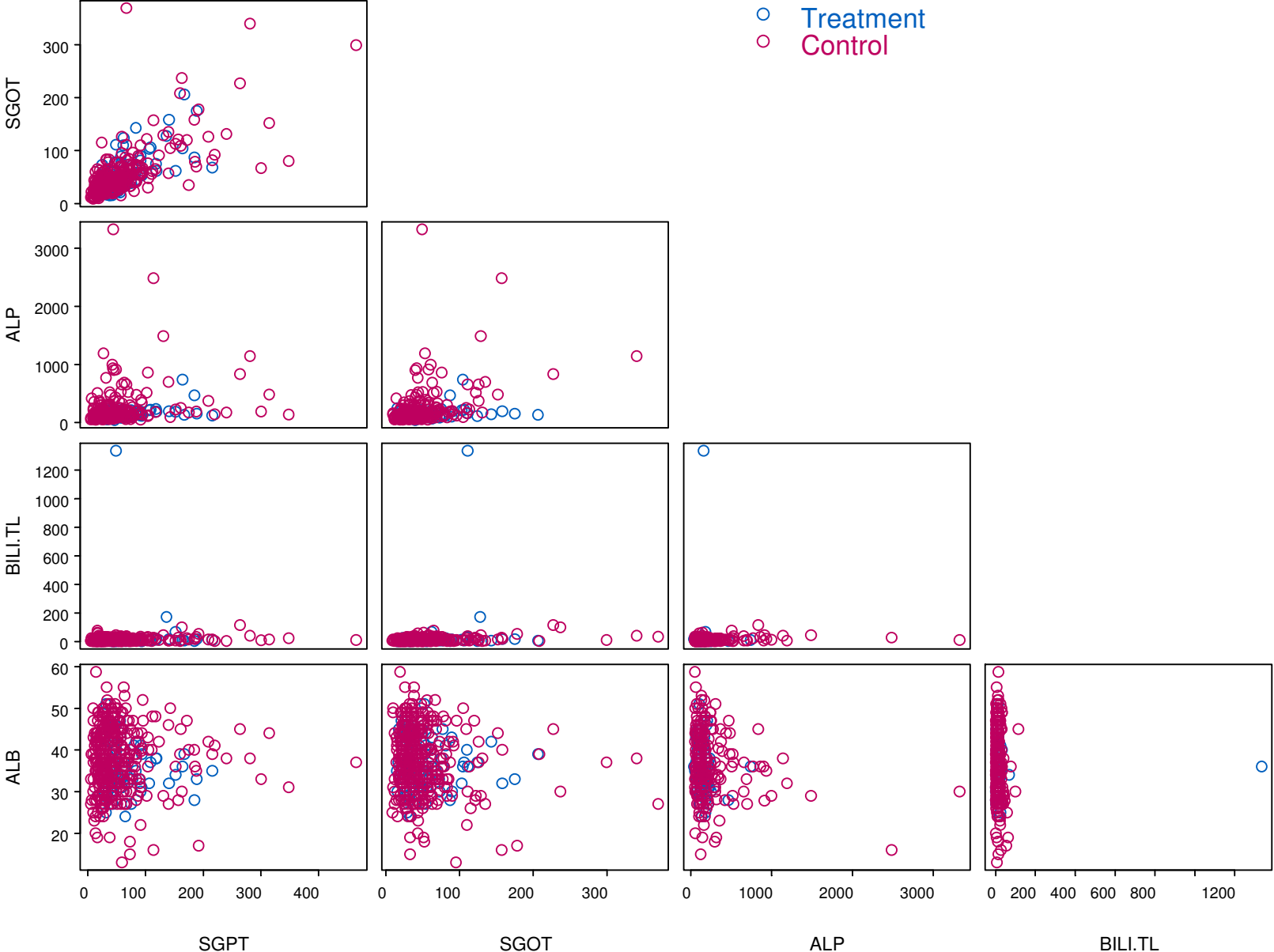


Summary of Safety Subjects Exposure by Treatment

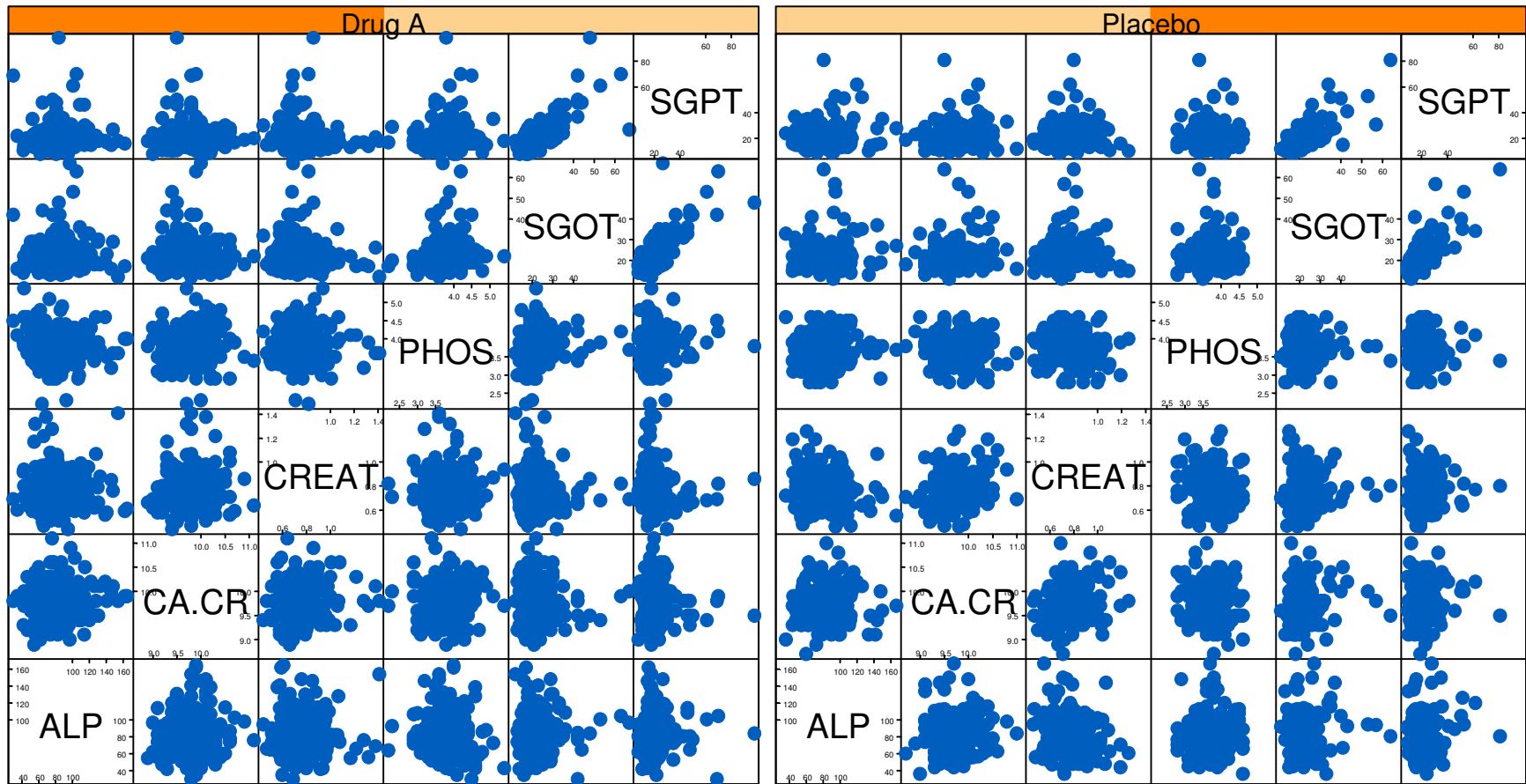


Drug A	Placebo
n :224	n :182
Min.: 32.0	Min.: 6.0
1st Qu.: 737.0	1st Qu.:1074.0
Median:1094.0	Median:1094.0
Mean: 916.3	Mean: 947.2
3rd Qu.:1100.0	3rd Qu.:1100.0
Max.:1149.0	Max.:1179.0

Lab Scatter Plot



Baseline Lab Values



Glucose by Time

