General Principles, Illustrations and Wiki Resources for Improving Statistical Graphs

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

SFDS – September 17, 2011

Acknowledgements: Andreas Bruckner (Novartis), Brenda Crowe (Eli Lilly), Susan Duke (GSK) , Richard Forshee (FDA), Mat Soukup (FDA)

Agenda

- Current Situation
- Safety Graphics FDA/Industry/Academia working group
- Catalog of clinical questions and associated graphs
- Graph Design Navigator
- Best graphing principles : do’s and don’ts
- Conclusions

CTSPEDIA

Motivation

We All Would Agree

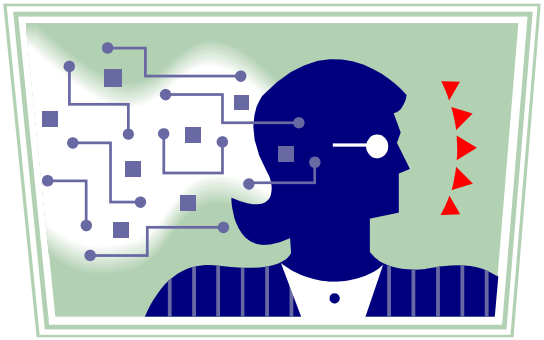
Study teams

Decision-makers

Prescribers

Patients

Benefit from easy ways to understand results



Obvious?

Then why aren't there more graphs in submissions?

CTSPEDIA

Lack of regulatory opinion / advice ?

ICH E9 – Statistical Principles (... 1998 ...)

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.

NOVARTIS

Are graphs less effective than tables ?

Example: Understanding the Trend

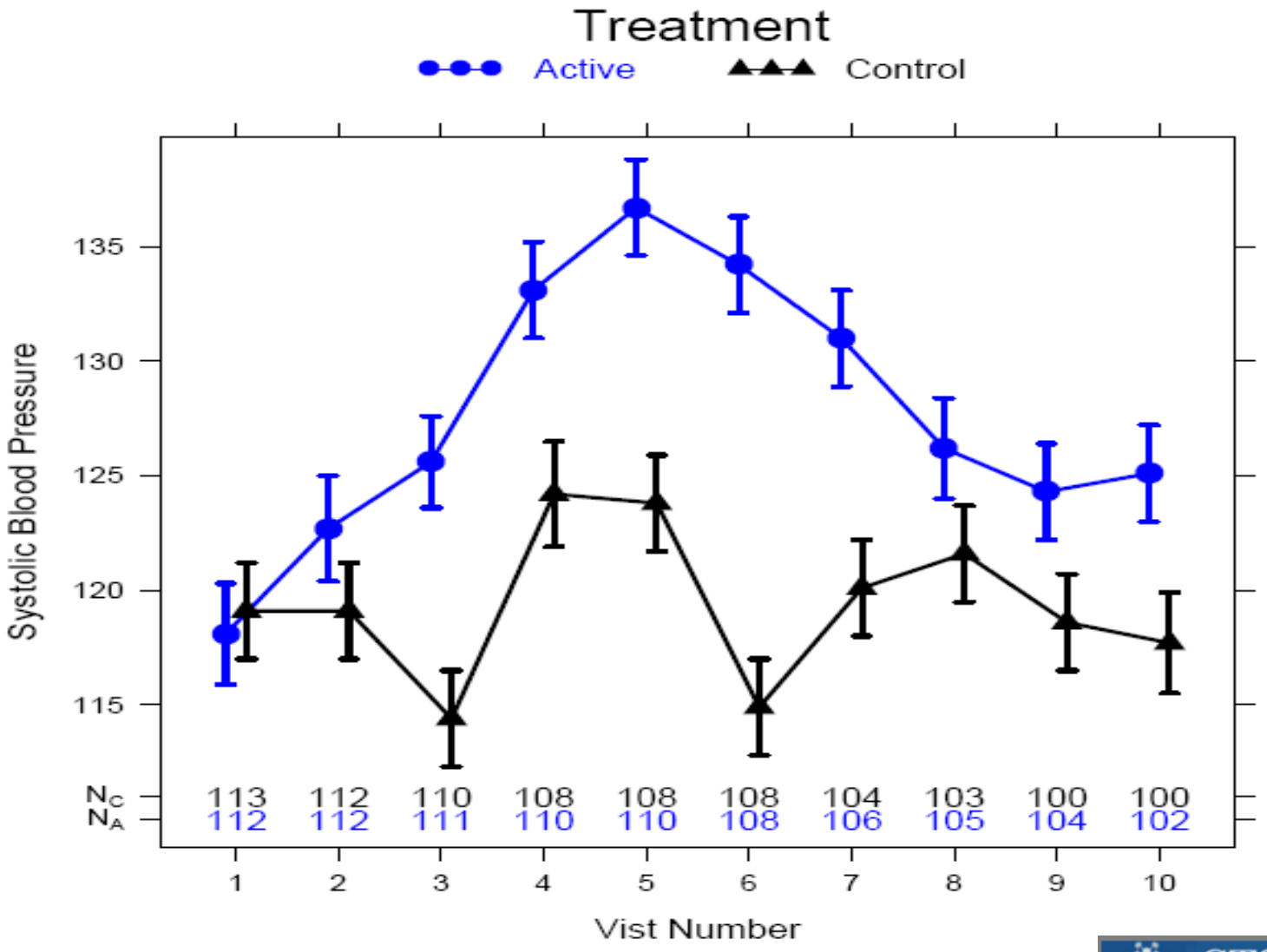
Tabular Summary of Systolic Blood Pressure Over Time:

	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)

CTSPEDIA

Are graphs less effective than tables ?

Example : Understanding the Trend



CTSPEDIA

Why are graphs underused ?

Imbalance ?

Time/Resources to
- Design
- Implement
- Fine-tune

Added value beyond existing tables/listings

- Encourage use of more graphs in medical research by developing supporting material for
  - Implementation of common graphs
  - Designing graphs for other data domains
  - Making graphs more **effective**

CTSPEDIA

Effective graph ?

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 …

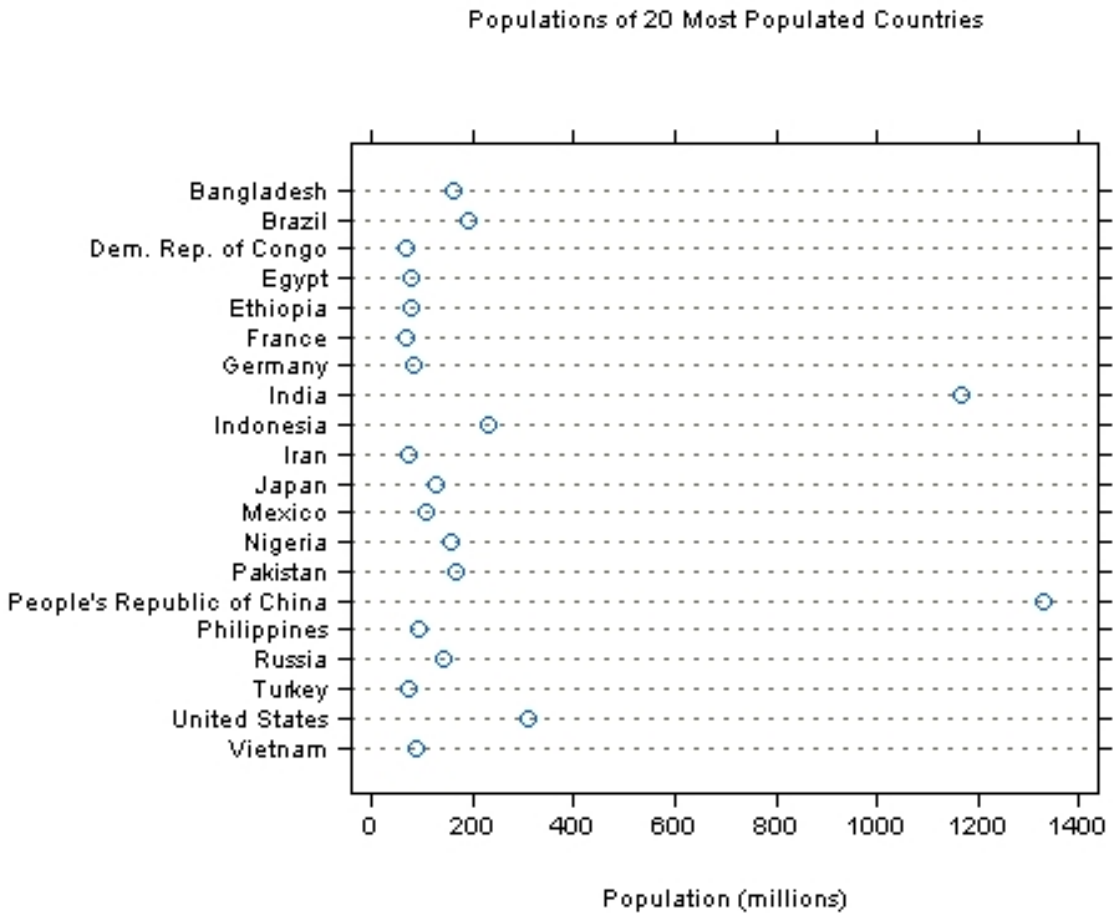
No matter how ingenious the encoding … and no matter how technologically impressive the production, a graph is a failure if the visual decoding fails."

William Cleveland, The Elements of Graphing Data

CTSPEDIA

Effective graph ?

Not all graphs are effective

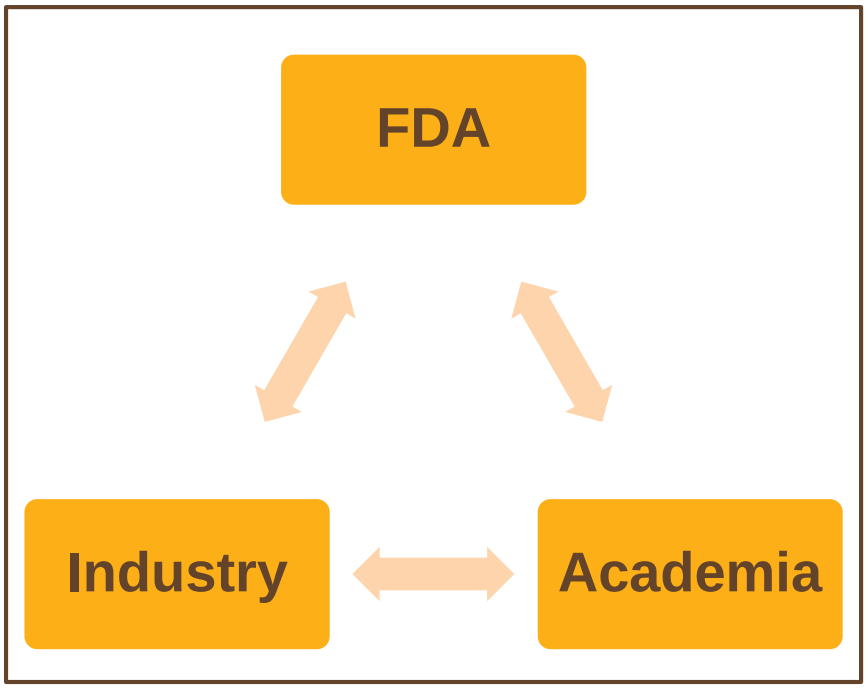


Concept from William Cleveland, *The Elements of Graphing Data*

CTSPEDIA

Framework

Joint Collaboration



Themes / Subteams

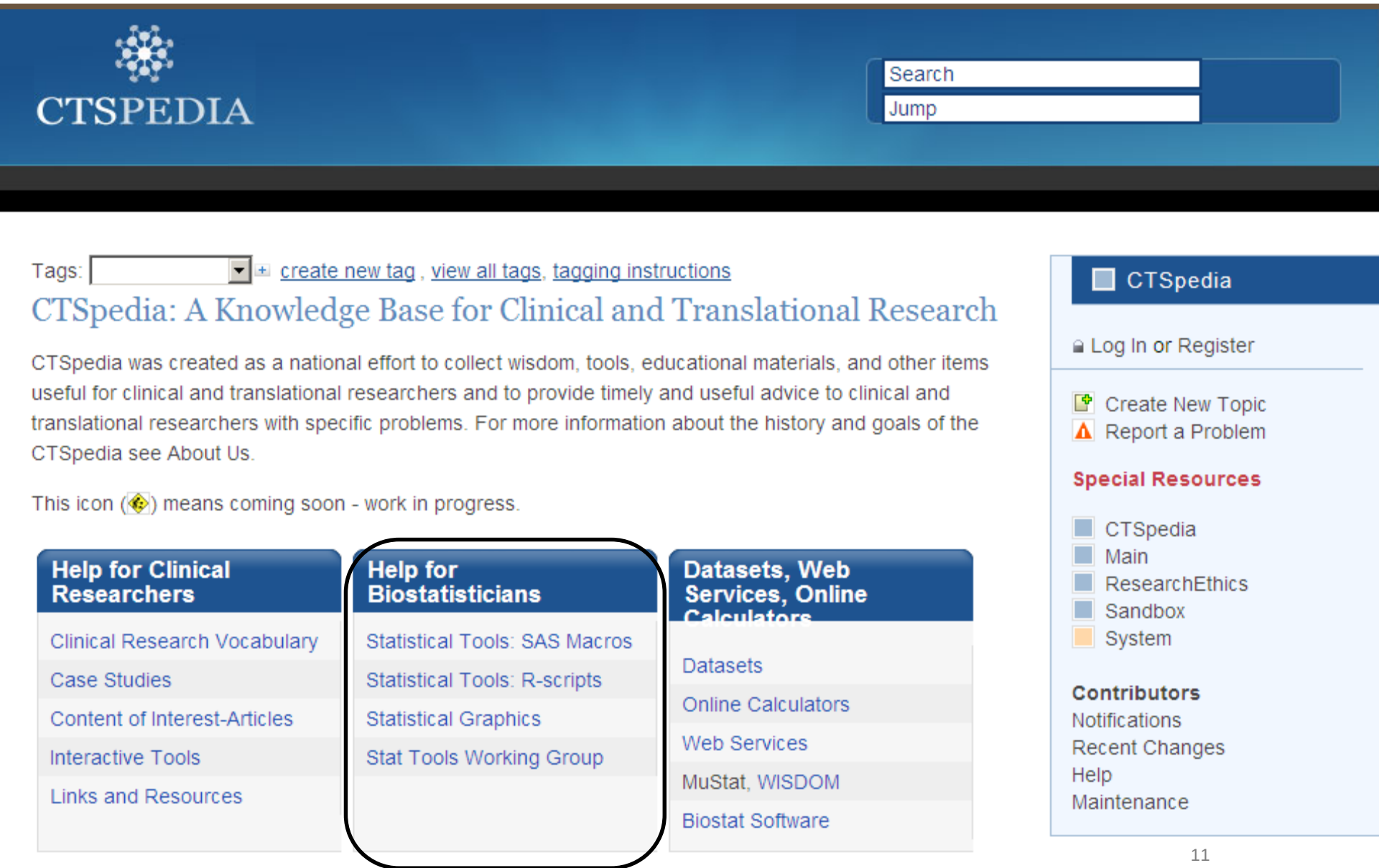
- General Principles
- ECG / Vital Signs
- Labs / Liver
- Adverse Events

http://www.ctspedia.org

CTSPEDIA

CTSPEDIA

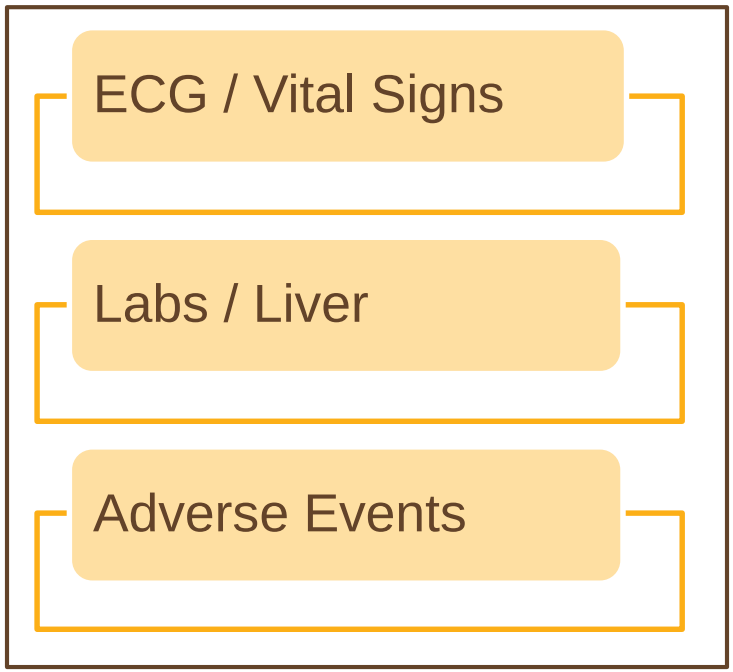
CTSpedia Screenshot (www.ctspedia.org)



Implementation of common graphs

Catalog of clinical questions and associated graphs

Themes



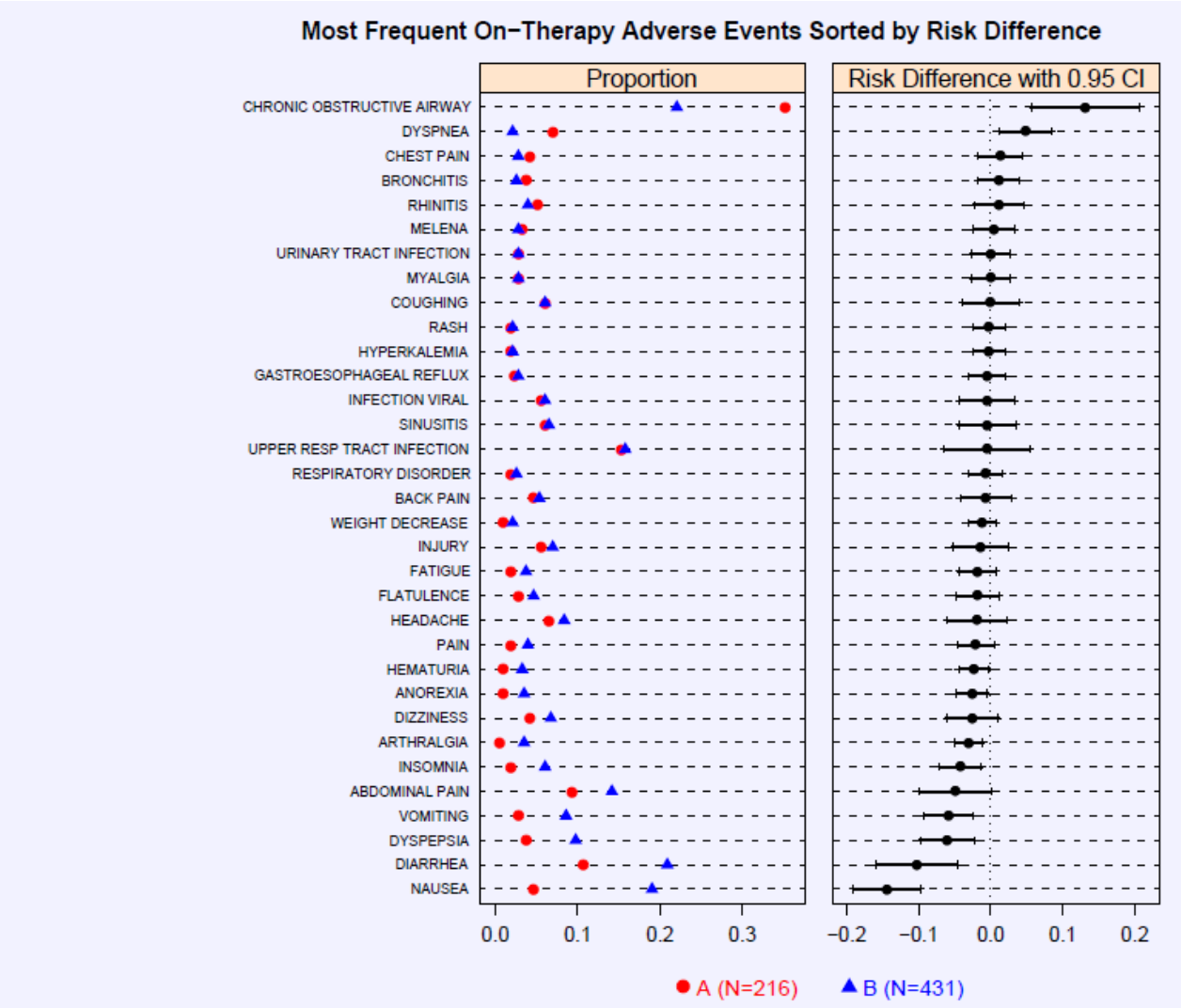
Catalog Entries

- 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 ...)

CTSPEDIA

Example 1 - Incidence of AE

Which AEs have a higher incidence (trt vs. control) ?



Use of Graphics in Clinical Trials

Frank E Harrell Jr

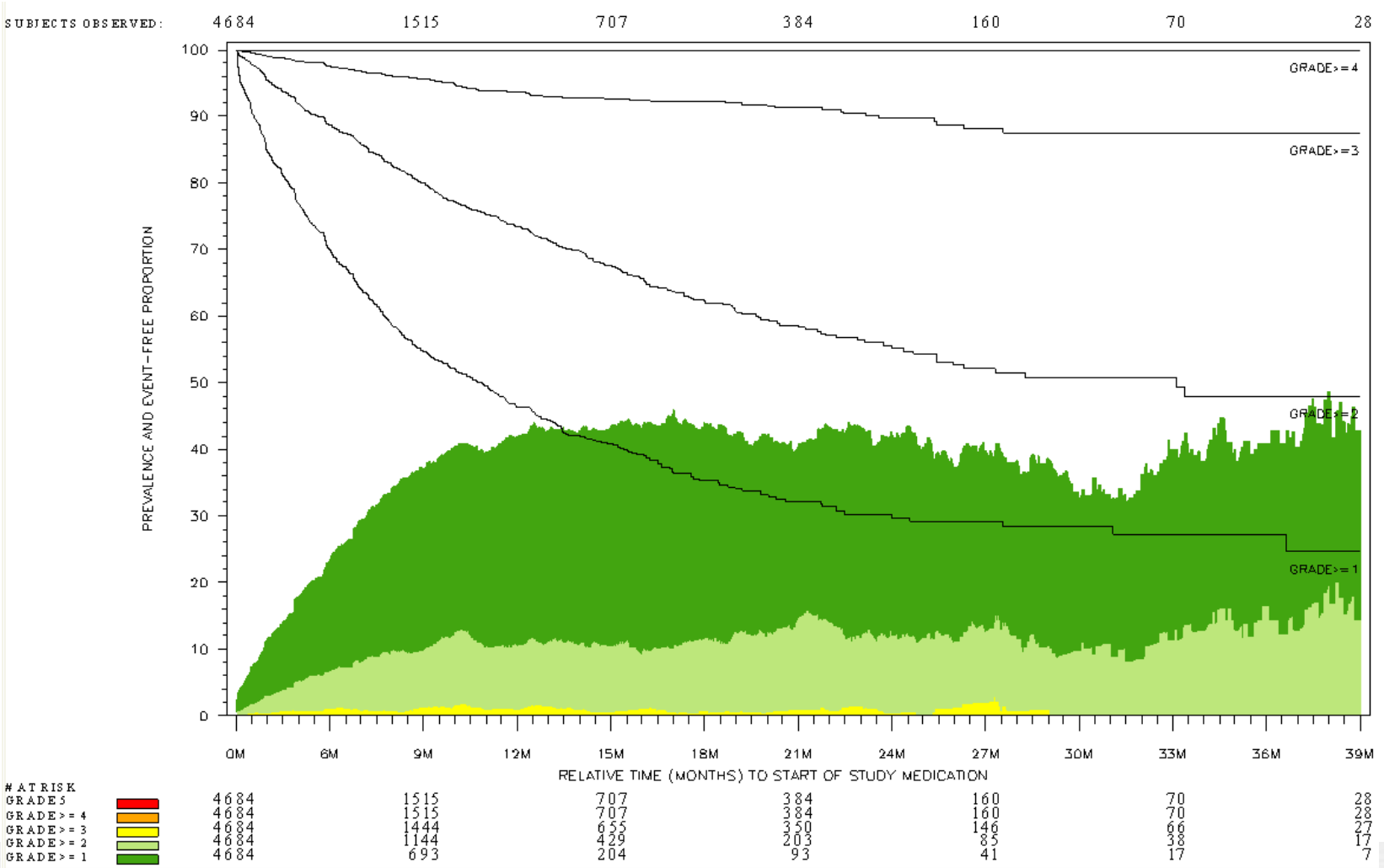
Department of Biostatistics, Vanderbilt University School of Medicine

Joint Statistical Meetings 3 August 2010

CTSPEDIA

Example 2 - AE Occurrence over time

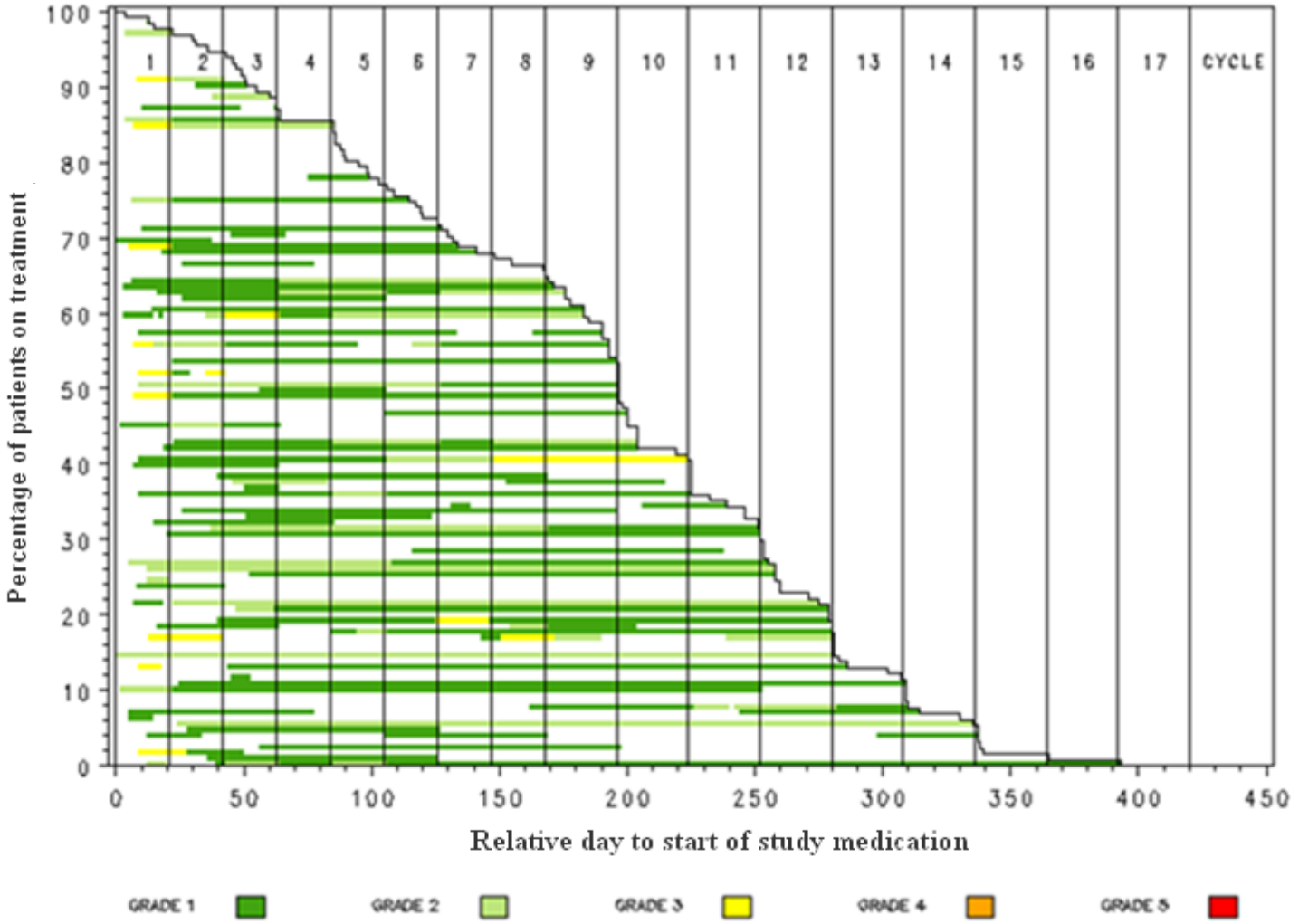
Incidence Prevalence Plot



CTSPEDIA

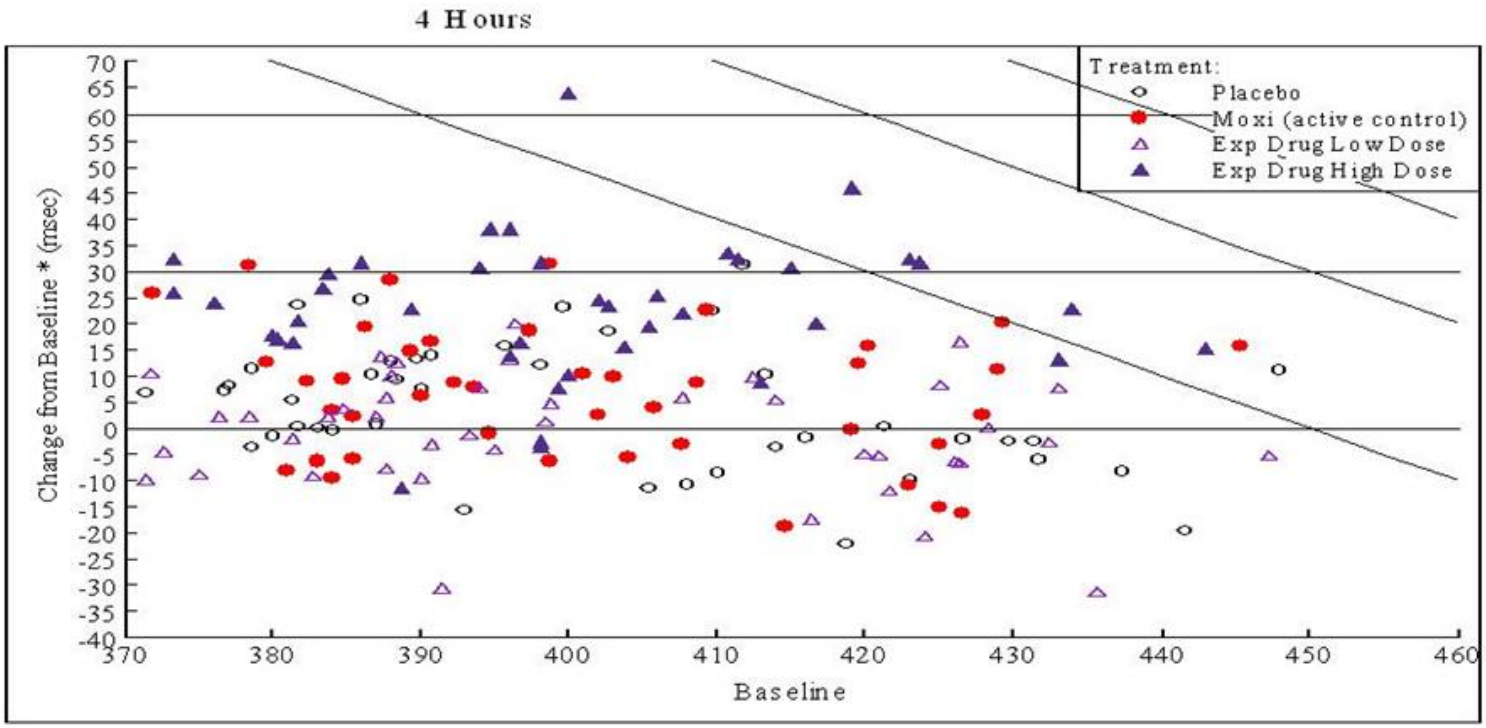
Example 3 - AE Occurrence over time

Event History Plot



CTSPEDIA

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 rigl

CTSPEDIA

General Principles

Designing graphs for other data domains

Graphics Navigator

Do's and Don'ts

Glossary

Making graphs more **effective**

CTSPEDIA

General Principles

Designing graphs for other data domains

Graphics Navigator

Do's and Don'ts

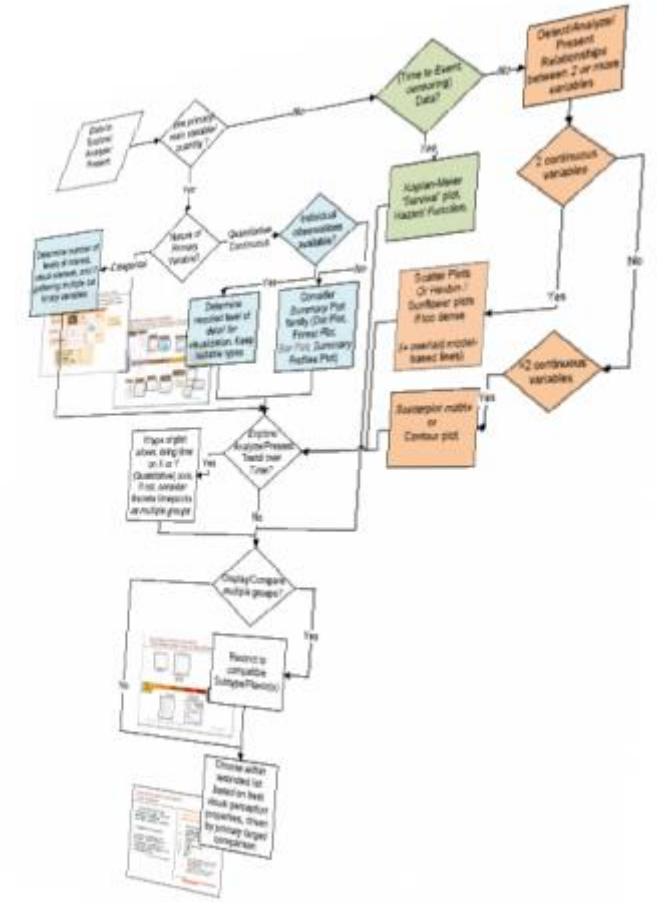
Glossary

Making graphs more **effective**

CTSPEDIA

Graph Design Navigator - Main Flow Diagram

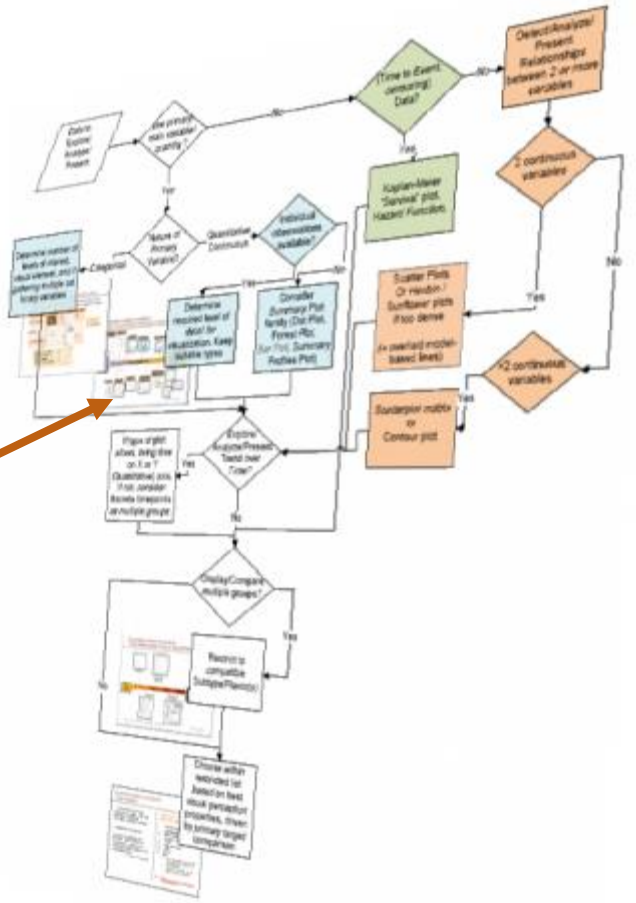
- Main drivers
  - Type (categ., quant.) of variables
  - Number of Variables
  - Number of levels of categorical variables
  - Level of detail needed for the distribution (quant.),
  - Visual Perception Criteria



CTSPEDIA

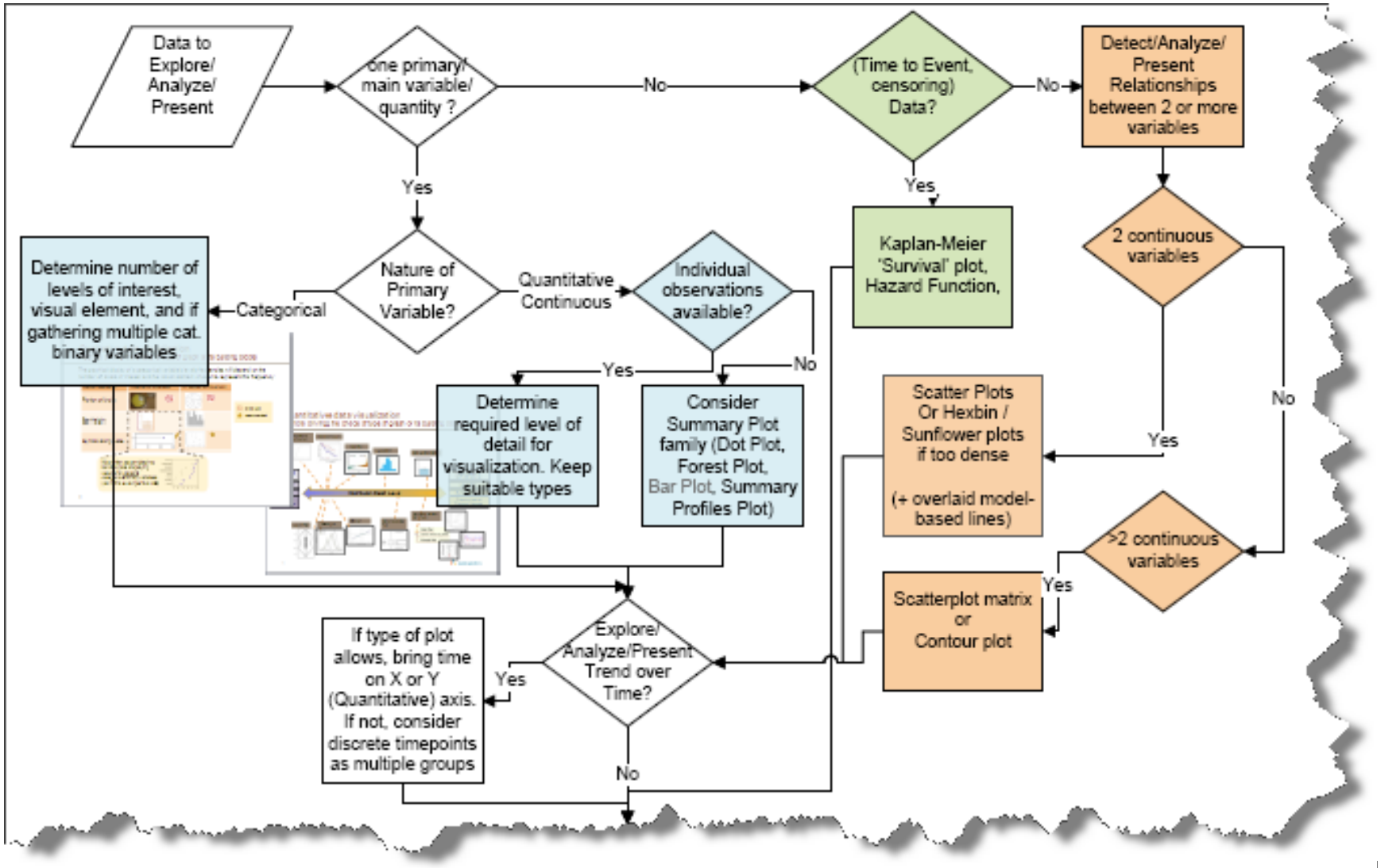
Graph Design Navigator - Main Flow Diagram

- 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



CTSPEDIA

Graph Design Navigator - Main Flow Diagram

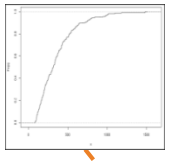


CTSPEDIA

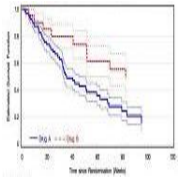
Graph Design Navigator– Navigator Slide 1

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

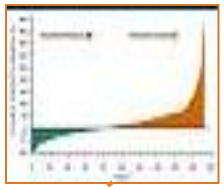
Cumulative Distribution



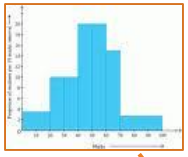
Kaplan-Meier



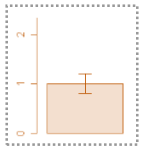
Waterfall



Histogram



Bars & Error Bars



Fine-Grained Distribution

High Detail

Raw data

Analysis/ Exploration

Distribution Detail Level

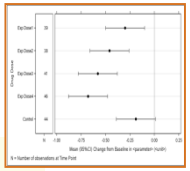
Mean/Median & IQR/SE/95%CI

Low Detail

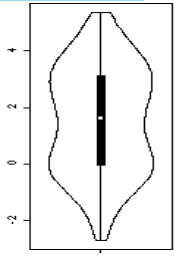
Summarized data

Communication/ Concise Message

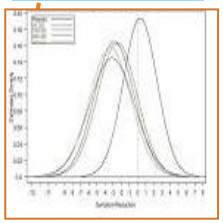
"Symbols & Error Bar"



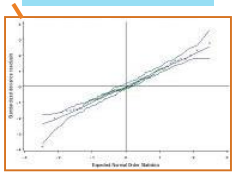
Violin Plot



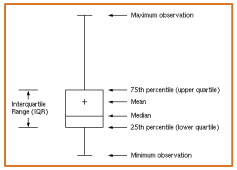
PDF plot



QQ plot



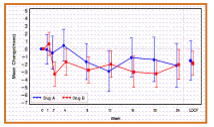
[Extended] Box Plot

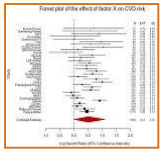


Dot Plot

Over-Time CI plots

Forest Plot



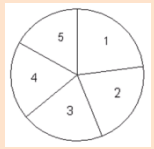
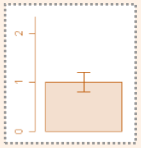
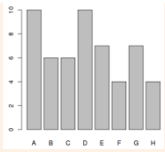
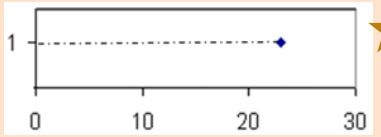
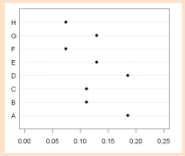


CTSPEDIA

Graph Design Navigator – Navigator Slide 2

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

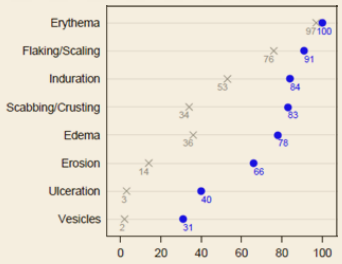
The graphical display of a categorical variable's levels frequencies will depend on the **number of levels** of interest and the **visual element** chosen to represent this frequency

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

: avoid use

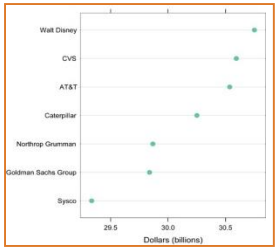
: recommended

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

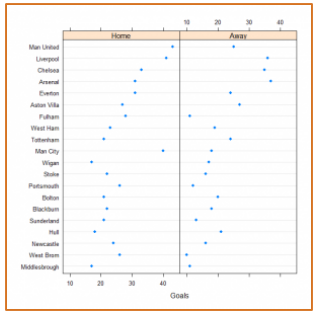


CTSPEDIA

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



Simple



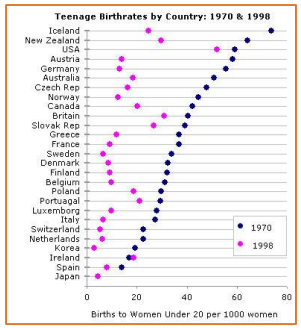
Multipanel of simple

0 or 1 grouping Variable

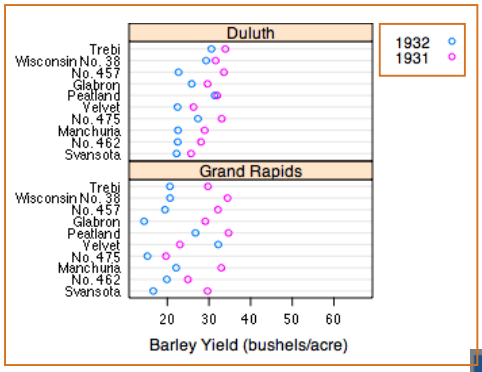
Graph Subtype/Flavor

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

Grouped



Multipanel of grouped



CTSPEDIA

General Principles

Designing graphs for other data domains

Graphics Navigator

Do's and Don'ts

Glossary

Making graphs more **effective**

CTSPEDIA

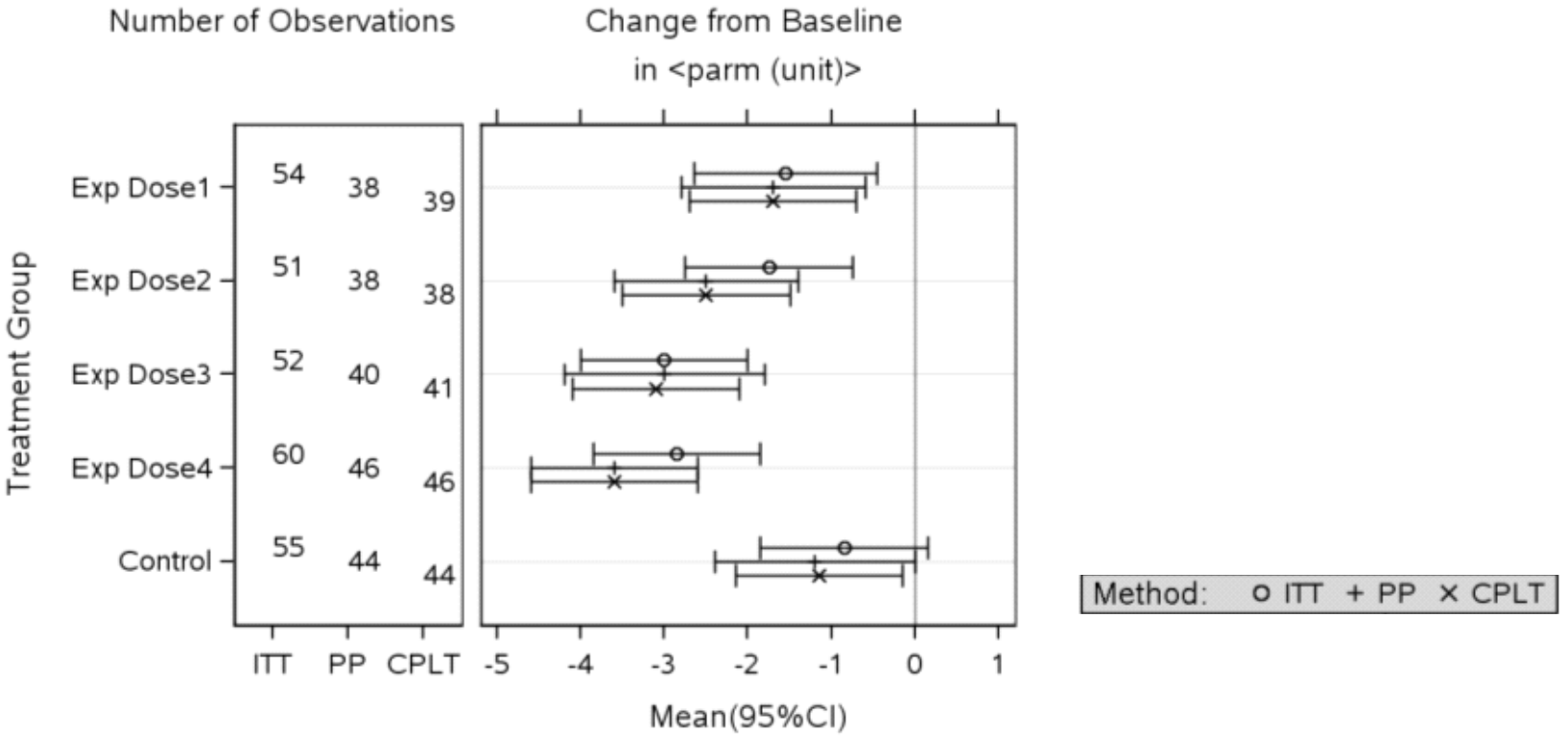
Do’s and dont’s

- 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

CTSPEDIA

Do's and don'ts

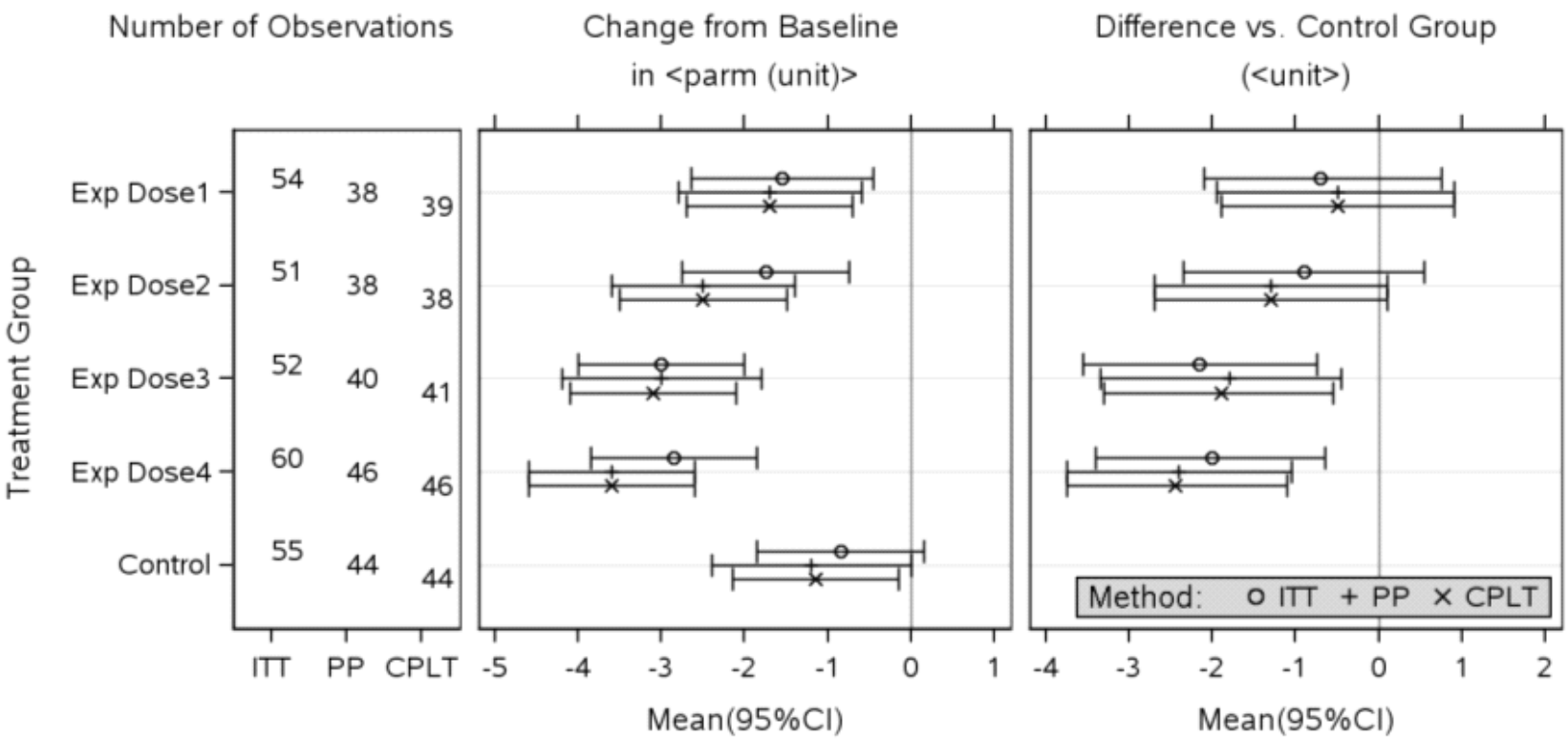
- Display the quantity of interest
  - *Don't assume the reader can 'visually subtract' displayed quantities*



CTSPEDIA

Do's and don'ts

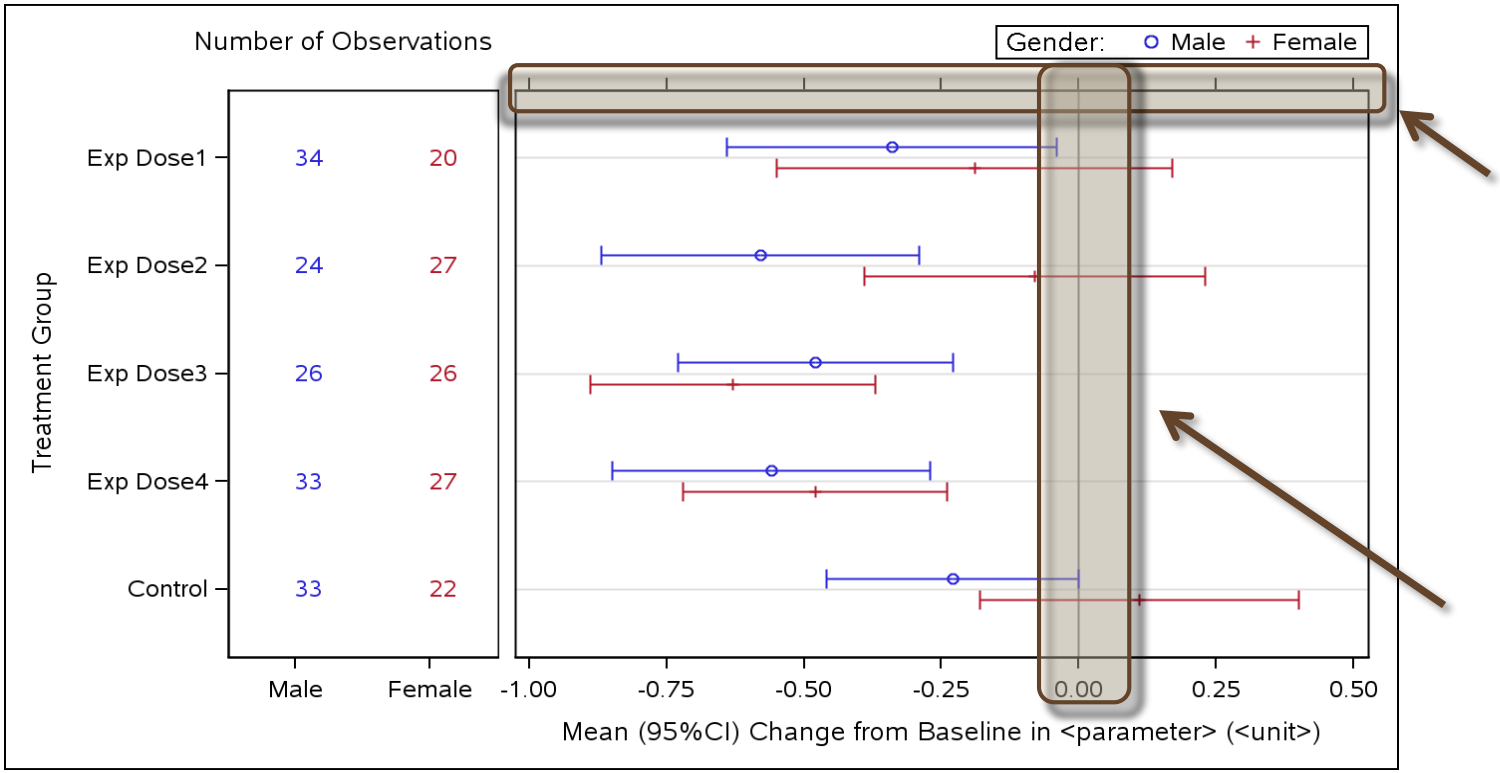
- Display the quantity of interest
  - *Don't assume the reader can 'visually subtract' displayed quantities*



CTSPEDIA

Do's and don'ts

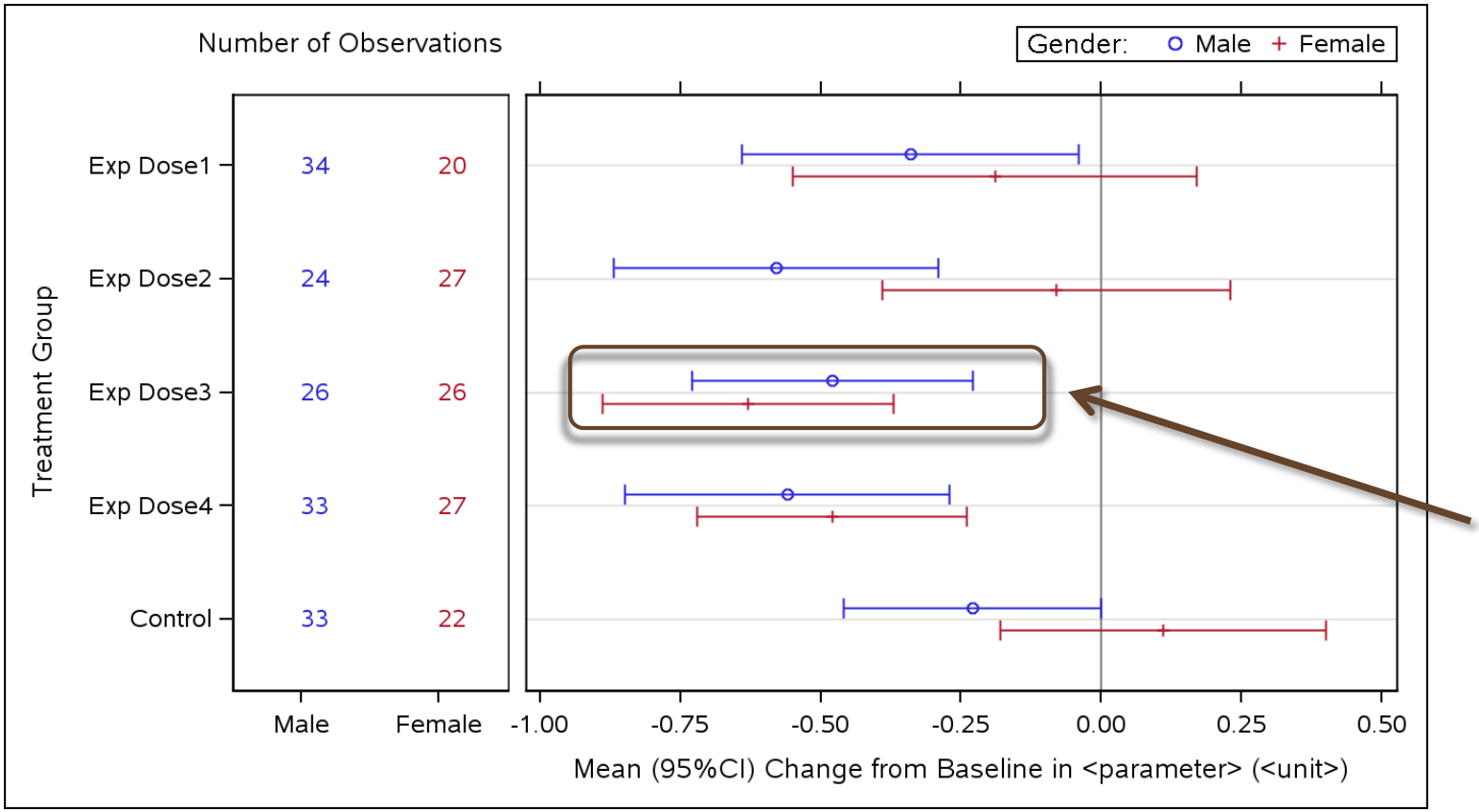
- Provide visual anchors (but less prominent than data)
  - *Use meaningful reference lines, mirror tick mark onto right and upper axes, regression lines / curves, smoothed curves*



CTSPEDIA

Do's and don'ts

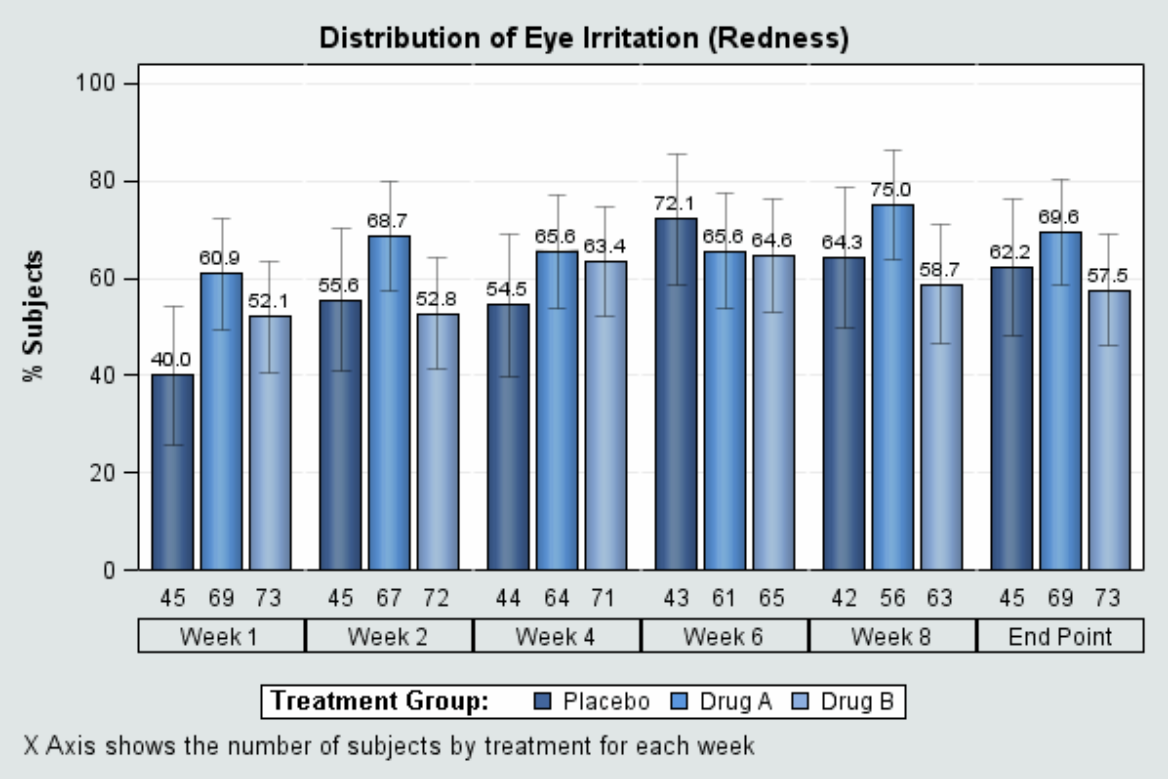
- Bring closer items the reader needs to compare
  - Dose-Response relationship ? Consistent effects across subgroups?



CTSPEDIA

Do's and don'ts

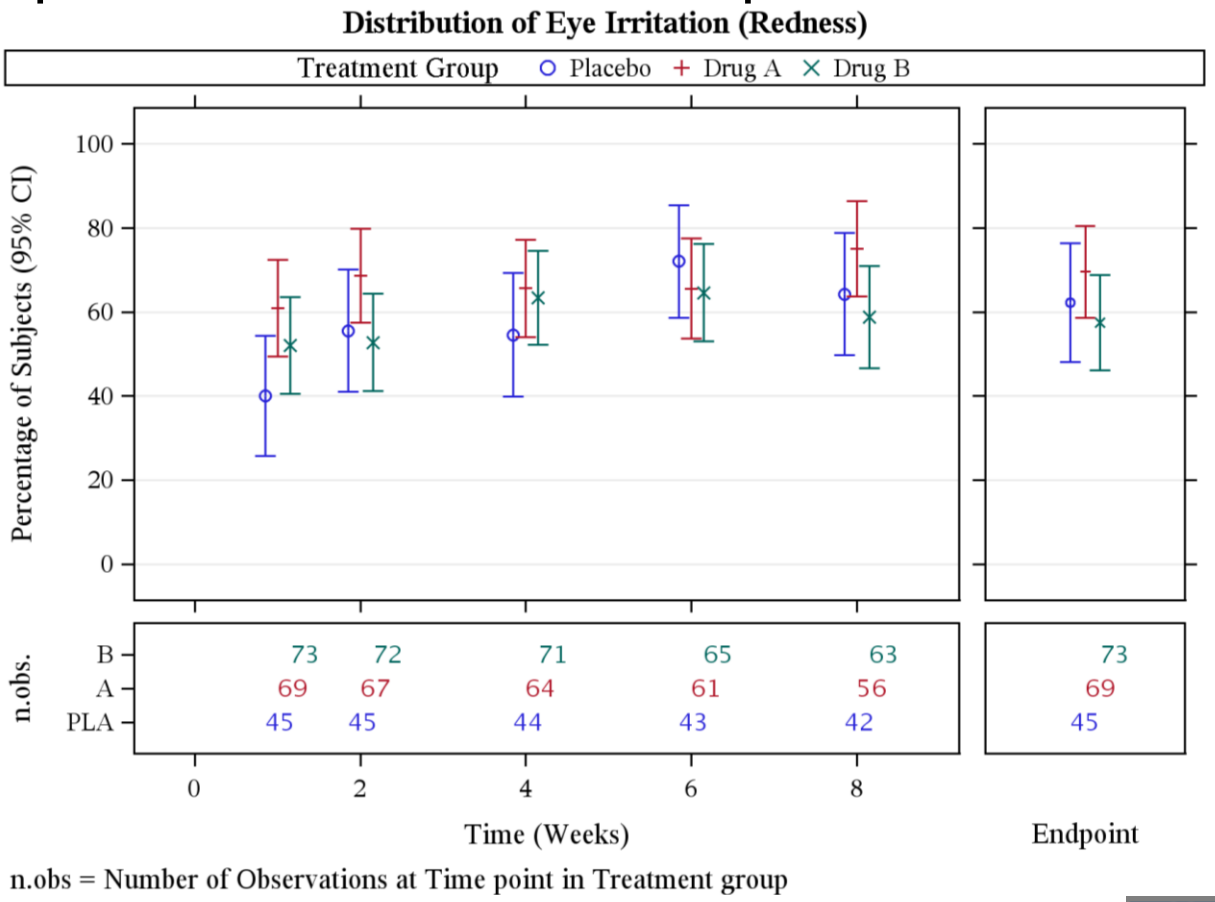
- Maximize the data-to-ink ratio
- Use quantitative scales ... for quantitative variables
  - 'Lot of ink' version ... with timepoint considered as categorical



CTSPEDIA

Do's and don'ts

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

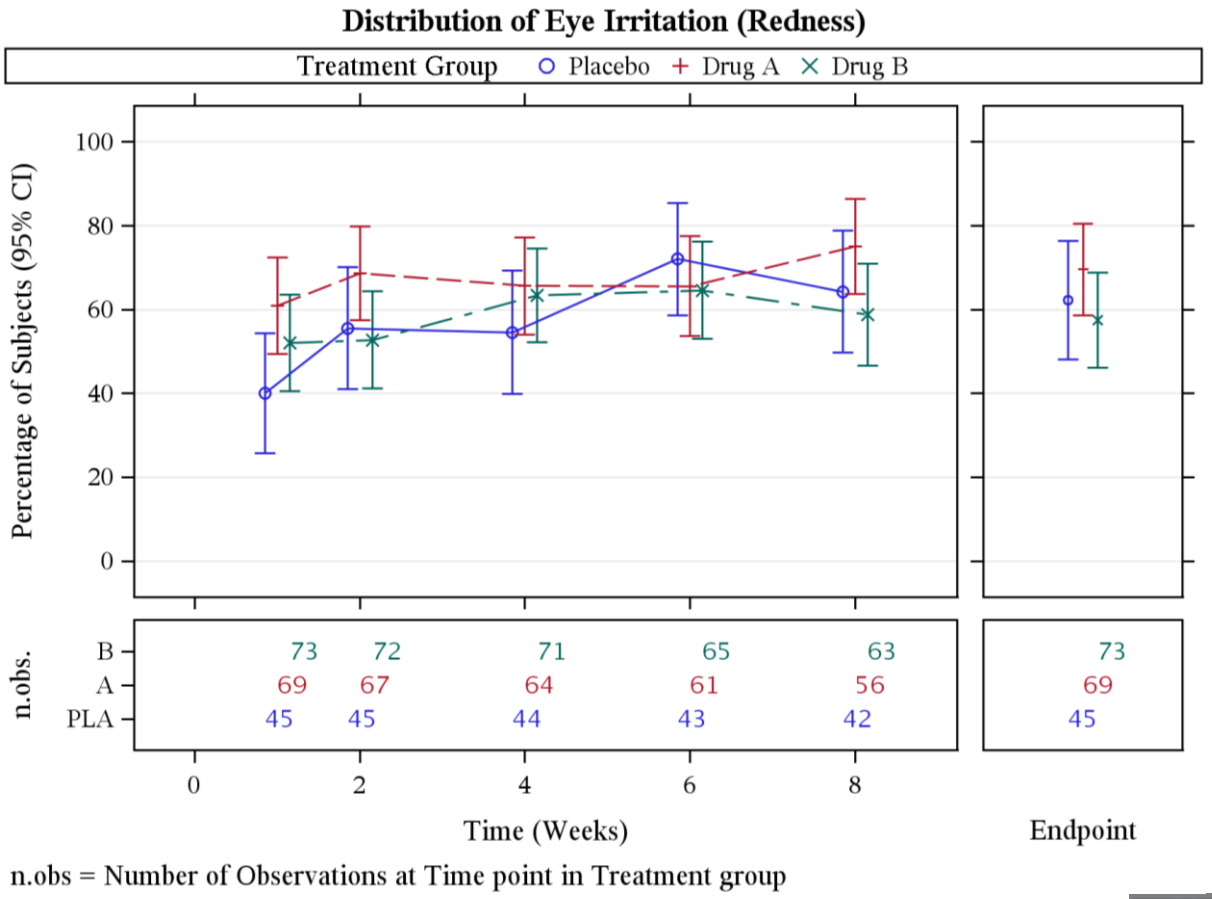


n.obs = Number of Observations at Time point in Treatment group

CTSPEDIA

Do's and don'ts

- Another variation with connecting lines

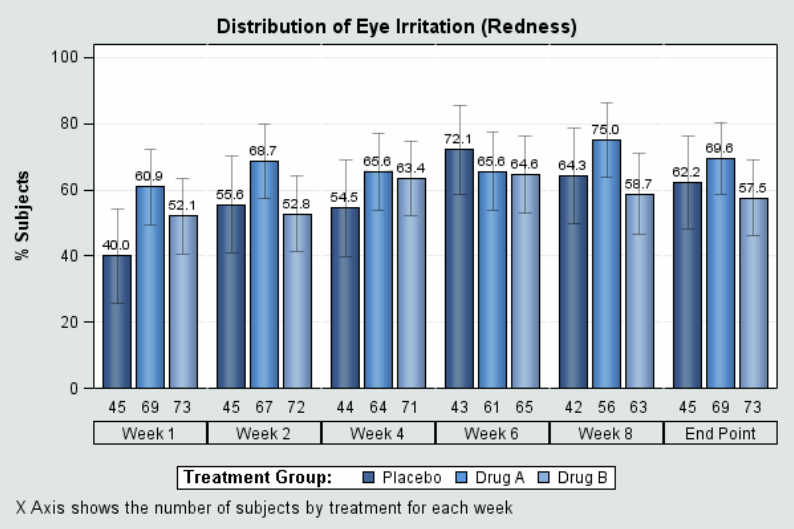


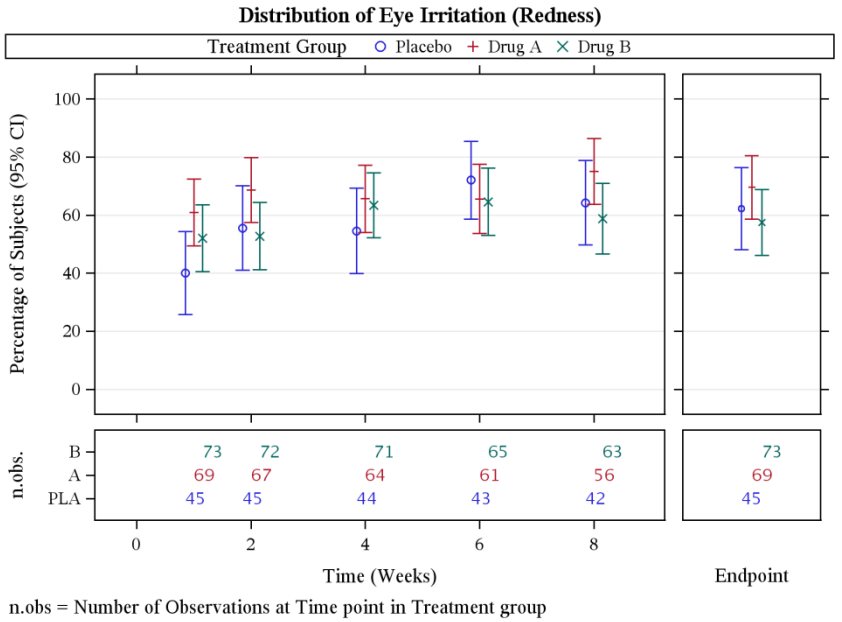
n.obs = Number of Observations at Time point in Treatment group

CTSPEDIA

Do's and don'ts

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

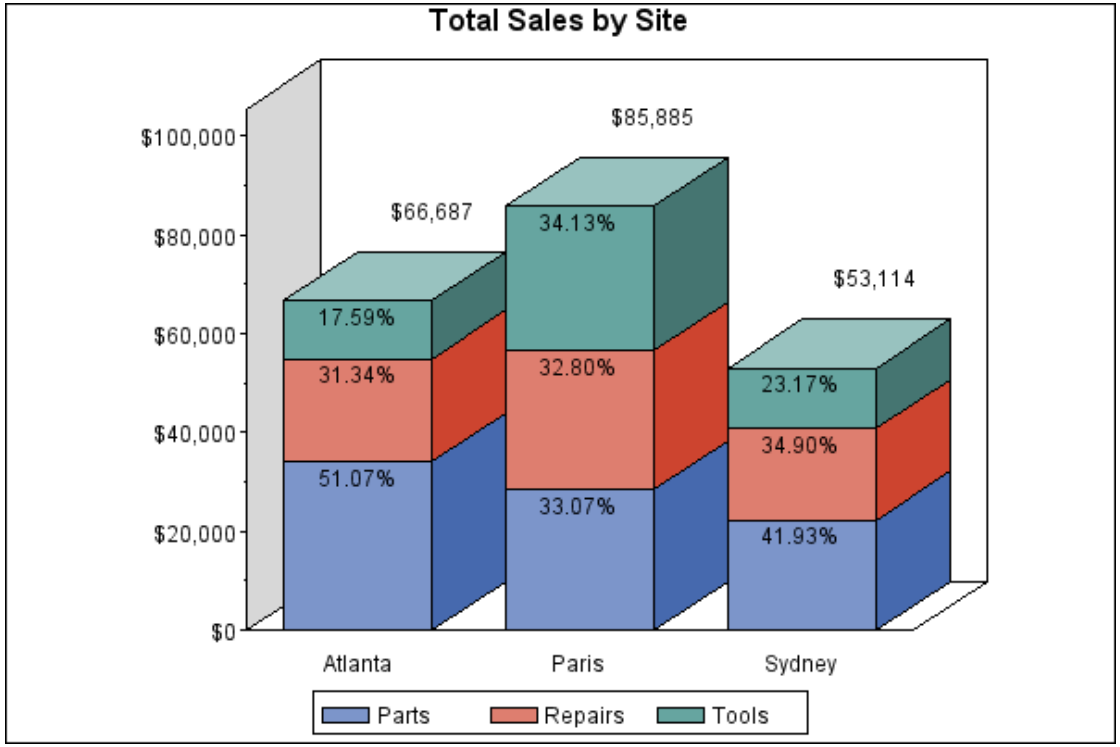


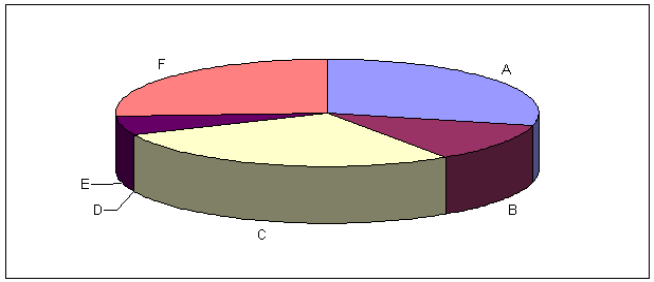


CTSPEDIA

Do's and don'ts

- Maximize the data-to-ink ratio
- Don't use unnecessary dimensions
- Stacked bar plots or pie charts not efficient for comparisons

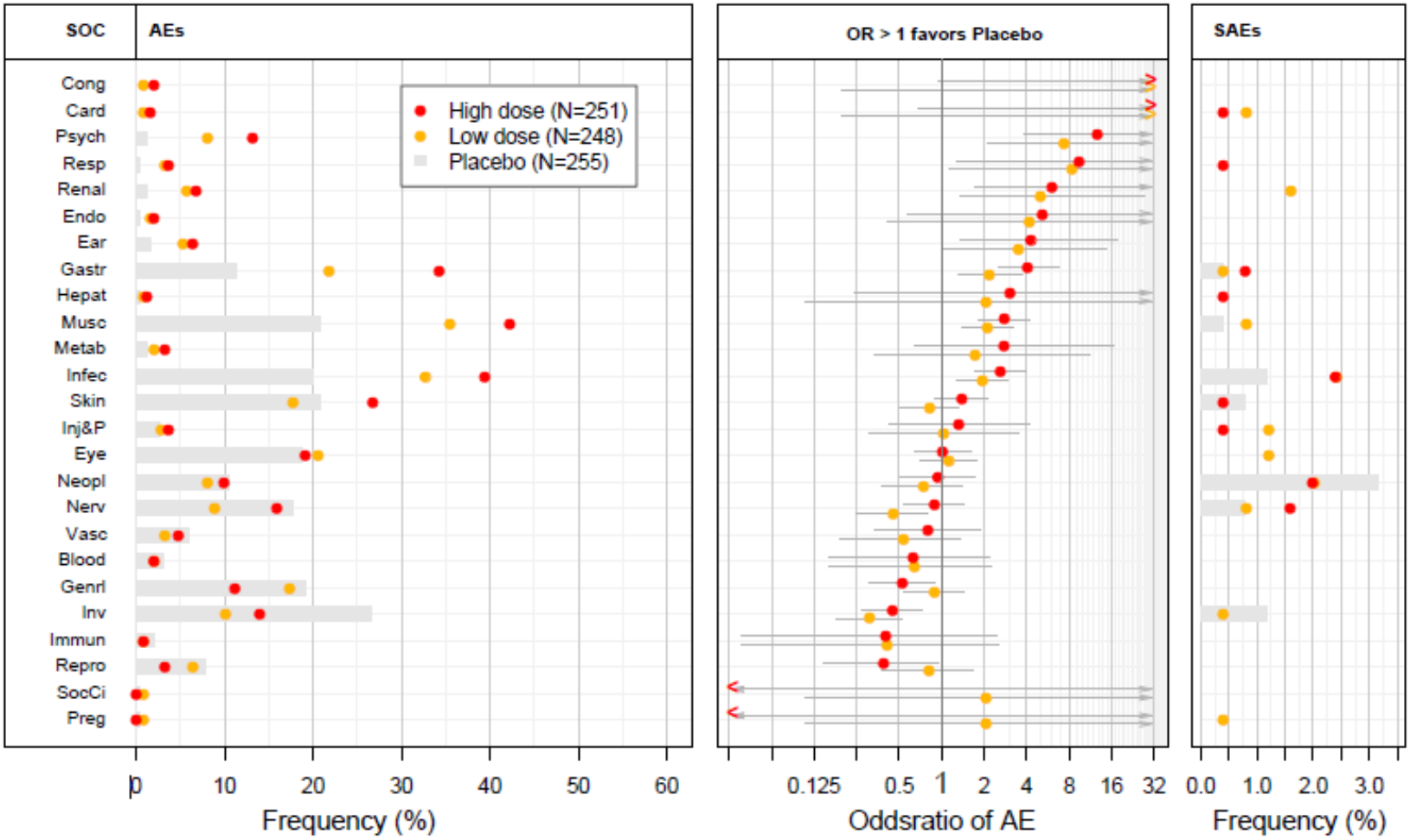




CTSPEDIA

Do's and don'ts

- Bring different components of the answer together



CTSPEDIA

General Principles

Designing graphs for other data domains

Graphics Navigator

Do's and Don'ts

Glossary

Making graphs more **effective**

CTSPEDIA

Conclusions

- Stakeholders benefit from easy ways to understand and remember clinical messages
- Using more graphs and more effective graphs will help reaching that goal
- Material developed and available on the wiki should allow to more rapidly design and optimize your graphs
  - Graphs for common clinical questions
  - Process for designing graphs for less common questions
  - Best graphing principles

You are welcome to share experience and provide feedback to the wiki ctspedia.org !

CTSPEDIA

References and Useful Links

Amit, O., Heiberger, R. and Lane, P. (2007). Graphical approaches to the analysis of safety data in clinical trials. Pharmaceut. Stat. 7(1):20-35.

Cooper, A. J. P., Lettis, S., Chapman, C. L., Evans, S. J. W., Waller, P. C., Shakir, S., Payvandi, N. and Murray, A. B. (2008), Developing tools for the safety specification in risk management plans: lessons learned from a pilot project. Pharmacoepidemiology and Drug Safety, 17: 445–454.

W.S. Cleveland. Visualizing Data. Hobart Press, Summit, NJ, 1993.

W.S. Cleveland. Elements of Graphing Data. Hobart Press, Summit, NJ, 1993.

Heiberger, R. and Holland, B., Statistical Analysis and Data Display. Springer, New York, NY, 2004.

N.B. Robbins, Creating More Effective Graphs. Wiley-Interscience, 2004.

E.R. Tufte, The Visual Display of Qualitative Information. Graphics Press, Chesire, CT, 1983.

E.R. Tufte, Envisioning Information. Graphics Press, Chesire, CT, 1990.

E.R. Tufte, Visual Explanations. Graphics Press, Chesire, CT, 1997.

Michael Friendly's Gallery of Data Visualization - The Best and Worst of Statistical Graphics http://www.math.yorku.ca/SCS/Gallery/

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

CTSPEDIA

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

CTSPEDIA