General Principles, Illustrations and Wiki Resources for Improving Statistical Graphs

F. Bancken (Novartis) on behalf of FDA-Industry-Academia Safety Graphics Working Group

BBS Meeting – September 5, 2011

Acknowledgements: Andreas Bruckner (Bayer), Susan Duke (GSK) , Richard Forshee (FDA)

Agenda

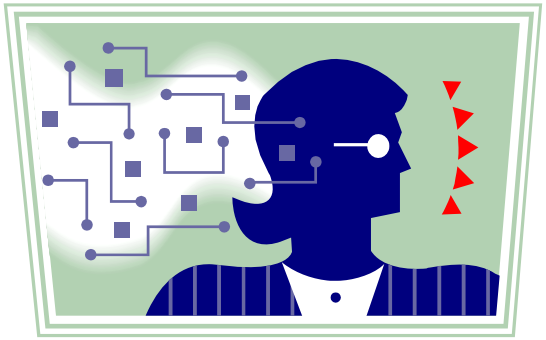
- Motivation
  - Graphs make a difference
  - Graphical Perception
- Framework
  - Catalog of clinical questions and associated graphs
  - Examples
- General Principles
  - Graph Navigator, Glossary, Do's and Don'ts
- Conclusions

Motivation

We All Would Agree

- Study teams
- Decision-makers
- Prescribers
- Patients

Benefit from easy ways to understand results



Obvious?

Then why aren't there more graphs in submissions?

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Recommended for Adoption

at Step 4 of the ICH Process

on 5 February 1998

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group

ICH E9 – Statistical Principles

3.3.3 Trials to Show Dose-response Relationship

For this purpose the application of procedures to estimate the relationship between dose and response, including the construction of confidence intervals and the **use of graphical methods,** is as important as the use of statistical tests.

6.4 Statistical Evaluation

In most trials the safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation. **It is also valuable to make use of graphical presentations in which patterns of adverse events are displayed** both within treatment groups and within subjects.

Motivation

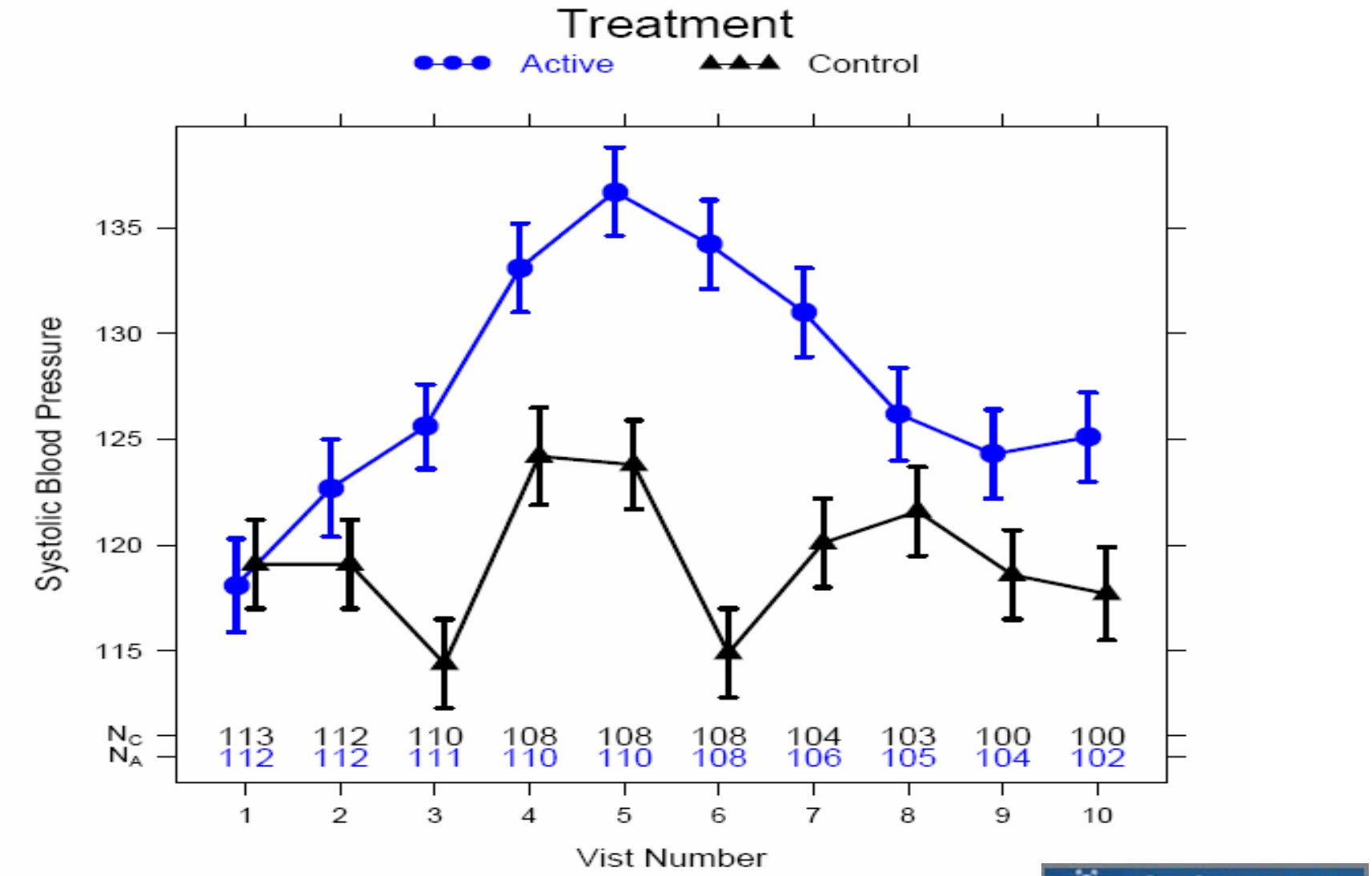
Example 1: Understanding the Trend

Tabular Summary of Systolic Blood Pressure Over Time:

	Active Drug				Control Drug			
Visit	**N**	**Mean**	**SD**	**95% CI**	**N**	**Mean**	**SD**	**95% CI**
1	112	118.1	1.3	(115.9, 120.3)	113	119.1	1.2	(117.0, 121.2)
2	112	122.7	1.4	(120.4, 125.0)	112	119.1	1.1	(117.0, 121.2)
3	111	125.6	1.0	(123.6, 127.6)	110	114.4	1.2	(112.3, 116.5)
4	110	133.1	1.2	(131.0, 135.2)	108	124.2	1.4	(121.9, 126.5)
5	110	136.7	1.2	(134.6, 138.8)	108	123.8	1.2	(121.7, 125.9)
6	108	134.2	1.1	(132.1, 136.3)	108	114.9	1.1	(112.8, 117.0)
7	106	131.0	1.2	(128.9, 133.1)	104	120.1	1.2	(118.0, 122.2)
8	105	126.2	1.3	(124.0, 128.4)	103	121.6	1.2	(119.5, 123.7)
9	104	124.3	1.2	(122.2, 126.4)	100	118.6	1.1	(116.5, 120.7)
10	102	125.1	1.2	(123.0, 127.2)	100	117.7	1.3	(115.5, 119.9)

Motivation

Example 1: Understanding the Trend



Motivation
Example 2: Detecting patterns in AE profiles

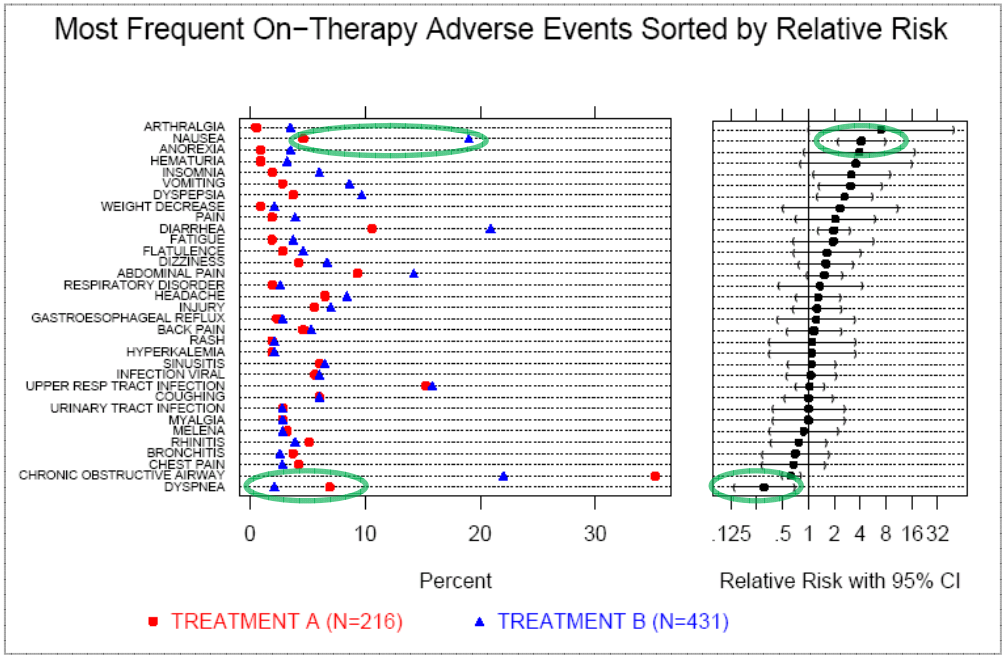
- *40-60% of the human brain is devoted to visualization*
- *Human visual capability is far ahead of the computer*

Data in Table Format

Event	Drug A (%)	Drug B (%)	RelRisk	Low95%	Up95%
ARTHRALGIA	3.5	0.5	7.0	1.6	31.5
NAUSEA	19.0	4.6	4.1	2.5	6.9
ANOREXIA	3.5	0.9	3.9	1.2	13.1
HEMATURIA	3.2	0.9	3.6	1.0	12.2
INSOMNIA	6.0	1.9	3.2	1.3	7.5
VOMITING	8.6	2.8	3.1	1.5	6.2
DYSPEPSIA	9.7	3.7	2.6	1.4	4.9
WEIGHT DECREASE	2.1	0.9	2.3	0.6	9.0
PAIN	3.9	1.9	2.1	0.8	5.3
DIARRHEA	20.9	10.6	2.0	1.4	2.9
FATIGUE	3.7	1.9	1.9	0.7	5.1
FLATULENCE	4.6	2.8	1.6	0.7	3.7
DIZZINESS	6.7	4.2	1.6	0.8	3.1
ABDOMINAL PAIN	14.2	9.3	1.5	1.0	2.4
RESPIRATORY DISORDER	2.6	1.9	1.4	0.5	4.0
HEADACHE	8.4	6.5	1.3	0.7	2.3
INJURY	7.0	5.6	1.2	0.7	2.3
GASTROESOPHAGEAL REFLUX	2.8	2.3	1.2	0.4	3.3
BACK PAIN	5.3	4.6	1.2	0.6	2.3
HYPERKALEMIA	2.1	1.9	1.1	0.4	3.4
RASH	2.1	1.9	1.1	0.4	3.4
SINUSITIS	6.5	6.0	1.1	0.6	2.0
INFECTION VIRAL	6.0	5.6	1.1	0.6	2.1
UPPER RESP TRACT INFECTION	15.8	15.3	1.0	0.7	1.5
MYALGIA	2.8	2.8	1.0	0.4	2.6
URINARY TRACT INFECTION	2.8	2.8	1.0	0.4	2.6
COUGHING	6.0	6.0	1.0	0.5	1.9
MELENA	2.8	3.2	0.9	0.3	2.2
RHINITIS	3.9	5.1	0.8	0.4	1.7
BRONCHITIS	2.6	3.7	0.7	0.3	1.8
CHEST PAIN	2.8	4.2	0.7	0.3	1.6
CHRONIC OBSTRUCTIVE AIRWAY	22.0	35.2	0.6	0.5	0.8
DYSPNEA	2.1	6.9	0.3	0.1	0.8

Where is the signal?

Identical Data in Graph



Signals easily identified
(the human brain is good at pattern recognition)

Motivation
Graphical Perception

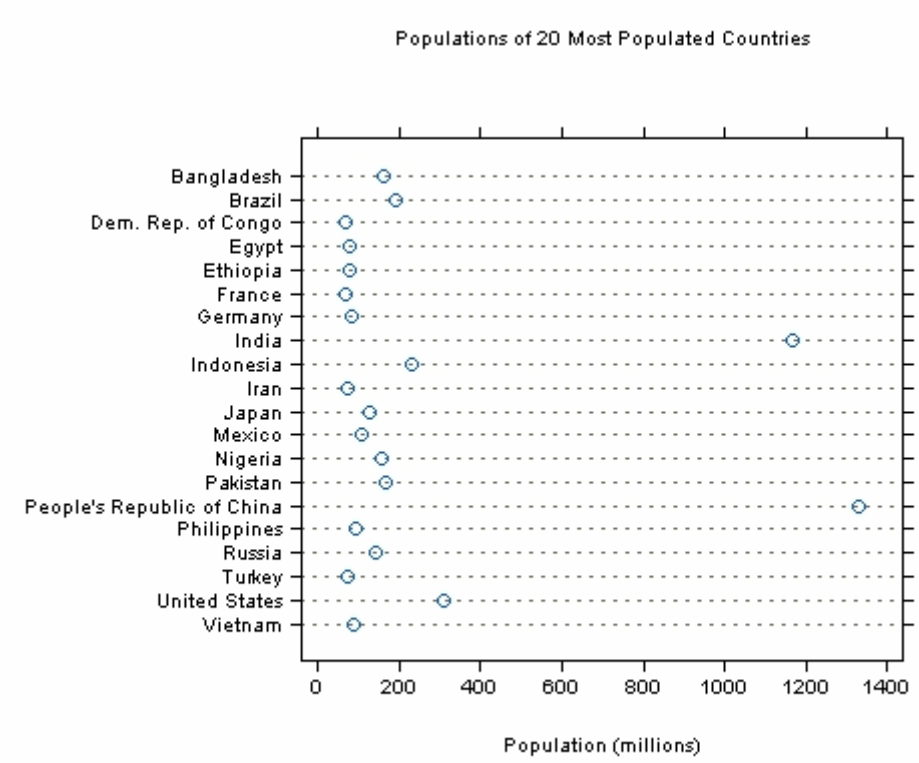
"When a graph is constructed, information is *encoded*. The *visual decoding* of this encoded information is *graphical perception*.

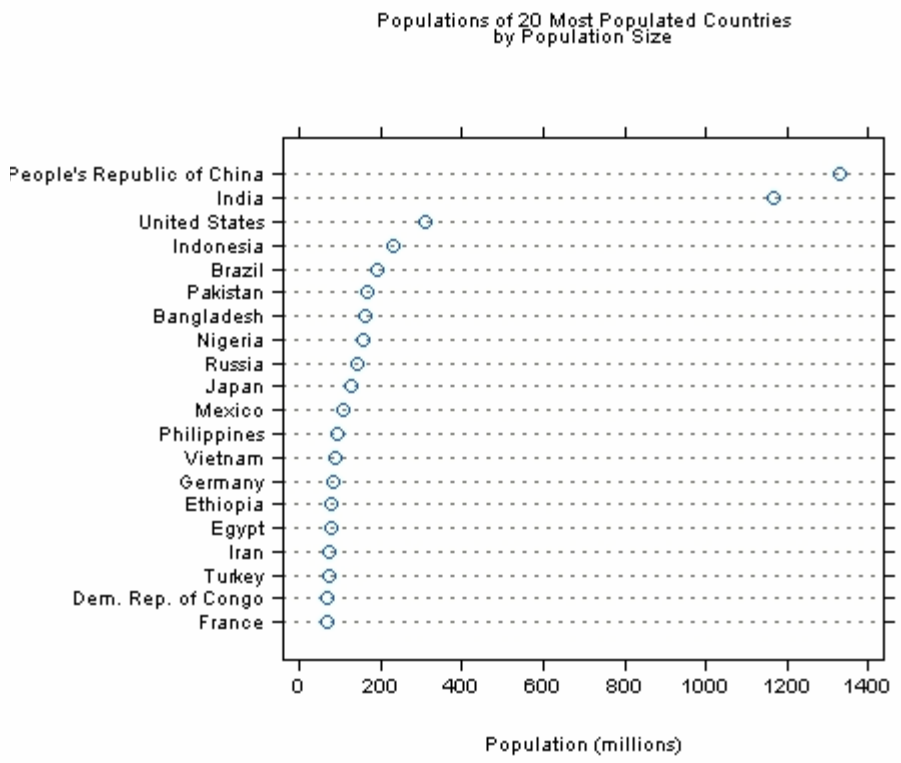
The decoding is the vital link …

No matter how ingenious the encoding … and no matter how technologically impressive the production, a graph is a failure if the visual decoding fails."

William Cleveland, The Elements of Graphing Data

Motivation
Graphical Perception





Source: Wikipedia

Concept from William Cleveland, *The Elements of Graphing Data*

Motivation

- Graphical vizualisation of a product‘s safety and efficacy data should be
  - More used (internal review, reports for submission)
  - When used,

    The choice of graph and its detailed design should allow a quick decode of the information

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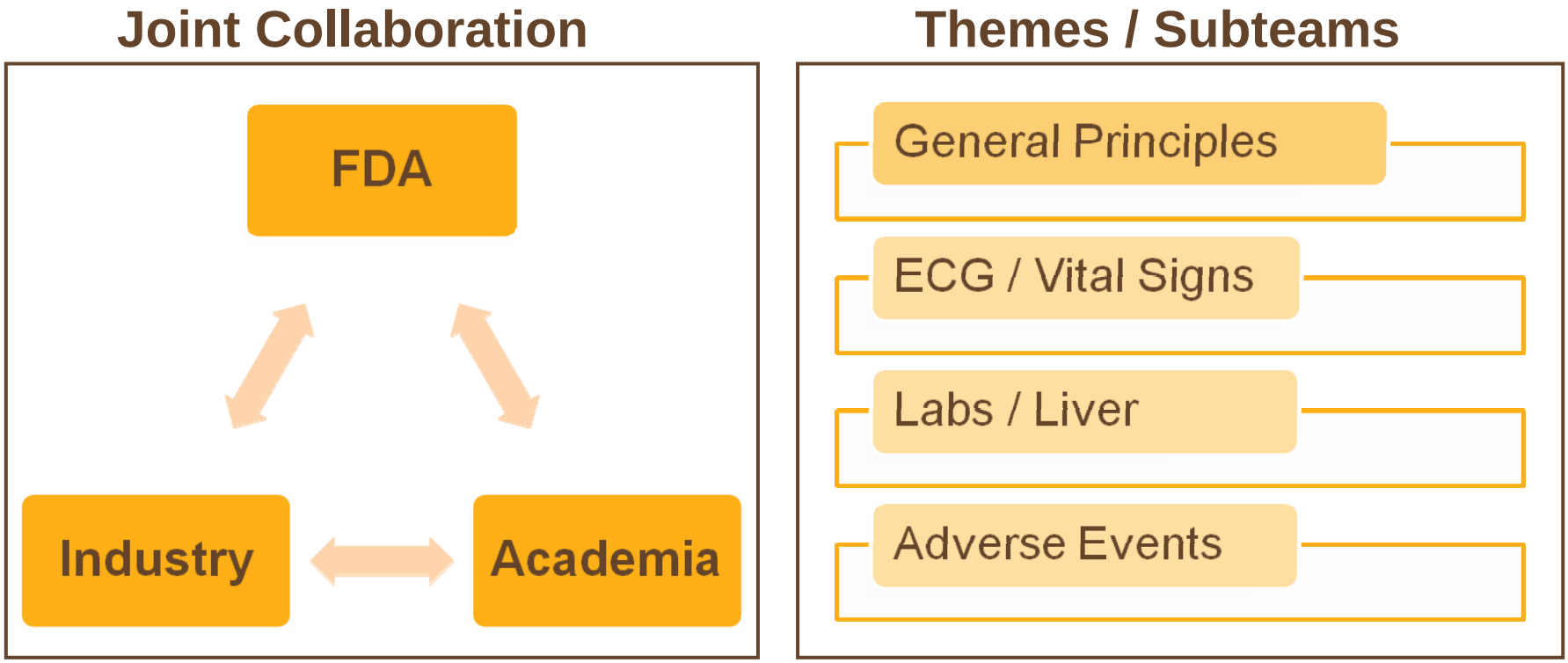
Framework



http://www.ctspedia.org

Members of the FDA/Industry/Academia Safety Graphics Working Group

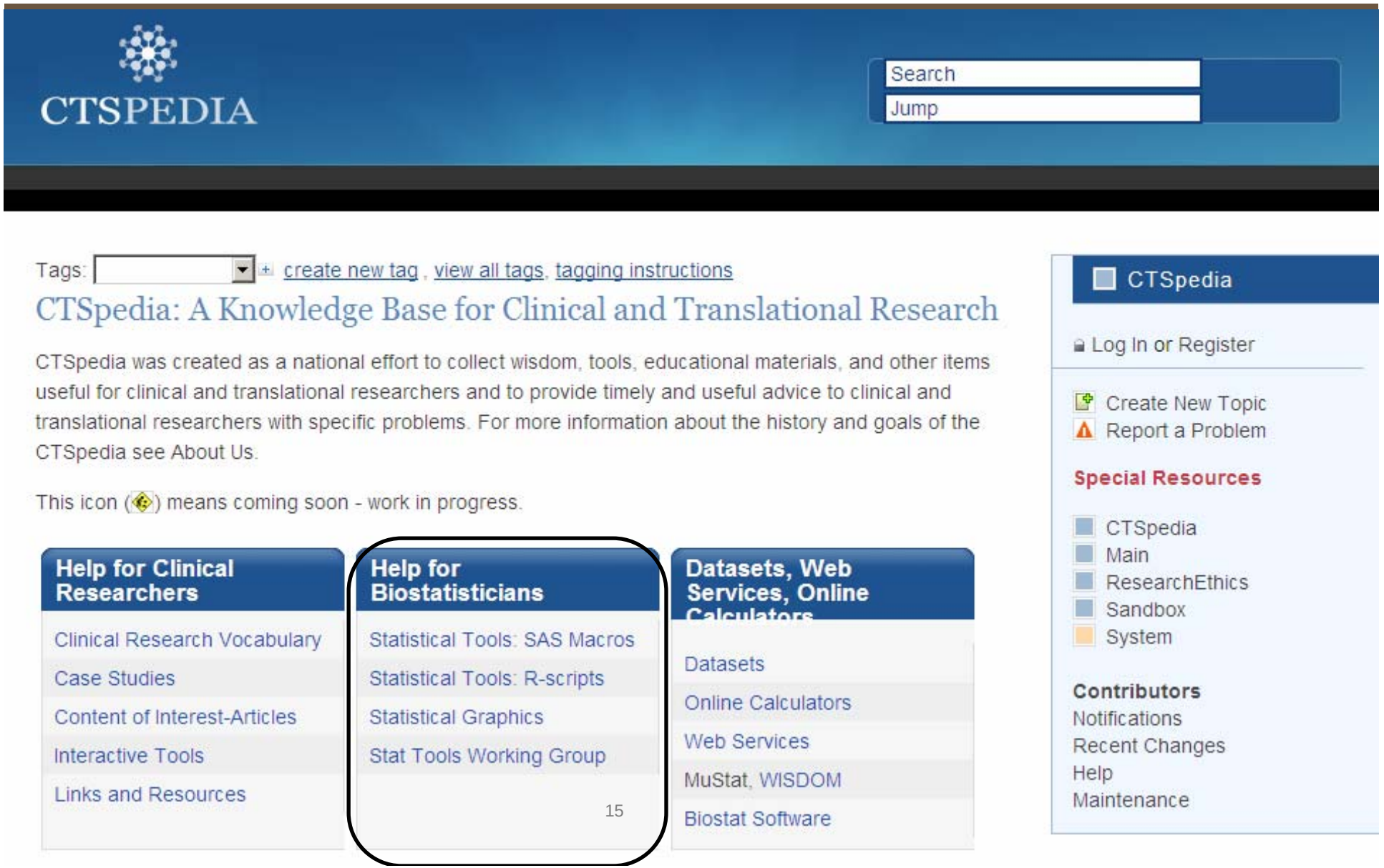
- *Regulatory*: **Mat Soukup, George Rochester**, Antonio Paredes, Chuck Cooper, Eric Frimpong, Hao Zhu, Janelle Charles, Jeff Summers, Joyce Korvick, Leslie Kenna, Mark Walderhaug, Pravin Jadjav, Richard Forshee, Robert Fiorentino, Suzanne Demko, Ted Guo, Yaning Wang,
- *Industry*: **Ken Koury, Brenda Crowe,** Andreas Brueckner, Andreas Krause, Fabrice Bancken, Larry Gould, Liping Huang, Mac Gordon, Matthew Gribbin, Navdeep Boparai, Qi Jiang, Rich Anziano, Susan Duke, Sylvia Engelen,
- *Academia*: Frank Harrell, Mary Banach

Co-leads are in bold font

Project Objectives

1. Develop a palette of statistical graphics for reporting on clinical trial safety data.
2. Identify areas particularly applicable or useful to regulatory review in which graphics can enhance understanding of safety information.
3. Recommend graphics for clinical data based on good scientific principles and best practices.
4. Create a publicly-available repository of sample graphics (ensuring appropriate credits are given for contributions), including data sets and code.
5. Educate and engage stakeholders through outreach activities.

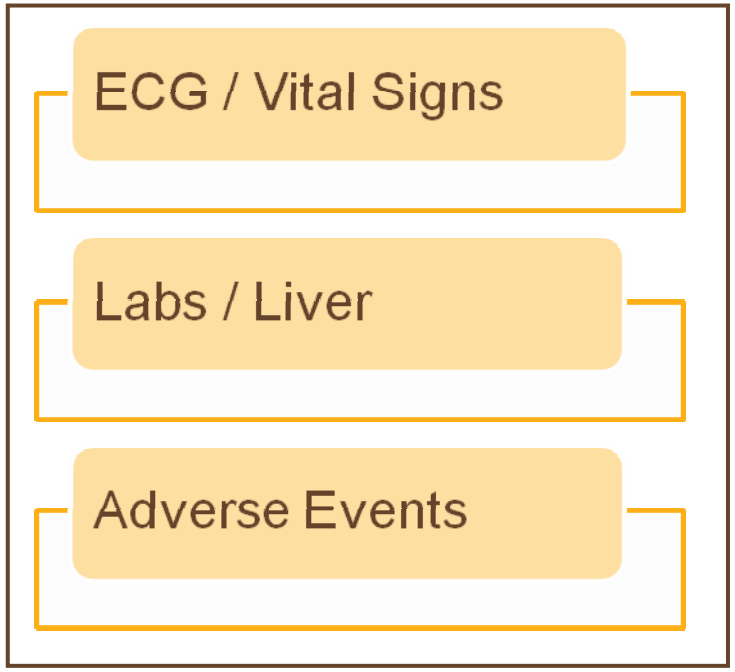
CTSpedia Screenshot (www.ctspedia.org)



CTSpedia Screen

Catalog of clinical questions and associated graphs

Themes



Catalog Entries

- Required Fields
  - **Illustration**,
  - Title, Description,
  - Background [**clin.question**],
  - Use (reporting / exploratory),
  - Keywords
  - Author,
  - Software used, **Code,**
- Optional Fields
  - References, Data
- Categorization
  - **Graph Type** (bar, box plot, dot plot ...)

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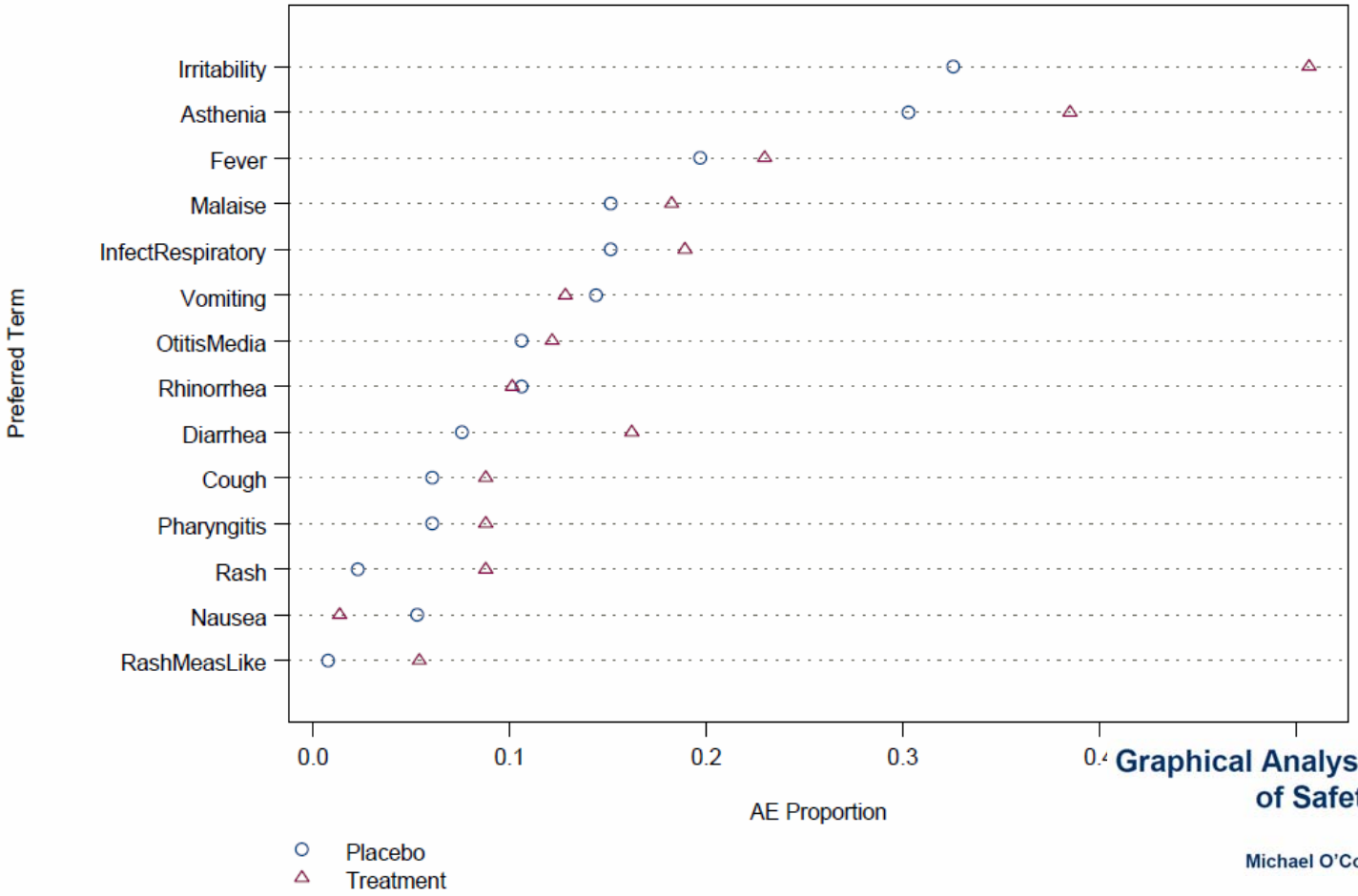
Example 1 - Incidence of AE

Which AEs are elevated in treatment vs. control?

Grouped Dotplot



Graphical Analysis and Reporting of Safety Data

Michael O'Connell, Ph.D.

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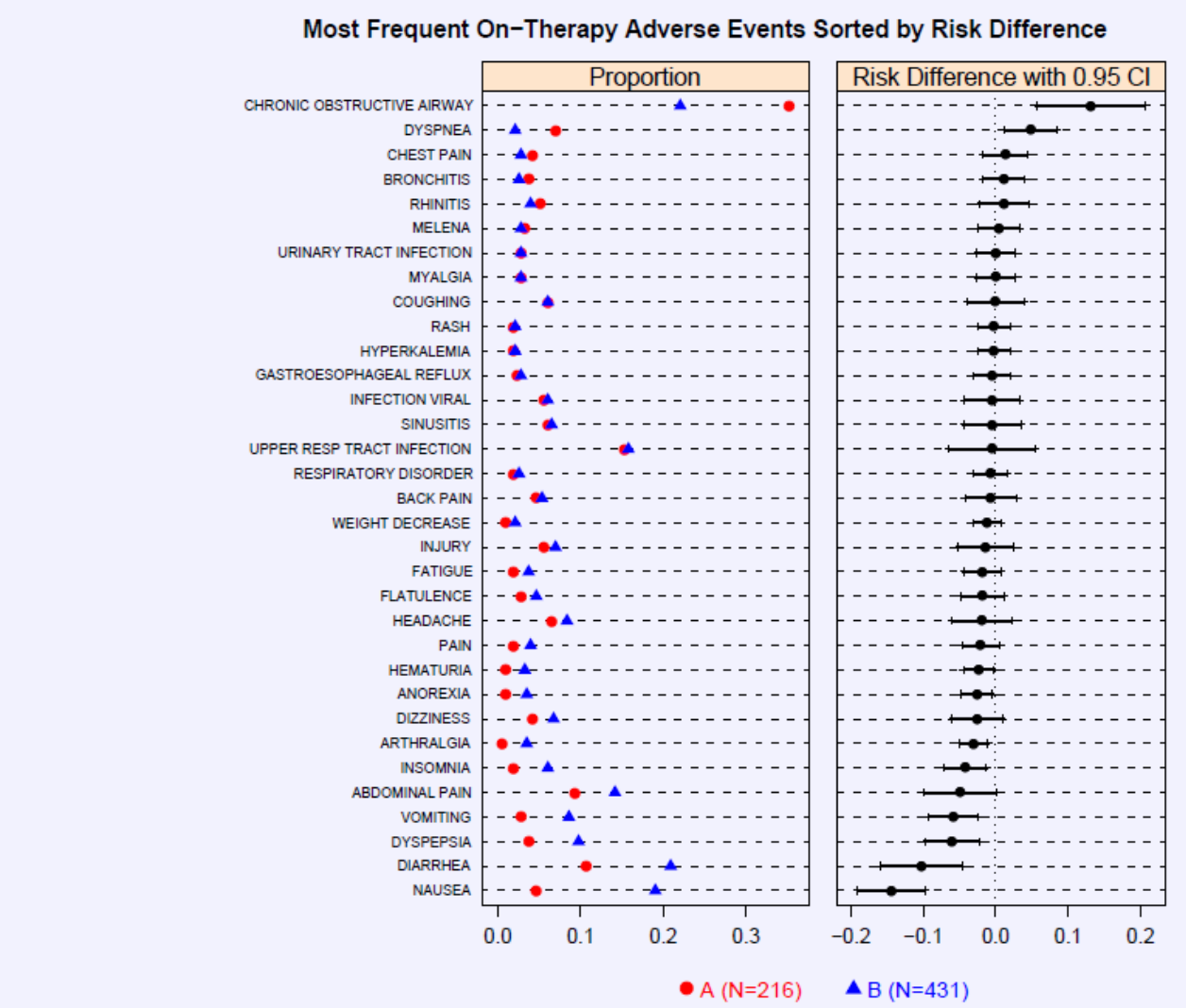
Example 2 - Incidence of AE

Which AEs are elevated in treatment vs. control?



Use of Graphics in Clinical Trials

Frank E Harrell Jr

Department of Biostatistics, Vanderbilt University School of Medicine

Joint Statistical Meetings 3 August 2010

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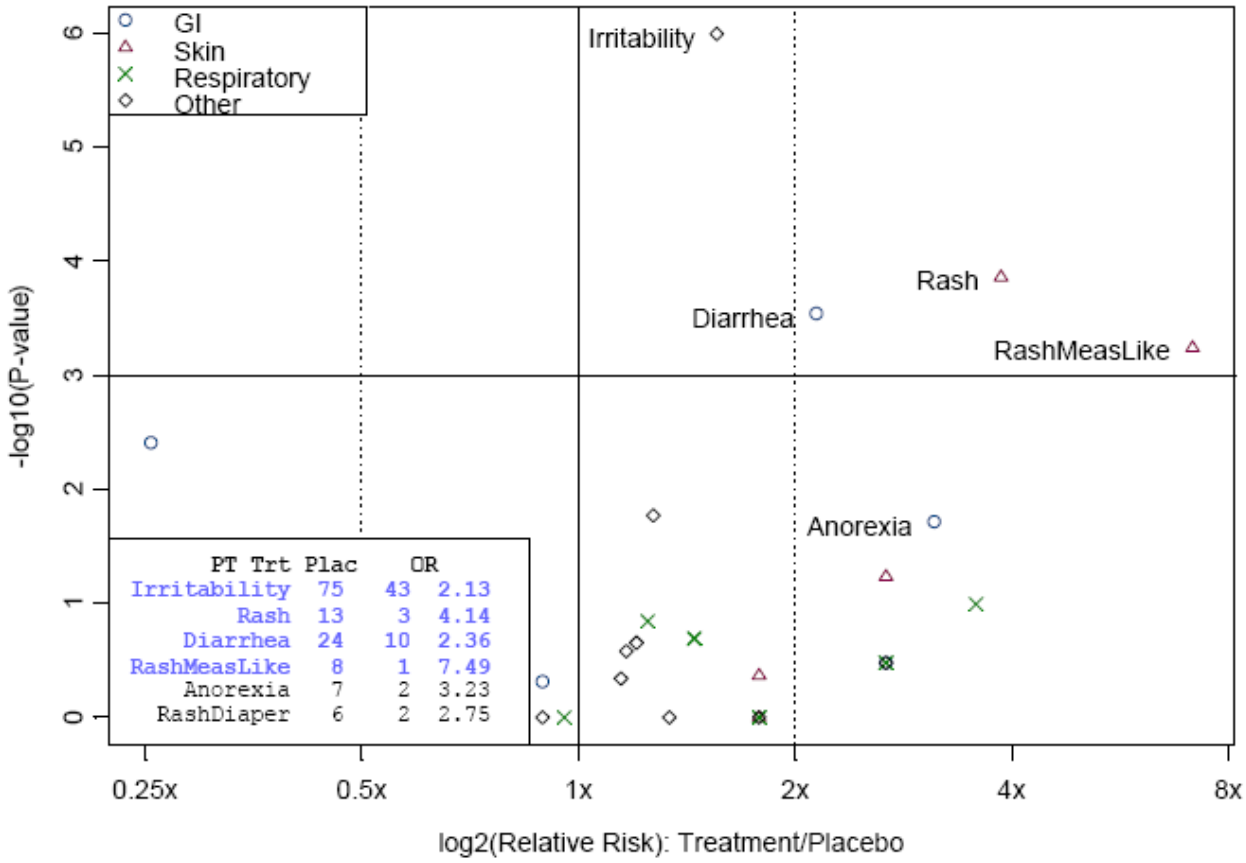
Example 3 – What is the safety profile of the drug?

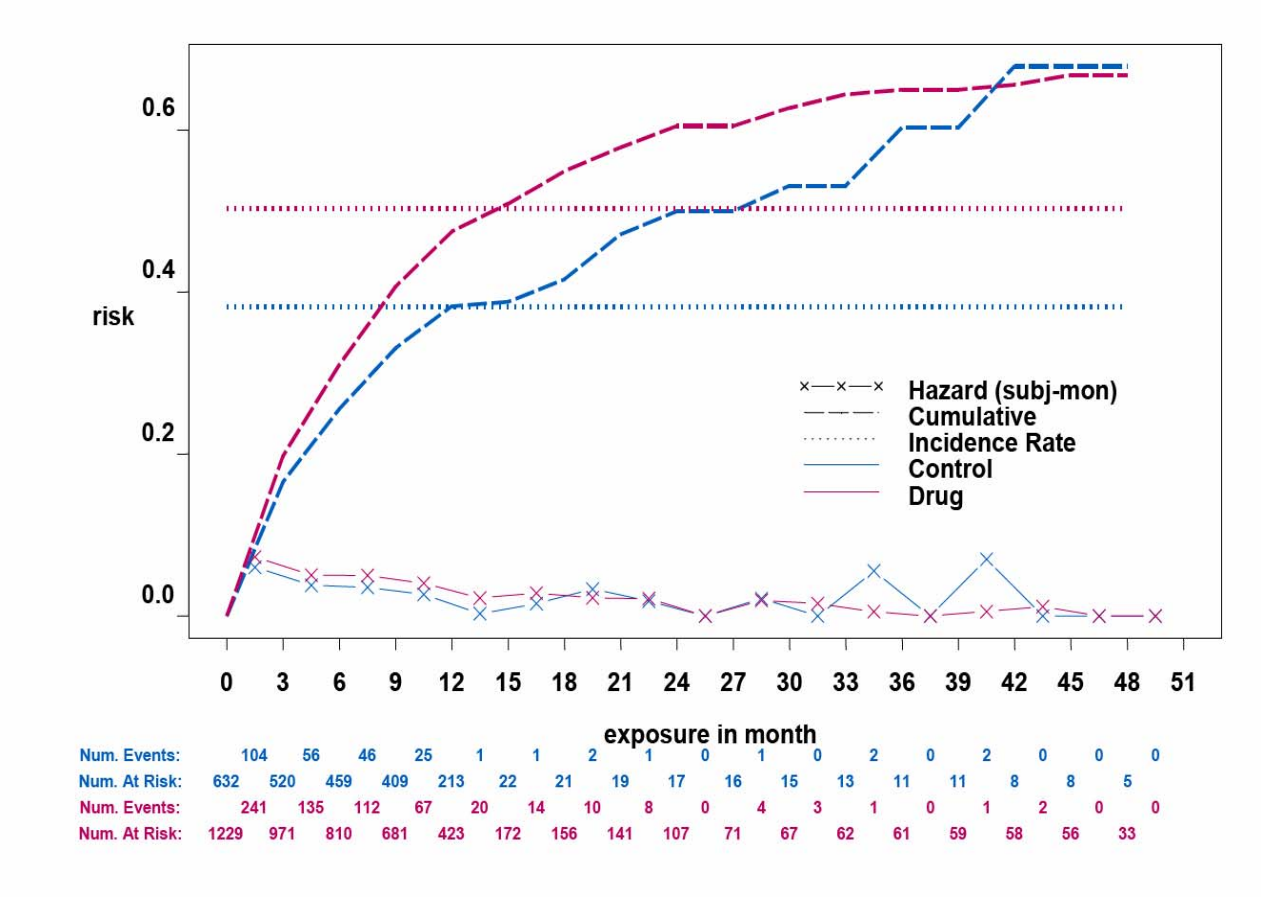
Which AEs are elevated in treatment vs. control?



*It shows the relative risk or ratio of the adverse event rates on the x-axis and the p-value comparing treatment and control on the y-axis. The additional information on the p-value of the treatment effect is important since it incorporates the number of observed events and confidence in the treatment effect.

Example 4 - AE Occurrence over time

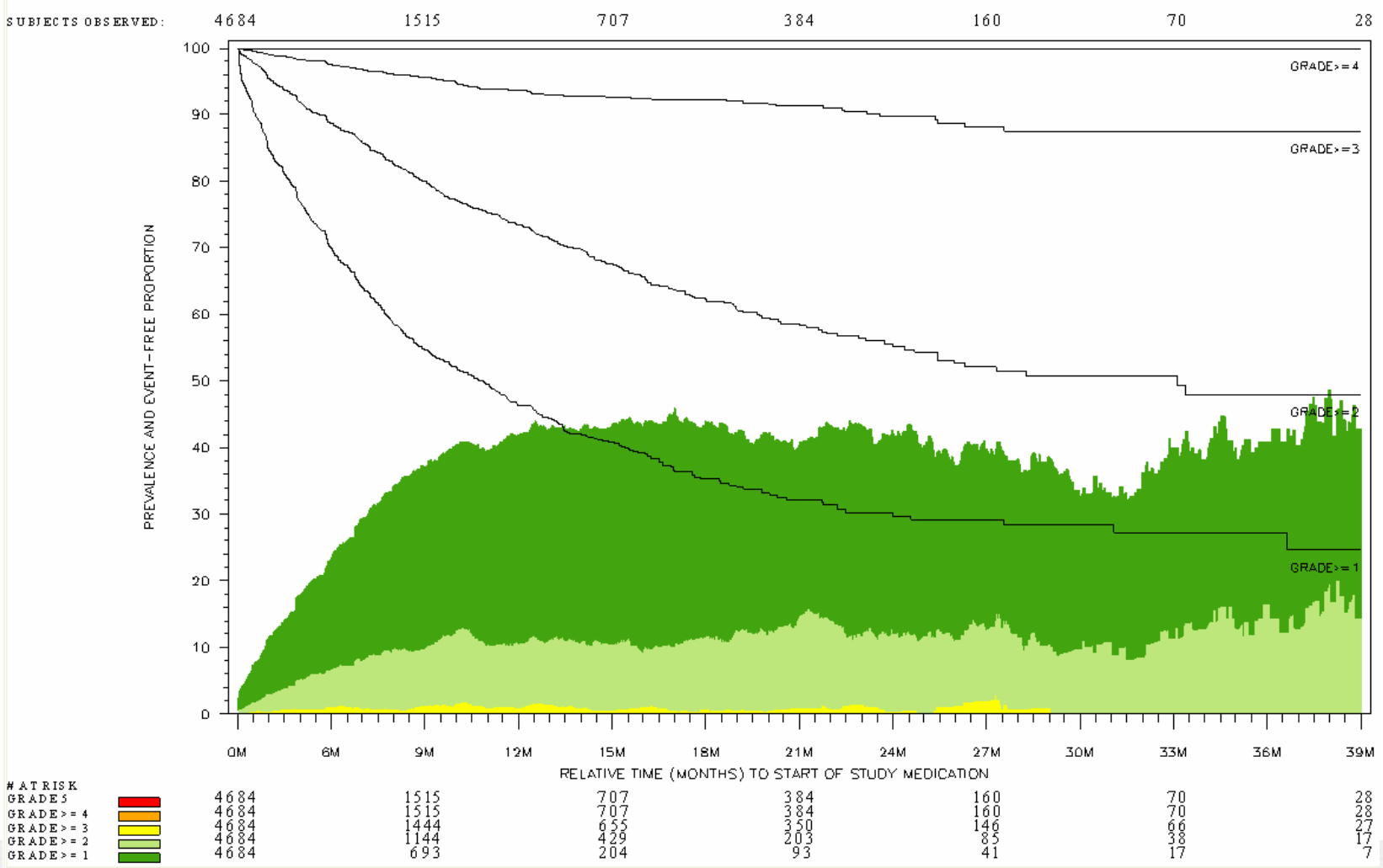
Is there a difference in the time to event?



Source: Xia A, 2011

Example 5 - AE Occurrence over time

Incidence Prevalence Plot



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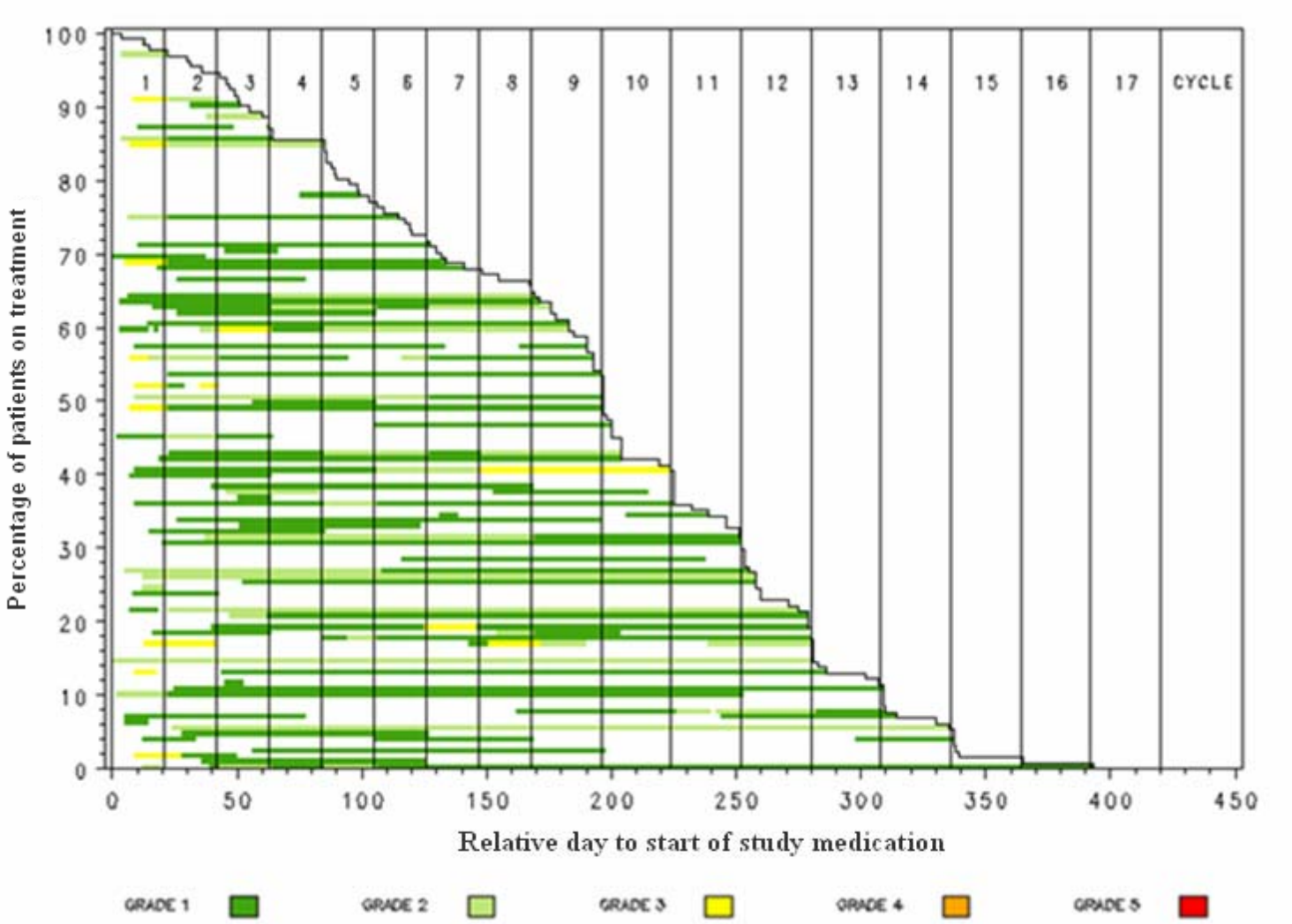
Example 6 - AE Occurrence over time

Event History Plot



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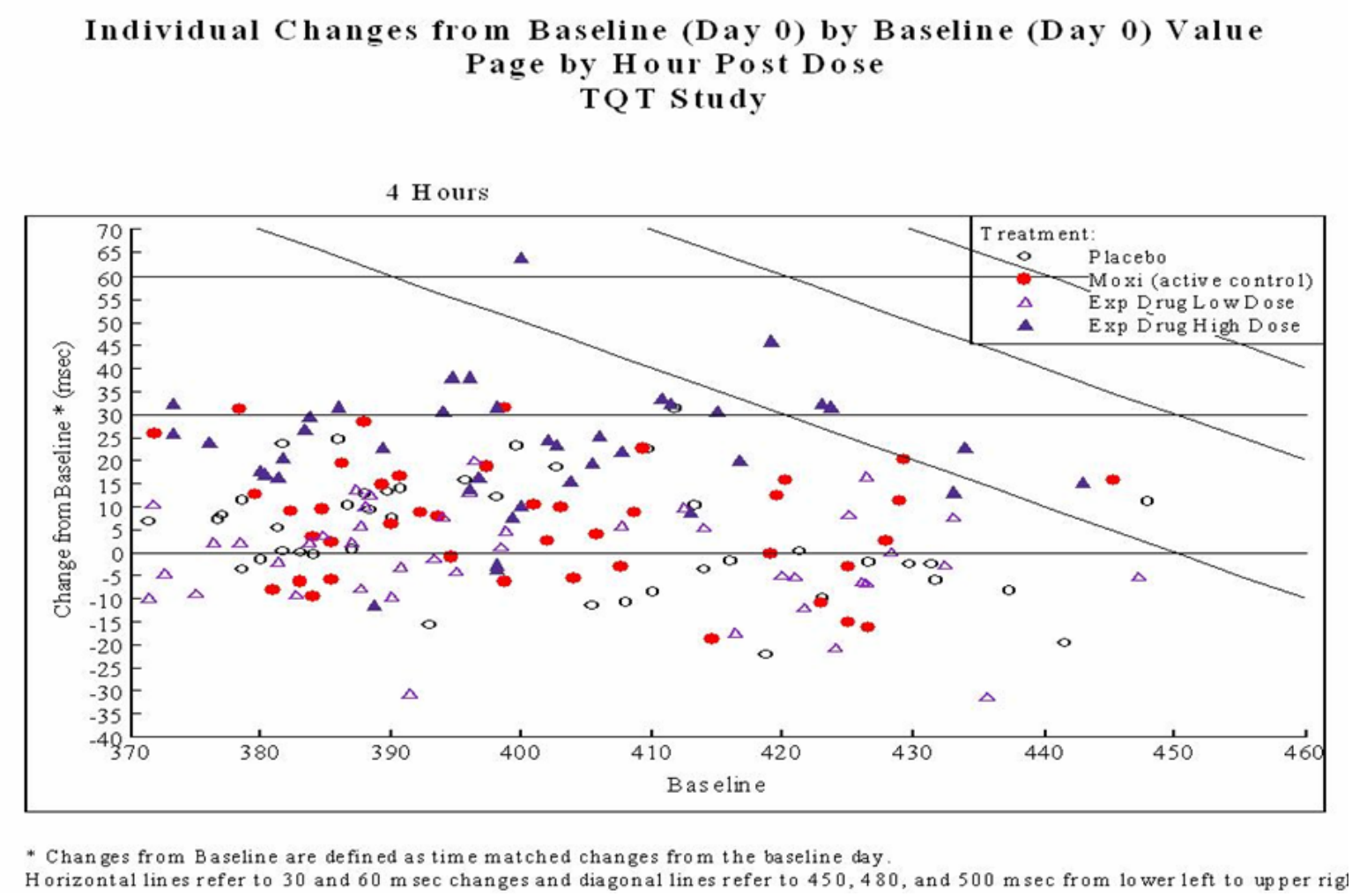
ECG example

Subjects with significant changes and absolute values of QTc



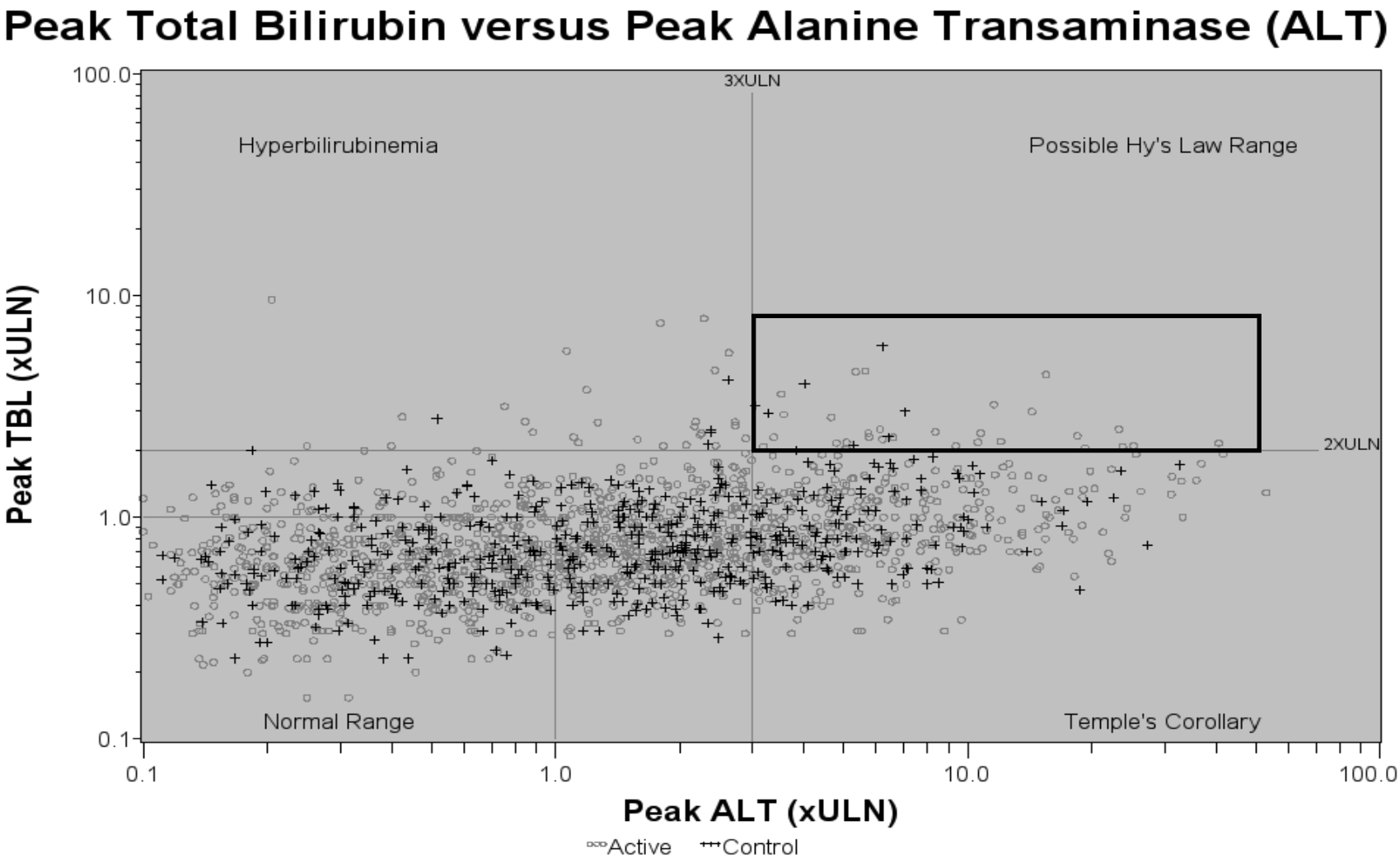
* Changes from Baseline are defined as time matched changes from the baseline day.
Horizontal lines refer to 30 and 60 msec changes and diagonal lines refer to 450, 480, and 500 msec from lower left to upper rig

ECG example

Subjects with significant changes and absolute values of QTc

- Design shortcoming of this graph type: regression to the mean
- The majority of large changes occur in subjects with low baseline
- Values of real concern are large changes with large absolute values – upper right is area of concern
- This couldn't be assessed with a table where absolute and changes are presented separately – the dependence of one on the other is lost with tabular displays

LFT example
Subjects with elevated ALT and Bilirubin



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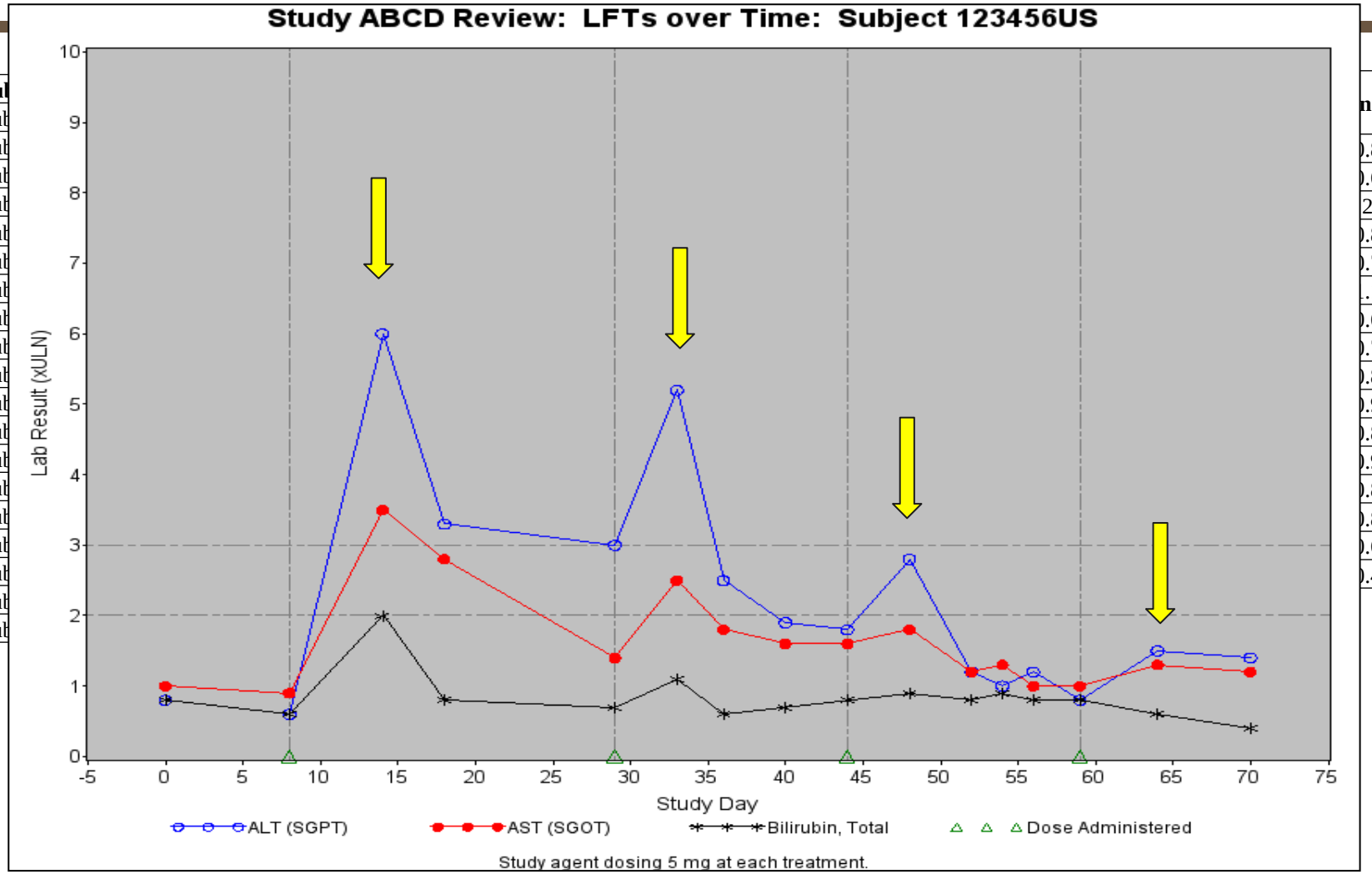
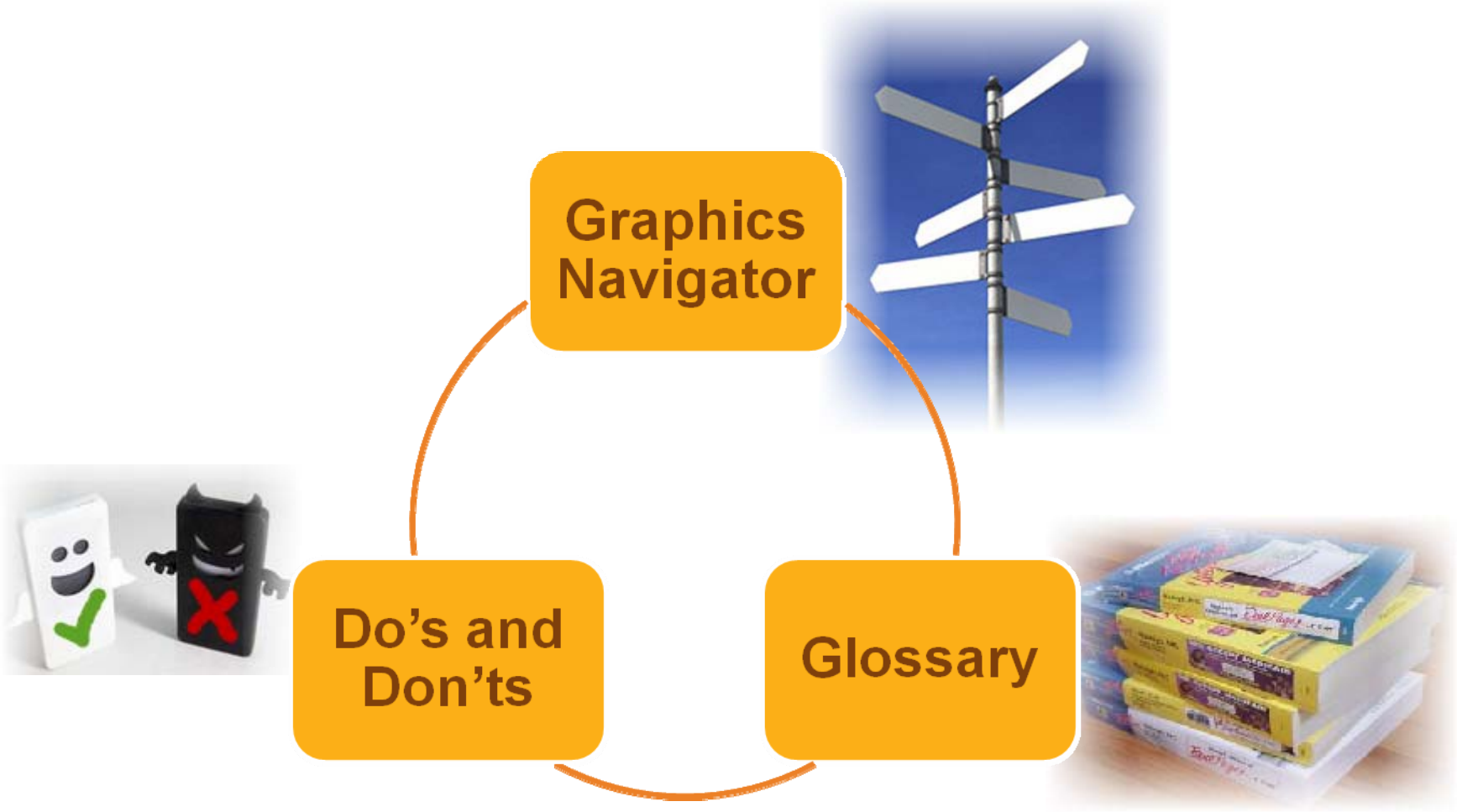
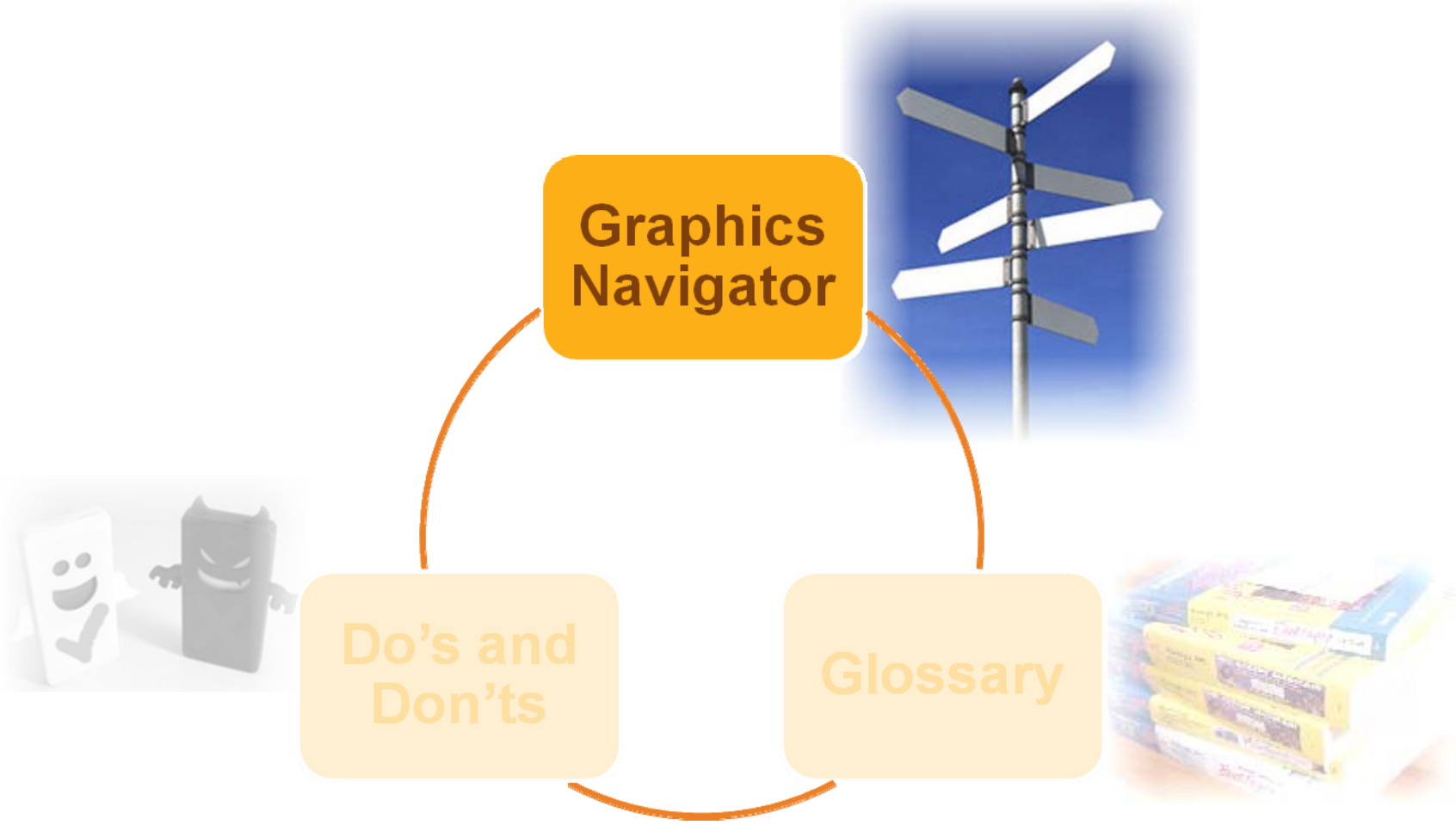
Simple and Powerful



General Principles

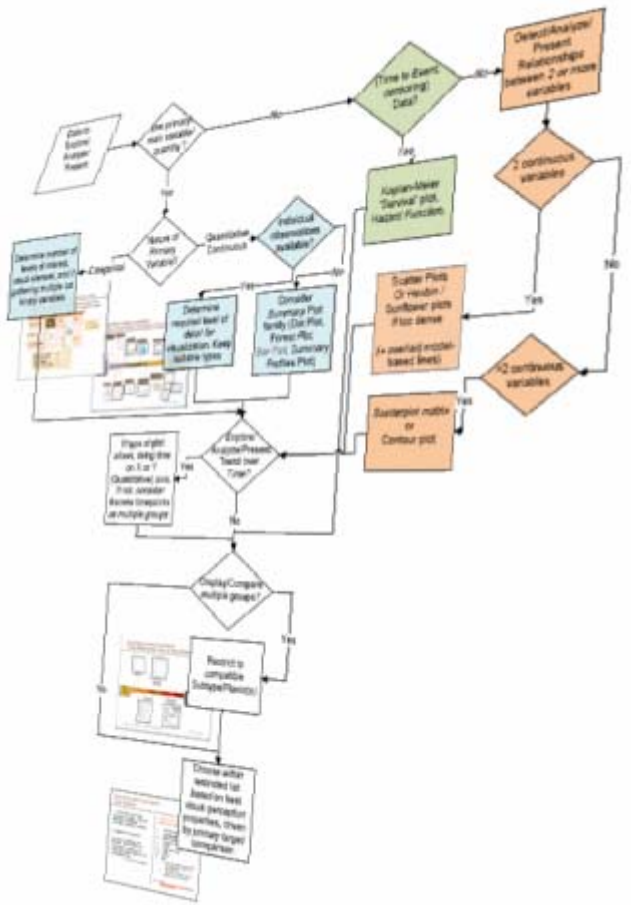


General Principles



Graphics Navigator - Main Flow Diagram

- Main drivers
  - Type (categ., quant.) of variables
  - Number of Variables
  - Number of levels of categorical variables
  - Level of detail needed for the distribution (quant.),
  - Visual Perception Criteria



Graphics Navigator - Main Flow Diagram

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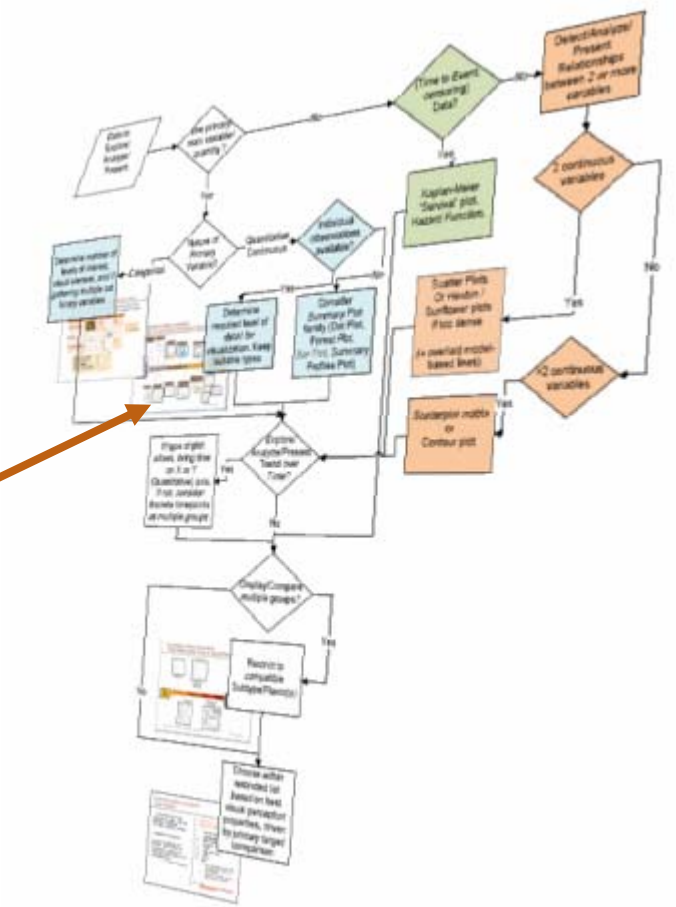
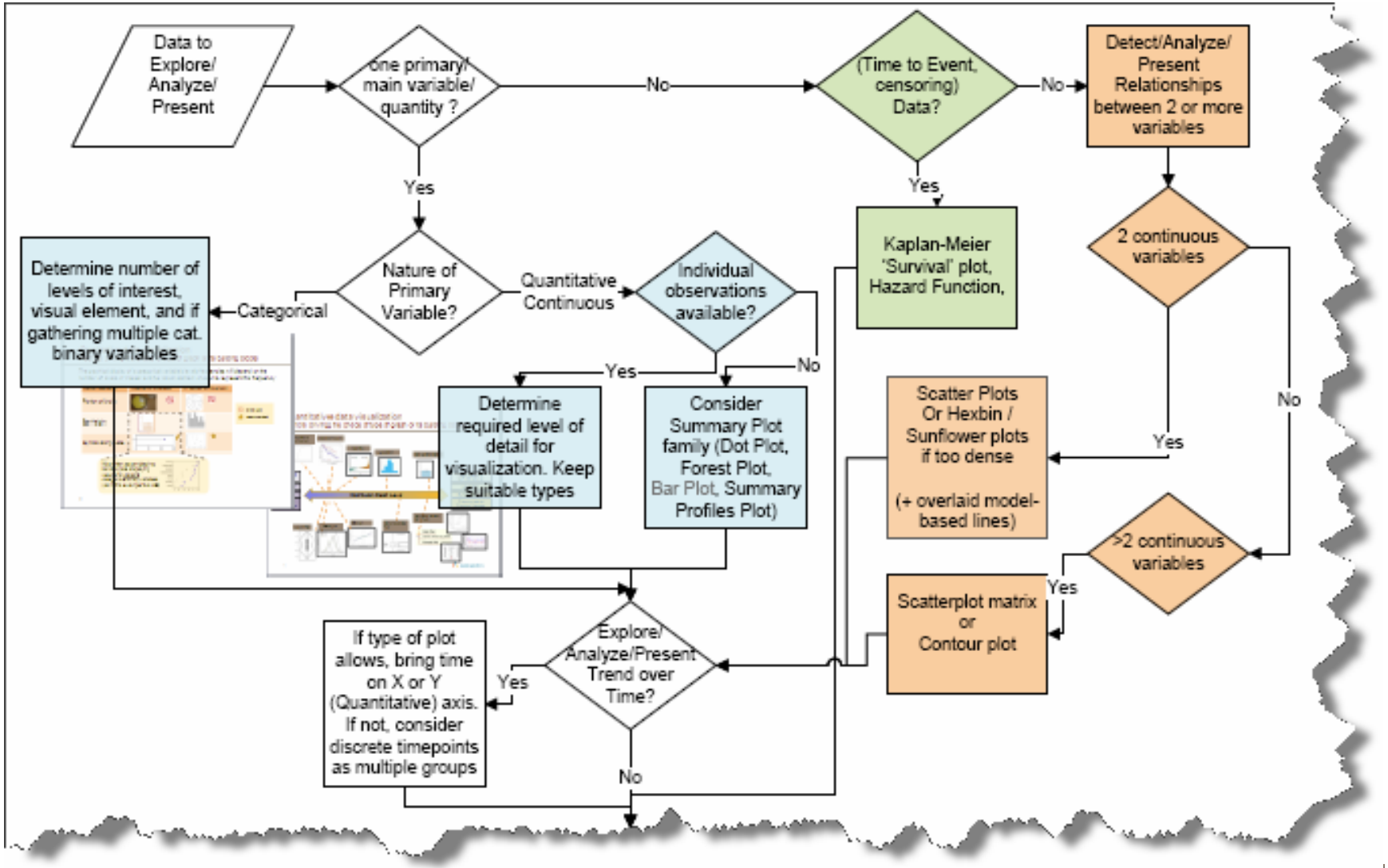
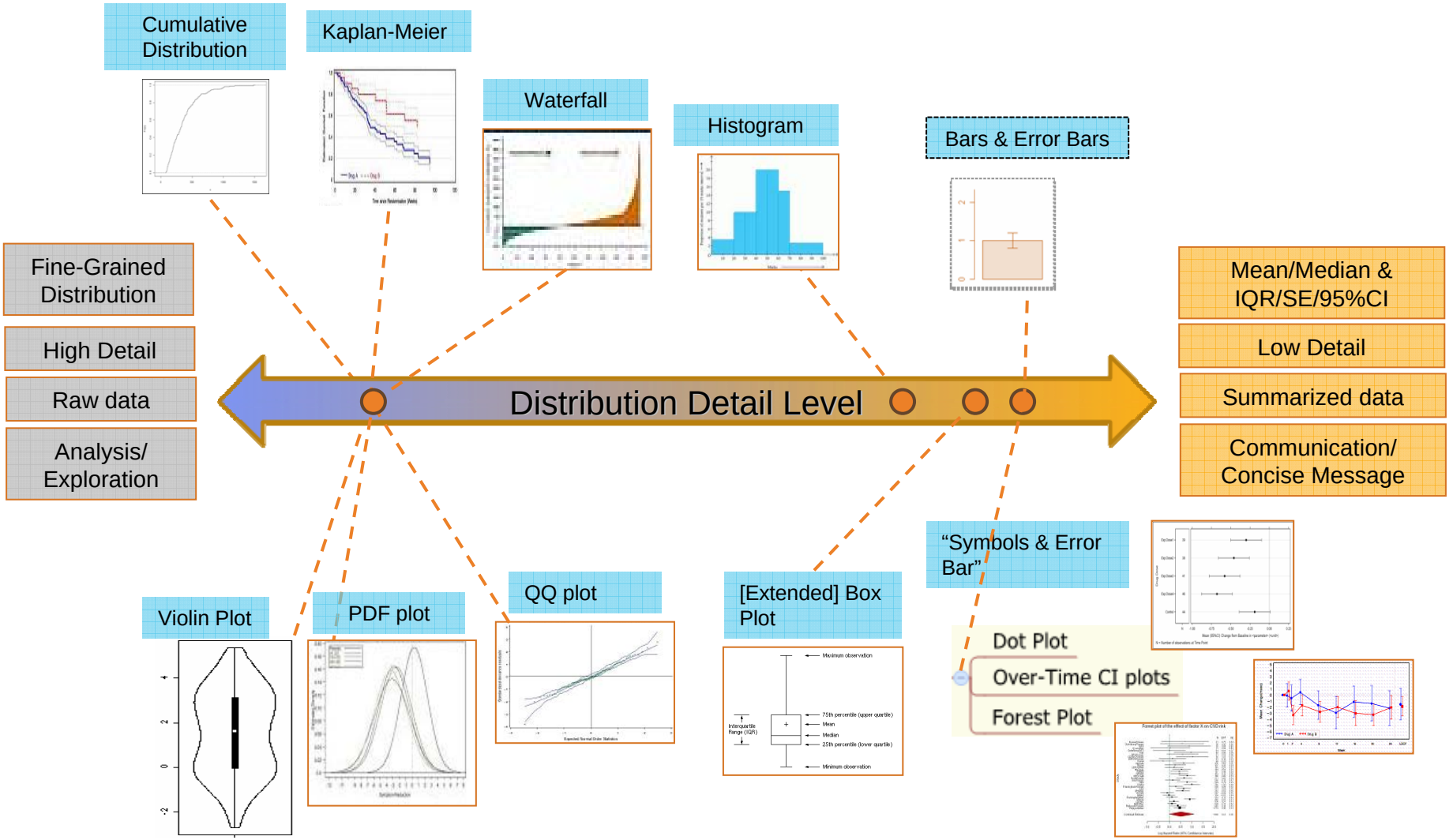


Graphics Navigator - Main Flow Diagram



Graphics Navigator– Navigator Slide 1

Factors driving the choice of type of graph/building blocks (1 quant. var)



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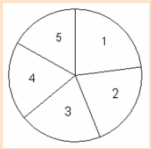
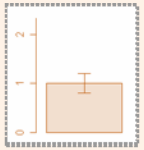
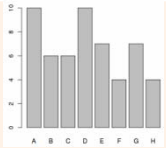
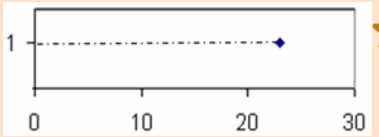
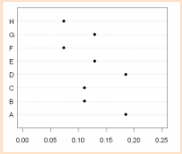
Graphics Navigator – Navigator Slide 2

Factors driving the choice of type of /building blocks (1 main categ. var)

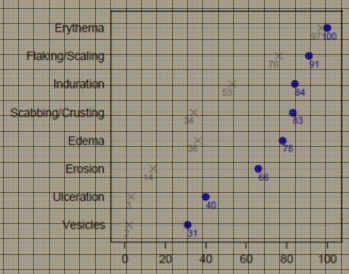
The graphical display of a categorical variable's levels frequencies will depend on the **number of levels** of interest and the **visual element** chosen to represent this frequency

Visual Element	1 Level of interest	>1 Level of interest
Portion of circle		
Bar Height		
Symbol along scale		

: avoid use

: recommended

Most often assembled into bar/dot plots displaying results for **several** categorical binary variables (as in this example for 8 AEs)



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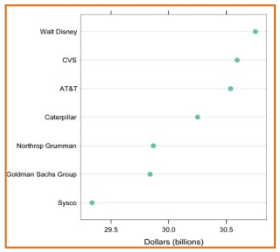
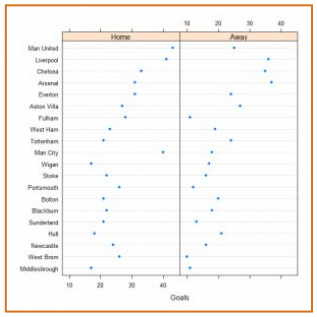
Graphics Navigator – Navigator slide 3
Factor influencing the choice of Graph Subtype



Simple



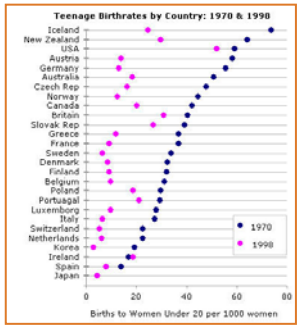
Multipanel of simple

0 or 1 grouping Variable

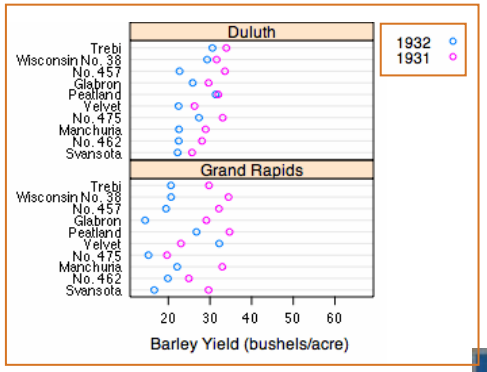
Graph Subtype/Flavor

Multiple grouping Variables (e.g., age category x gender x treatment group)

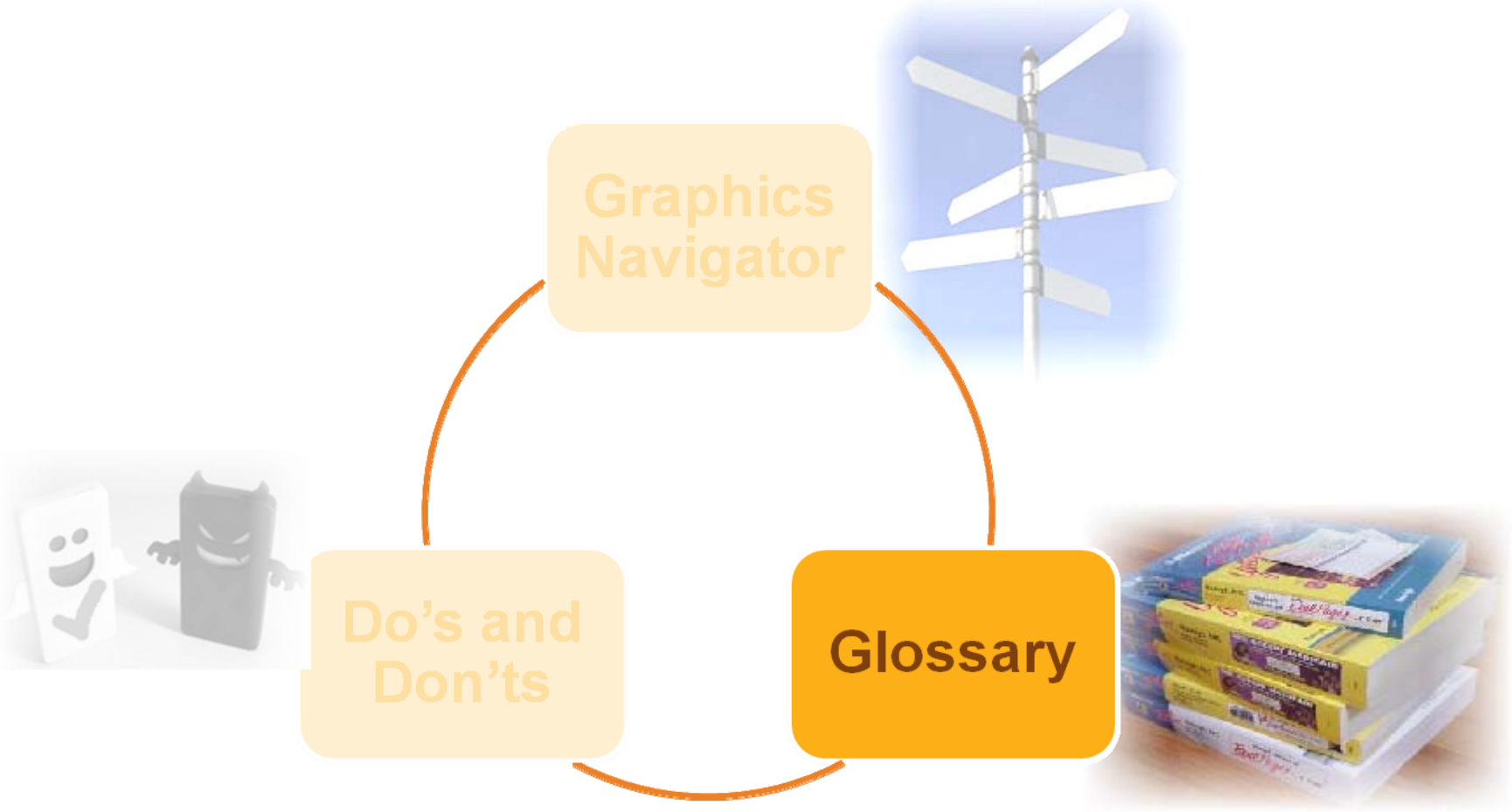
Grouped



Multipanel of grouped



General Principles



CTSPEDIA

Glossary

- Graph Types
  - Histogram, Violin, Box plot ...

    ➡ Description, typical use,

    Illustration(s), sample code, limitations
- Graph Subtypes
  - Simple, Grouped, Multipanel
- Graph Terms
  - Shift, Jitter, axis frame,
  - Major, minor tick marking, tick mark mirrorring ...

Glossary

CTSPedia Snapshot – Graph Type

Histograms

Last updated by Richard Forshee on September 17, 2010

Type of data: continuous

Type of analysis: univariate

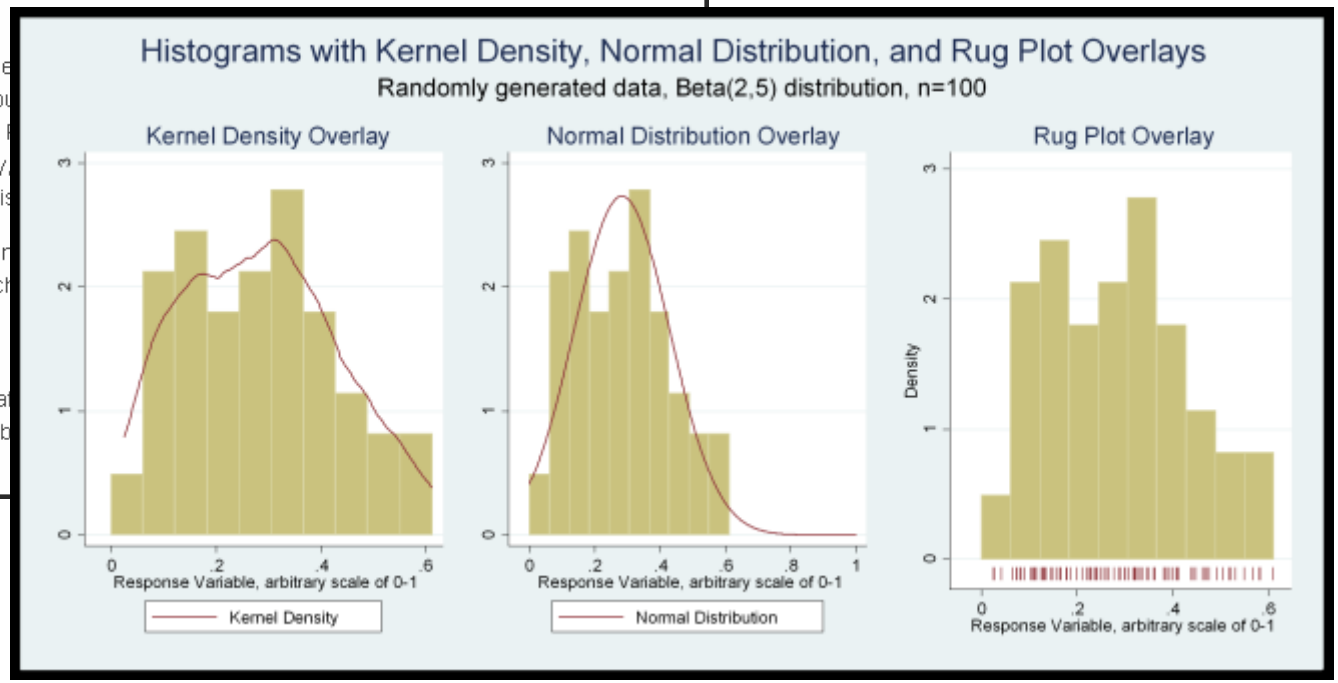
Description and purpose:

Histograms are used to represent the
individual observations into bins (mou
number of observations in each bin.
histogram) represents the frequency.
By convention, the rectangles in a his

Histograms are distinct from bar char
rectangles in a bar chart do not touch

Examples:

All examples use 100 data points that
(2,5) is a skewed distribution that is b
leaf plot.



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Glossary

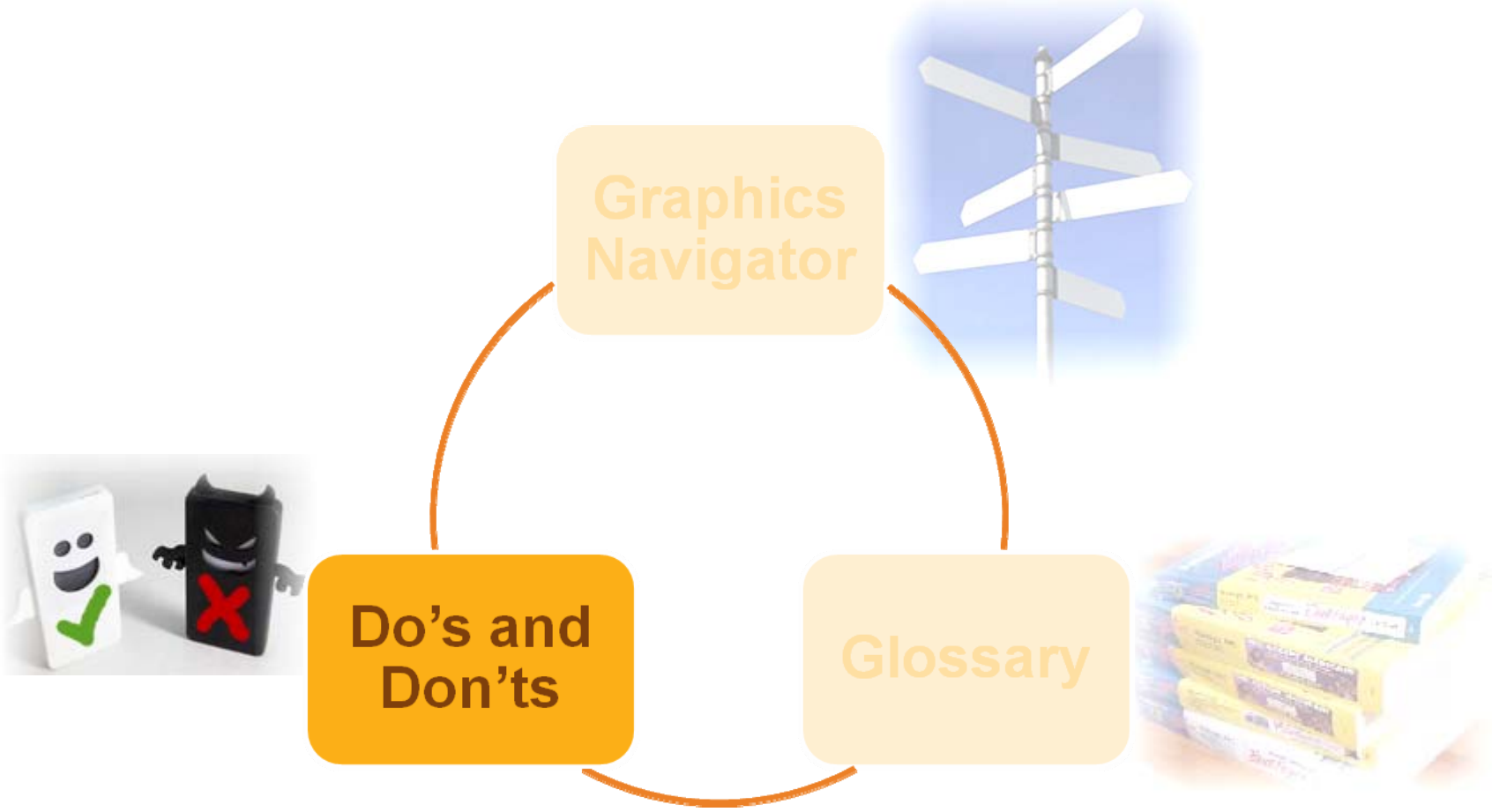
CTSPedia Snapshot – Graph Terms

- Graph Types
  - Histogram, Violin, Box plot ...

    ➡ Description, typical use,

    Illustration(s), sample code, limitations
- Graph Subtypes
  - Simple, Grouped, Multipanel
- Graph Terms
  - Shift, Jitter, axis frame,
  - Major, minor tick marking, tick mark mirrorring ...

General Principles

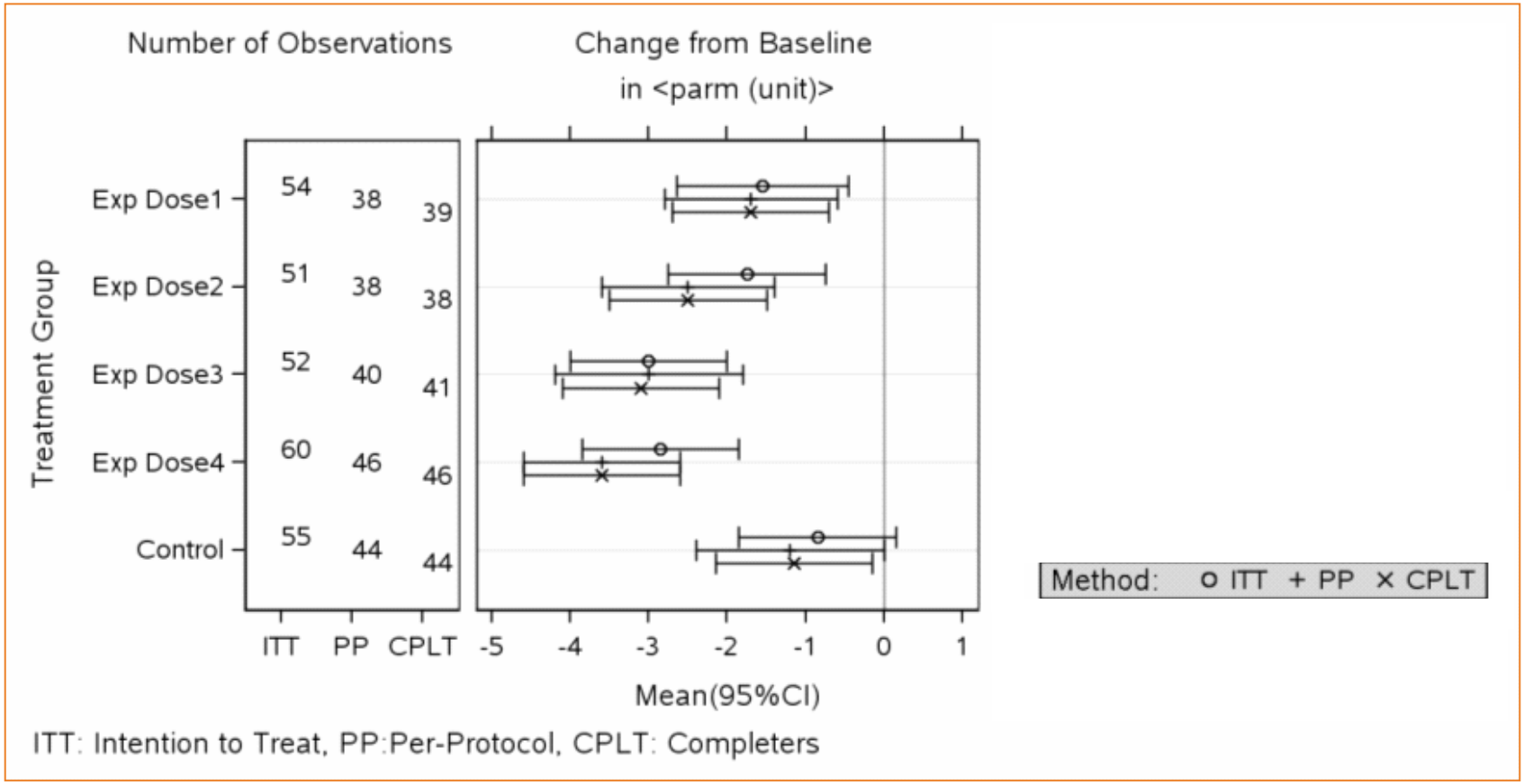


Do’s and dont’s

- Display the quantity of interest
- Provide visual anchors
- Bring closer items the reader needs to compare
- Maximize the data-to-ink ratio
- Use quantitative scales ... for quantitative variables
- Don’t use unnecessary dimensions
- Avoid using stacked bar plots
- Bring different components of the answer together

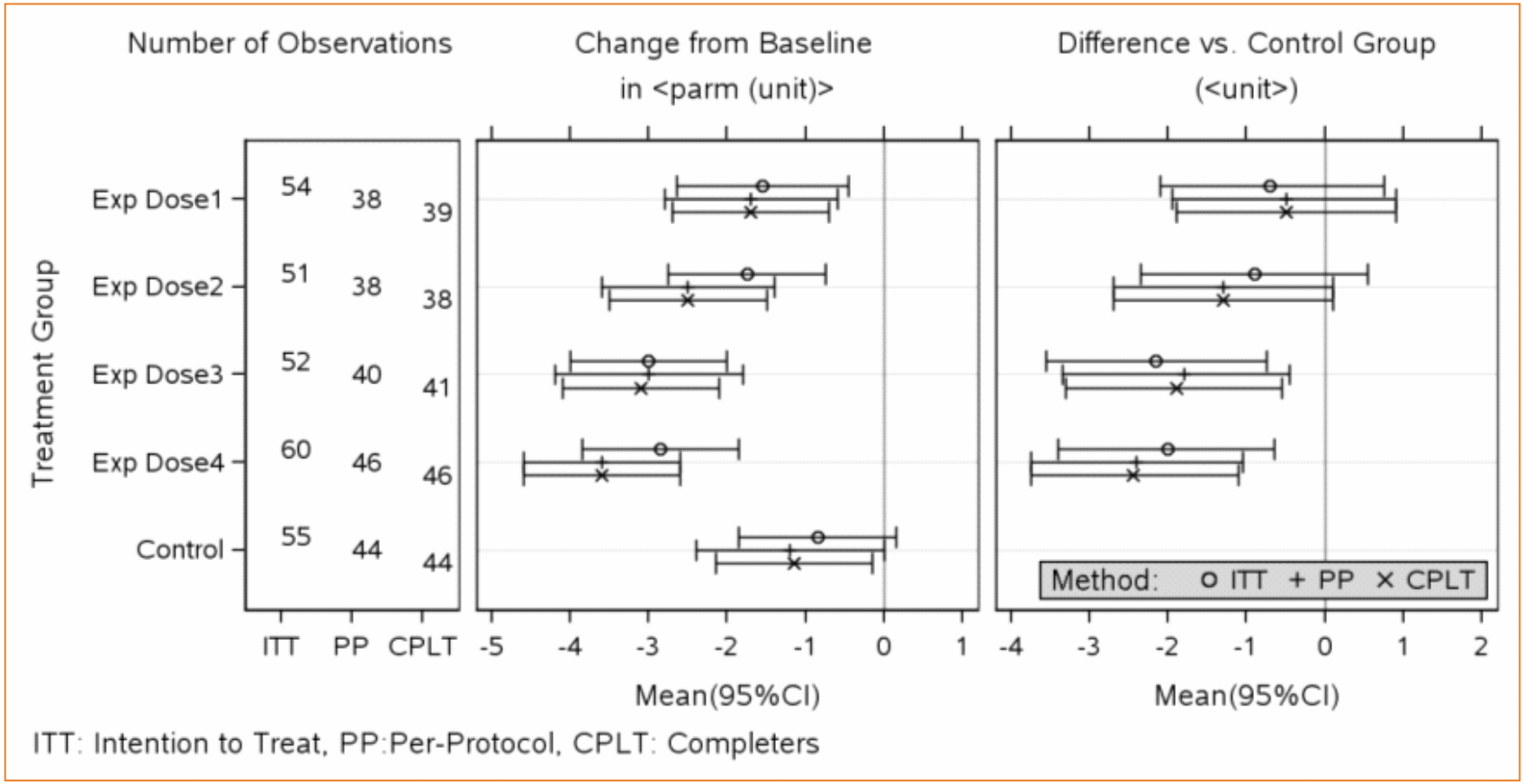
Do's and don'ts

- Display the quantity of interest
  - *Don't assume the reader can 'visually subtract' displayed quantities*



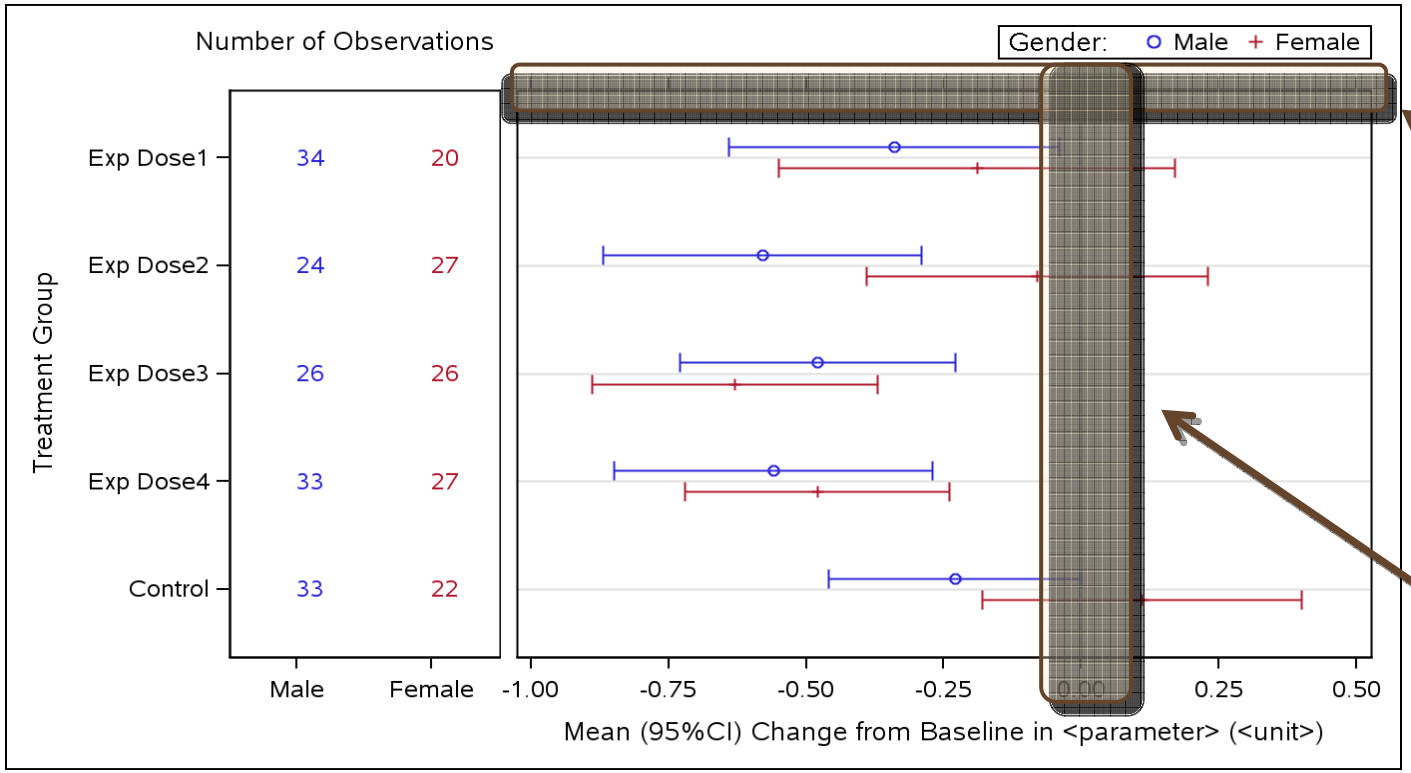
Do's and don'ts

- Display the quantity of interest
  - *Don't assume the reader can 'visually subtract' displayed quantities*



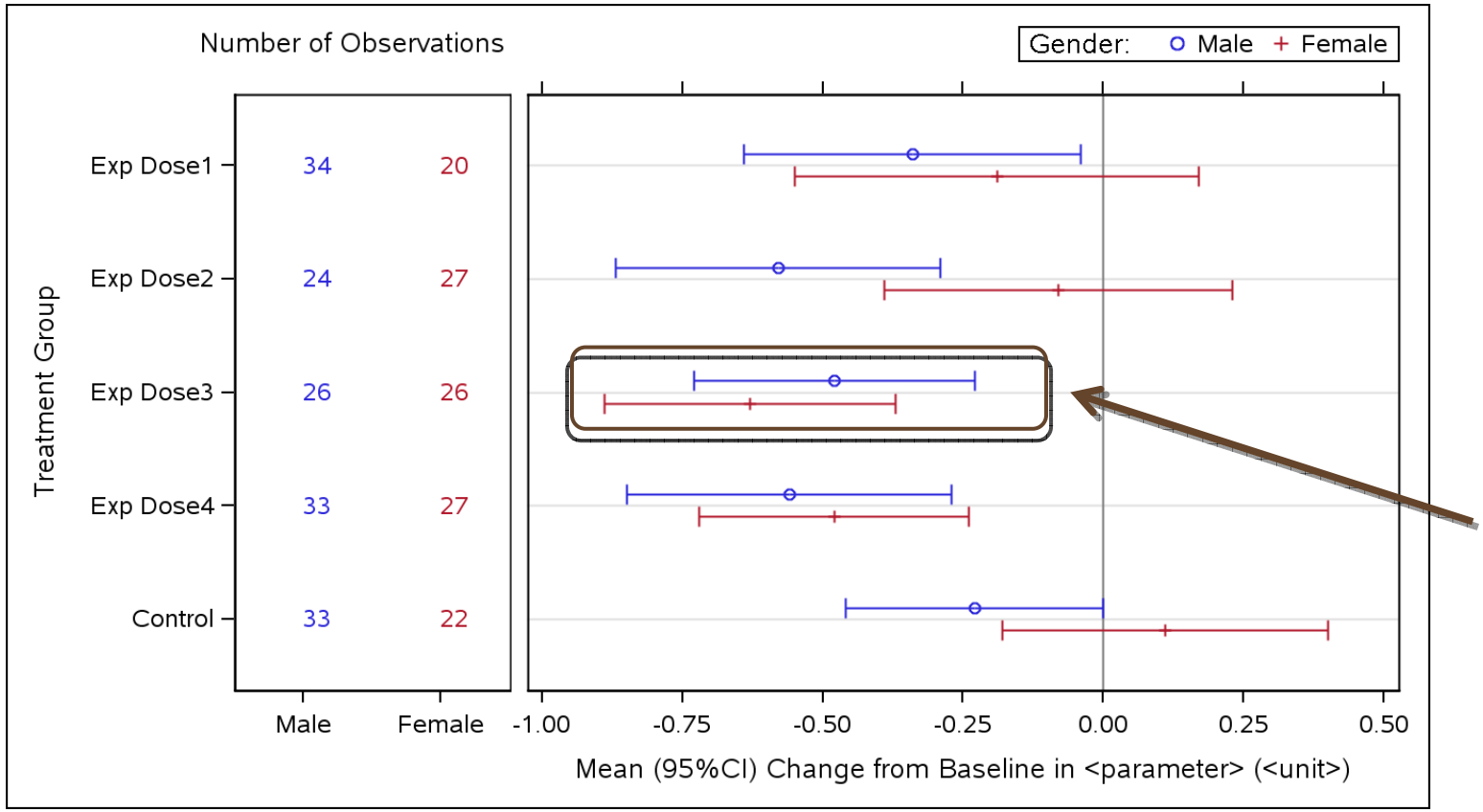
Do's and don'ts

- Provide visual anchors (but less prominent than data)
  - *Use meaningful reference lines, mirror tick mark onto right and upper axes, regression lines / curves, smoothed curves*



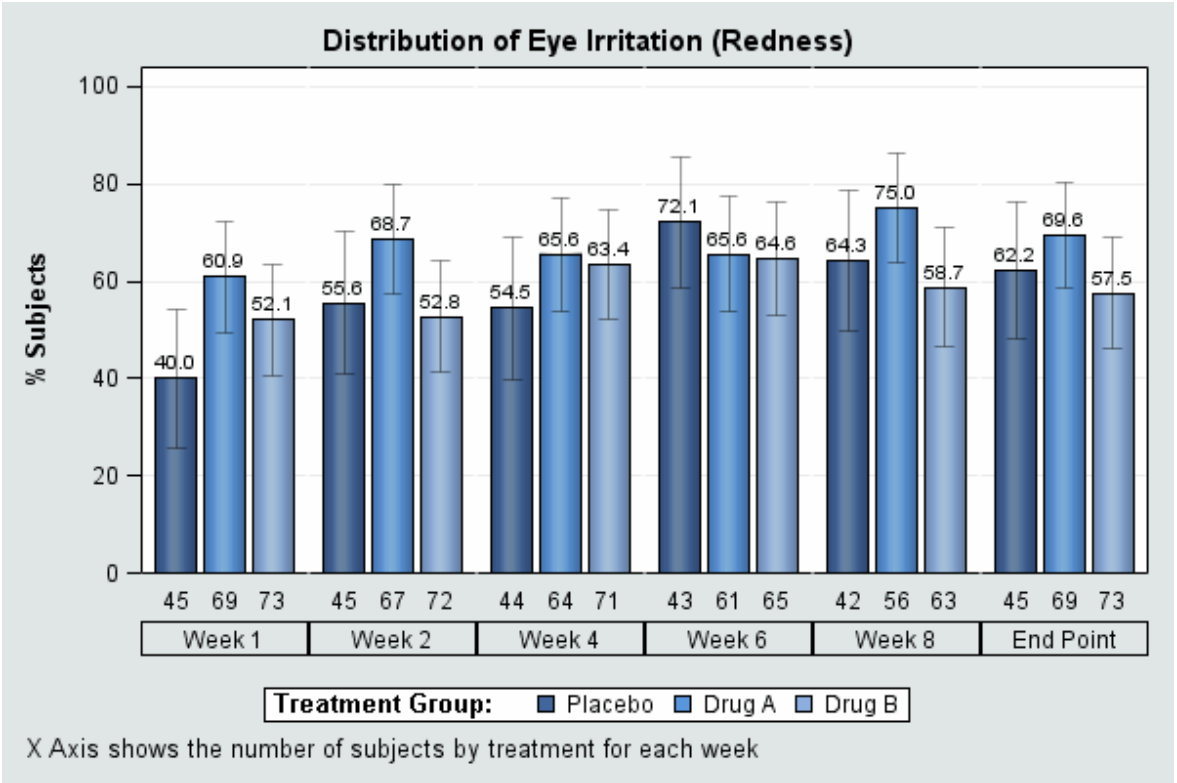
Do’s and don’ts

- Bring closer items the reader needs to compare
  - Dose-Response relationship ? Consistent effects across subgroups?



Do's and don'ts

- Maximize the data-to-ink ratio
- Use quantitative scales ... for quantitative variables
  - 'Lot of ink' version ... with timepoint considered as categorical



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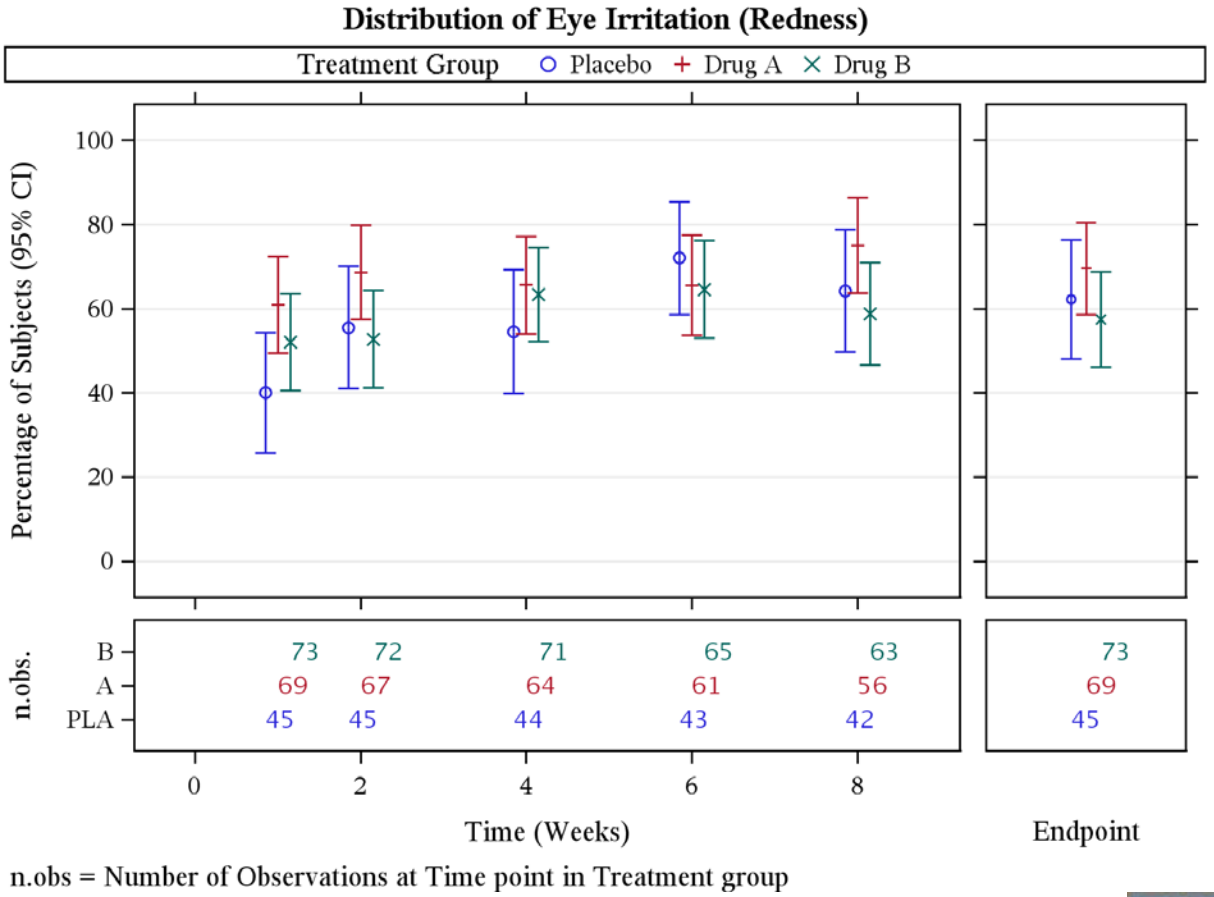
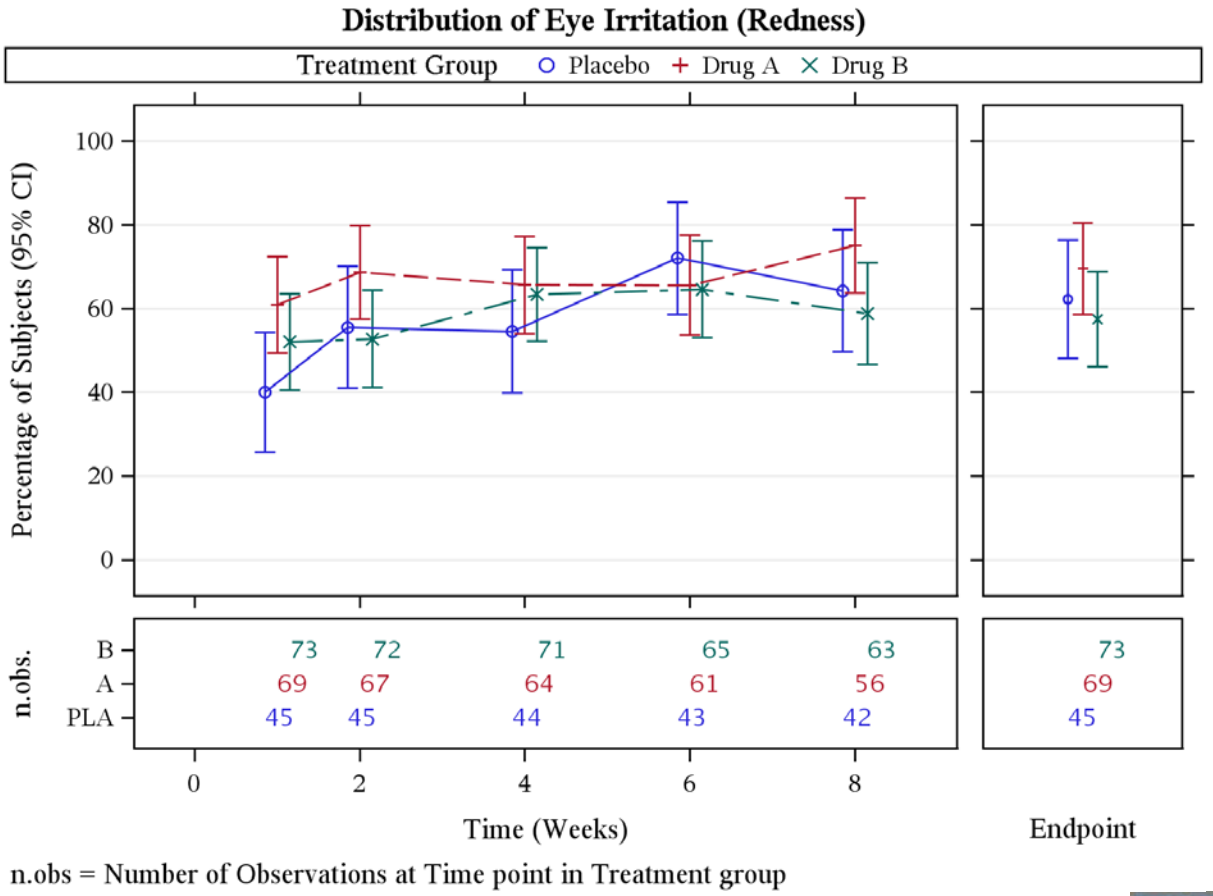
Do's and don'ts

- Maximize the data-to-ink ratio
- Use quantitative scales ... for quantitative variables



Do's and don'ts

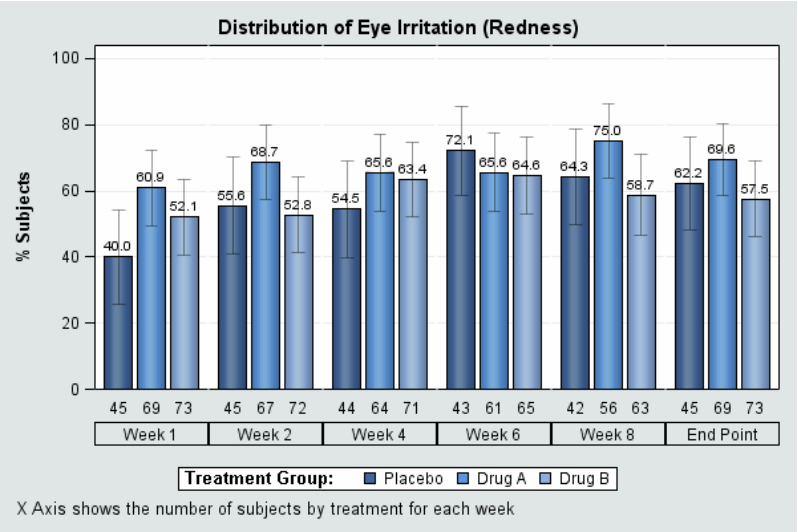
- Another variation with connecting lines

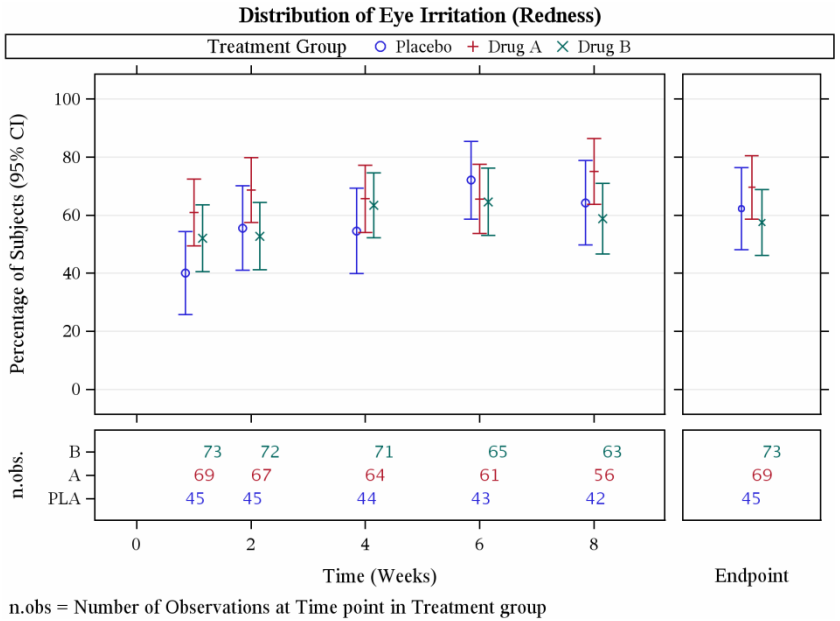


n.obs = Number of Observations at Time point in Treatment group

Do's and don'ts

- Maximize the data-to-ink ratio
- Use quantitative scales ... for quantitative variables





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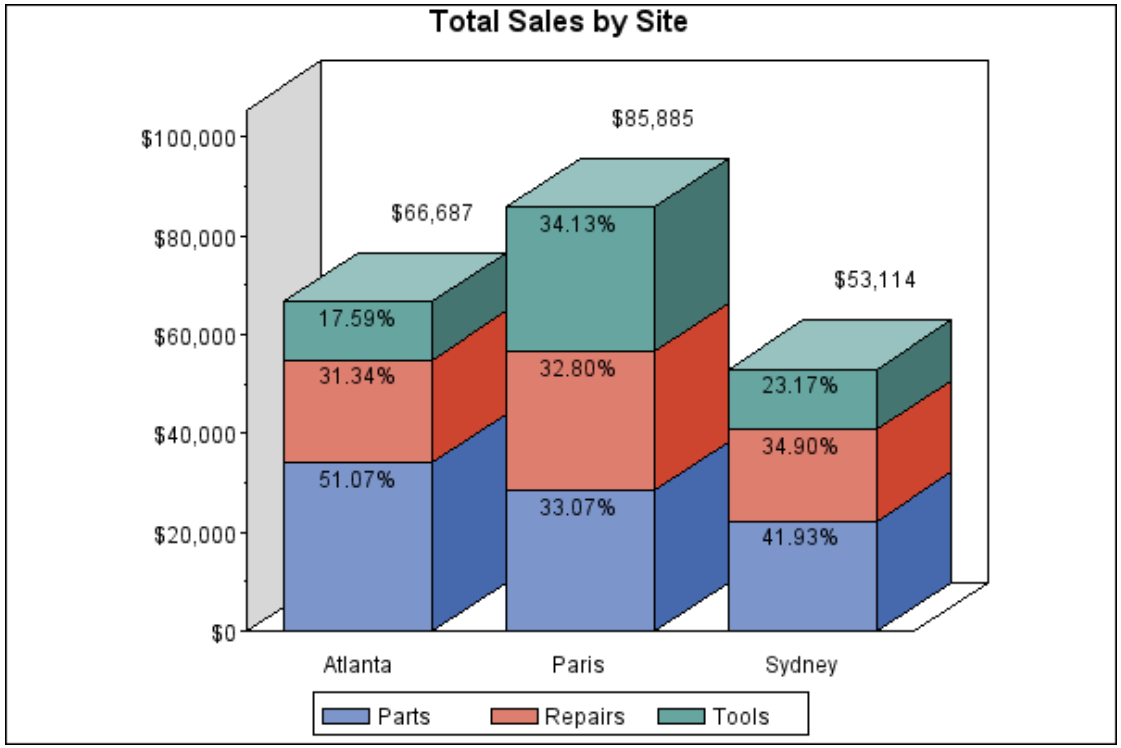
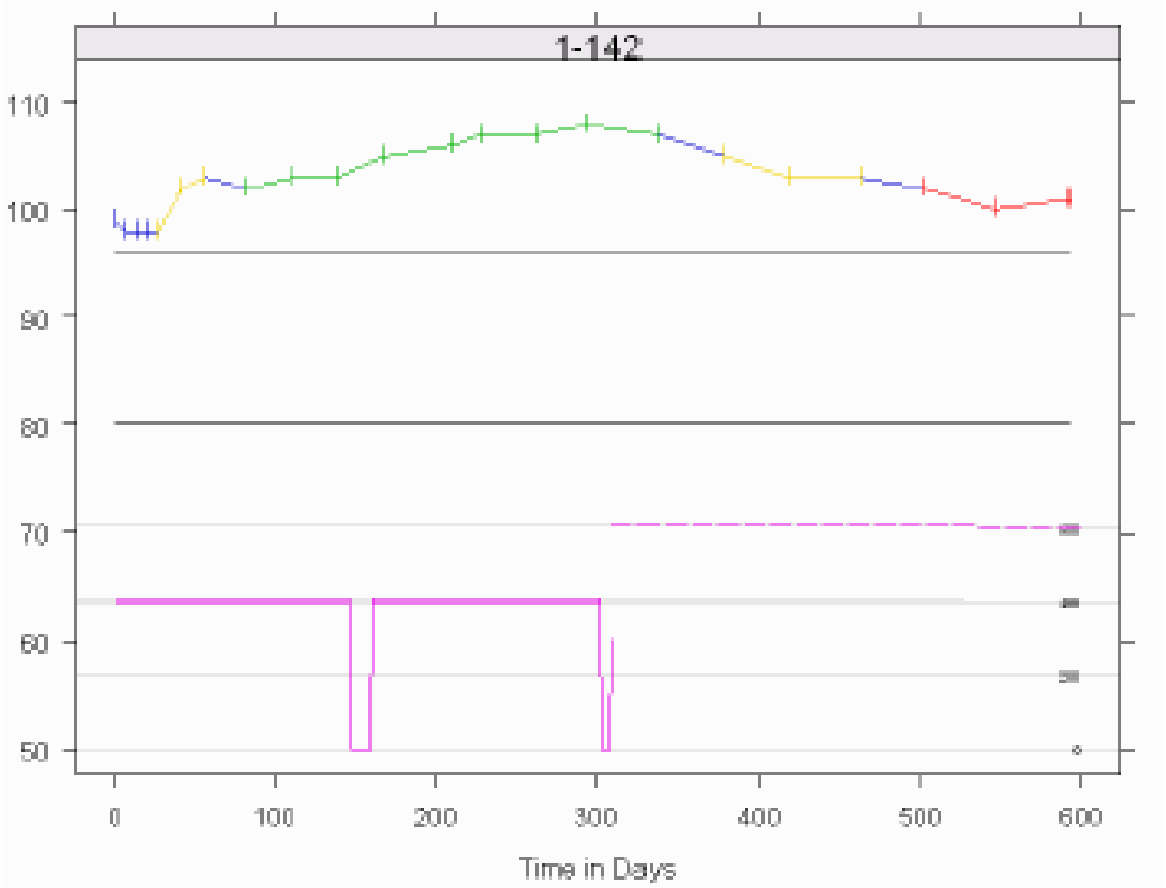
Do’s and don’ts

- Maximize the data-to-ink ratio
- Don’t use unnecessary dimensions
- Stacked bar plots are not efficient for comparisons

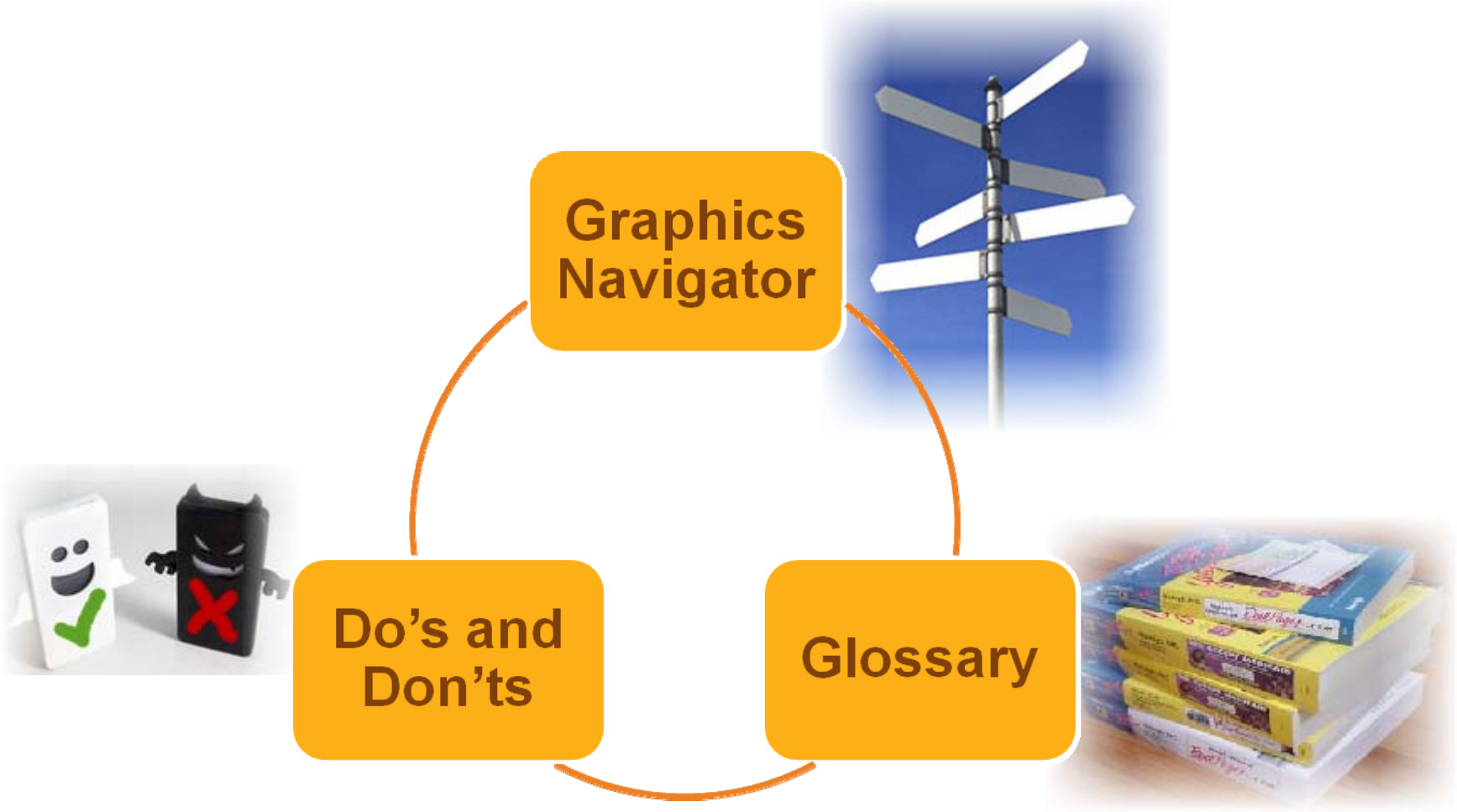


Do’s and don’ts

- Bring different components of the answer together



General Principles



Conclusions

- Use more graphical visualization to support messages
- Make reader's life easier in decoding the information
- Share experience

References and Useful Links

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Robert Allison's SAS/Graph Examples - http://robslink.com/SAS/Home.htm

http://stat-computing.org/events/2010-jsm - Use of Graphics in Clinical Trials

Frank Harell's Tutorial: Statistical Presentation Graphics

http://biostat.mc.vanderbilt.edu/twiki/pub/Main/StatGraphCourse/graphscourse.pdf

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Backup Slides

NOVARTIS

Graphics Navigator – Navigator Slide 4
Visual Perception

"When a graph is constructed, information is *encoded*. The *visual decoding* of this encoded information is *graphical perception*.

The decoding is the vital link …

No matter how ingenious the encoding … and no matter how technologically impressive the production, a graph is a failure if the visual decoding fails."

William Cleveland, The Elements of Graphing Data

Hierarchy of human graphical perception abilities

1. Position along a common scale (most accurate)
2. Position along identical nonaligned scales
3. Length
4. Angle and slope
5. Area
6. Volume
7. Color
    1. Hue (red, green, blue, etc) can give good discrimination but poor ordering
    2. Saturation (pale/deep) can be useful if order is important

Source: W.S. Cleveland - Elements of Graphing Data