Graphs are Statistical Methods Too!
The case for graphics in safety and benefit-risk analysis

Susan P Duke, MS, MS

Manager, Benefit Risk Evaluation

GlaxoSmithKline

Outline

- Statistical graphs are statistical methods too
- Visual perception
- Barriers to graph creation and what we can do about it *Best practices and standard graphs that elegantly answer commonly asked questions*
- Initial learnings about graphics techniques and impact in benefit-risk quantification at GSK

Graphical displays of data are encouraged in regulatory guidance documents:

Thanks to Andreas Brueckner, Novartis, for the original compilation of these regulatory guidance slides.

ICH E9

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

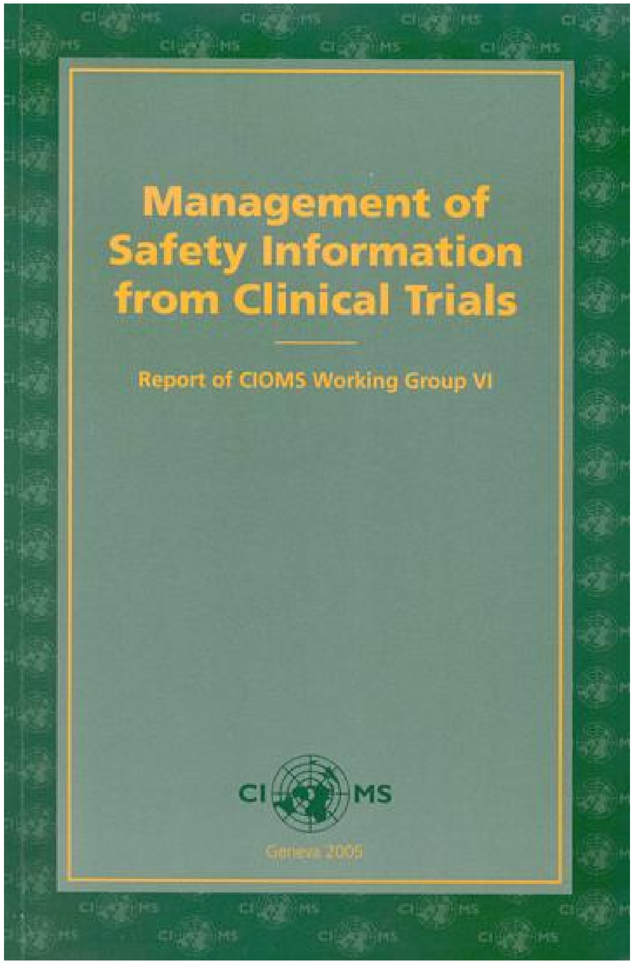
3.3.3 Trials to Show Dose-response Relationship

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.

CIOMS VI


Management of
Safety Information
from Clinical Trials
Report of CIOMS Working Group VI
Geneva 2005

From the perspective of illustrating the course of an adverse event, it is very much preferred to present the cumulative hazard.

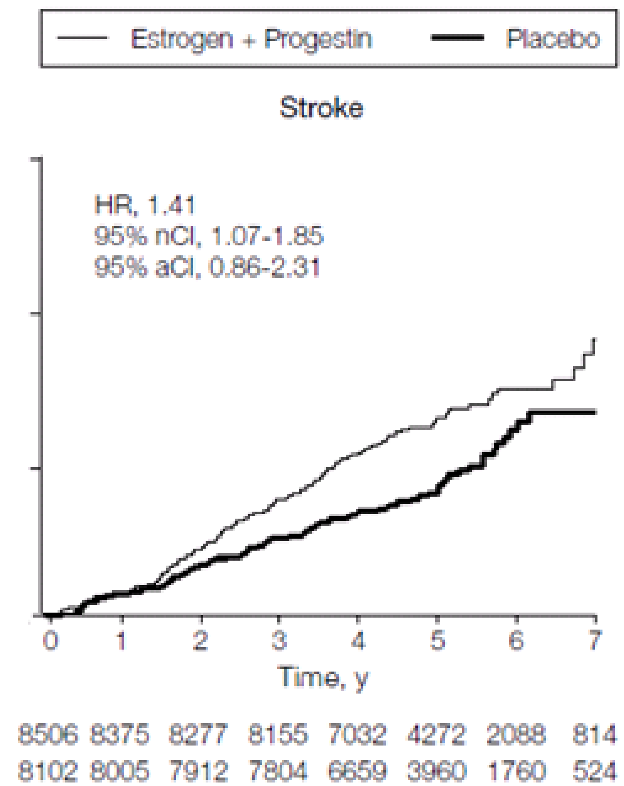


Figure 2 illustrates, for stroke, the cumulative hazard in each of the treatment groups. These curves show the rate at which new strokes are occurring in the two groups, as time from start of the study increases

FDA Reviewer Guidance

Reviewer Guidance

Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joseph J. DeGeorge, 301-594-5476.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2001

Pharmacology/Toxicology

FDA Reviewer Guidance – Adverse Findings

7.4.2.2 Explorations of Time-Dependency for Adverse Findings
The reviewer should explore time dependency of adverse reactions:

For important adverse reactions that occur later in treatment, there should be explorations of the time dependency of the reaction. Possible methods include:

- A life table (Kaplan-Meier graph) describing risk as a function of duration of exposure (i.e., cumulative incidence)
- Plotting risk for discrete time intervals over the observation period (i.e., a hazard rate curve) reveals how risk changes over time.

In spite of all this encouragement, let's check where we're at:

- Graphs for key safety parameters in study reports?
- Graphs for key efficacy?
- When clinicians ask for more details, do you respond with a graph?
- Graphs of key safety & efficacy in internal presentations?

Evidence for Graphs as Statistical Methods

- **Statistics** is the study of the collection, organization, analysis, interpretation, and presentation of data.

  -Wikipedia

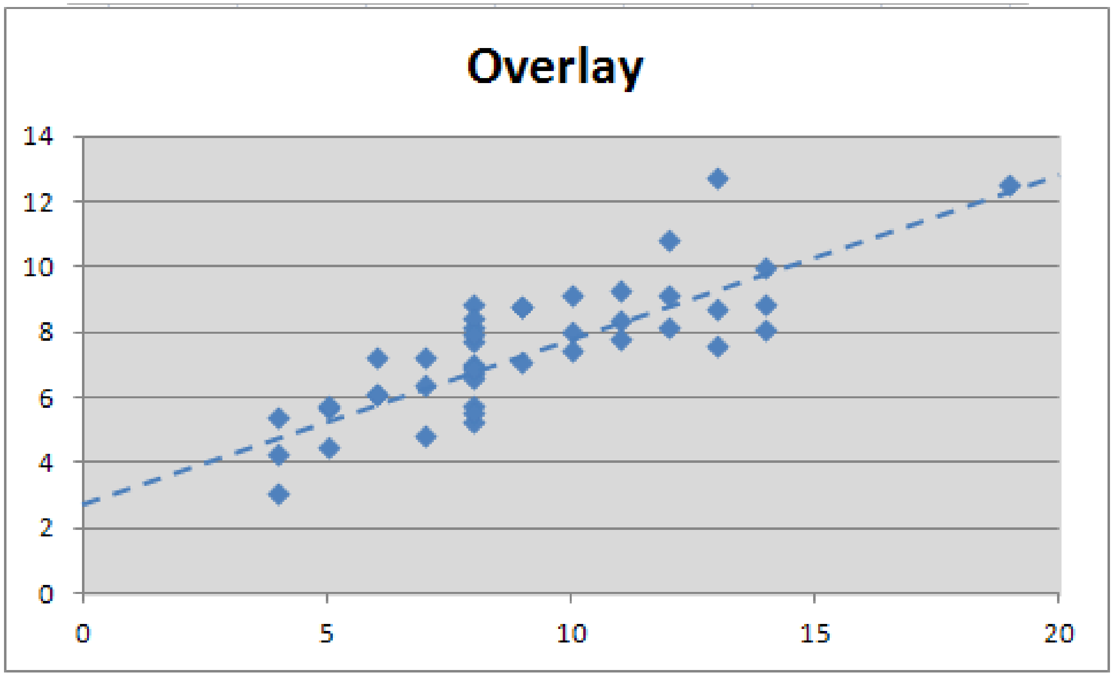
- Organization
  - What is the thought task of the graph? *What is the thought task of the analysis?*
- Analysis
  - What is being analyzed? *Do you know if you've never looked at it graphically?*
- Interpretation, Presentation
  - Whose responsibility is it to clearly convey the interpretation of the analysis? To present clearly to the intended audience? *If the statistician doesn't, who will?*

Interpretation – ‘Graphics Reveal Data’ (Tufte)

ANSCOMBE’s QUARTET							
Graph 1		Graph 2		Graph 3		Graph 4	
X	Y	X	Y	X	Y	X	Y
10	8.04	10	9.14	10	7.46	8	6.58
8	6.95	8	8.14	8	6.77	8	5.76
13	7.58	13	8.74	13	12.74	8	7.71
9	8.81	9	8.77	9	7.11	8	8.84
11	8.33	11	9.26	11	7.81	8	8.47
14	9.96	14	8.1	14	8.84	8	7.04
6	7.24	6	6.13	6	6.08	8	5.25
4	4.26	4	3.1	4	5.39	19	12.5
12	10.84	12	9.13	12	8.15	8	5.56
7	4.82	7	7.26	7	6.42	8	7.91
5	5.68	5	4.47	5	5.73	8	6.89

Mean of Y's	7.5
Mean of X's	9
Regression line	Y = 0.5X + 3

From Robert Gordon, J&J



From Robert Gordon, J&J

Graphs as Statistical Methods *Statistics as an Art*

- Have you noticed how your eye is drawn to figures more than words and tables? *This very fact can be powerfully used to transparently and succinctly communicate the key points of a clinical study or submission.*
- Descriptive *but often confidence intervals are included*
- Often a necessary adjunct to inferential statistics *if clinical interpretation is meant to be clear*
- Statisticians have many statistical tools available
  - We choose those tools most appropriate for the situation *Consider graphs here too!*

Better use of statistical graphics

- Is it a lack of respect as a statistical method?
- Lack of knowledge of effective graphics?
- Both?

Visual Perception

I Can't Think!

The Twitterization of our culture has revolutionized our lives, but with an unintended consequence—our overloaded brains freeze when we have to make decisions.

by Sharon Begley (/contributors/sharon-begley.html) | February 27, 2011 10:0 AM EST

Illustration by Matt Mahurin for Newsweek

- *Brain scans confirm - parts of the brain best at decision-making can get overloaded*
- *Too much information results in poorer decisions*

The Science of Making Decisions Newsweek 27 Feb 2011

Imagine the most mind-numbing choice you've faced lately, one in which the possibilities almost paralyzed you: buying a car, choosing a health-care plan, figuring out what to do with your 401(k). The anxiety you felt might have been just the well-known consequence of information overload, but Angelika Dimoka, director of the Center for Neural Decision Making at Temple University, suspects that a more complicated biological phenomenon is at work. To confirm it, she needed to find a problem that overtaxes people's decision-making abilities, so she joined forces with economists and computer scientists who study "combinatorial auctions," bidding wars that bear almost no resemblance to the eBay version. Bidders consider a dizzying number of items that can be bought either alone or bundled, such as airport landing slots. The challenge is to buy the combination you want at the lowest price—a diabolical puzzle if you're considering, say, 100 landing slots at LAX. As the number of items and combinations explodes, so does the quantity of information bidders must juggle: passenger

Pattern Recognition is a Key Feature of Effective Graphics

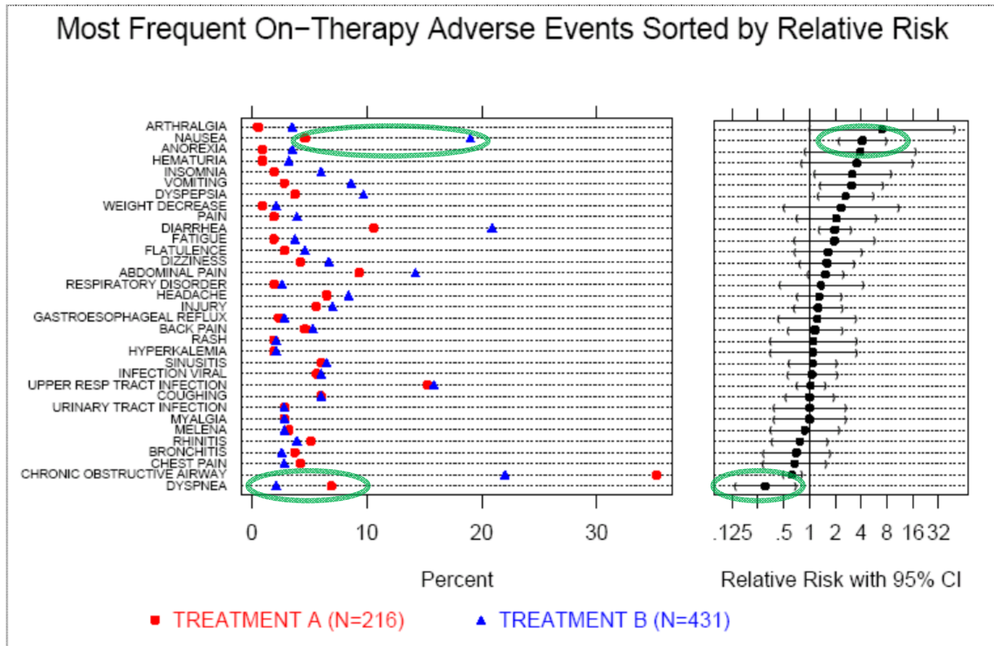
- *40-60% of the human brain is devoted to visualization*
- *Human visual capability is far ahead of the computer*

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)

Graphical Perception

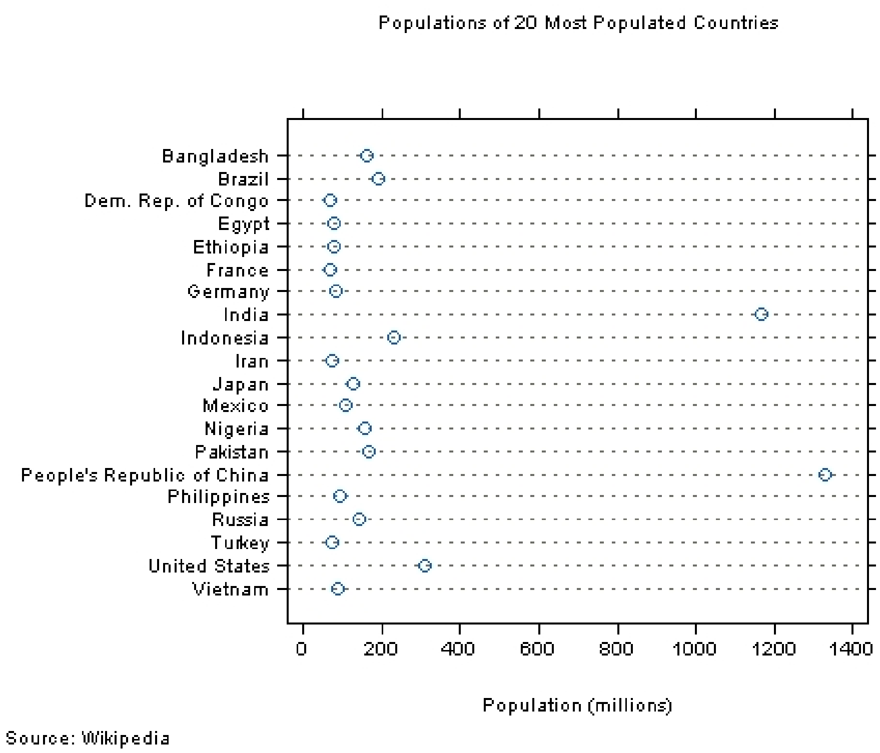
"When a graph is constructed, information is *encoded*. The *visual decoding* of this encoded information is *graphical perception*.

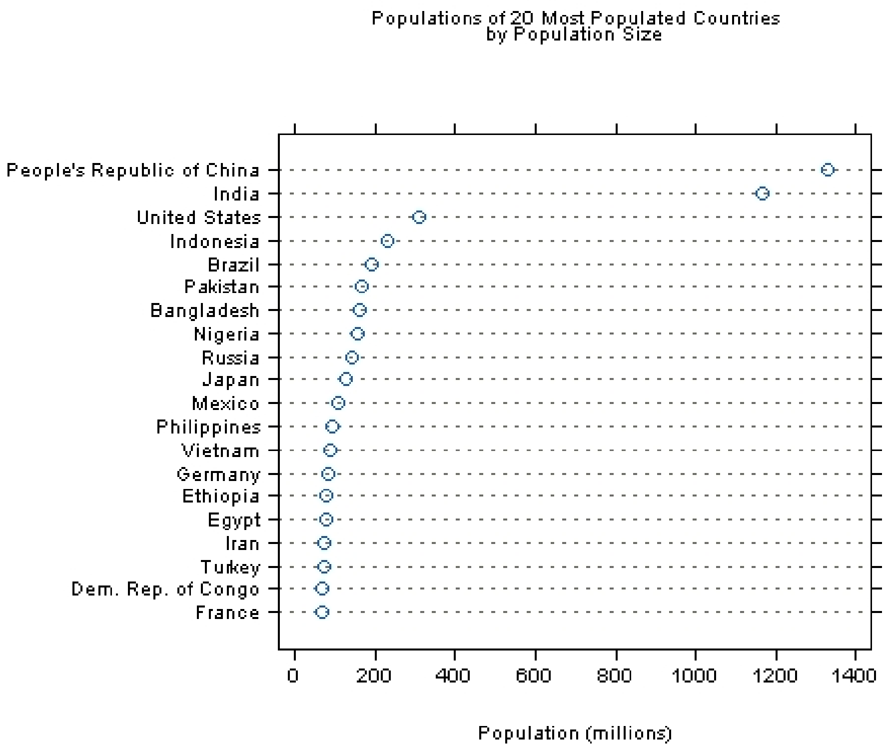
The decoding is the vital link …

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

Table Look-Up and Pattern Perception





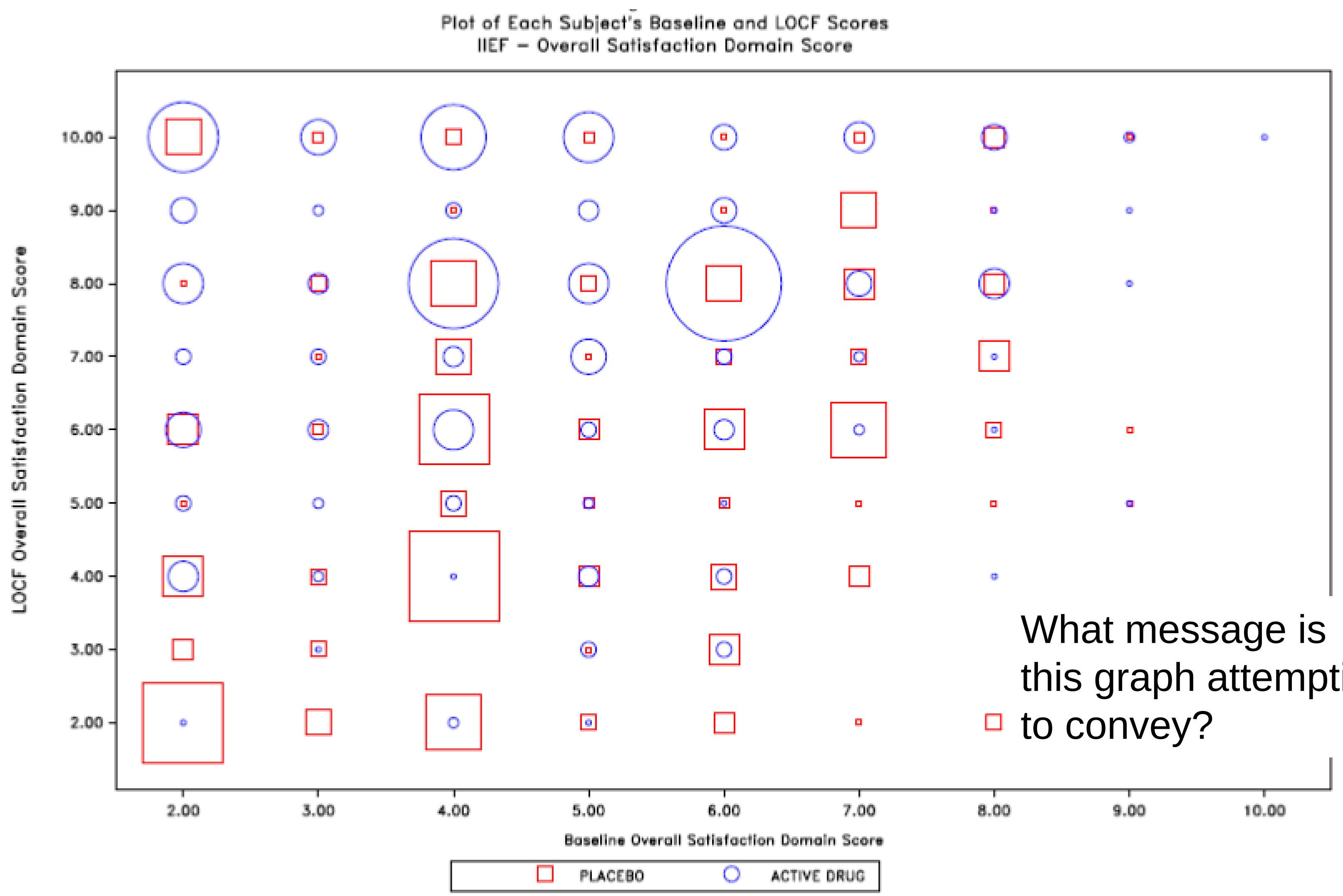
Concept from William Cleveland, The Elements of Graphing Data
Graphs by Susan Duke, GSK

Barriers to Graph Creation

- What's in it for me/my group?
  - The value of clear communications inherent in graphs is typically downstream from the group who creates them

- Graphs take time!
  - **Thought time**: how best to design the graph for its intended purpose?
    - What is the purpose of this graph? Who is the audience? What type of data?
  - **Programming time**
    - How to reduce the time needed for programming?

Comparative Bubble-plot

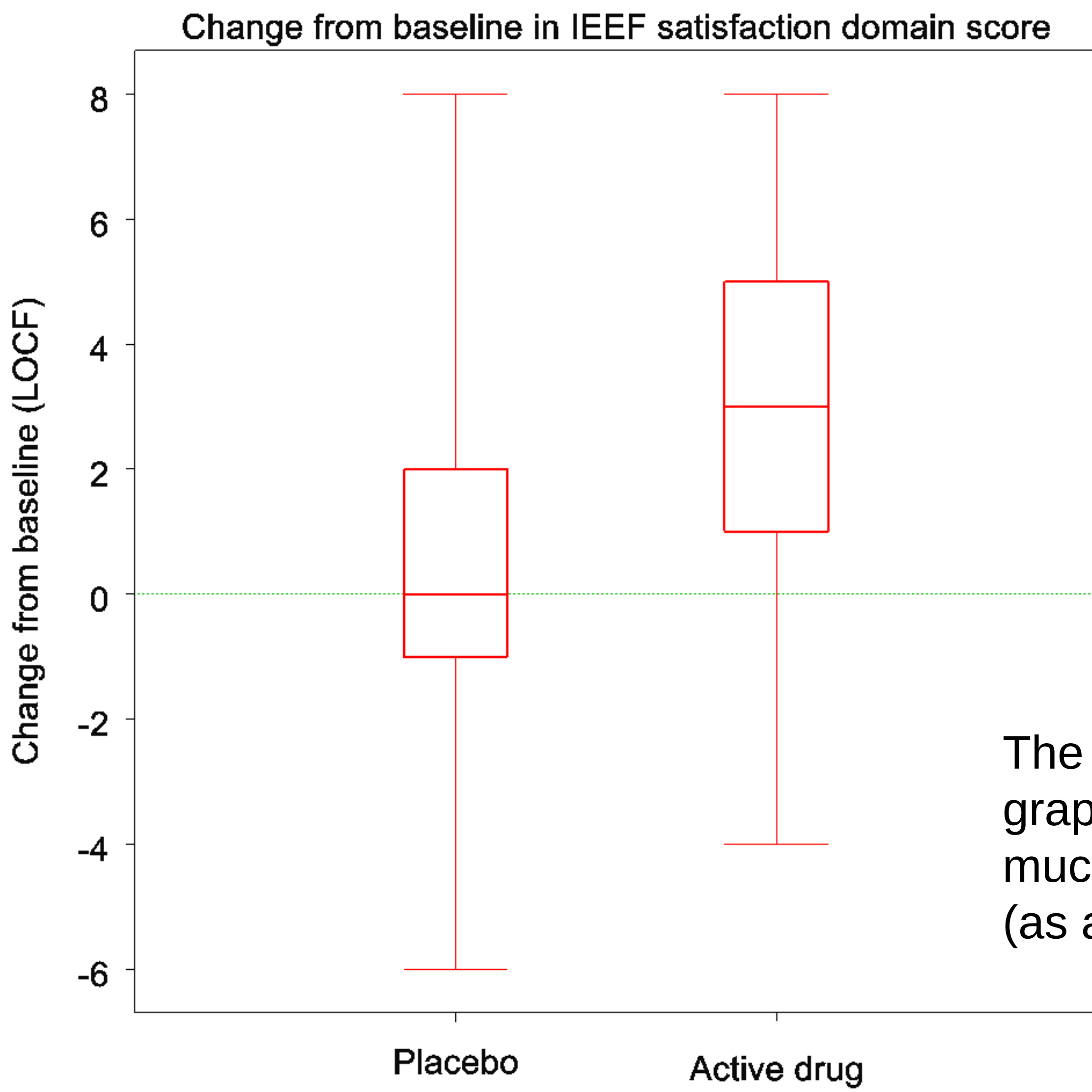


What message is this graph attempting to convey?

Note: The size of the circles and squares indicate the freqency of subjects at the respective coordinates.

Graph from GSK Graphics Design Course

The Same Data in a Boxplot



The intent of the graphics message is much clearer here (as are the results!)

Graph by Peter Lane, GSK Graphics Design Course

Graphics Best Practices

1. **Content** Every graph should stand on its own
2. **Communication** Tailor each graph to its primary communication purpose
3. **Information** Maximize the data-to-ink ratio
4. **Annotation** Provide legible text and information
5. **Axes** Design axes to aid interpretation of a graph
6. **Styles** Make symbols and plot lines distinct and readable
7. **Colors** Make use of color if appropriate for the medium of communication
8. **Techniques** Use established techniques to clarify the message
9. **Types of plots** Use the simplest plot that is appropriate for the information to be displayed

http://www.ctspedia.org/do/view/CTSpedia/BestPractices

Endorsed by General Principles subteam, FDA/Industry/Academia Safety Graphics Working Group
Adapted from GlaxoSmithKline Graphics Principles

How to reduce programming time?

- Let's face it - time needed to make graphs is typically longer than time needed for tables and listings

- Learnings from GSK Graphics Initiative:
  - Stats & programming teams with a reputation for sustainably creating impactful graphs have a "graphics guru" (or two)
    - Encourage 'community of practice' amongst those with strong graphics interest
  - Make graph creation easier
    - We focused on safety, specifically standard graphs for common safety questions
    - We use a software tool (TSCG) that has a template for each of the standard graphs. Graphs are created with a GUI interface and it's easy to put into our reporting system

- Industry-wide, FDA has encouraged a similar approach with the FDA/Industry/Academia Safety Graphics Working Group

How to Make Quality Graphs More Quickly?
Use Standard Graphs for Common Safety Questions

- Two references:
  - Graphical approaches to the analysis of safety data from clinical trials (Amit, Heiberger & Lane, 2008)

PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. 2008; 7: 20–35
Published online 26 February 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/pst.254

WILEY InterScience DISCOVER SOMETHING GREAT

Graphical Approaches to the Analysis of Safety Data from Clinical Trials

MAIN PAPER

Ohad Amit[1], Richard M. Heiberger[2,‡] and Peter W. Lane[3,*,†]
[1] *Oncology Medicine Development Center, GlaxoSmithKline, USA*
[2] *Department of Statistics, Temple University, USA*
[3] *Research Statistical Unit, GlaxoSmithKline, UK*

Patient safety has always been a primary focus in the development of new pharmaceutical products. The predominant method for statistical evaluation and interpretation of safety data collected in a clinical trial is the tabular display of descriptive statistics. There is a great opportunity to enhance evaluation of drug safety through the use of graphical displays, which can convey multiple pieces of information concisely and more effectively than can tables. Graphs can be used in an exploratory

  - FDA/Industry/Academia Safety Graphics Working Group
    - Each graph entry in the wiki has a description of use, sample program code & data
    - The wiki is searchable, has a glossary and many other features
    - ctspedia.org/StatGraphHome

How to Make Quality Graphs More Quickly?

Use Standard Graphs for Common Safety Questions

You are here: CTSPedia > CTSpedia Web > StatGraphHome (23 Aug 2012, MaryBanach) Edit Attach

Tags: create new tag , view all tags, tagging instructions

Welcome to the Clinical Trials Safety Graphics Home Page

Graphs that answer common clinical trial safety questions

Recommendations from the FDA/Industry/Academia Safety Graphics Working Group

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

for general information about graph types and where to use them

Select the Right Graph for Your Data

See all graphical entries in the library

Search for a graph entry

Resources:

- 9 Best Practices for Making Graphs
- Graphics Glossary
- FDA/Industry/Academia Safety Graphics Presentation Archive
- Graphics References

CTSpedia

Log In or Register

Webs on CTSpedia

- CTSpedia
- Main
- ResearchEthics
- Sandbox
- System

Recent Changes
Help

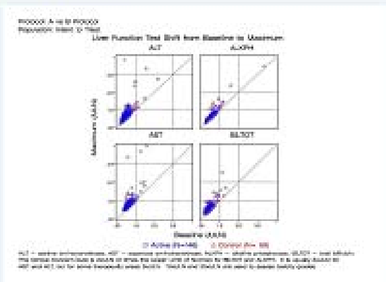
Thanks to Mary Banach, UC Davis, for her webmaster role on the FDA/Industry/Academia Safety Graphics Working Group

Graphs that answer common lab questions

Baseline and Trending over Time

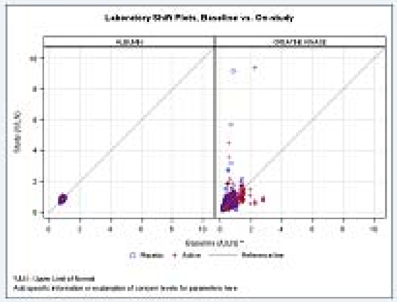
1. What are the changed and percent changes from baseline over time? ie, are abnormal lab values a result of an abnormal baseline or have values changed on study?

Example 1



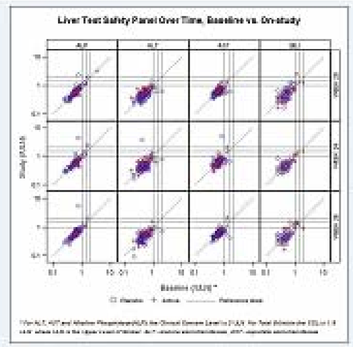
Click here for Example 1 Data

Example 2



Click here for Example 2 Data

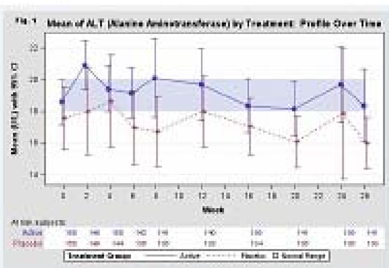
Example 3



Click here for Example 3 Data

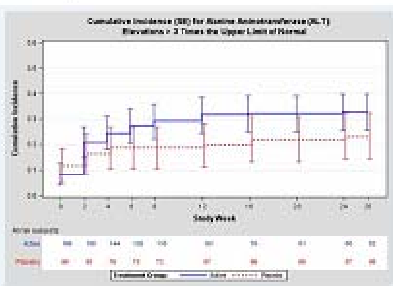
2. Is there a temporal relationship between treatment and lab values?

Example 1



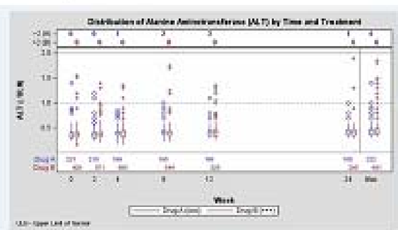
Click here for Example 1 Data

Example 2



Click here for Example 2 Data

Example 3



Click here for Example 3 Data

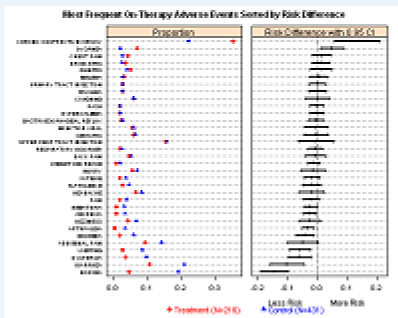
See more questions and graphs at ctspedia.org/StatGraphHome

Contributed by Safety Graphics Working Group Lab/Liver subteam, lead by Robert Gordon, J&J

Graphs that answer common adverse event questions

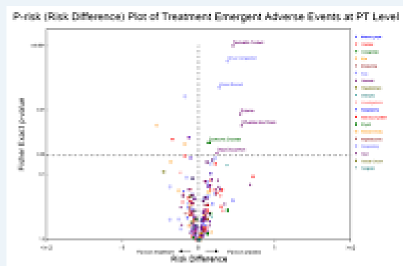
1. Which AEs are elevated in treatment vs. control? Which AE could be a safety signal?

Example 1



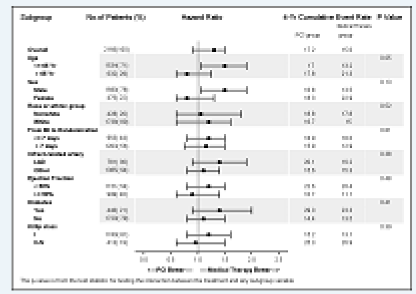
Click here for Example 1 Data

Example 2



Click here for Example 2 Data

Example 3

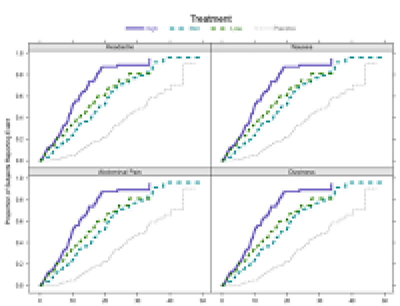


Click here for Example 3 Data

2. What is the risk trend of an Adverse Event of Special Interest?

3. Is there a difference in the time to the first event across treatment groups?

Example 1



Click here for Example 1 Data

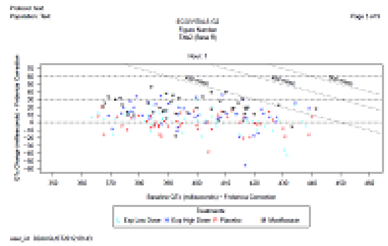
See more questions and graphs at ctspedia.org/StatGraphHome

Contributed by Safety Graphics Working Group AE subteam, lead by Qi Jiang, Amgen & Liping Huang, CSL Behring

Graphs that answer common ECG/Vital Signs questions

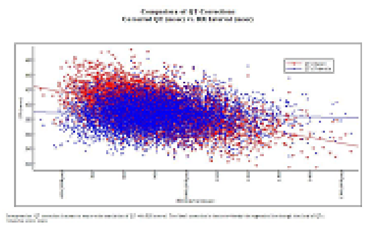
1. What are the longitudinal trends in the data?

2. Are there outlier individuals that have large changes or raw values?



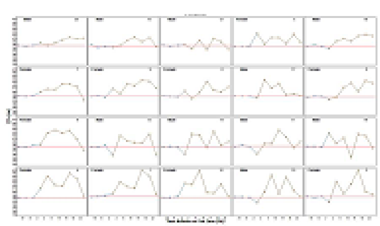
Click here for more information

3. How do the different QT correction compare w.r.t relationship with RR?



Click here for more information

4. How do individuals' values track over time?



Click here for more information

See more questions and graphs at ctspedia.org/StatGraphHome

Contributed by Safety Graphics Working Group ECG/Vitals subteam, lead by Rich Anziano, Pfizer

Solutions to Graph Creation

- What's in it for me/my group?
  - See it as an opportunity for empowerment!
- Graphs take time!
  - **Thought time**: how best to design the graph for its intended purpose?
    - What is the purpose of this graph? Who is the audience? What type of data?
    - **Use the 9 Best Practices to review the first draft**
  - **Programming time**
    - How to reduce the time needed for programming?
    - **Use the Safety Graphics Wiki for ideas and code**
    - **Use software that's *designed* for graphing (eg, R)**
    - **Work together (many teams have a 'graphics guru' – share ideas!)**

Switching Gears

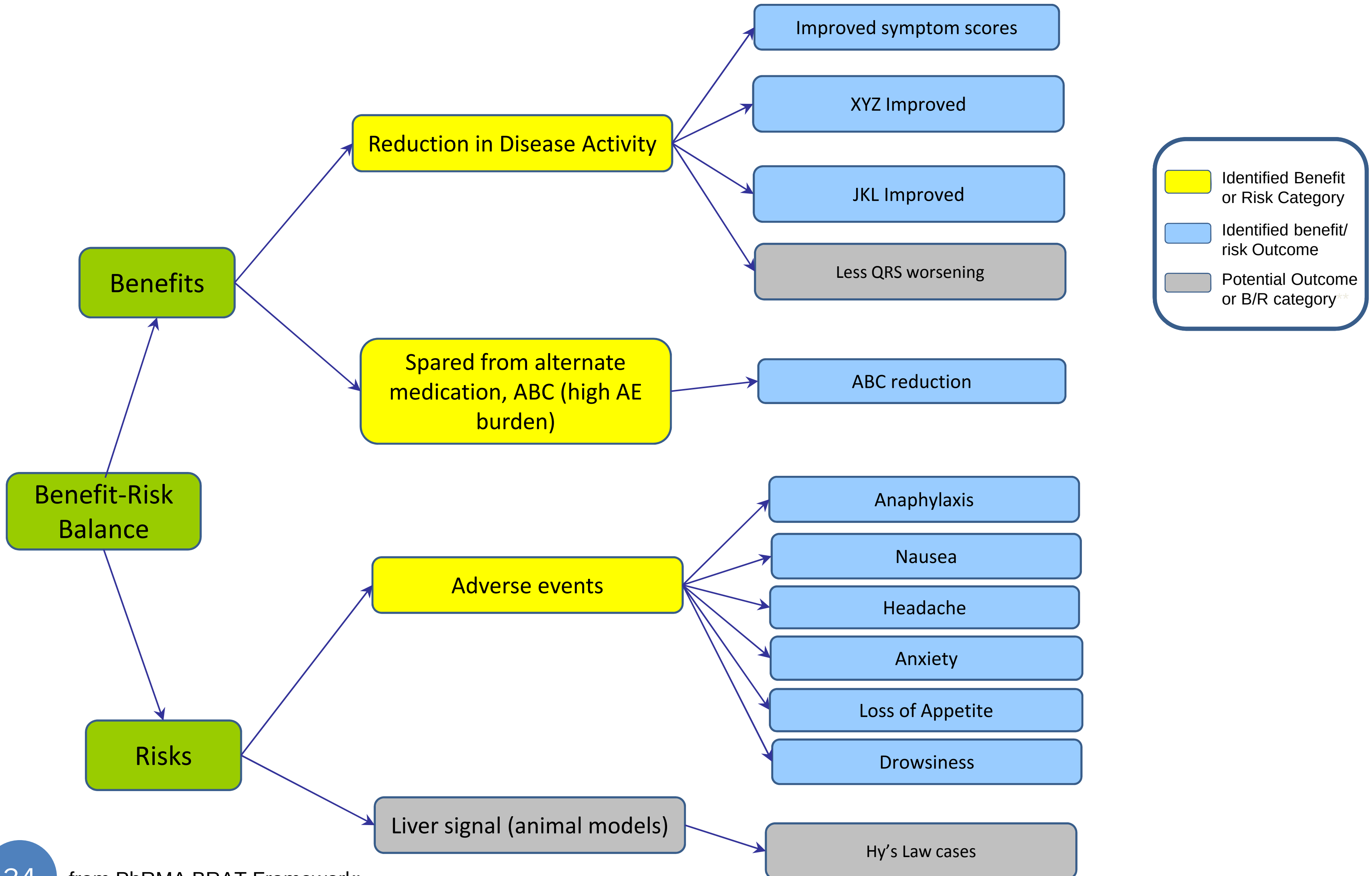
from Safety

to Benefit-Risk…

Impact of Graphics on Benefit-Risk

- Value Tree and Graphic are making an impact!

Value Tree: Drug X added to Standard of Care

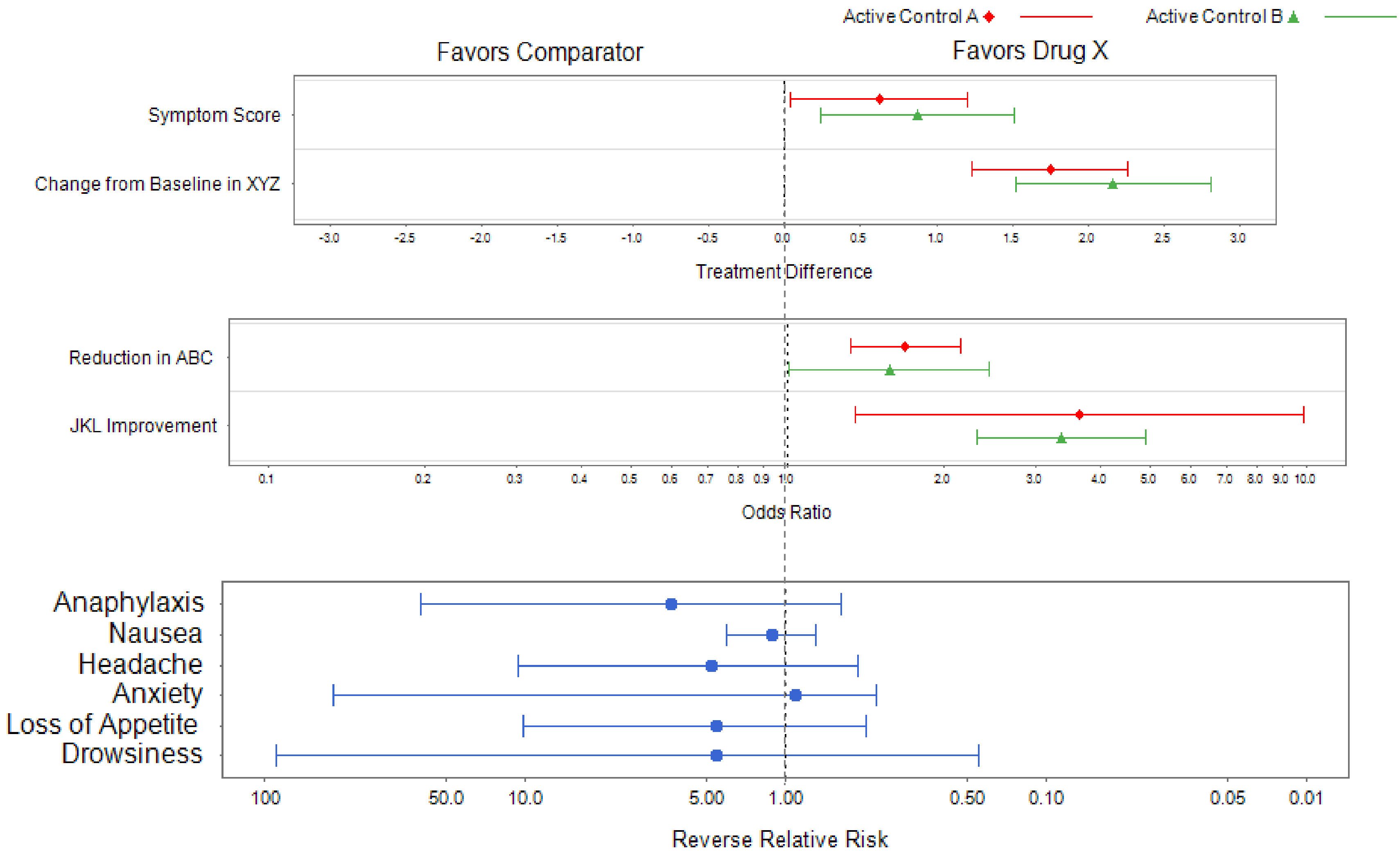


from PhRMA BRAT Framework;

EMA has successfully field tested a similar "effects tree"

Drug X Benefit-Risk Interval Plot

Risks by order of clinical importance

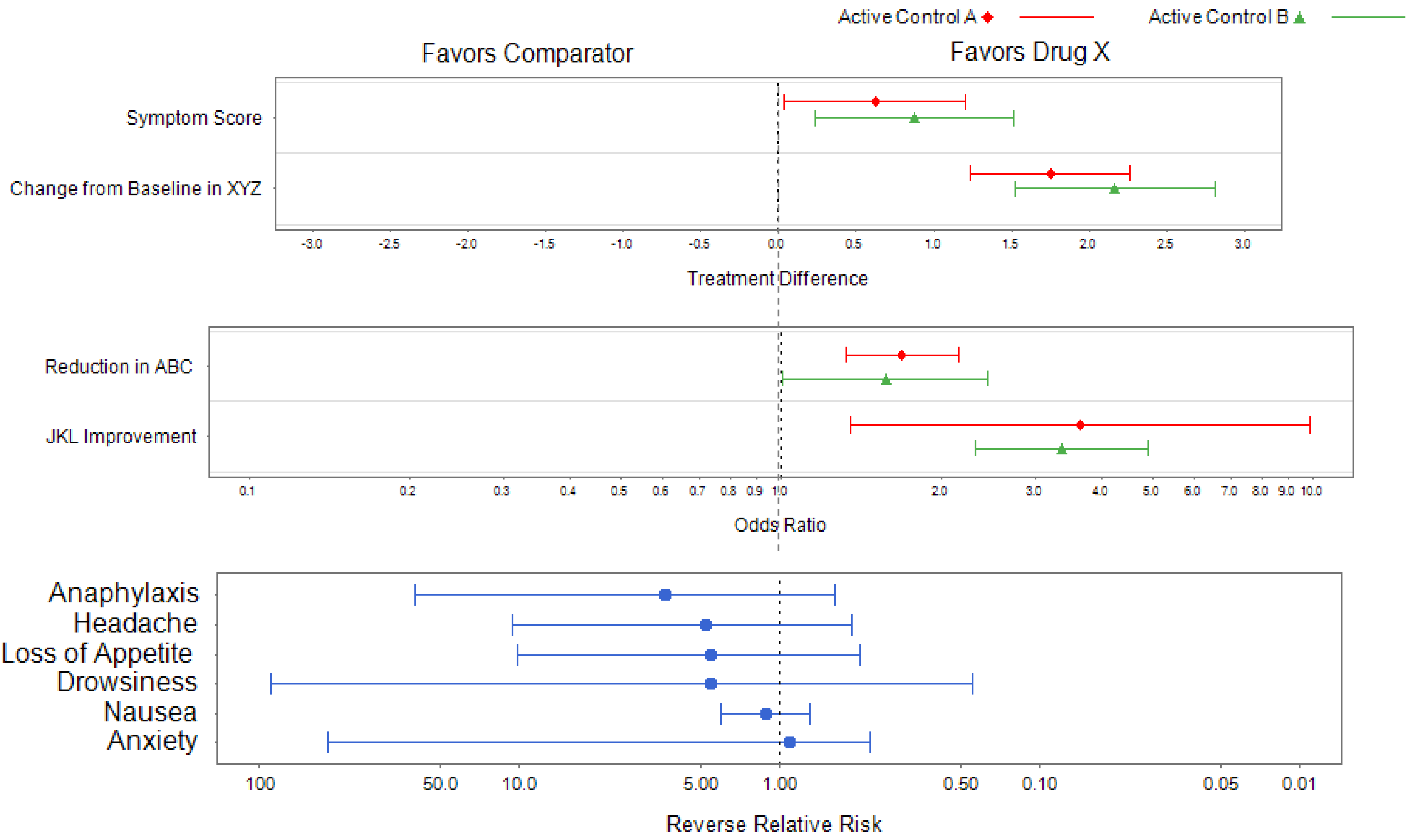


Comparator (Active Controls A + B combined) vs.Drug X (point estimate and

Benefits are from ?? Population: xx Phase 3 studies (xx-xx weeks) (n=xxx);
Risks are from Primary Safety Population: xx phase 3 studies (xx-xx weeks) and xx phase 2 study (xx weeks) (n=xxx)

Drug X Benefit-Risk Interval Plot

Risks by order of point estimate



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Benefits are from ?? Population: xx Phase 3 studies (xx-xx weeks) (n=xxx);
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Impact of Graphics on Benefit-Risk

- Value Tree and Graphic are making an impact!
- Challenge of different scales
  - Training opportunity
- Quantification beyond the graph
  - EFSPI Benefit-Risk Working Group
  - GSK Statistical Methods Benefit-Risk Working Group

Conclusions

- Clear and informative graphs enhance the ability to understand the data
- Suitable graphical presentation could increase the likelihood of detecting safety signals
- Graphs convey information more efficiently and better meet regulatory requirements for ongoing safety evaluation

From Ken Koury, Merck

Thanks to

- The FDA/Industry/Academia Safety Graphics Team
  - ***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, Robert Makowsky
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  - ***Academia*****:** Frank Harrell, Mary Banach
  - ***Programmers:*** Max Cherny, Sanjay Mantage, Sally Rodriquez
- GSK Graphics Team (variously lead by Ohad Amit, Peter Lane, Susan Duke, Mark Jones, Jay Hilliard, Michael Durante)
- GSK Benefit Risk Evaluation Team (Marilyn Metcalf, Alfons Lieftucht, Susan Duke)
- Special thanks to Peter Lane (formerly GSK, now retired)
  - Peter had the original idea to create a Graphics Catalogue at GSK. He drafted the initial best practices, created the glossary and wrote or reviewed many of the GSK graphics entries
  - Much of Peter’s work has found its way into the Safety Graphics wiki