

# Visual Analytics in Safety Monitoring – Beyond the Usual Graphs and Available Tools

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Takeda

2017 MBSW

# Outline

- Overview
- Safety Monitoring
- Visual Analytics
- Visual Analytics Efforts
- Enhancing Visual Analytics and Safety Monitoring
- Tool of Choice
- Concluding Remarks

# ASA Safety Monitoring Working Group

**Established in 2015** by the ASA Biopharmaceutical Section Safety Statistics WG



## Goal

- To empower the biostatistics community to play a more proactive role and better enable quantification in safety monitoring

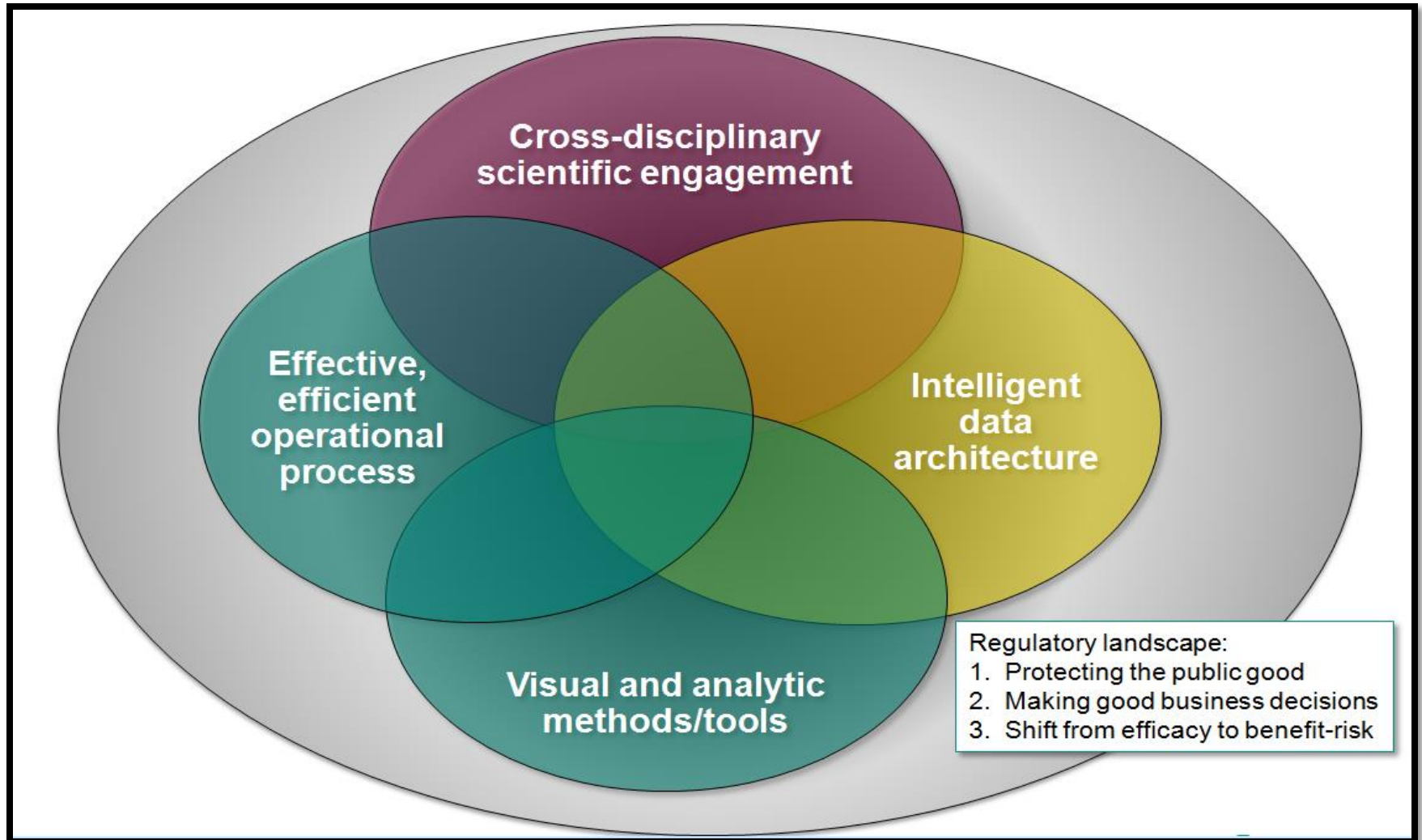
## Key activities

- Two Work Streams
  - WS 1 - Review safety regulations, survey industry, and interview thought leaders
  - WS 2 - Review statistical methodologies

# Background – Some Thoughts and Questions

- What are the roles and opportunities for statisticians supporting safety monitoring?
- How do we collaborate effectively with safety physicians and scientists?
- Are we facing a gap between our current practices and new methods, tools and regulatory guidance?

# Foundation - Four Pillars of Safety Statistics



# Who We Are (original team)

## **WS1: Industry Practice Regulation**

- Faiz Ahmad (Galderma)
- Greg Ball (Co-lead, Merck)
- Michael Colopy (UCB)
- Susan Duke (Co-lead, AbbVie)
- Robert (Mac) Gordon (Janssen)
- Qi Jiang (Amgen)
- Wenquan Wang (Morphotek)
- William Wang (Chair, Merck)

## **WS2: Methodology**

- Michael Fries (Behring)
- Karolyn Kracht (AbbVie)
- Judy Li (Co-lead, FDA)
- Melvin Munsaka (Co-lead, Takeda)
- Matilde Sanchez (SanchezKam)
- Krishan Singh (GSK)
- Ed Whalen (Pfizer)
- William Wang (Chair, Merck)
- Kefei Zhou (Amgen)

## **Safety Monitoring Statistical Advisors**

- Aloka Chakravarty (FDA)
- Brenda Crowe (Lilly)
- Larry Gould (Merck)
- Qi Jiang (Amgen)
- Olga Marchenko (Quintiles)
- Amy Xia (Amgen)
- Janet Wittes (Statistics Collaborative)

We are indebted to the 18 thought leaders who each spent at least an hour with us discussing their views on quantitative assessment of safety monitoring

*Interviewed by Greg Ball, Susan Duke, Mac Gordon, and Bill Wang*

# Thought Leaders

- Aloka Chakravarty (FDA)
- Bob Temple (FDA)
- Brenda Crowe (Lilly)
- Christy Chuang-Stein (Pfizer)
- Conny Berlin (Novartis)
- Dave DeMets (UW)
- Frank Rockhold (GSK, now Duke)
- Frank Shen (AbbVie)
- Janet Wittes (Statistics Collaborative)

- Jose Vega (Merck)
- Juergen Kuebler (CSL Behring)
- Lily Krasulja (Janssen)
- Mark Levenson (FDA)
- Mondira Bhattacharya (AbbVie)
- Olga Marchenko (Quintiles)
- Steve Snapinn (Amgen)
- Valerie Simmons (Eli Lilly)
- Walter Offen (AbbVie)

# Thought Leader Interviews: Cross-Disciplinary Scientific Engagement

- “Safety is the new efficacy” - a public health issue
  - No longer just PV and spontaneous reports
  - Requires experienced statisticians to interact with other departments
- Safety physicians need to rely heavily on quantitative expertise for aggregate data analysis and interpretation
- Siloed discussions of safety and benefit are not in the patients’ best interest
- Statisticians need a safety mindset and need to closely engage other disciplines (e.g., safety physicians) to increase our impact
- Statisticians need to understand about “why” before jumping into “how”



# Safety Monitoring

# Working definition

Safety  
Monitoring

Processes

Methods

Data

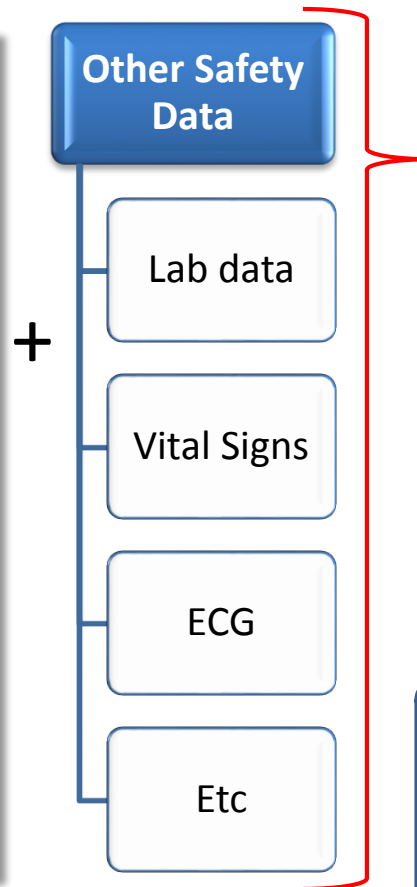
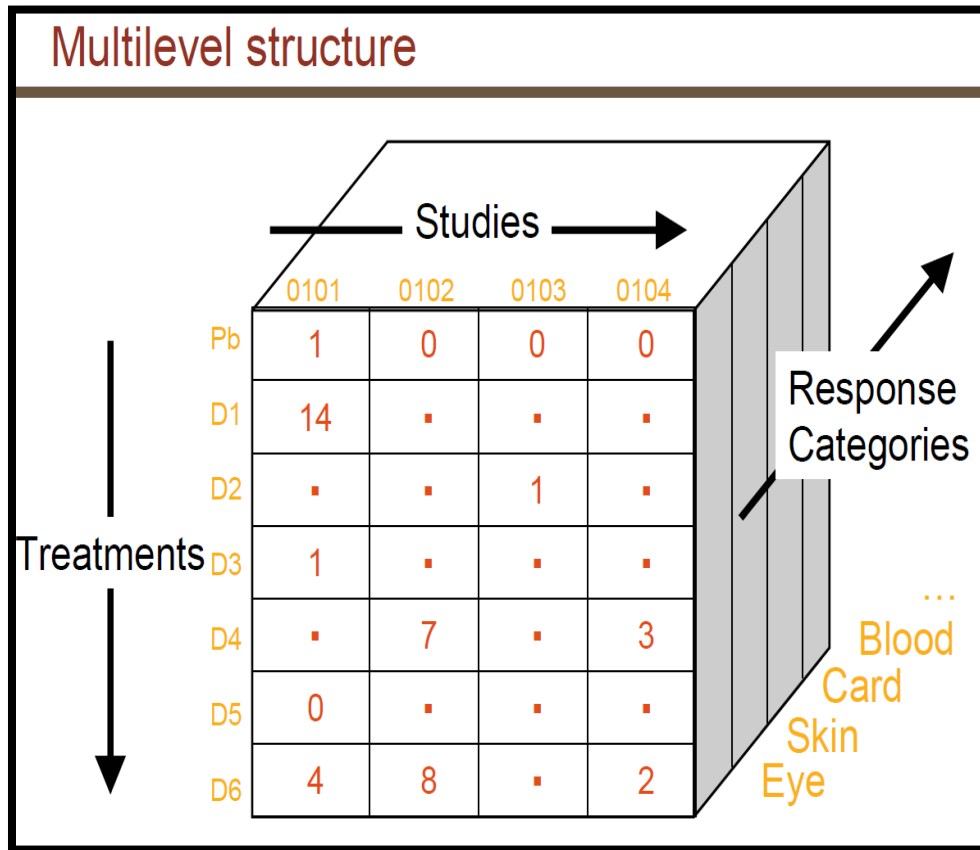


- ① Used to assess both the frequency and magnitude of the side effects, ranging from easily detected to rarely occurring, but of potential high impact on patient well-being
- ② It also serves to lay out the foundation for Integrated Analysis of safety preparation and benefit-risk analysis in the Clinical Overview and possible Advisory Committee Meeting
- ③ Can be dynamic or static

# Importance of Safety Monitoring/Challenges

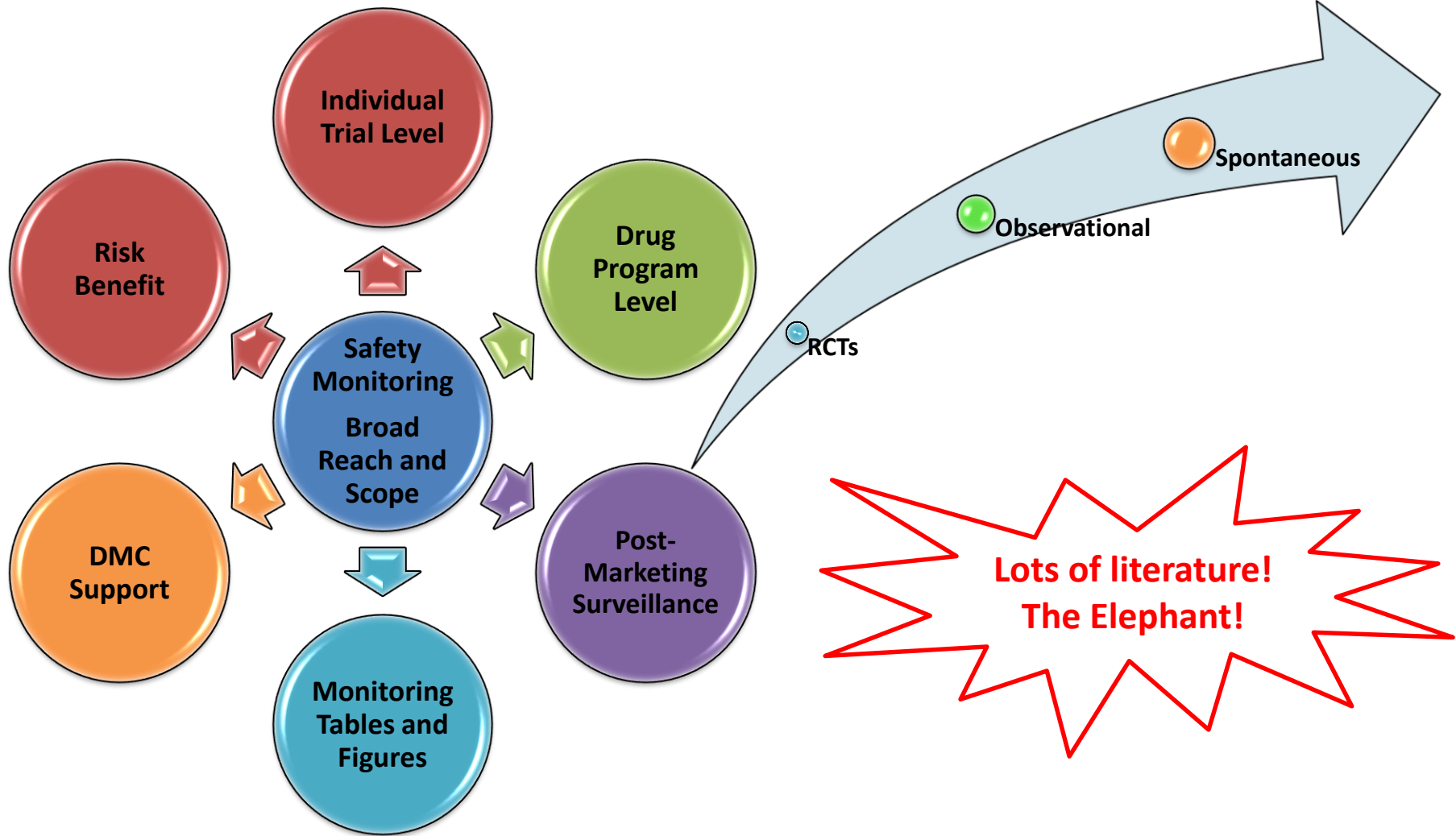
- Why is this important/challenging?
  - Monitoring of safety information - accumulation of evidence on the safety profile of a drug
  - Ideally want early detection of potential safety signals
  - Prediction - what safety signals are likely to be seen in future studies
  - Monitoring and interpreting safety data is not easy – rare events, multiplicity, safety data are complex, etc

# Complexity of Safety Data

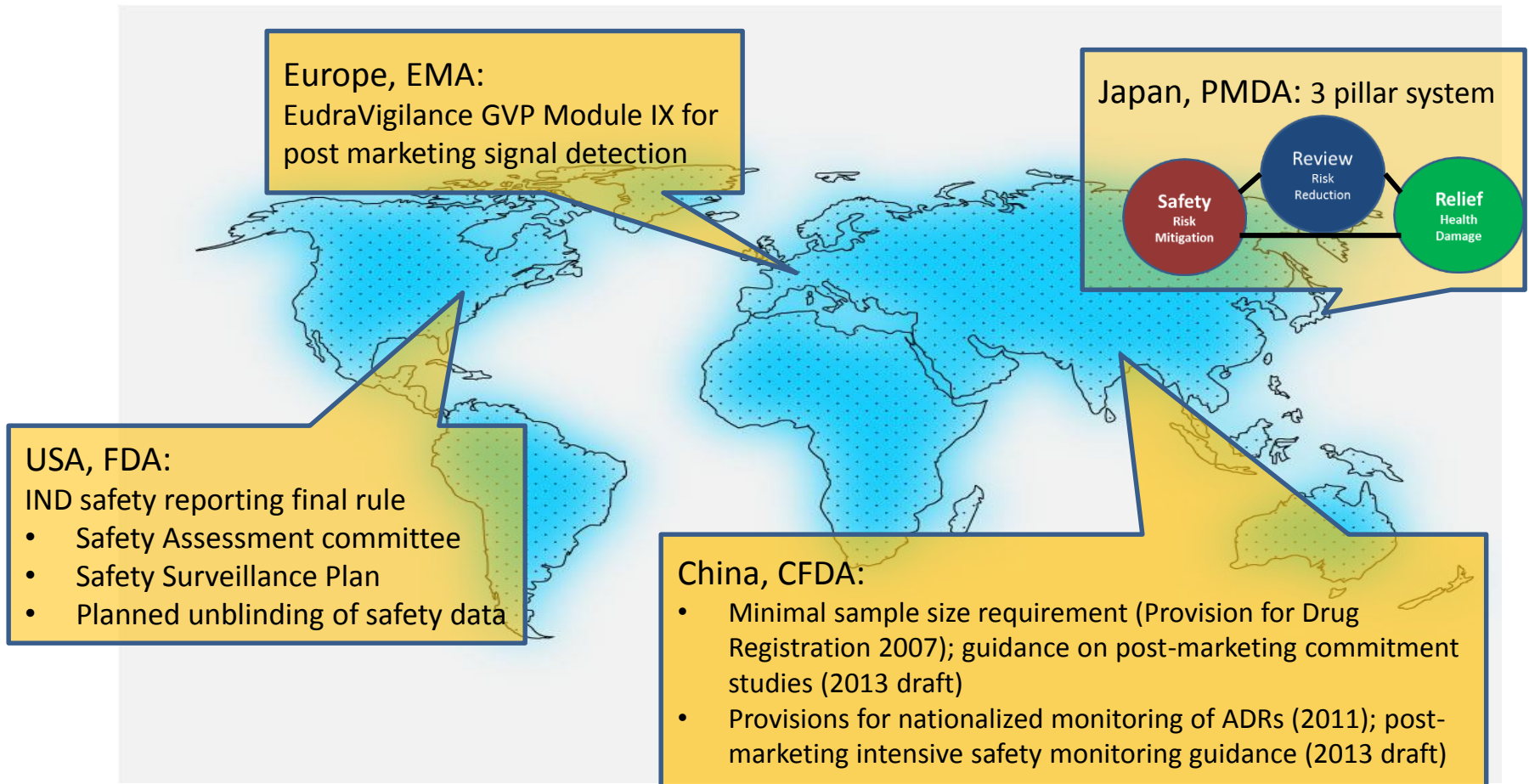


**Characterize safety profile of drug...this may evolve over time**

# What does it entail and where is it done?



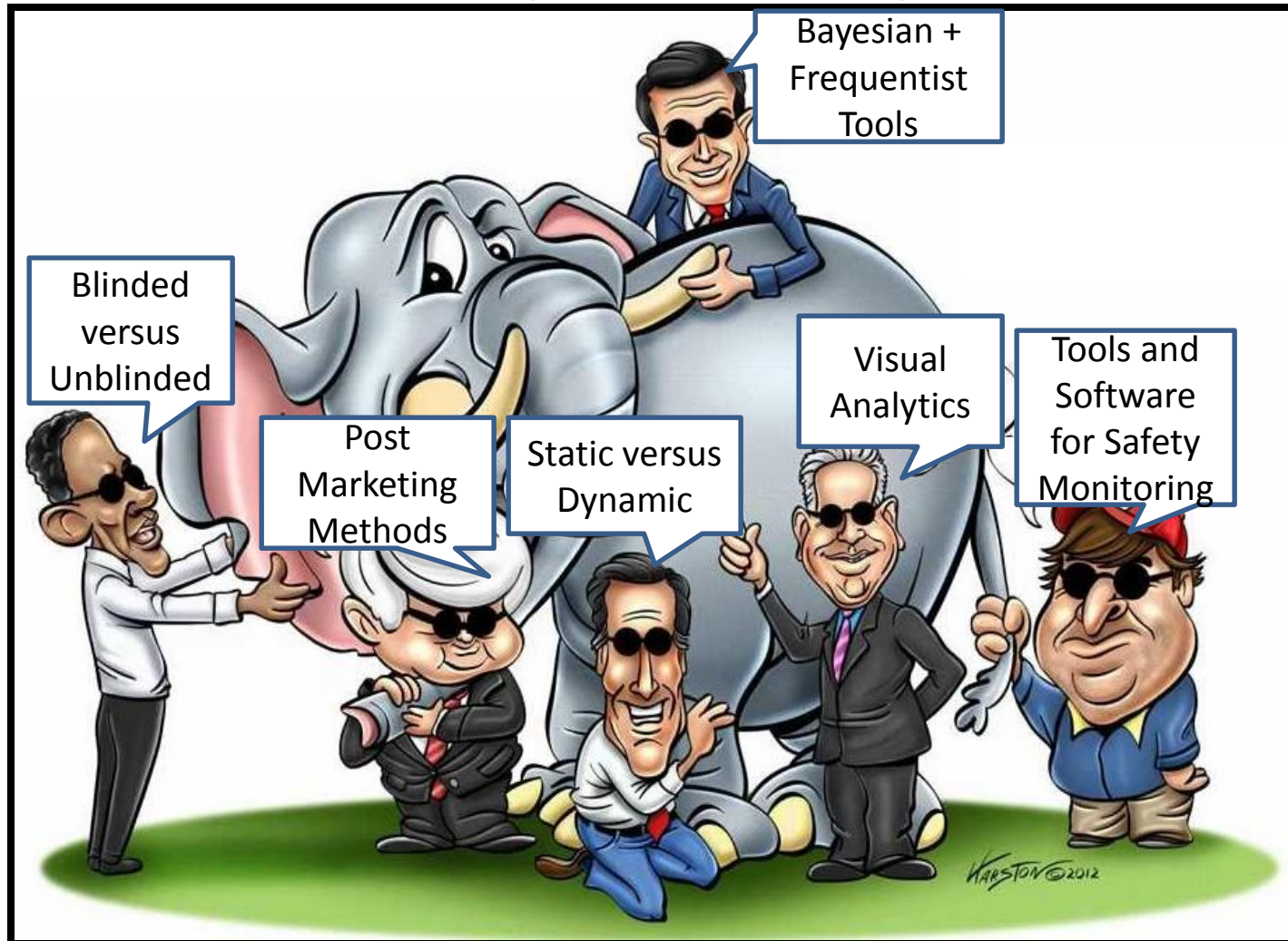
# WS 1 - Regulations Vary Greatly Across Regional Jurisdictions



# WS 2 - Literature Landscape

## An Approach to Look at Safety Monitoring

### Use Elephant Metaphor



# WS 2

## Deliverables

### 2016 deliverables

- August
  - JSM Biopharm Section
  - DIA China Quantitative Science Forum
- September
  - FDA Regulatory-Industry Statistics Workshop
- December
  - Deming Conference (tutorial)
- Manuscripts

### 2017 deliverables

- Deep dive
- Cross functional/organization engagement, physicians, epidemiologists, PhUse, DIA BSWG, etc
- Conferences and workshops
- Manuscripts





# Visual Analytics

# Need for Graphs

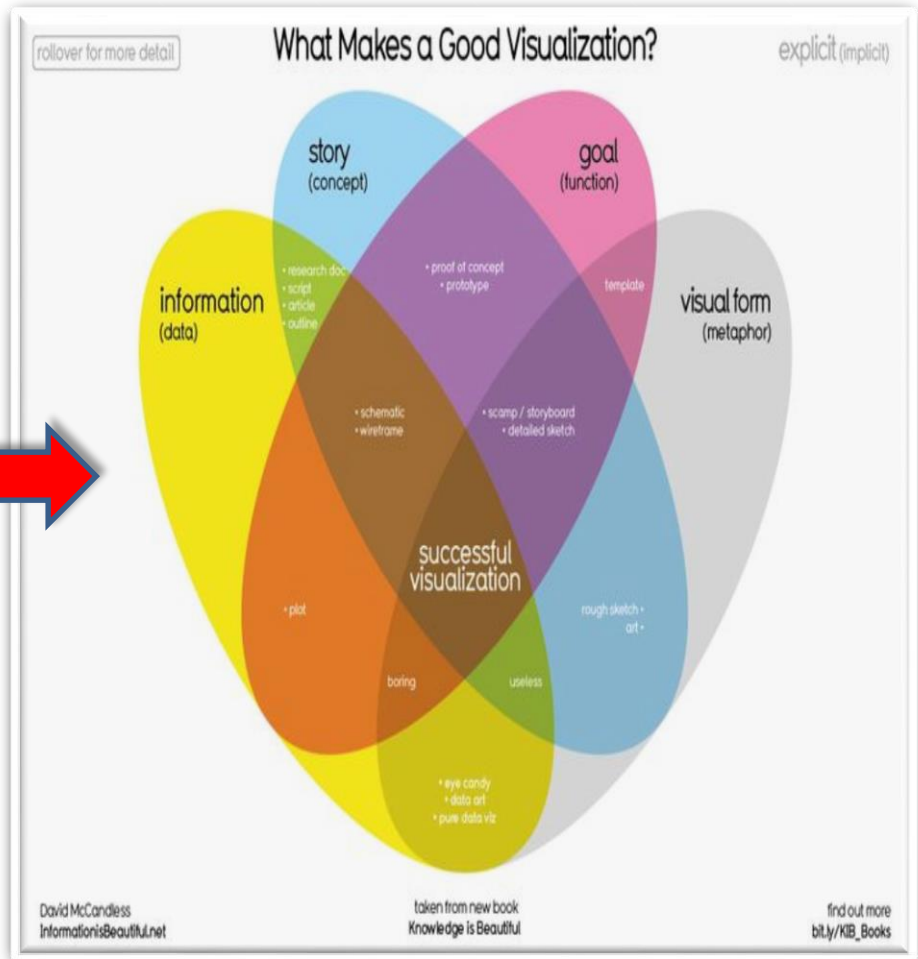
- Safety data present many challenges with regard to analysis and interpretation:
  - Nature of safety data makes it challenging to analyze using conventional statistical methods
  - Typical clinical trials generally not sufficient to detect safety signals
  - Pathological features of diseases lead to asymmetric non-normal distributions and heterogeneous subpopulations
  - Safety data are multidimensional and interrelated in nature and some key safety concerns may not be unknown prior to trial
- Using tabular formats for safety data results in large volumes of output leading to problems in generation, assessment validation, and assembly
- Descriptive summary tabular outputs and individual patient data are rarely analytical
- Comprehension, interpretation, and communication of safety findings has many challenges
- Generally recognized that there is great benefit to use visual methods to accompany or can be jointly use with tabular formats or replace tabular formats altogether

# Need for Graphs

|                     |   |
|---------------------|---|
| Harrell (2005)      | <ul style="list-style-type: none"><li>• <i>Graphs, Not Tables!</i><ul style="list-style-type: none"><li>• <i>Have pity on statistical and medical reviewers</i></li><li>• <i>Difficult to see patterns in tables</i></li><li>• <i>Substituting graphs for tables increases efficiency of review</i></li></ul></li></ul> |
| Wittes (1996)       | <i>A plethora of tables and graphs that describe safety may bury some true signal in a cacophony of numbers</i>   |
| Vlachos (2015)      | <i>Graphics are an underutilized resource in safety</i>   |
| McKain et al (2015) | <i>Traditional case reviews and TLs not sufficient for safety surveillance principles – use graphs</i>  |
| Regulatory Guidance | <i>ICH-E3, FDA Safety Review Guidance - recommendations for using visuals</i>   |

# Graphs Principles

- *Duke (2014), Duke et al (2015) - Good graphing principles and good graphic design*
  - Graphs for safety data must also adhere to good graphing principles and good design for graph construction
  - There must be a goal, a story, information to be delivered and a visual form to make visualization successful
  - These aspects are especially in the context of safety monitoring in order to help identify safety signals early using visual forms



Source: <http://www.informationisbeautiful.net/2015/workshops-are-beautiful-learn-our-dataviz-process/>

# Visualization Principles

- Some key graph principles include
  - Graph content
  - Communication
  - Information
  - Annotation, axes, and style
- All these are important to ensure that we have good and successful visualization of the data, especially in the context of safety monitoring

# Asking the Right Question

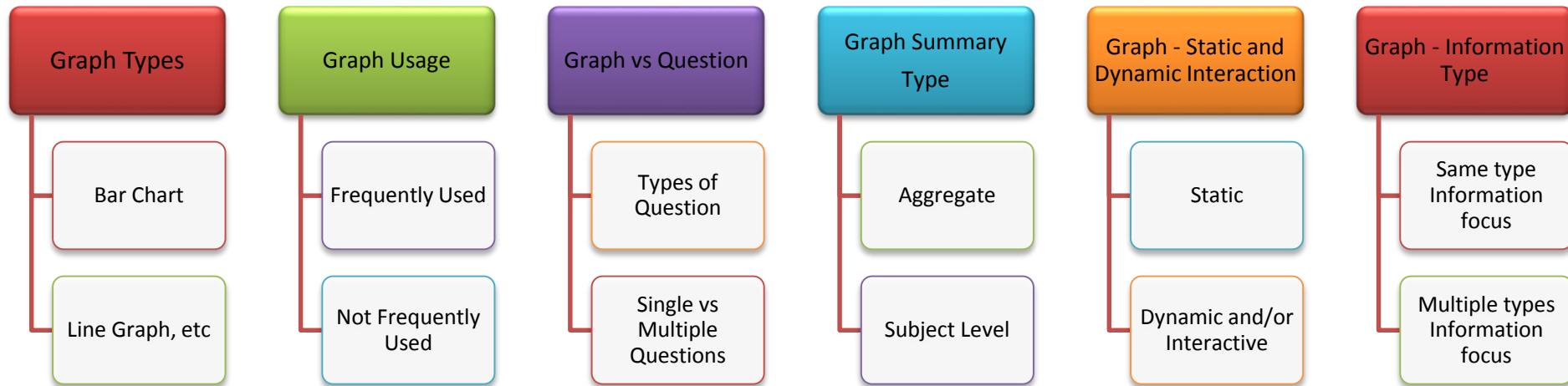
- In order to effectively use visual analytics in safety monitoring, it is a good idea to begin with some questions with regards to safety data under consideration
- More specifically, safety monitoring should be driven by asking the right question(s) of safety data

# Asking the Right Question

## Examples of some questions one may ask:

- What is the temporal relation of drug experience and exposure?
- Which AEs are elevated in treatment versus control?
- What is the constellation of AEs that come with the drug?
- Is there any evidence of a dose-response-relationship?
- Is the potential AE of interest increasing over time?
- Is there a difference in the time to the first event across treatment groups?
- What are the trends of time to the first event among different AEs?
- Which AEs are elevated in patient subgroups?
- What are the risk factors of the AE?
- Are there withdraws and/or interruption due to AE of interest?
- Is there a relationship with other AEs?
- What is the severity of the AEs ?
- Are the most prevalent AEs suggestive of more serious events or medical concern?
- Is there a relationship with use of concomitant medications?
- For multiple studies, does a meta analysis reveal a degree of heterogeneity of event across studies?
- Which AEs could be a safety signal? Are there any surprises in the data?
- Under what circumstances is the event most important to the patient?

# Graph Complexity



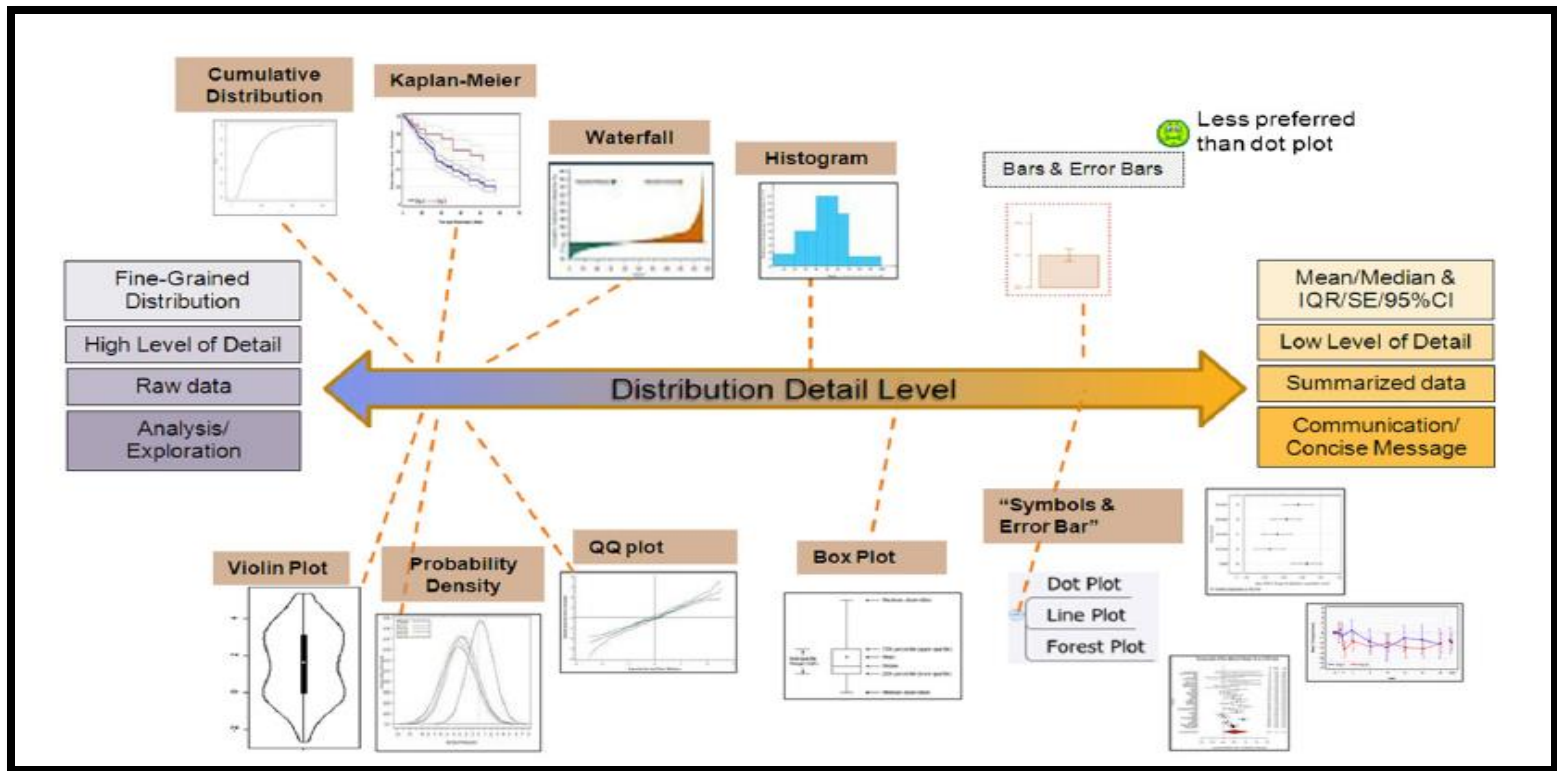


# Safety Monitoring Objective and Graph Type

- Safety monitoring question will ultimately determine the graph type, i.e., the choice of the visual that will be used
- Selection of the visual type or graph type may also be driven by the nature of the event in terms of AE Tier categories (Crowe *et al*, 2009)
- Ultimately, the safety question and graph type will dictate the right tool to use in safety monitoring

# Choosing the Right Graph Type

- The most appropriate graph type depends on the clinical question and data available



Source: <https://blogs.fda.gov/fdavoice/index.php/2015/09/seeing-is-believing-making-clinical-trial-statistical-data-from-medical-product-testing-easy-to-understand/>

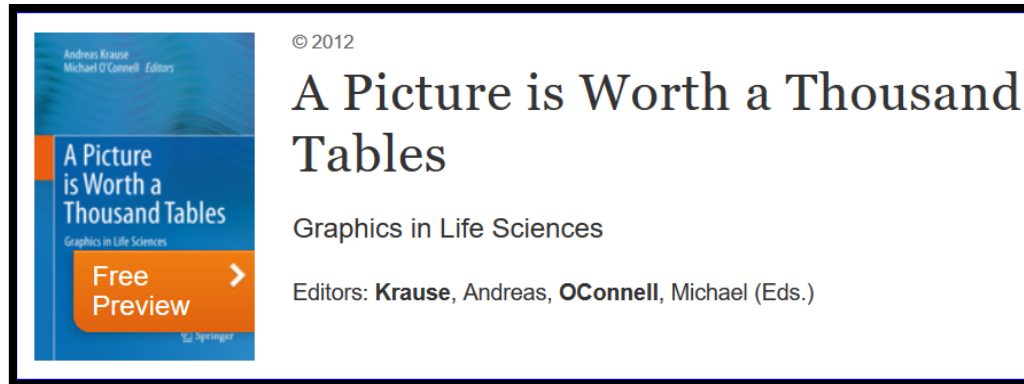
# Visual Analytics Efforts

# Visual Analytics and Safety Monitoring Efforts

- Use of graphs in safety is well recognized
  - Some individual commendable efforts, e.g.,
    - Frank Harrel
      - <http://biostat.mc.vanderbilt.edu/wiki/pub/Main/FHHandouts/gksafety.pdf>
      - <http://biostat.mc.vanderbilt.edu/wiki/Main/RCTGraphics>
    - Shi-Tao Yeh
      - <http://www.lexjansen.com/pharmasug/2007/po/PO10.pdf>
      - <http://www2.sas.com/proceedings/forum2007/164-2007.pdf>
      - <http://www.lexjansen.com/nesug/nesug07/po/po23.pdf>
      - <http://www2.sas.com/proceedings/sugi31/181-31.pdf>
    - Jonathan Levine
      - <http://www.gersonides.com/r/>

# Visual Analytics and Safety Monitoring Efforts

- Some collaborative commendable efforts, e.g.,
  - CTSPedia
    - <http://www.ctspedia.org/do/view/CTSpedia/AllGraphicalEntries>
  - A Picture is Worth a Thousand Tables
    - <http://www.elmo.ch/doc/life-science-graphics/>



- Above individual and collaborative efforts cover common industry practice

# Visual Tool Selection

- There are many tools (commercial and free) available that can be used in visual analytics in safety monitoring
- Tools have different functionality
- Selected tool should consider tool functionality, for example
  - static versus interactive and/or dynamic visualization
  - drill down to patient level data
  - graph types most effective for SMR question

# Visual Tool Selection

Older Tools

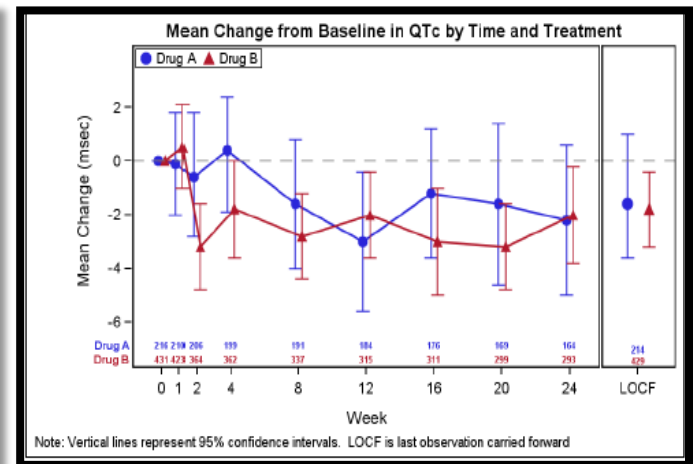
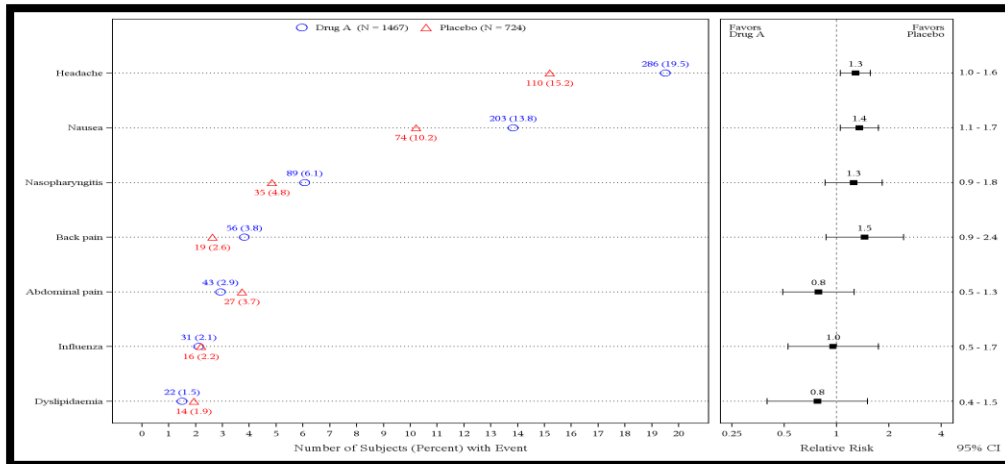
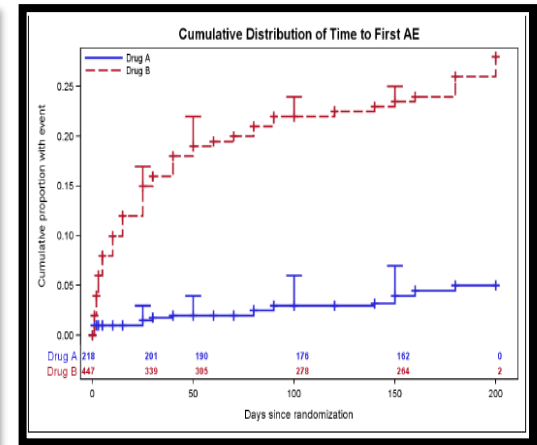
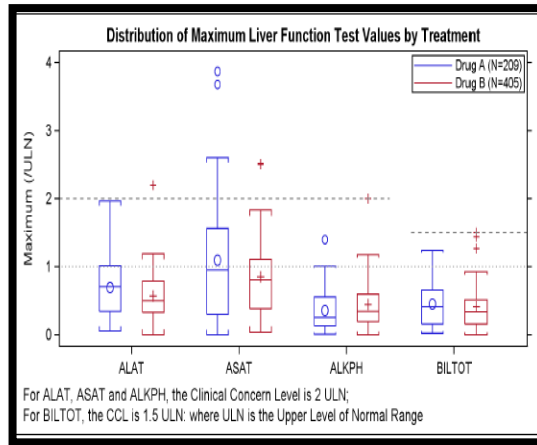
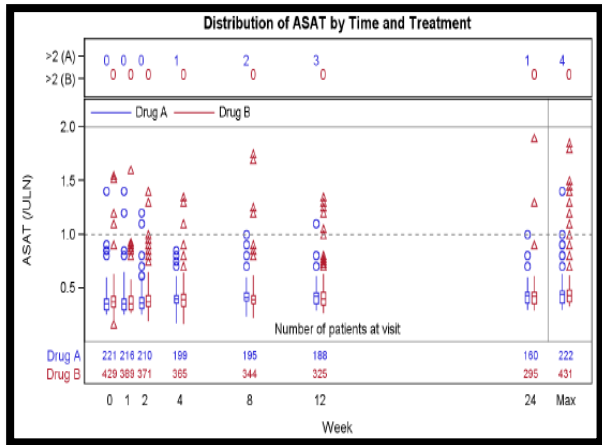
- SAS, SAS JMP,
- JReview
- Splus, Spotfire
- SAS, JMP
- J-Review

Newer Tools

- R, R Shiny, R html widgets, Numerous R Packages
- SAS JMP Clinical
- Python, Jypiter Notes, Rodeo
- Tableau, QlikView
- Java, D3.js

# Some Considerations and Graph Choices

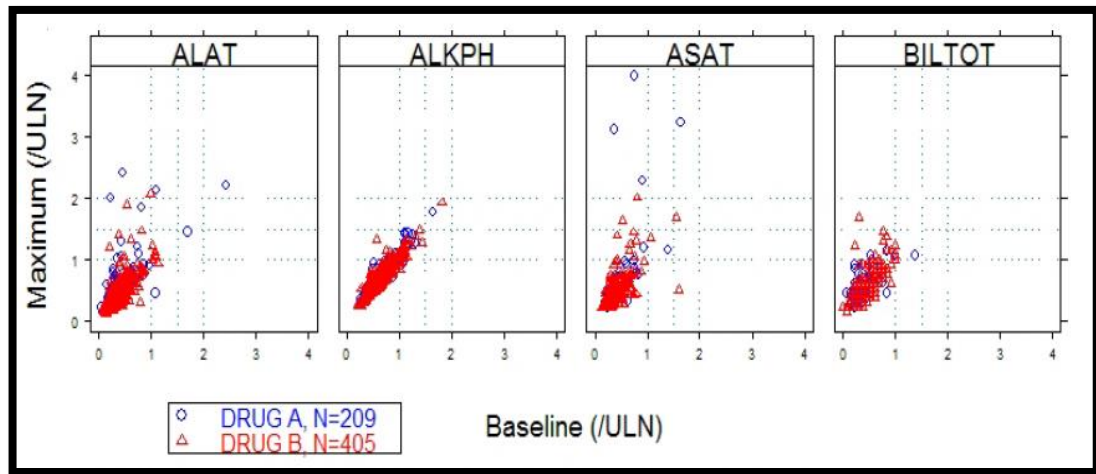
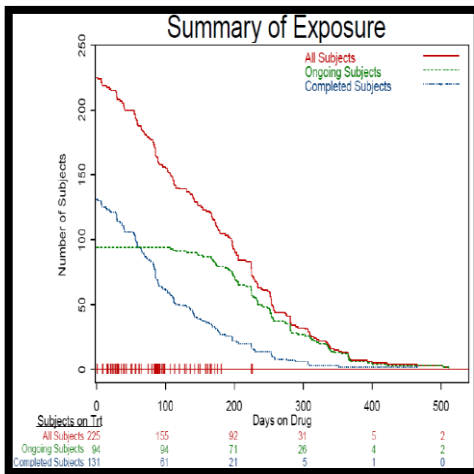
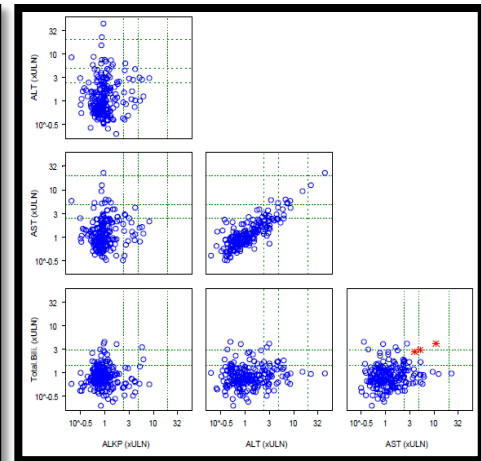
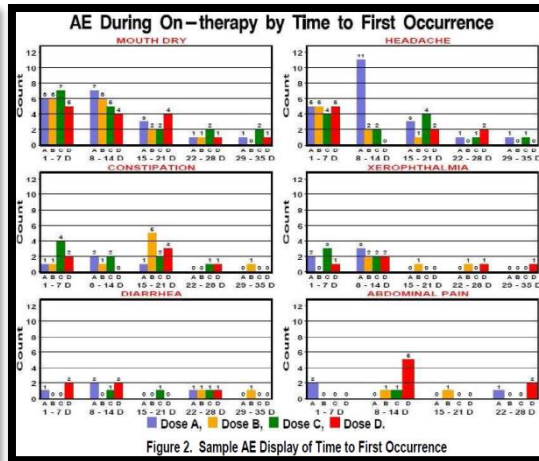
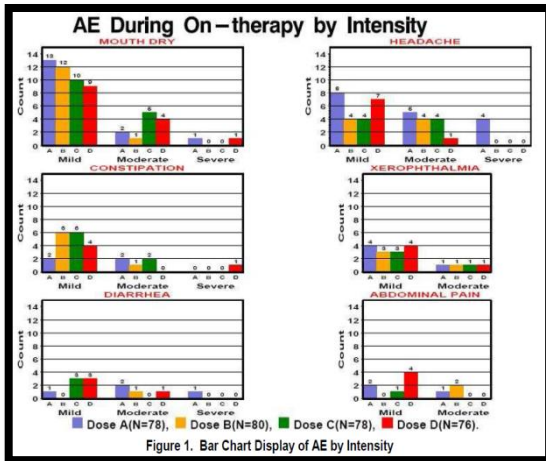
## Main stream graphs in the analysis of safety data





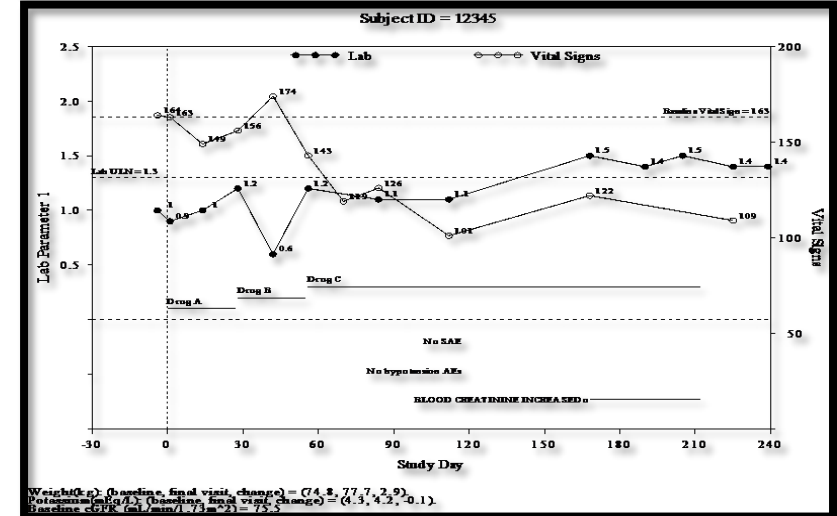
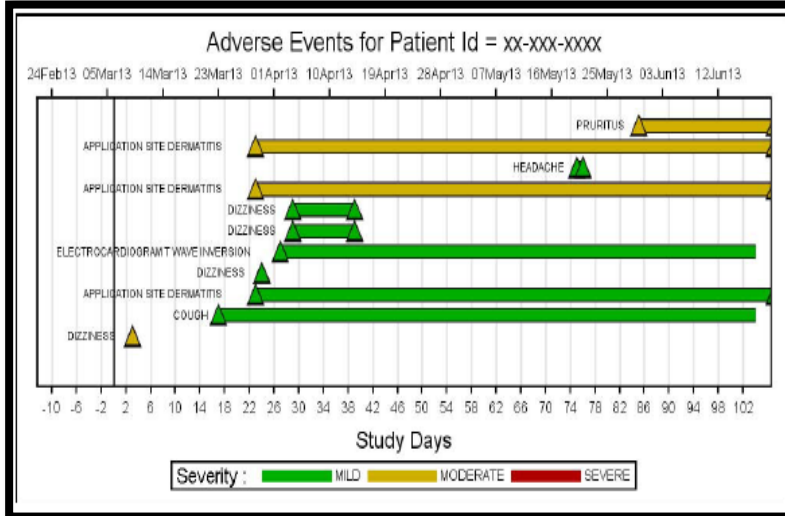
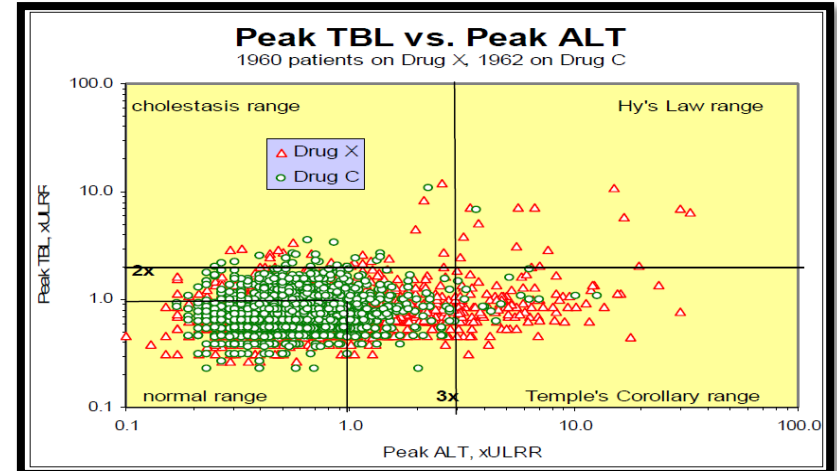
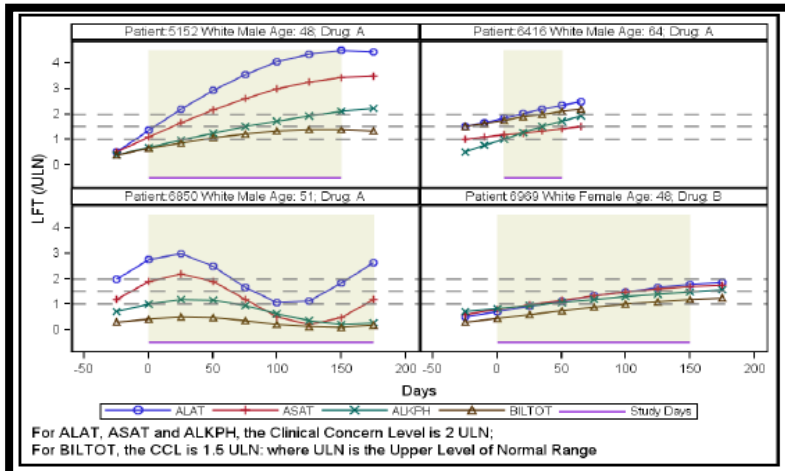
# Some Considerations and Graph Choices

Main stream graphs in the analysis of safety data



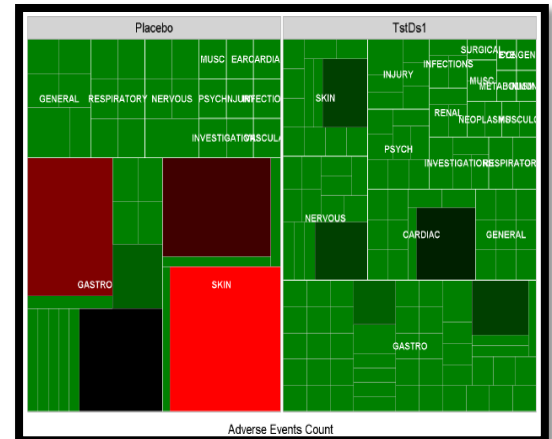
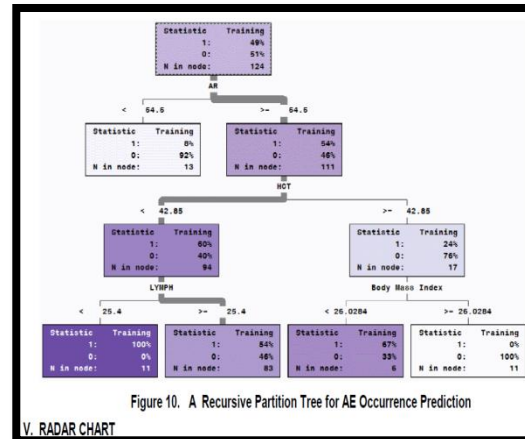
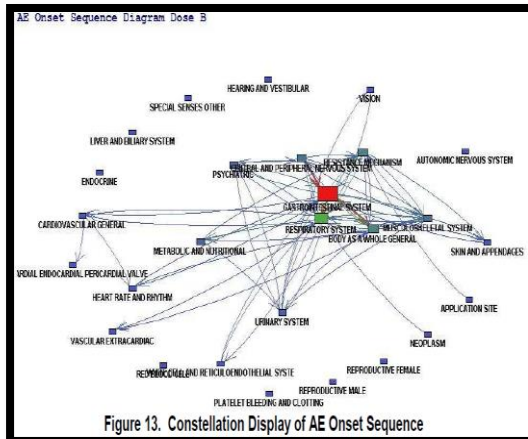
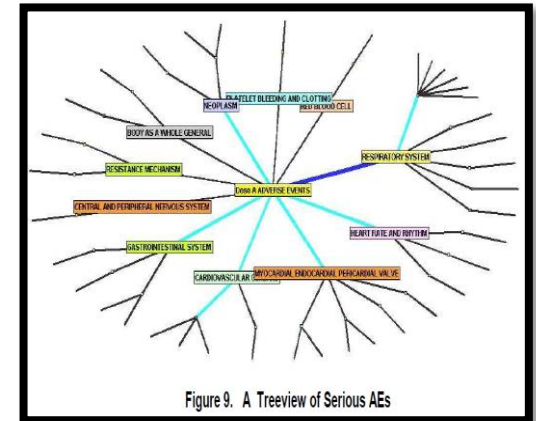
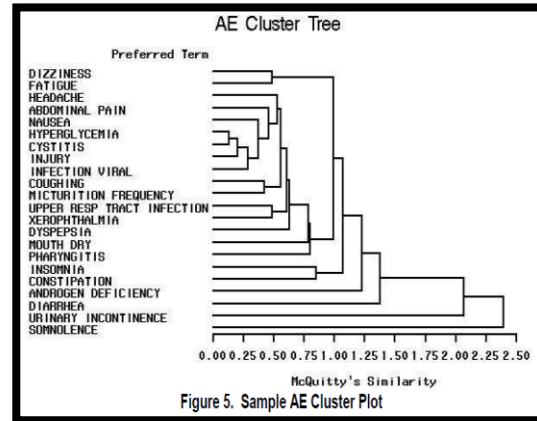
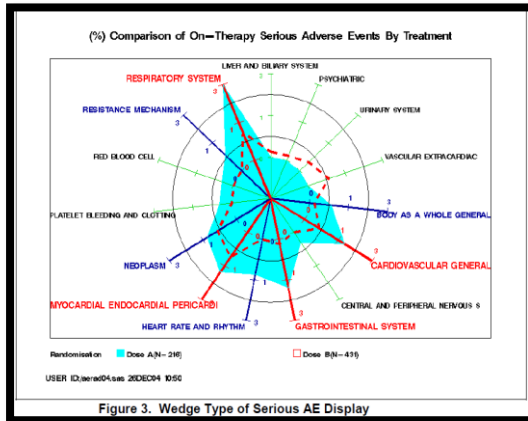
# Some Considerations and Graph Choices

## Main Stream Graphs in the Analysis of Safety Data



# Some Considerations and Graph Choices

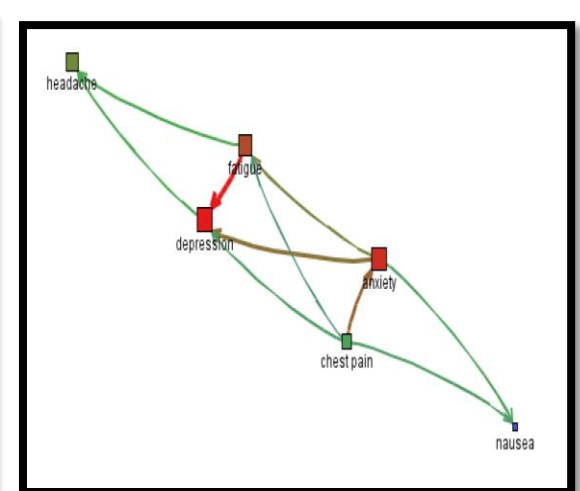
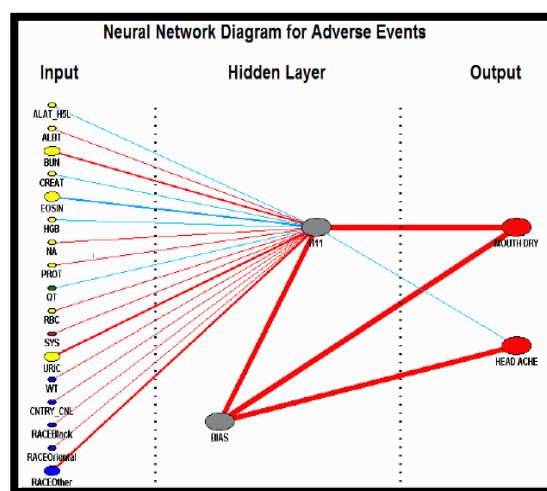
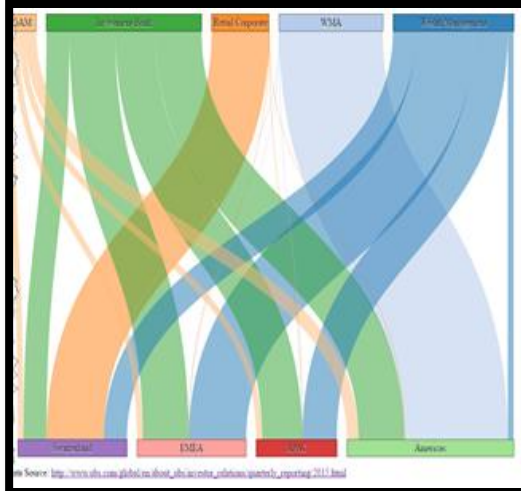
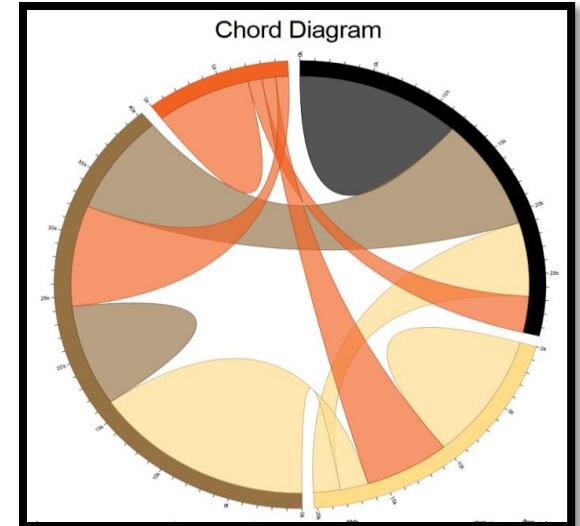
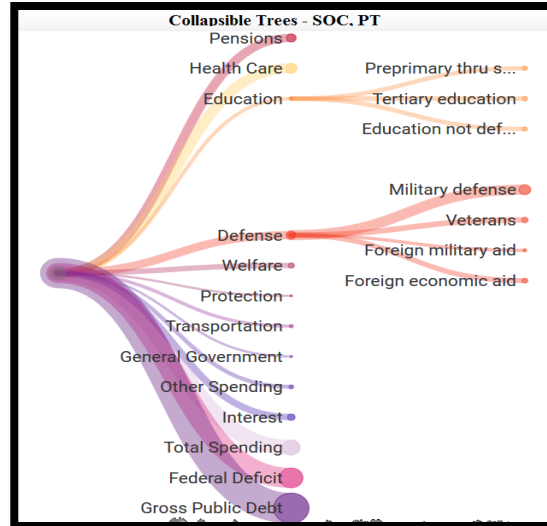
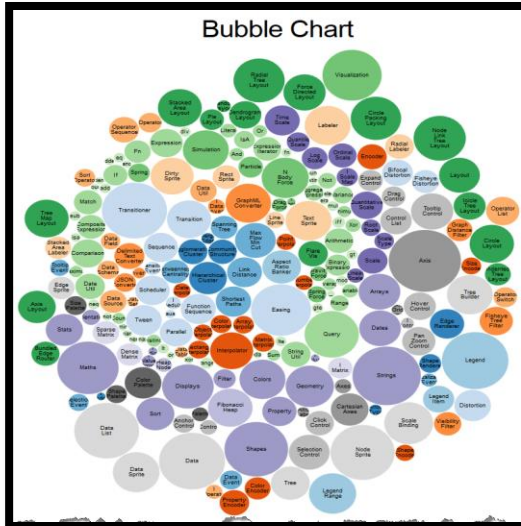
- Not so main stream graphs in the analysis of safety data



Graph enhancement? Interactivity, dynamic, animation, drill down, connectivity, etc

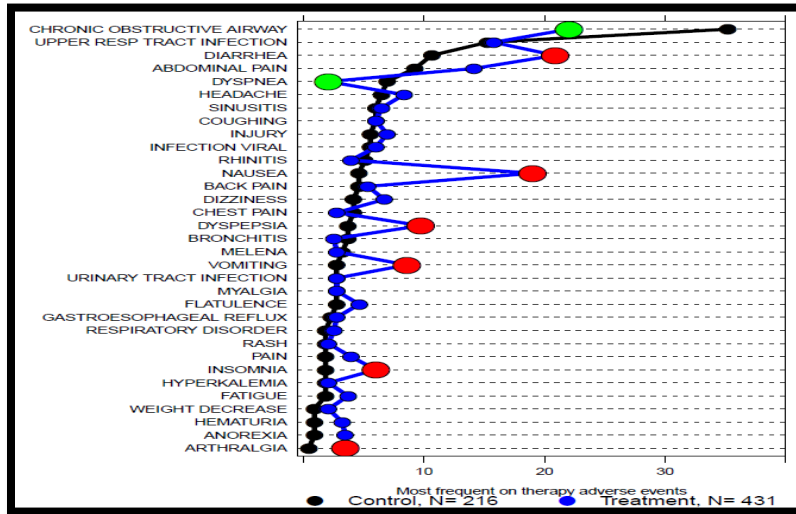
# Some Considerations and Graph Choices

- *Borrow ideas from other areas*

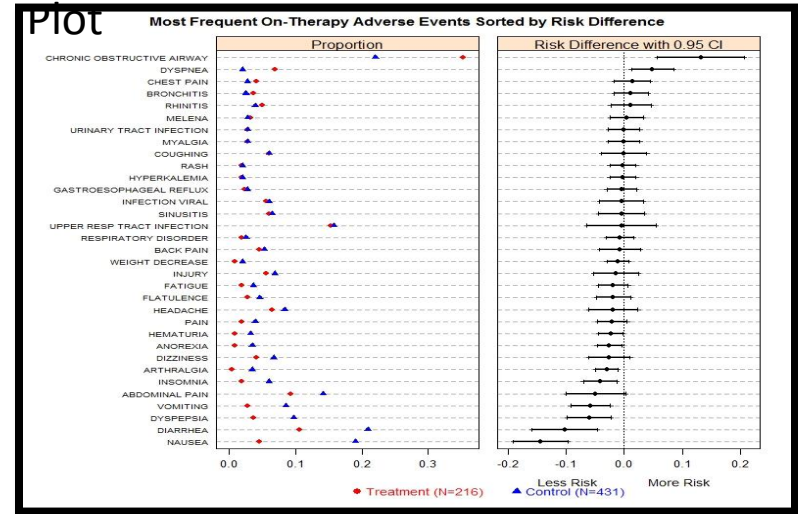


# Some Considerations and Graph Choices

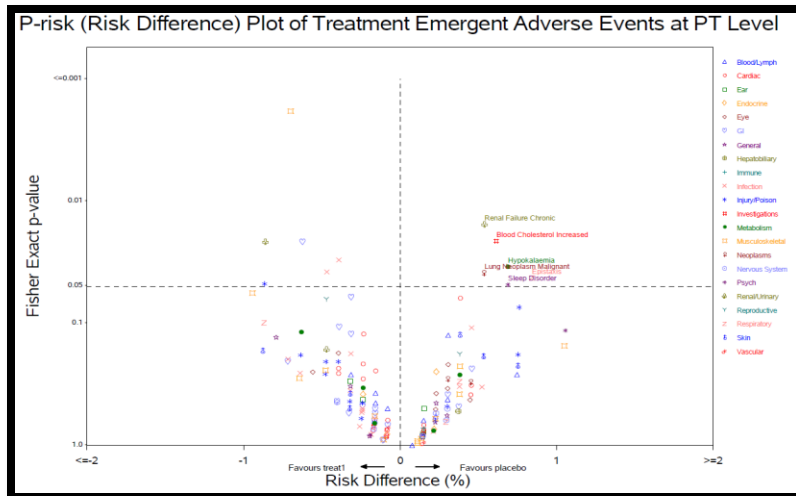
TIER 1, Dot plot



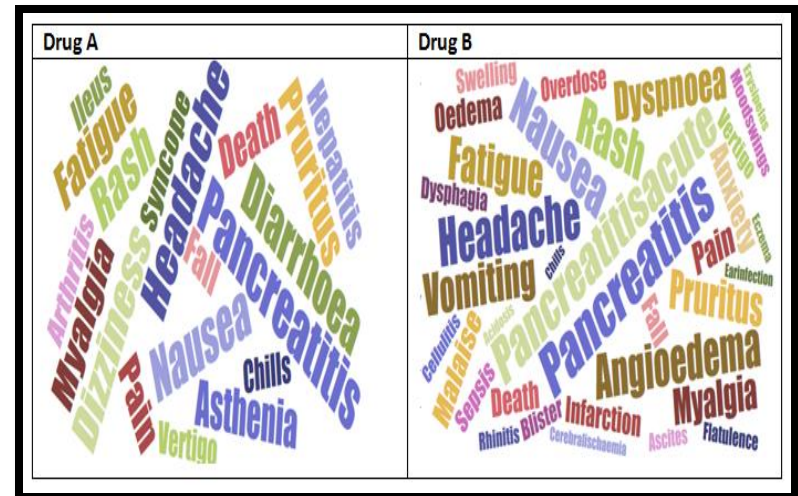
TIER 1, Dot plot, Risk Plot



TIER 2, Volcano plot



TIER 2, Word Cloud



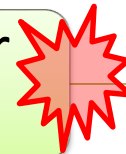
# Enhancing Visual Analytics and Safety Monitoring

# Enhancing Visual Analytics and Safety Monitoring

Enhancement of available visual analytics



New visualization ideas – borrow from other areas



Bayesian versions – incorporate Bayesian ideas

Consider method driven visualization

Tools – versatile, flexibility, customization, open source, wide use, resourceful, etc



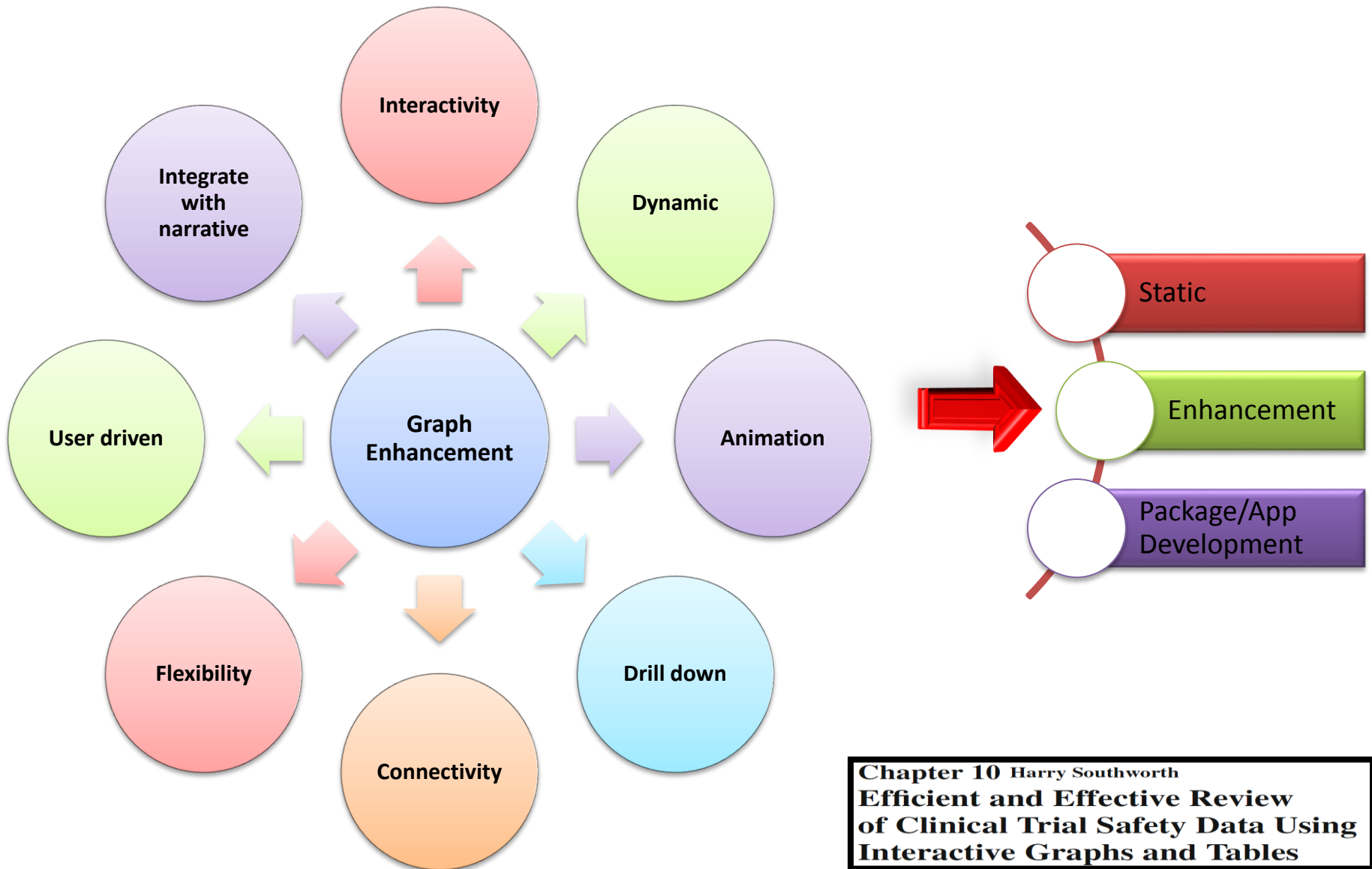
# Enhancing Visual Analytics and Safety Monitoring

- Considerations

- Enhance - make the graphs more useful in some sense
- Consider using other graphics outputs by borrowing new useful and informative visualization and tools, e.g., from visual analytics of big data, e.g., D3.js:  
<https://github.com/d3/d3/wiki/Gallery>
- Consider incorporating Bayesian ideas in graphs, where applicable
- Graphs related to safety monitoring and reporting method
- Use of readily available open source resources that are freely available and yet versatile and use highly flexible software platforms and good IDEs



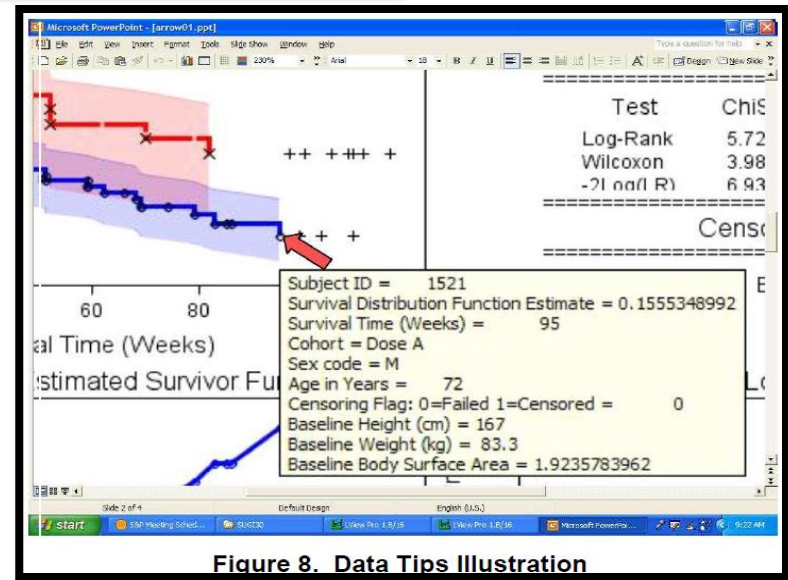
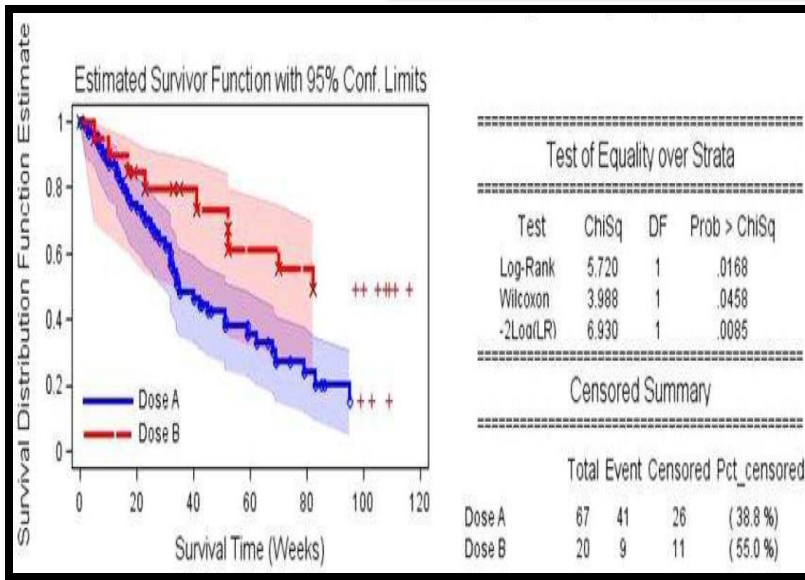
# Enhancing Visual Analytics and Safety Monitoring



# Enhancing Visual Analytics and Safety Monitoring

- Example: KM Plot – highlight details

Paper PO10  
**Clinical Adverse Events Data Analysis and Visualization**  
 Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.



Static



Enhancement



Package/App



Adobe Acrobat  
Document



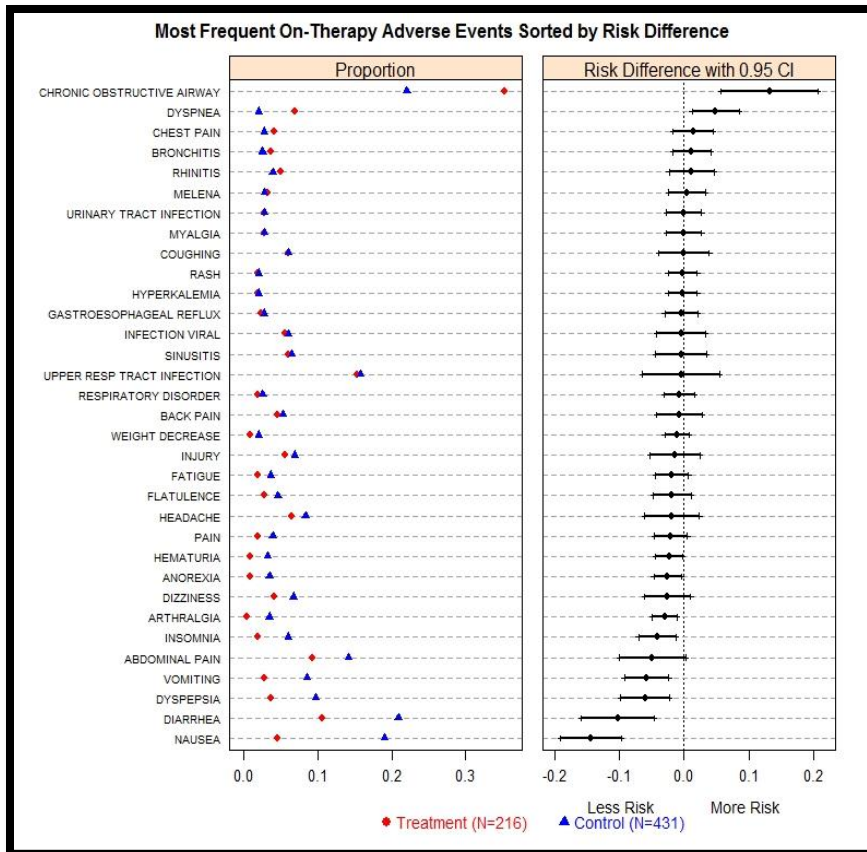
1\_KM\_Plot.html 2\_KM\_Plot.html

<https://sachsmc.github.io/interactive-KM/>

<https://github.com/selcukorkmaz/geneSurv>

# Enhancing Visual Analytics and Safety Monitoring

- Interactivity – Allow user to interact with the graphic - Examples



## Enhancements

- <https://www.rdocumentation.org/packages/HH/versions/3.1-34/topics/AEdotplot>
- <https://becca-krouse.shinyapps.io/aetableapp/>
- <https://rhoinc.github.io/viz-library/examples/0008-safetyExplorer-default/ae-table/>



# Enhancing Visual Analytics and Safety Monitoring

## Examples

- Word Cloud



WordCloudStatic.html



WordCloudInteractive.html

## Examples

- Collapsible Tree



8\_Java\_script.html



9\_Java\_script.html



collapsible\_tree.html

Tool of Choice

# Tool of Choice

## Tool Functionality

- IDE
- Reproducibility
- Open Source
- Applications development
- Ease of use
- Flexible
- Open source, free
- Abundant resources
- Can incorporate fairly complex applications
- Allow for different delivery modes – pdf, word, ppt, html, etc

## R + Tools

- R Studio, R Shiny, R Markdown, R Notebook, R htmlwidgets,
- R Studio IDE → R + Python + SAS + Java + Combining R + Java + D3.js, etc
- Numerous resources/packages for analysis and graphs with enhancements, e.g., ggplot2, plotly, etc
- Shared resources – github, Rpubs, etc
- Open source, flexibility, can use many tools, reproducibility, etc

By Michael Grogan September 07, 2016

**Shiny, R and HTML: Merging Data Science and Web Development**

**Developing Standardized Clinical Review Tools Using Shiny In R**

JIMMY WONG, STATISTICIAN

Food and Drug Administration/Center for Drug Evaluation and Research/Office of Biostatistics

# Tool of Choice

- R Toolset for Reporting

- R Markdown document: <http://rmarkdown.rstudio.com/>
- R Notebook: [http://rmarkdown.rstudio.com/r\\_notebooks.html](http://rmarkdown.rstudio.com/r_notebooks.html)
- R Flexdashboard: <http://rmarkdown.rstudio.com/flexdashboard/>
- R Bookdown: <https://bookdown.org/yihui/bookdown/>
- R Shiny App: <https://shiny.rstudio.com/>



RNotebookEx1.nb.html



Example\_Flexdashboard.html



# Tool Choice

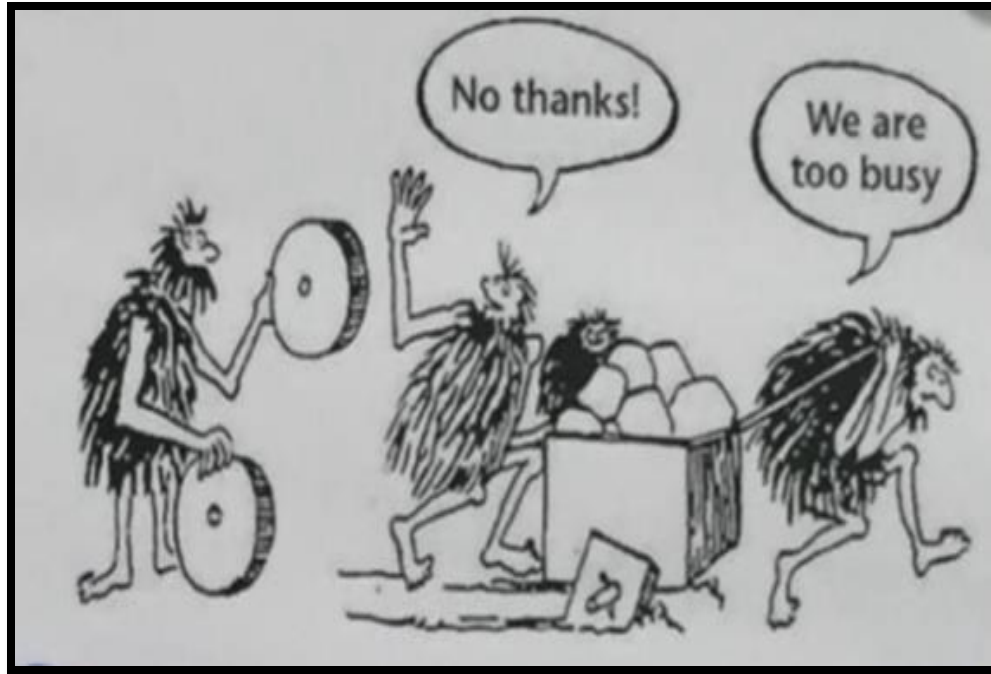
- Other tools
  - R Html Widgets: <http://www.htmlwidgets.org/>
    - **Bring the best of JavaScript data visualization to R**
    - Use JavaScript visualization libraries at the R console, just like plots
    - Embed widgets in R Markdown documents and Shiny web applications
    - Develop new widgets using a framework that seamlessly bridges R and JavaScript
  - R Crosstalk: <http://rstudio.github.io/crosstalk/using.html>
    - Crosstalk makes it easy to link multiple (Crosstalk-compatible) [HTML widgets](#) within an R Markdown page or Shiny app

## Concluding Remarks

# Concluding Remarks

- Visual analytics can help in safety monitoring and in safety data analysis in general
- Utilizing visualization tools can help exploration and substantially improve information gain for safety monitoring activities
- One should however take into consideration important principles of graph construction in order to render them visuals useful in safety monitoring
- Ultimately, the visual type and tool used will depend on the question or questions under consideration in the safety monitoring activity
- By considering various enhancements, one can select visualizations and tools that are most useful for the end-user and reporting to address various questions with a wide range of functionality to allow for efficient safety monitoring
- New skill set, not business as usual
- Embrace new ideas

# Time to Embrace New Ideas!



**It's easy to get stuck in your ways.. Don't be too busy to try new ideas.**

[buffer-media-uploads.s3.amazonaws.com](http://buffer-media-uploads.s3.amazonaws.com)

# Acknowledgement

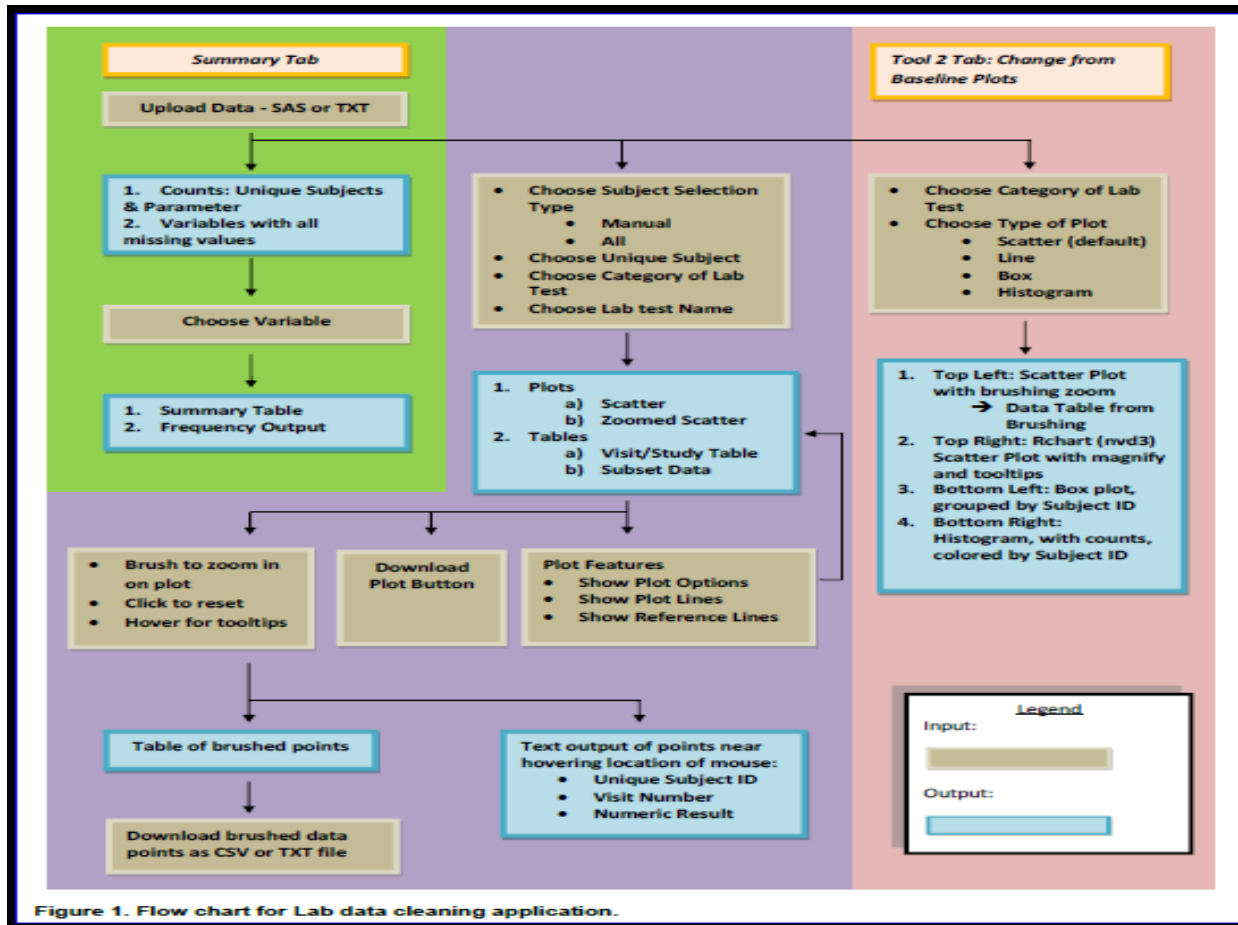
- Rebecca Krouse, Jeremy Wildfire, Ryan Bailey – Rho Inc.
  - SafetyExplorer Tool
- Junfang Chen – Takeda
  - Visual analytics implementation
- Collaborators in WS 2
  - Kefei Zhou – Theravance
  - Karolyn Kracht - AbbVie



# Many R Shiny Apps Out There!

**Empowering Users By Creating Data Visualization Applications In R/Shiny**  
 Sudhir Singh, Brian Munneke, Amulya R Bista, Jeff Cai, Pharmacyclics LLC, CA  
 PharmaSUG 2016 - Paper DG10

<http://www.lexjansen.com/pharmasug/2016/DG/PharmaSUG-2016-DG10.pdf>



# Many R Shiny Apps Out There!

- OpenFDA: <http://www.gersonides.com/openfda/>

**Shiny Applications for openFDA Data**

[Drug Apps](#)

[Dashboard- Overview of reports for a drug](#)

[PRR for a Drug- Calculate Proportional Reporting Rates for Common Events for a drug](#)

[PRR for an Event- Calculate Proportional Reporting Rates for Common Drugs that have a specified event](#)

[Dynamic PRR- Calculate Proportional Reporting Rates for a drug-event pair over time](#)

[Change Point Analysis- Change point analysis for a drug-event pair over time](#)

[Adverse Event Browser- View reports that meet search criteria](#)

[Label Browser- View labels that meet search criteria](#)

[Likelihood Ratio Test for Drug- Calculate Likelihood Ratio Tests for Common Events for a drug](#)

[Likelihood Ratio Test for Event- Calculate Likelihood Ratio Tests for Common Drugs for an event](#)

[Drug Enforcement Report Browser- View labels that meet search criteria](#)

[Device Apps](#)

[Adverse Event Browser- View reports that meet search criteria](#)

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