Advanced Visual Analytics of Safety Data from Different Data Sources

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On behalf of the ASA Safety Monitoring Work Group
BASS XXV, 2018

The Team

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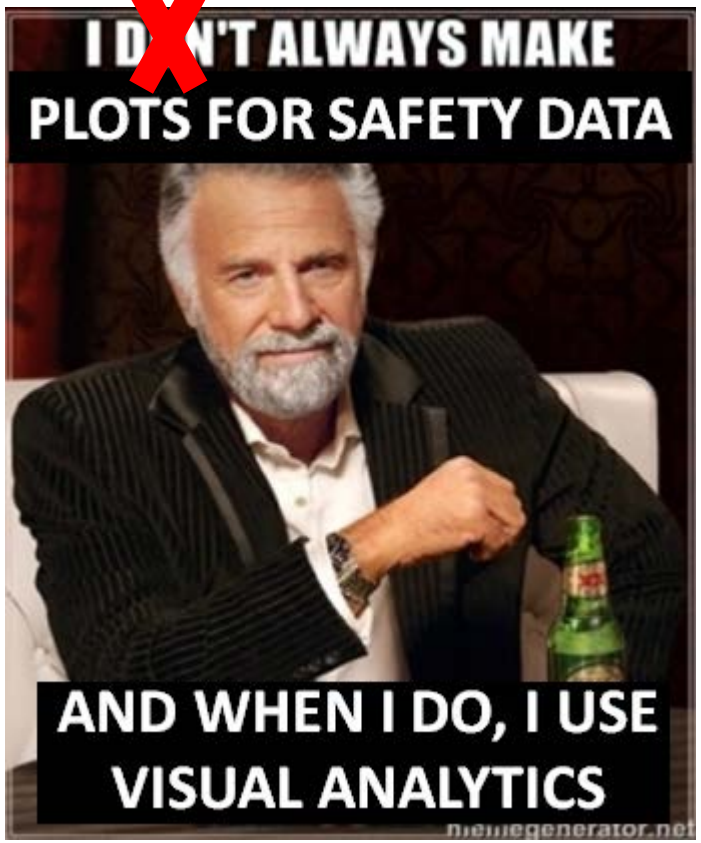
Disclaimer

- Opinions expressed in this presentation are the authors' own and do not represent in any way opinions of their respective employers

Mantra


I DON'T ALWAYS MAKE PLOTS
BUT WHEN I DO, I MAKE THEM PRETTY


PLOTS FOR SAFETY DATA
AND WHEN I DO, I USE VISUAL ANALYTICS

Motivation

ClinicalTrials.gov Data
https://www.mbcalliance.org/clinical-trials-in-metastatic-breast-cancer

Cause of Death
http://flowingdata.com/2016/01/05/causes-of-death/

How You Die
http://flowingdata.com/2016/01/19/how-you-will-die

Periodic Table of graphs
http://www.visual-literacy.org/periodic_table/periodic_table.html

D3.js Library
https://github.com/d3/d3/wiki/Gallery

Outline

- Introduction
- The Ever Expanding Data Sources for Safety Data
- Challenges of Safety Data
- Need for Graphs in the Analysis of Safety Data
- General considerations
- The Push Towards Quantitative Safety
- Defining Visual Analytics
- Examples
- Conclusion
- References

Introduction

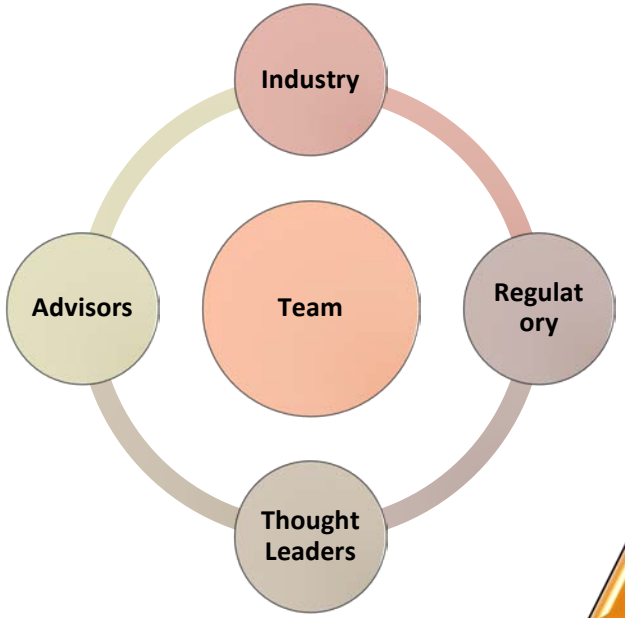
About the ASA Biopharm Safety Monitoring Work Group

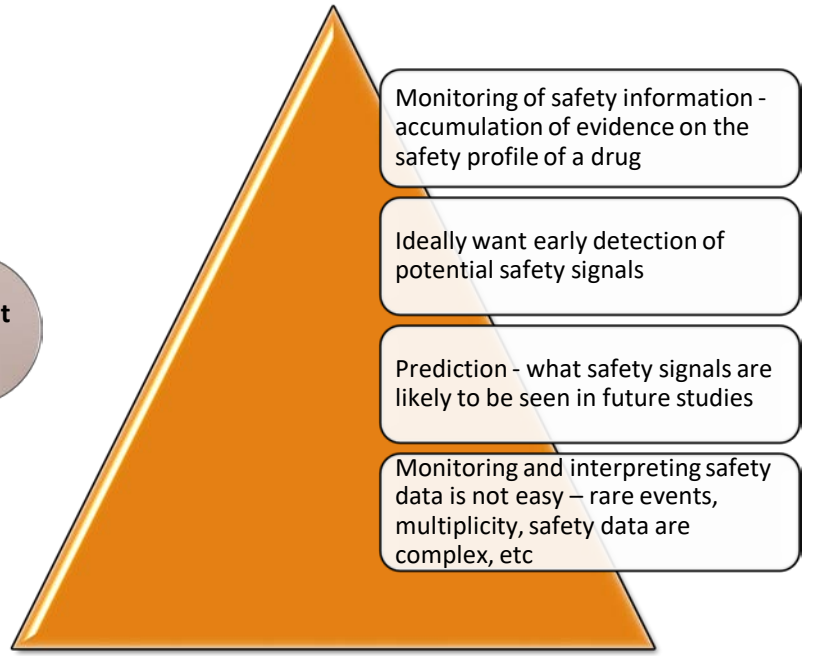
- http://community.amstat.org/biop/workinggroups/safety/safety-whoweare

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?

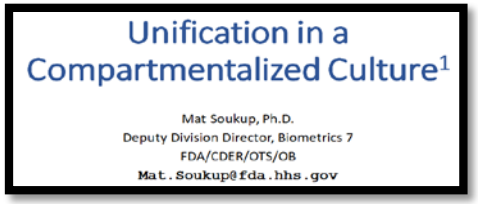




Currently 3 Subteams:

- WS 1: focusses on regulatory guidance and industry practice
- WS 2: focusses on methodology
- WS 3: focusses on real world data

Cross-functional collaboration

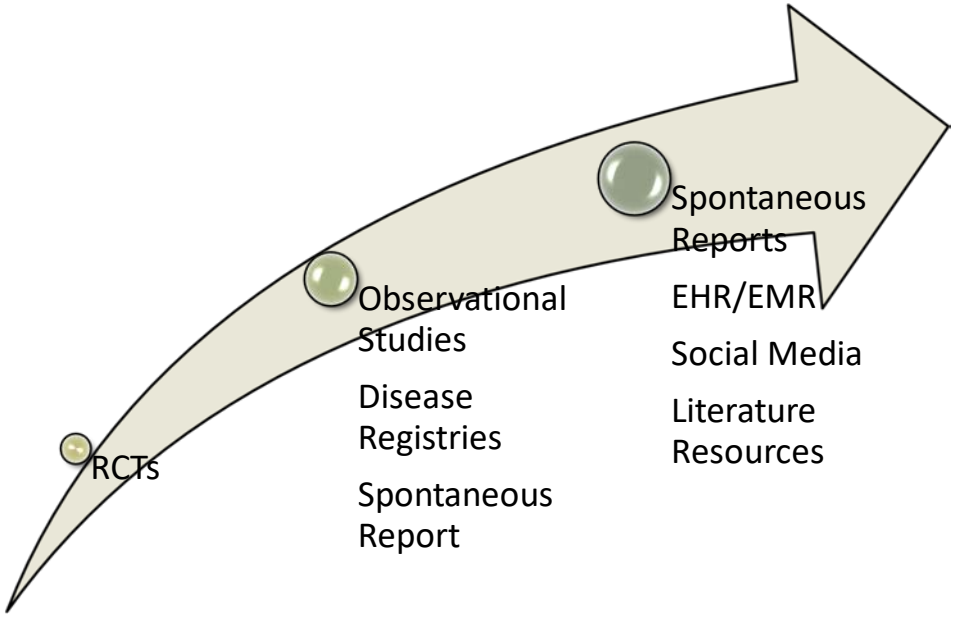


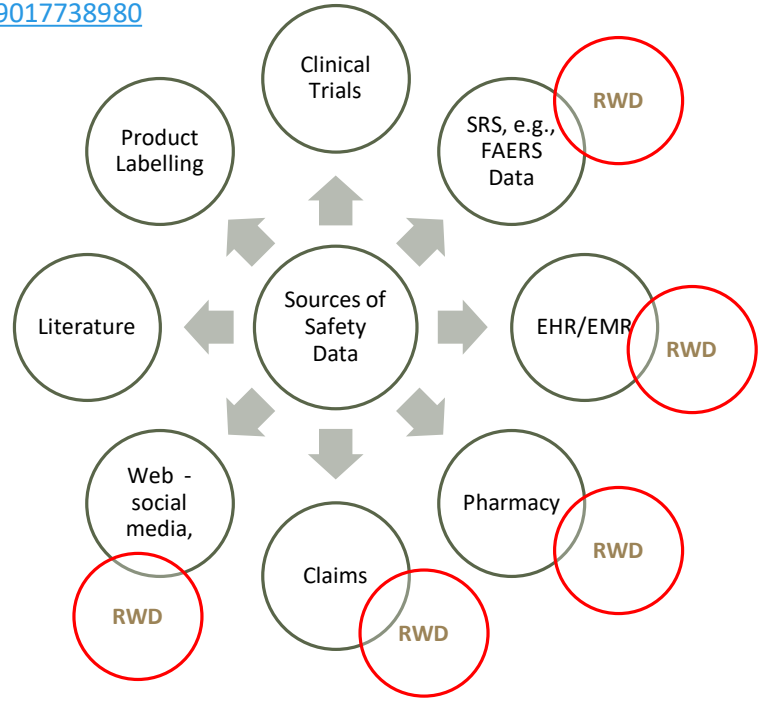
The Ever Expanding Data Sources for Safety Data

Safety assessment on a continuum

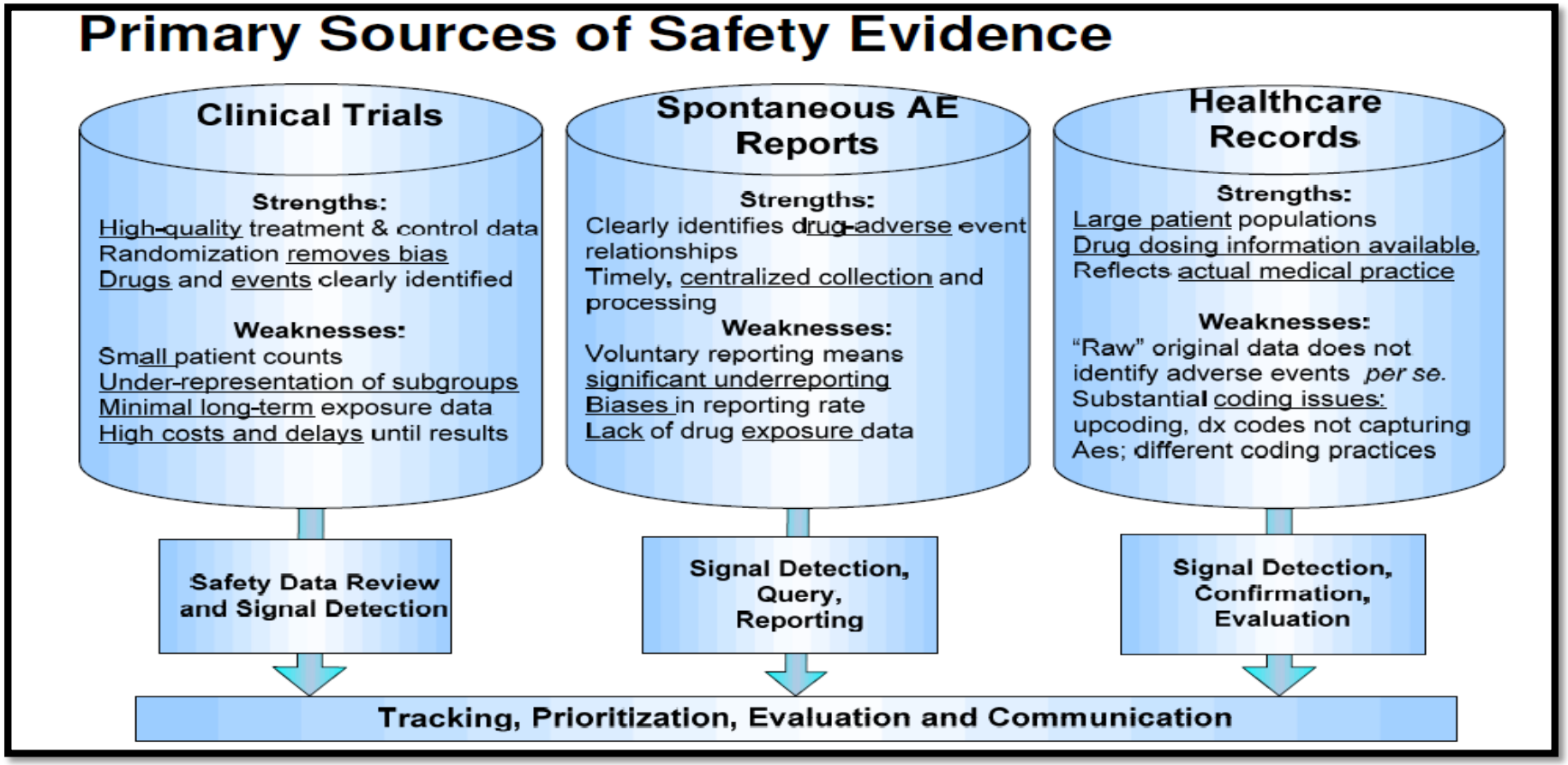
Ever expanding sources for safety data

- Challenge – finding ways to harness the data from these new sources in safety profiling of drugs
  - See: Zink et al (2018): sources of safety data - http://journals.sagepub.com/doi/abs/10.1177/2168479017738980



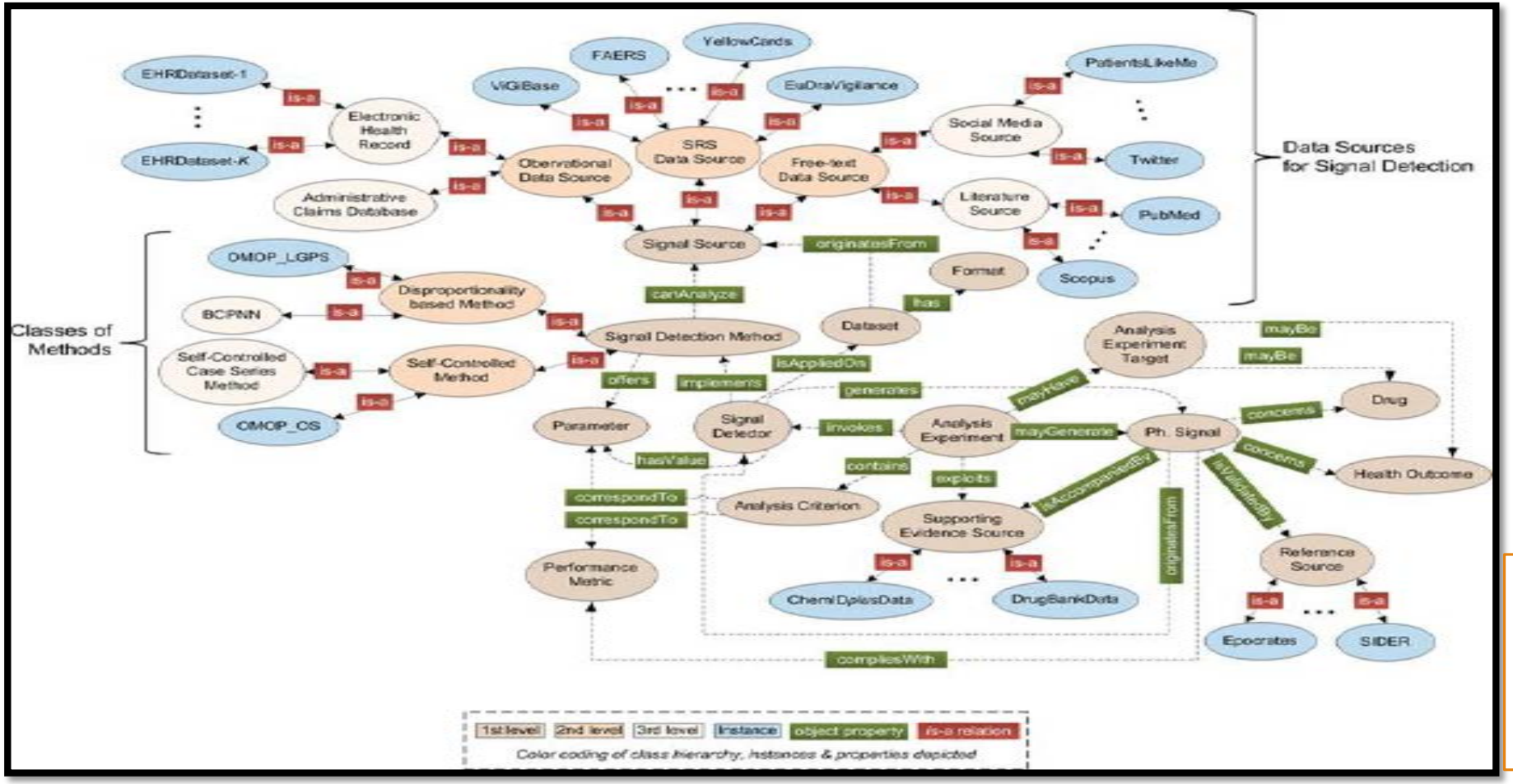


The Ever Expanding Data Sources for Safety Data



Source: https://www.diaglobal.org/productfiles/22993/day%202/303/s303%2005_wayne%20kubick.pdf

The Ever Expanding Data Sources for Safety Data



Source: ***Leveraging Post-marketing Drug Safety Research through Semantic Technologies: The PharmacoVigilance Signal Detectors Ontology,*** Vassilis Koutkias1 and Marie-Christine Jaulent1
Source: http://ceur-ws.org/Vol-1320/paper_17.pdf

Challenges of Safety Data

- Safety data present many challenges with regard to analysis and interpretation
- For example in the clinical space:
  - Clinical trials not powered to detect safety signals
  - Safety data are multidimensional and interrelated in nature
  - Pathological features of diseases lead to heterogeneous subpopulations and data with non-normal distributions
  - Using tabular formats for safety data results in large volumes of output
  - Descriptive summary tabular outputs, especially displays going over many pages are not easy to interpret
  - Patient data listings can be quite cumbersome and are rarely analytical

Need for Graphs in the Analysis of Safety Data

Need for use of graphical methods in safety data has been long recognized!

Wittes (1996)	*A plethora of tables and graphs that describe safety may bury some true signal in a cacophony of numbers*

Harrell (2005)	• *Graphs, Not Tables!*
	  • *Have pity on statistical and medical reviewers*
	  • *Difficult to see patterns in tables*
	  • *Substituting graphs for tables increases efficiency of review*

Amit, Heiberger, and Lane (2008)	*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.*
Krause and O'Connell (2012)	*A Picture is Worth a Thousand Tables* *Graphics in Life Sciences*
Vlachos (2015)	*Graphics are an underutilized resource in safety*
McKain, Jackson, and Elko-Simms (2015)	*Traditional case reviews and TLs not sufficient for safety surveillance principles – use graphs*
Regulatory Guidance	*ICH-E3, FDA Safety Review Guidance (2005) – some recommendations for using visuals*

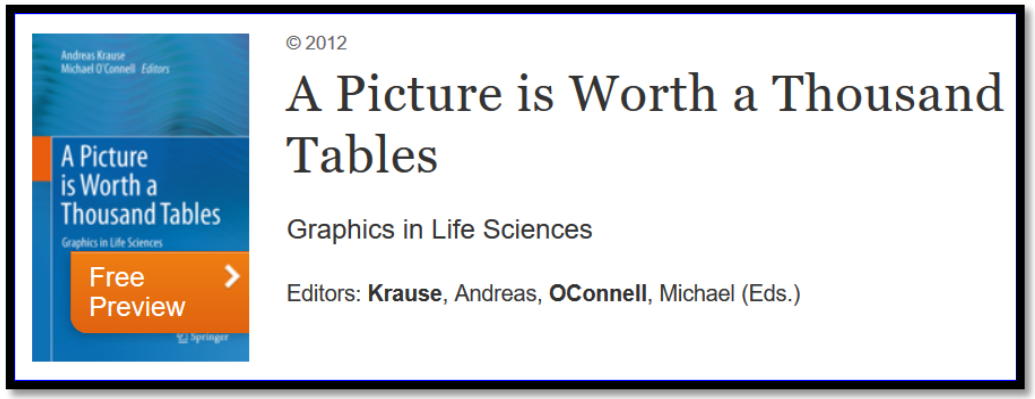
Need for Graphs in the Analysis of Safety Data

Some past efforts

- Individual commendable efforts, e.g.,
  - Frank Harrel
    - http://biostat.mc.vanderbilt.edu/wiki/pub/Main/FHHandouts/gsksafety.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/

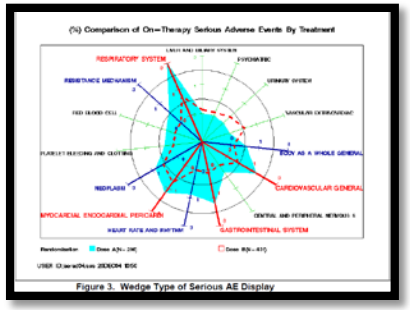
Need for Graphs in the Analysis of Safety Data

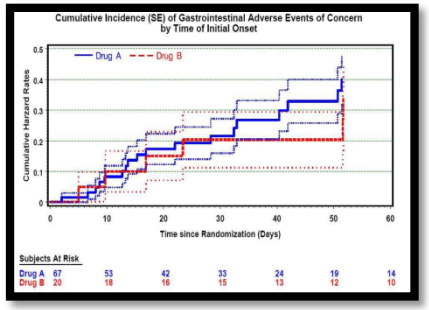
- Some collaborative commendable efforts, e.g.,
  - CTSPedia
    - http://www.ctspedia.org/do/view/CTSpedia/AllGraphicalEntries
  - A Picture is Worth a Thousand Tables
    - http://www.elmo.ch/doc/life-science-graphics/

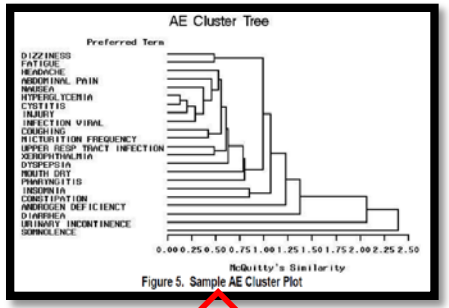


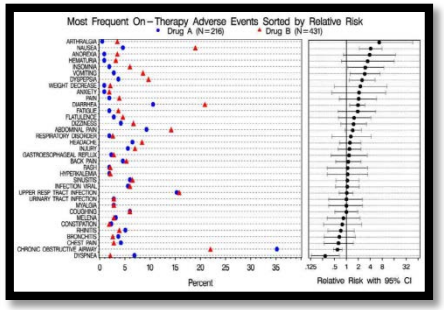
  - Above individual and collaborative efforts cover common industry practic

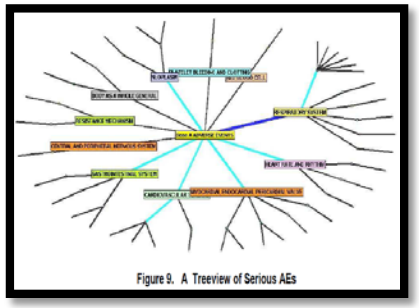
Need for Graphs in the Analysis of Safety Data

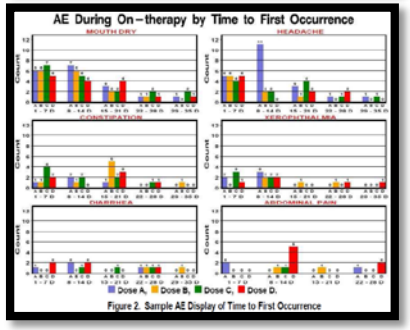


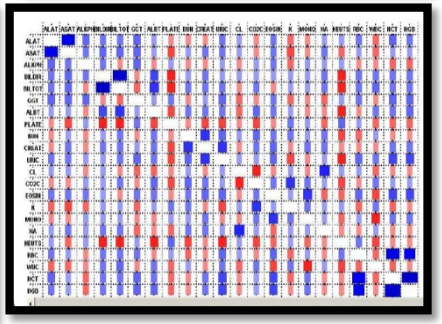


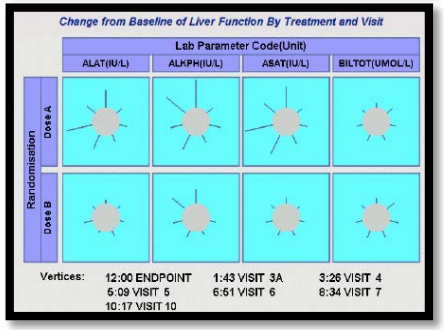


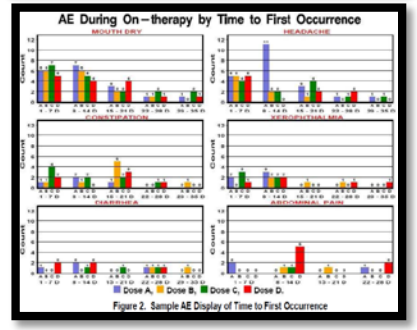


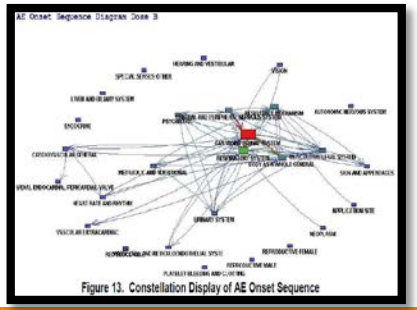


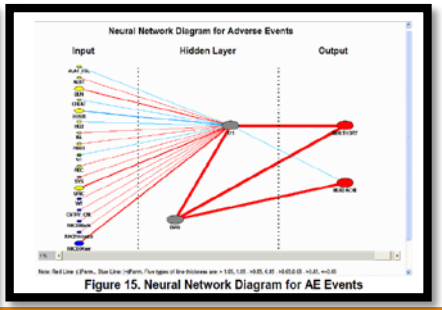


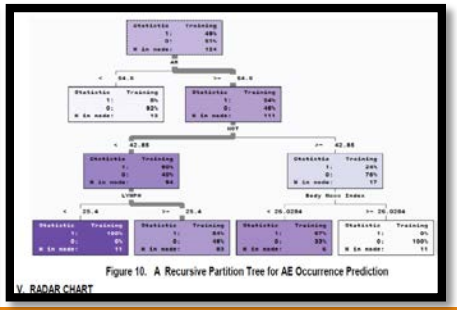


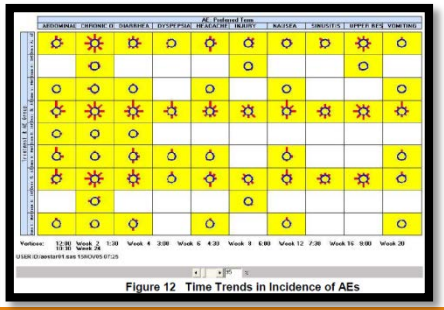










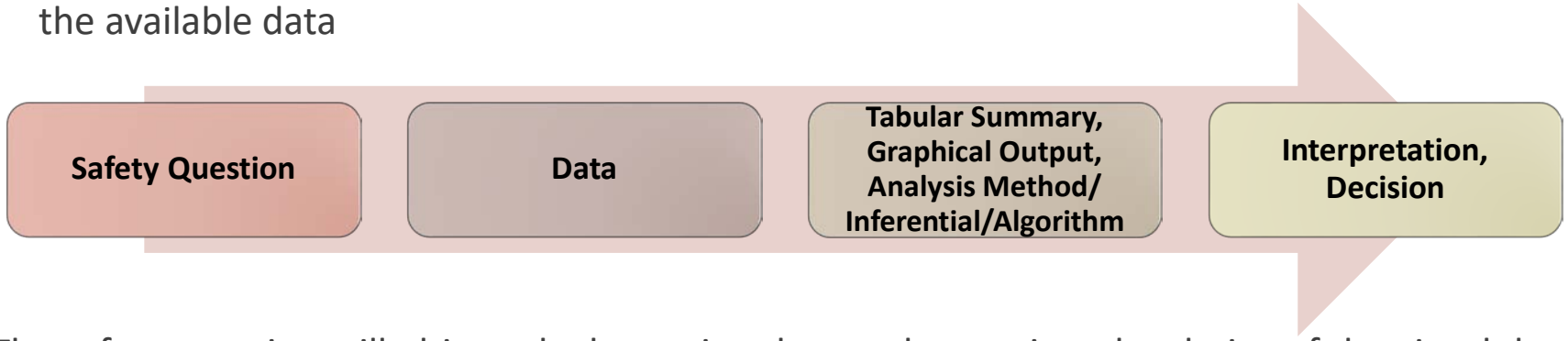


Shi-Tao Yeh

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

General considerations – Question-Based Approach

- First, we need to decide what is the safety question that we want to address?
- Determine what data will be used to address the question, or what sort of questions can be addressed with the available data

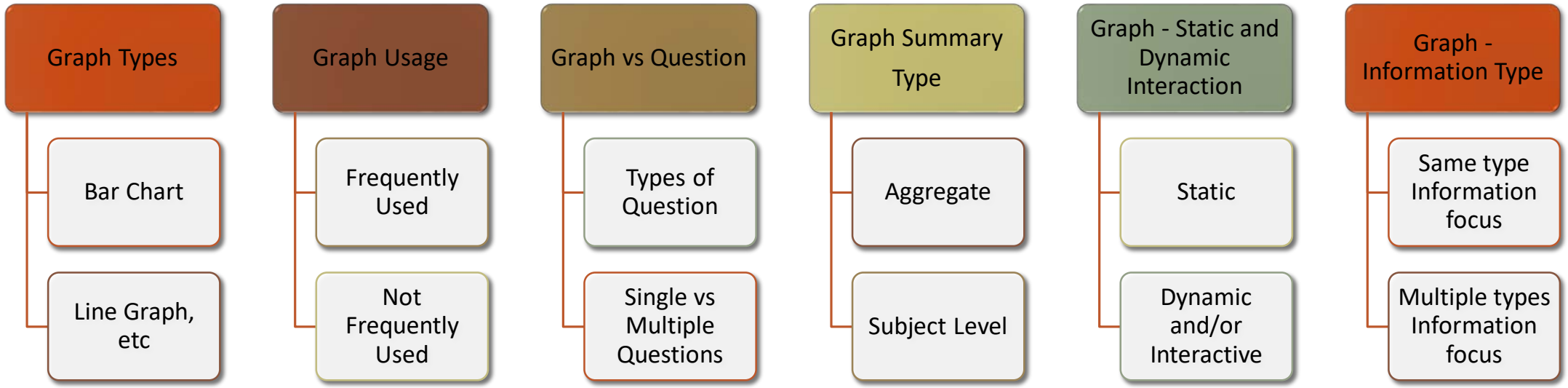



Chapter 11
A Question-Based Approach to the Analysis of Safety Data
Melvin S. Munsaka

K. E. Peace et al. (eds.), *Biopharmaceutical Applied Statistics Symposium*, ICSA Book Series in Statistics, https://doi.org/10.1007/978-981-10-7826-2_11

- The safety 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

General considerations – Graph Complexity



General considerations – Graphing Principles

Some key graph principles include

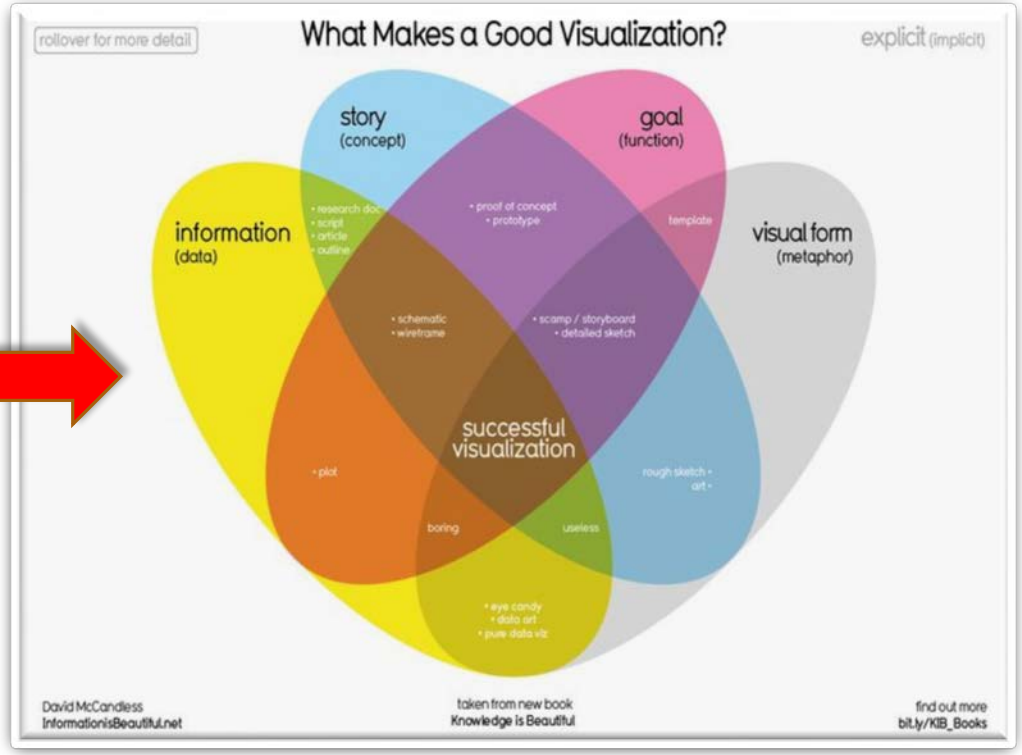
- Graph content
- Communication
- Information
- Annotation, axes, and style
  - All these are important to ensure that we have good and successful visualization of the data, especially in the context of safety monitoring

General considerations – Graphing Principles

Graph Principles

Duke (2014), Duke et al (2015) - Good graphing principles and good graphic design

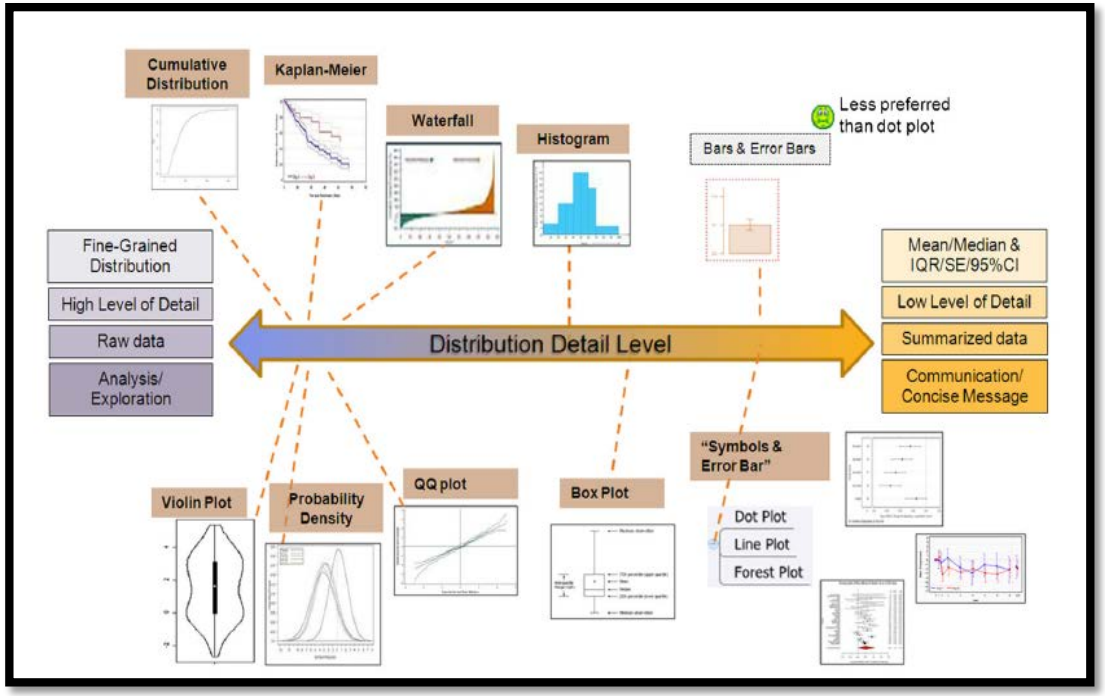
- Graphs for safety data must also adhere to good graphing principles and good design for graph construction
- There must be a goal, a story, information to be delivered and a visual form to make visualization successful
- These considerations are especially important in the context of safety in order to help identify safety signals early using visual forms



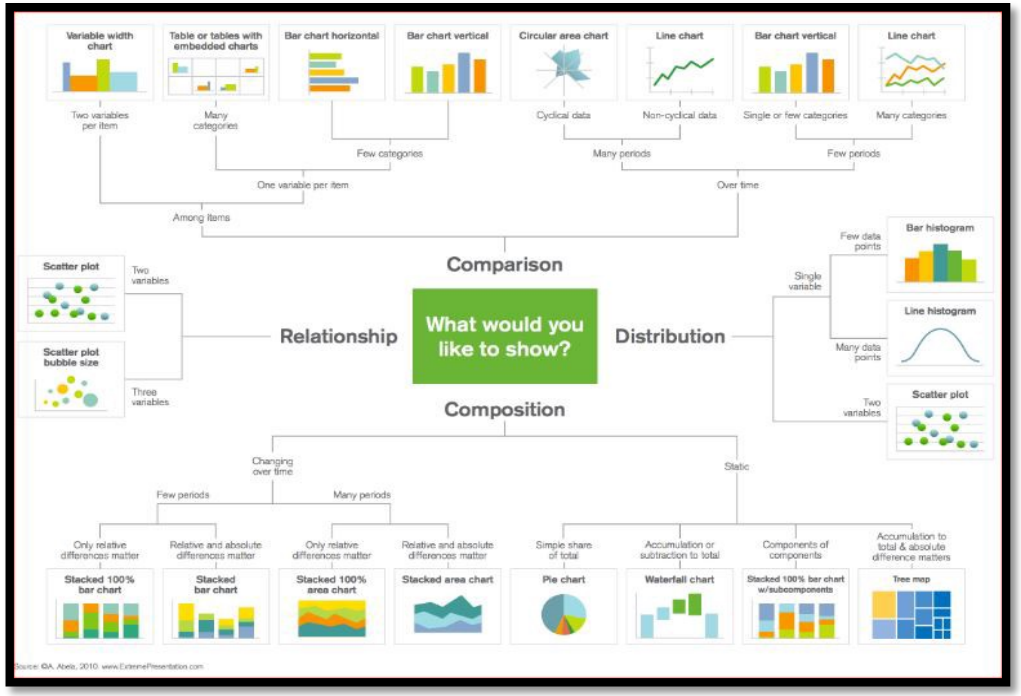
Source: https://infobeautiful4.s3.amazonaws.com/2015/05/2552_What-Makes-a-Good-Infoviz-frame01.png

General considerations – Choosing the Right Graph Type

- 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/



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The Push Towards Quantitative Safety

JOURNAL OF BIOPHARMACEUTICAL STATISTICS
2016, VOL. 26, NO. 1, 17–29
http://dx.doi.org/10.1080/10543406.2015.1092026
Taylor & Francis
Taylor & Francis Group

The role of quantitative safety evaluation in regulatory decision making of drugs

Aloka G. Chakravarty, Rima Izem, Stephine Keeton, Clara Y. Kim, Mark S. Levenson, and Mat Soukup

Division of Biometrics VII, Office of Biostatistics, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

Quantitative drug safety requires unique expertise.
DBVII provides this expertise in statistical methods relevant to safety evaluation, including:

- Design and analysis of safety clinical trials
- Design and analysis of observational studies
- Meta-analysis for safety evaluation
- Signal detection
- Survey methodology
- Time series analysis
- Graphical and computational tools.

Quantitative Safety Evaluation at CDER

Aloka Chakravarty,
Director, Division of Biometrics VII
Office of Biostatistics, OTS, CDER, FDA

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Biometrics VII (Safety)

- **Focus** on the **quantitative** assessment of safety
  - Development phase of product development
  - Pre-market risk assessment
  - Post-market risk assessment
- **Expertise** in areas **unique** to the safety assessment
  - Meta-analysis
  - Randomized trials primarily to evaluate safety
  - Design and analysis of observational studies
  - Graphical and computational methods
  - Analyses of registry and health care databases
- **Experience** in working across **multiple** divisions
  - Application of prior experience to new situations

On quantitative methods for clinical safety monitoring in drug development

Statistics in Biopharmaceutical Research

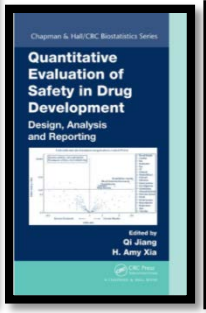
William Wang, Ed Whalen, Melvin Munsaka, Judy Li, Michael Fries, Karolyn Kracht, Matilde Sanchez-Kam, Krishan Singh & Kefei Zhou

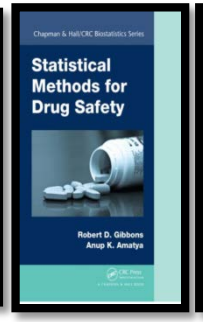
Received 18 Oct 2016, Accepted 19 Nov 2017, Accepted author version posted online: 19 Dec 2017

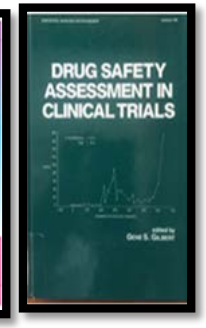
Pre-Market Safety Must Balance Statistics With Clinical Discernment – FDA

"The Pink Sheet" Nov. 10, 2008, Vol. 70, No. 045

Safety evaluation is probably much harder than efficacy evaluation because in many ways it's reading the tea leaves. It's a lot of multiplicity, a lot of false discovery, a lot of it-is-real or is-it-not-real…But nonetheless, you can't even approach that discussion if you can't quantify it in a reasonable way…statisticians for the most part have not been involved in safety evaluations…The sophistication is out there, it just has not been brought to bear on routine safety assessment for chronically used drugs.







The Push Towards Quantitative Safety

On the question of statistical inference of safety data

- Big question, many challenges! Controversial, varying opinions on what, when, how, and interpretation given the many statistical challenges! But value of inference on safety data is well recognized! Topic for another day!

MAKING DECISIONS ABOUT SAFETY IN CLINICAL TRIALS — THE CASE FOR INFERENTIAL STATISTICS
GREGORY G. ENAS, PHD
Drug Information Journal, Vol. 25, pp. 439–446, 1991

→ *While not required for every AE, inferential statistical methods can be used both formally and informally to help characterize the safety profile of a new drug and help guide the resulting inferences to the broader population.*

Reviewer Guidance
Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

→ *Although not strictly hypothesis testing, p-values give some feeling for the strength of the finding and should be produced for all new drug/placebo pair-wise comparisons and any p-values meeting a p < 0.05 level of significance should be noted*

Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team
Brenda J Crowe[a], H Amy Xia[b], Jesse A Berlin[c], et al *Clinical Trials* 2009; **6**: 430–440

→ *For TIER 1 and TIER 2 AEs - an estimate of the RD, RR, or OR is reported together with corresponding confidence intervals or p-values.*

ICH Topic E 9
Statistical Principles for Clinical Trials

→ *6.4 Statistical Evaluation - The calculation of p-values is sometimes useful, either as an aid to evaluating a specific difference of interest or as a flagging device applied to a large number of safety and tolerability variables to highlight differences worthy of further attention.*

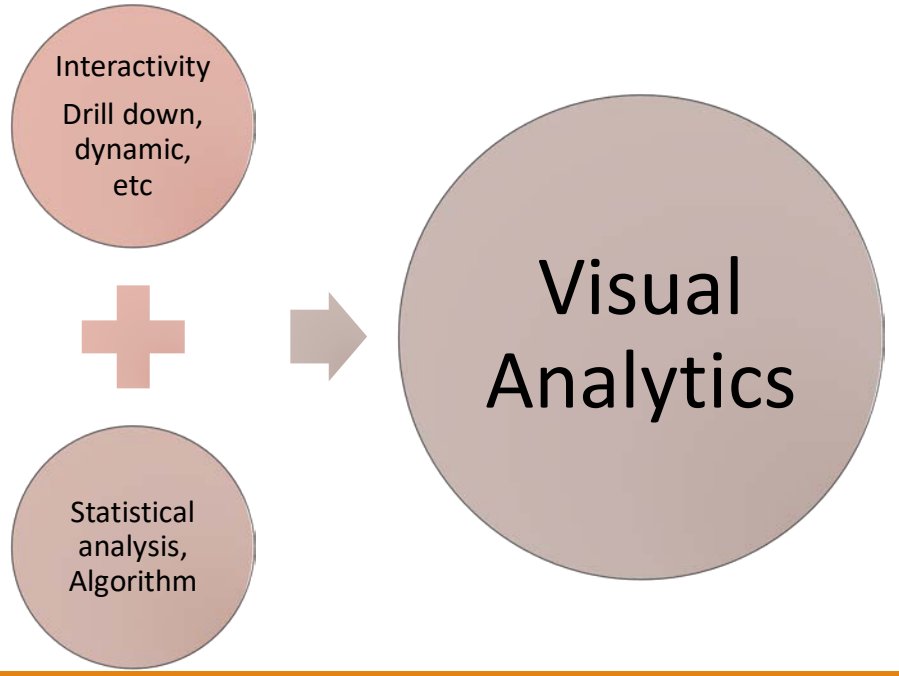
Carragher R (2015) A comparison of some methods for detection of safety signals in randomised controlled trials. In: Society for Clinical Trials 36th Annual Meeting

→ *Classical and Bayesian methods to control false positive results. R Package developed for the methods.*

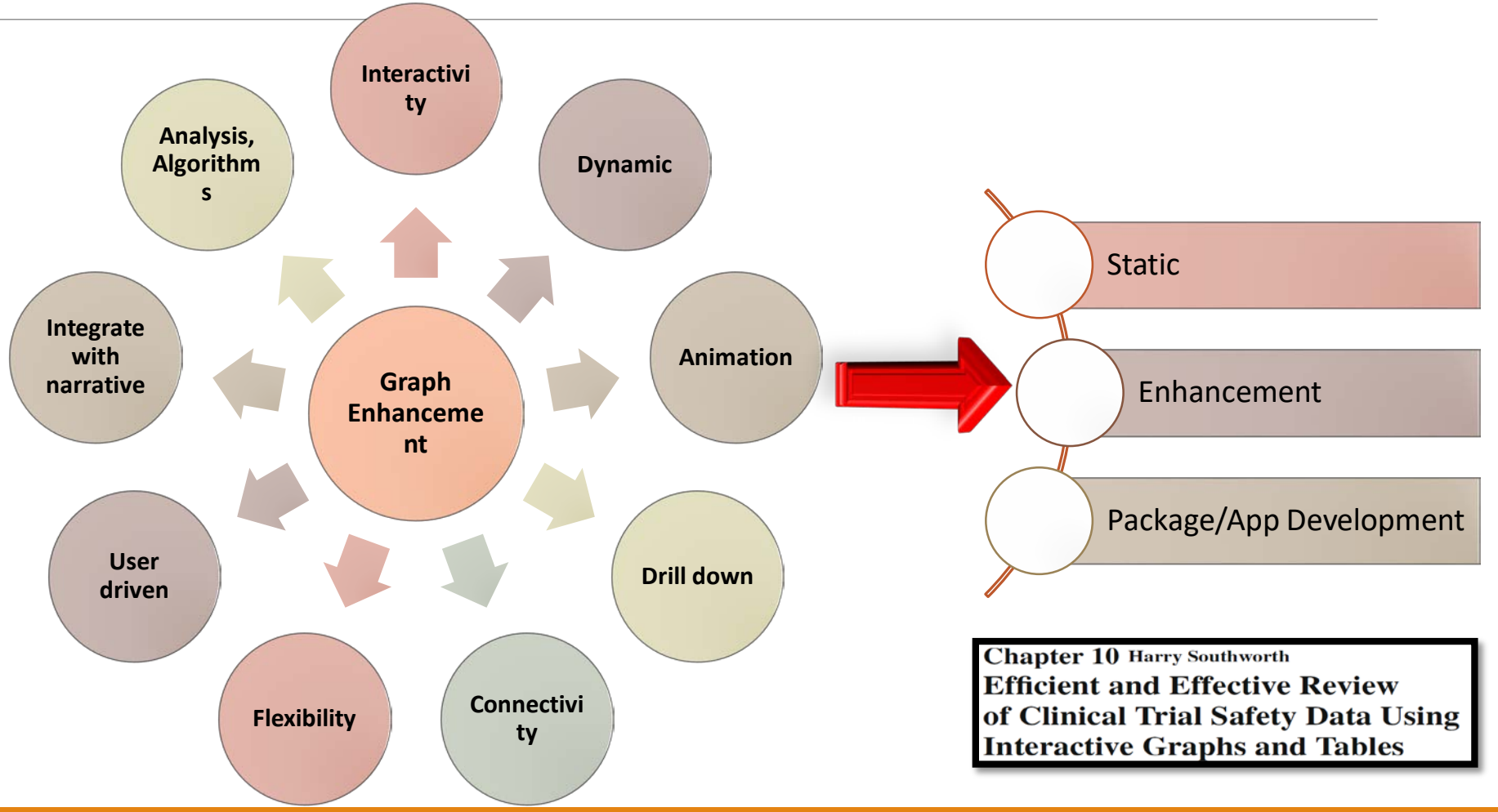
Defining Visual Analytics

Two broad views

- Bringing static graphs to life via some enhancement, e.g., interactivity, drill down, animation, dynamic, etc
- Statistical analysis and algorithms

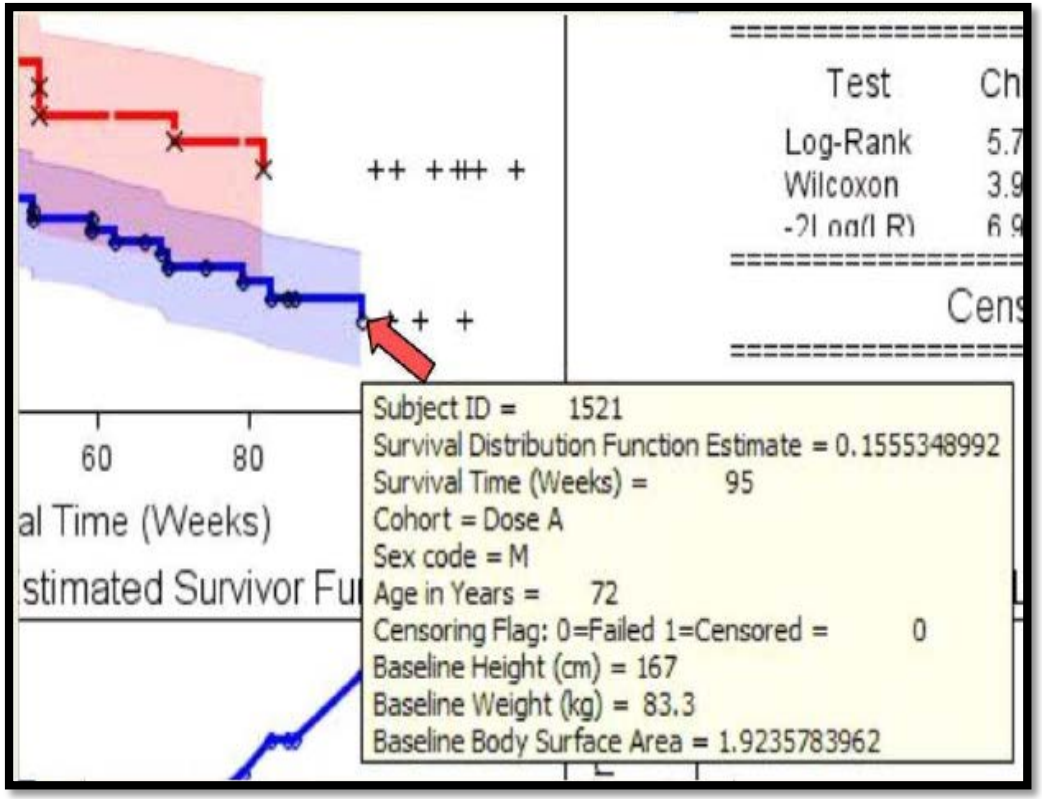


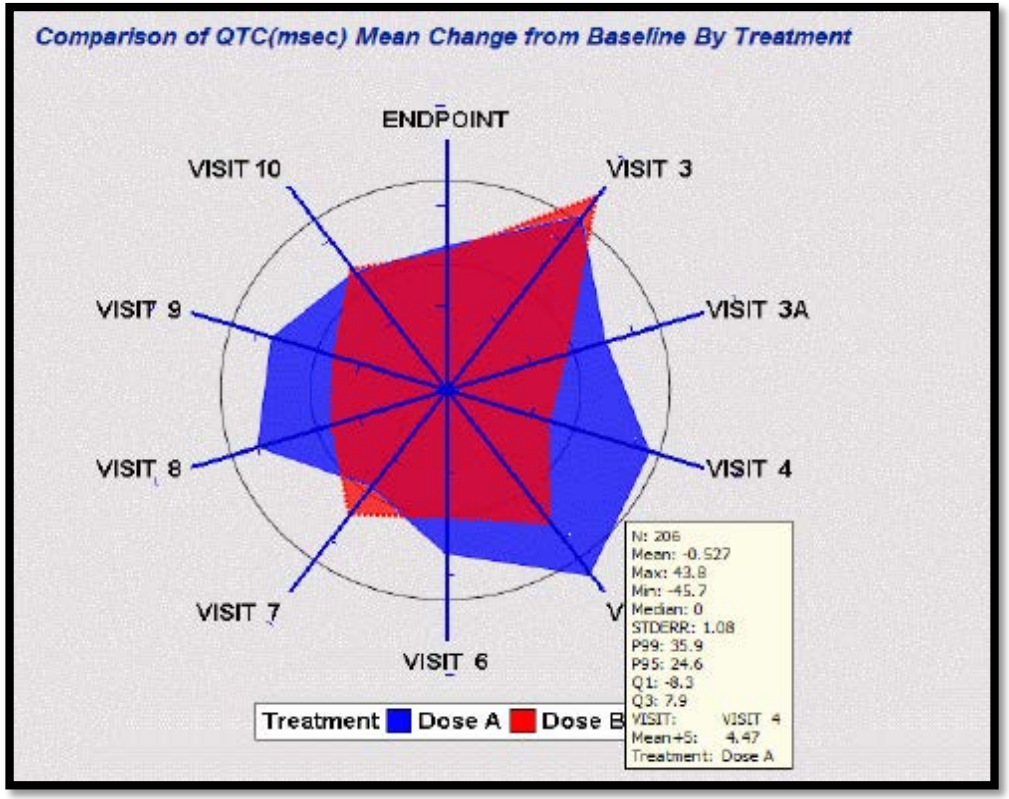
Defining Visual Analytics



Defining Visual Analytics

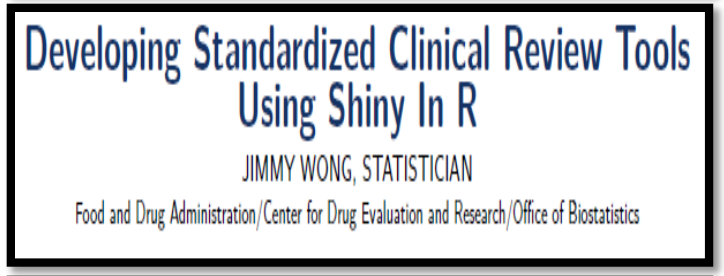
Some attempts using SAS and JAVA byYeh (2007)

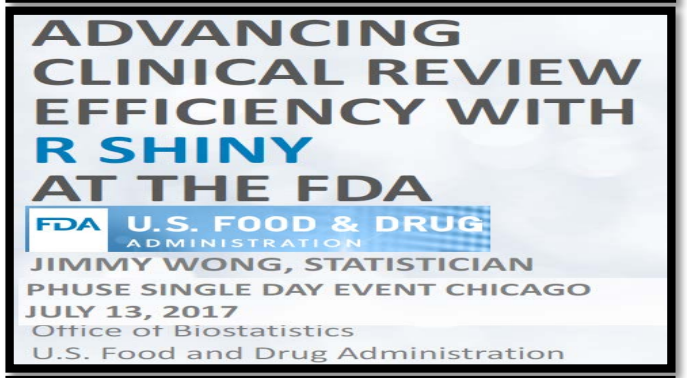


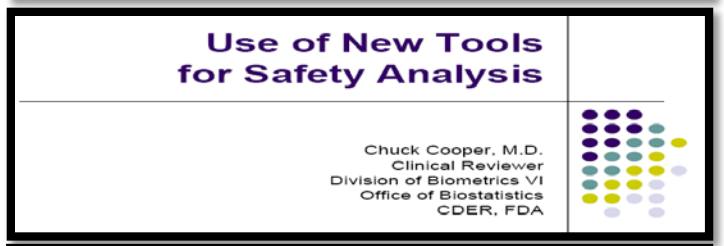


Defining Visual Analytics

…and FDA is doing it too!

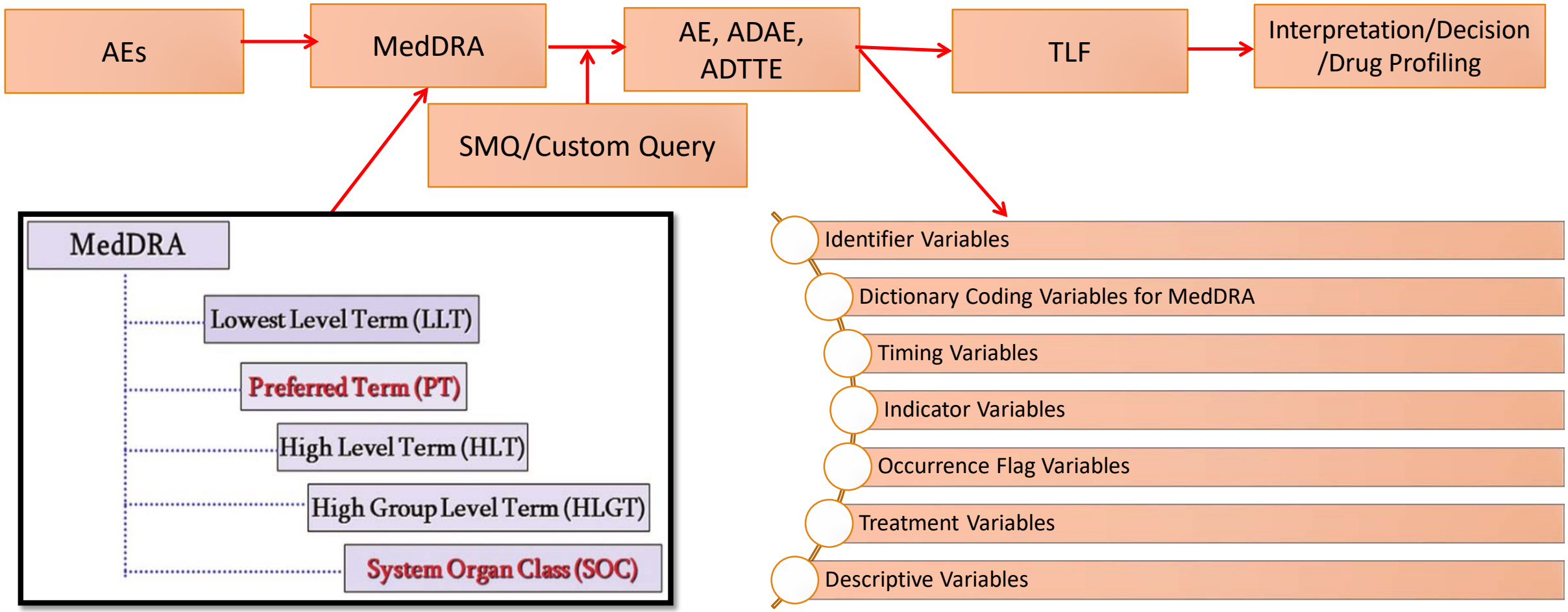






Examples – Clinical Trial Data, Adverse Events

AE Data Flow


AEs
MedDRA
AE, ADAE, ADTTE
TLF
Interpretation/Decision /Drug Profiling
SMQ/Custom Query
MedDRA
Lowest Level Term (LLT)
Preferred Term (PT)
High Level Term (HLT)
High Group Level Term (HLGT)
System Organ Class (SOC)
Identifier Variables
Dictionary Coding Variables for MedDRA
Timing Variables
Indicator Variables
Occurrence Flag Variables
Treatment Variables
Descriptive Variables

Some Questions to Ask on AEs

Incidence Rate

- What is the constellation of AEs that come with the drug?
- Which AEs are elevated in treatment versus control?
- What are the most common AEs in treatment?

Severity , Duration, Relationship to Study Drug

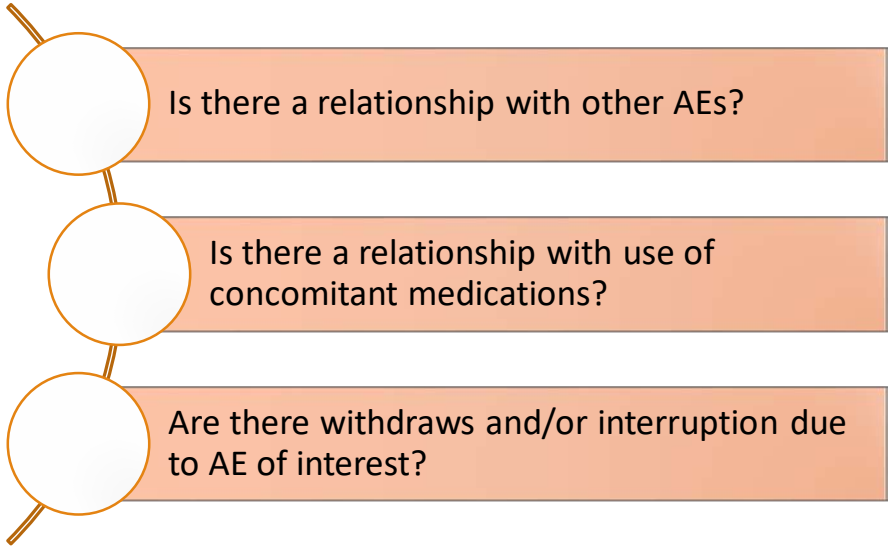
- What is the severity of the AEs ?
- What is the duration of the AEs?
- What is the relationship to study drug?

Temporal Relationship

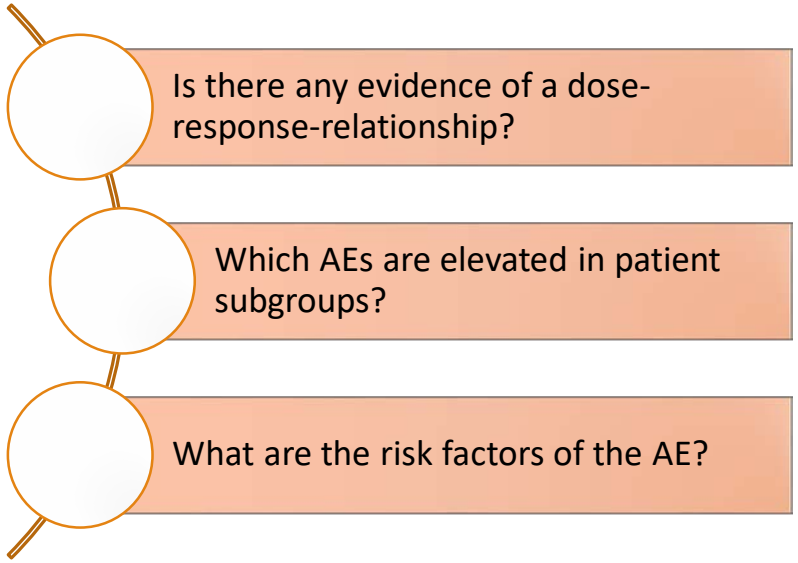
- Is there a difference in the time to the first event across treatment groups?
- What are the trends of time to the first event among different AEs?
- Is the potential AE of interest increasing over time?

Some Questions to Ask on AEs

Concurrent and Intercurrent Events

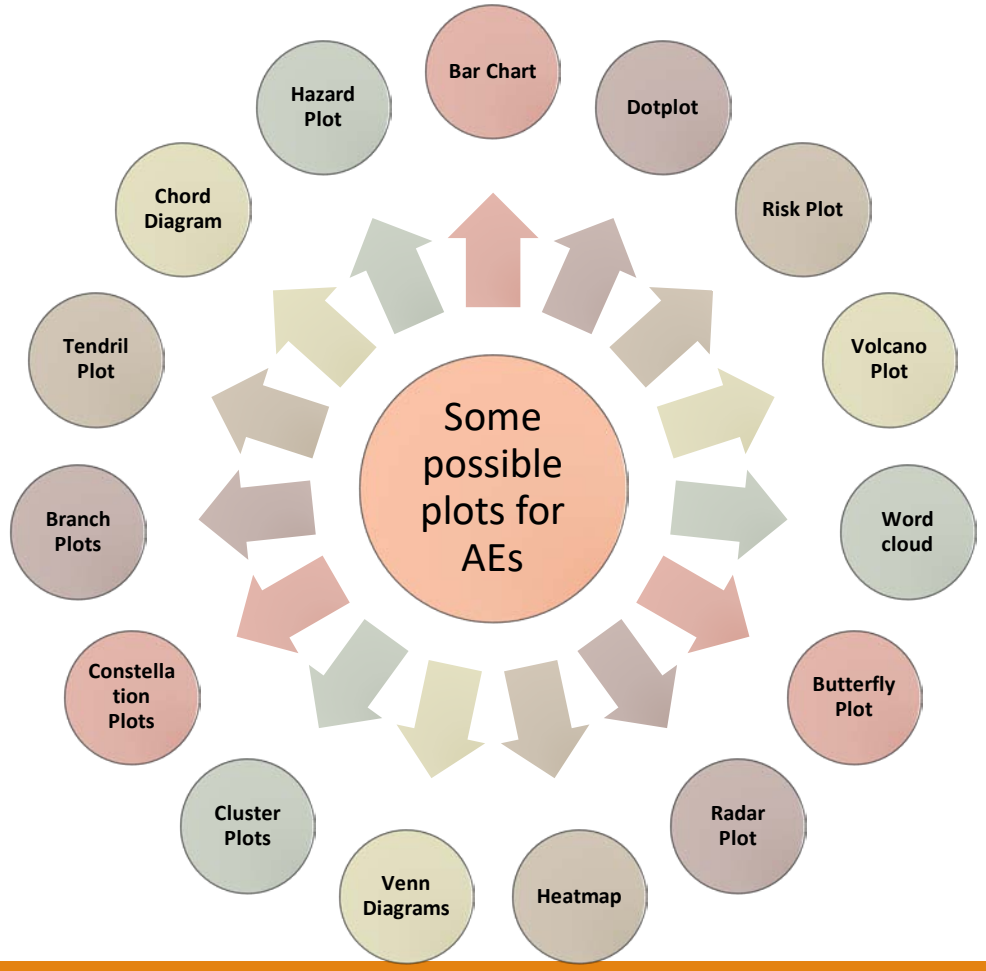


Dose relationship, Subgroups, Risk Factors



AE Plots – Many Available Charts to Graphically Present AEs

Examples



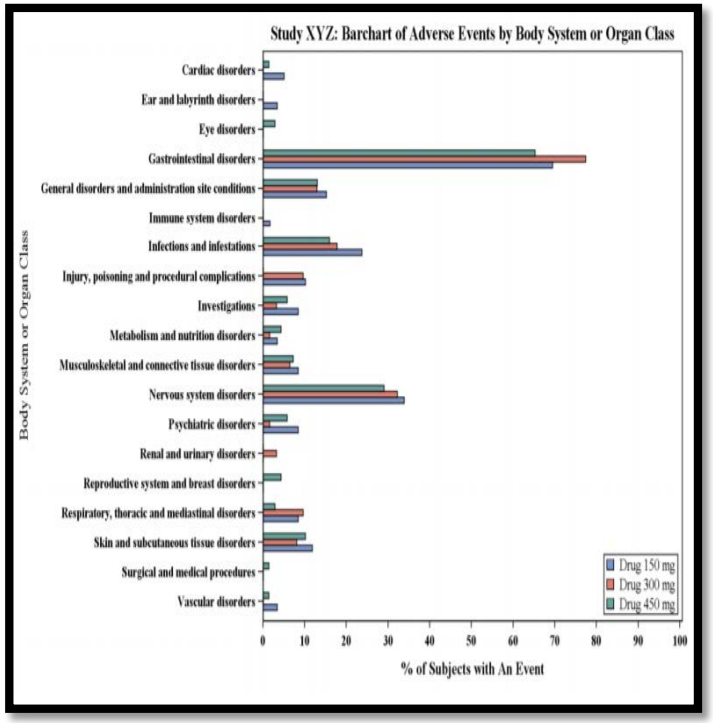
AE Magnitudes Bar Charts

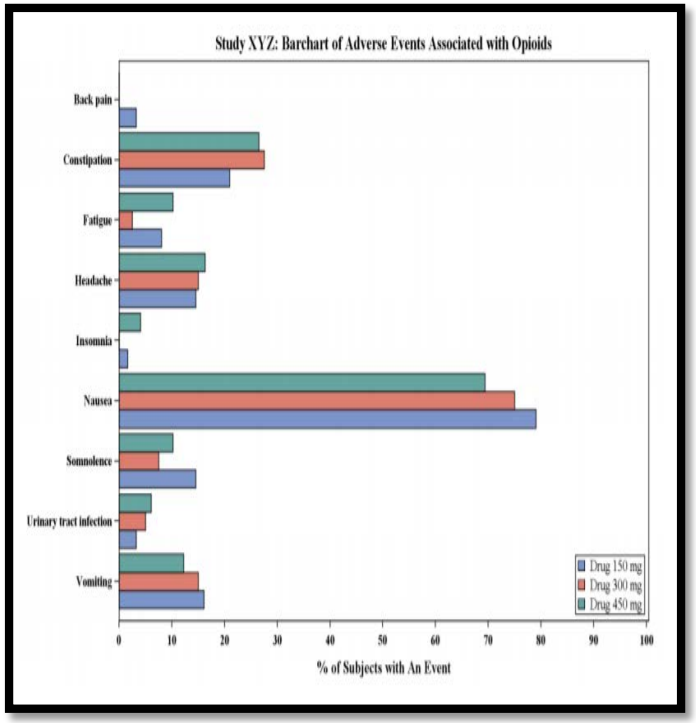
Bar Charts

Table AE 3
Incidence of Treatment Emergent Adverse Event by System Organ Class, Preferred Term, and Treatment
(Format 2)
All Randomized Subjects

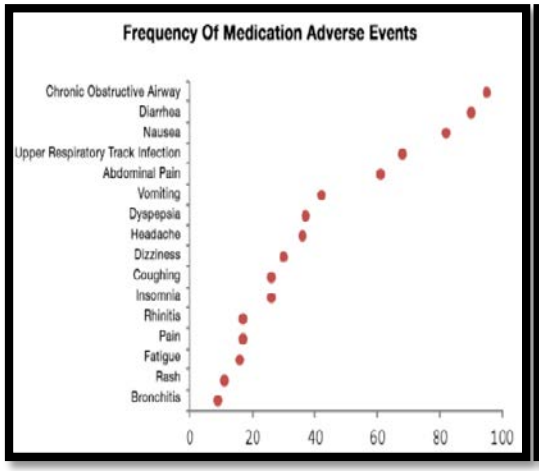
Body Class or System Organ Class	Preferred Term	Placebo N=xxx	Demo Dose 10 mg N=xxx	Demo Dose 30 MG N=xxx	Demo Dose 60 MG N=xxx
With Any Adverse Event	Overall	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 1		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
..... '		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 2		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
..... '		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 3		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
..... '		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)

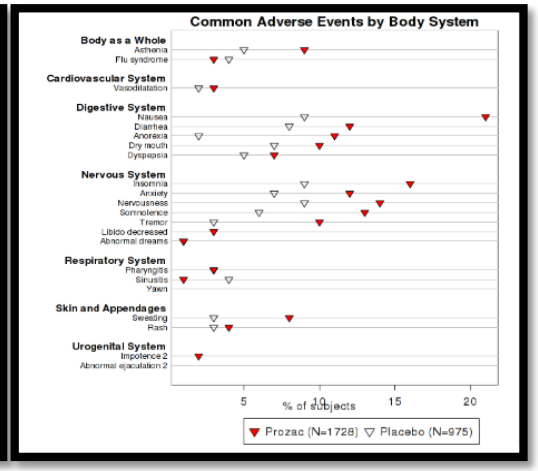
Note: denominator of percentage is the number of subjects in the column
Percentage is based on the number of subjects who had event not the number of events.

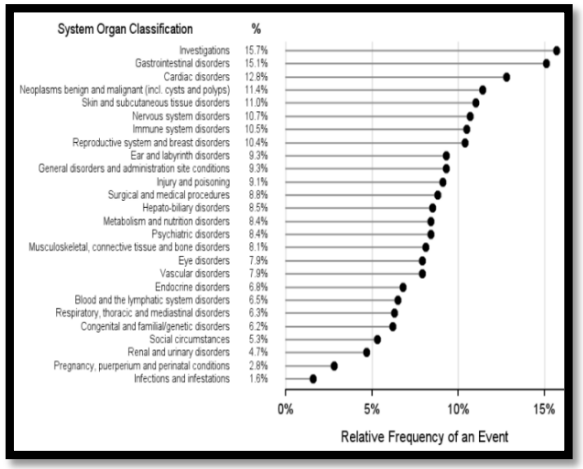


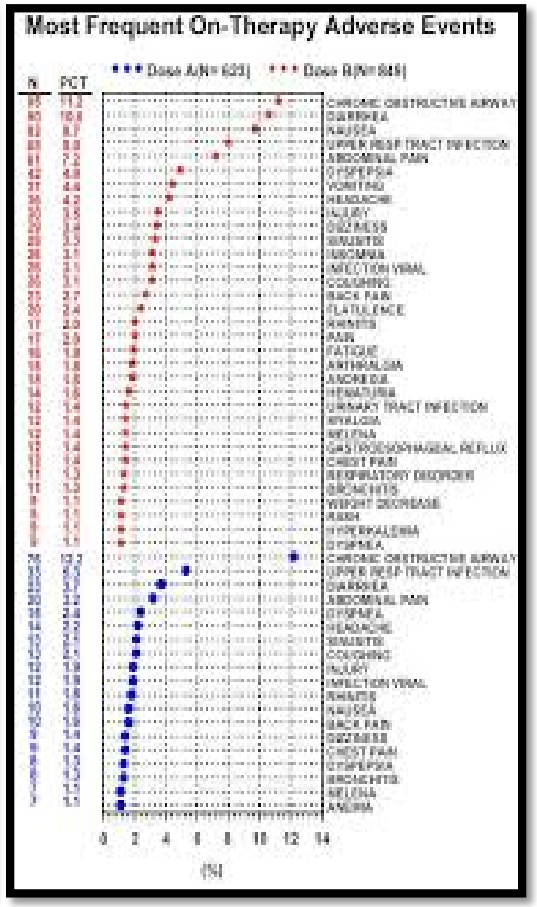


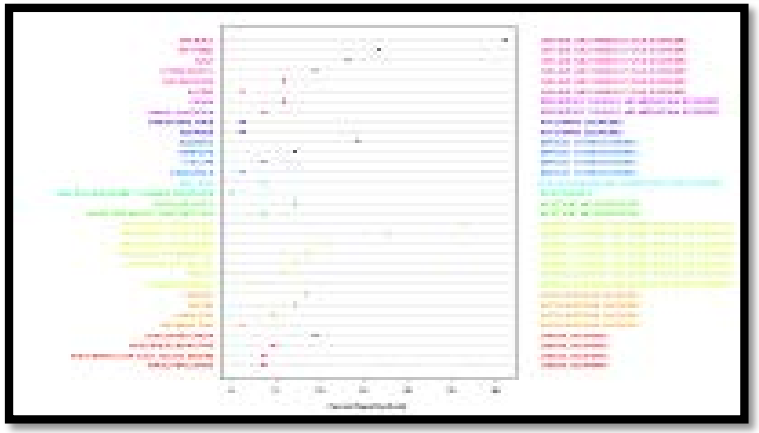
AE Magnitudes Dot Plots – Many variations

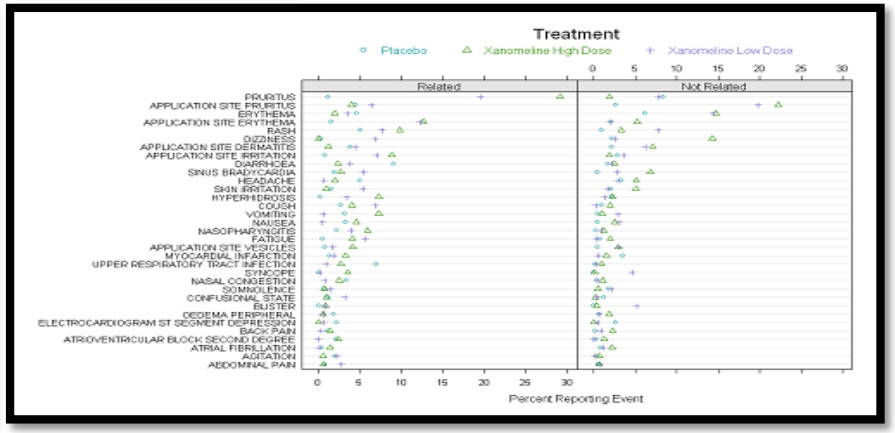




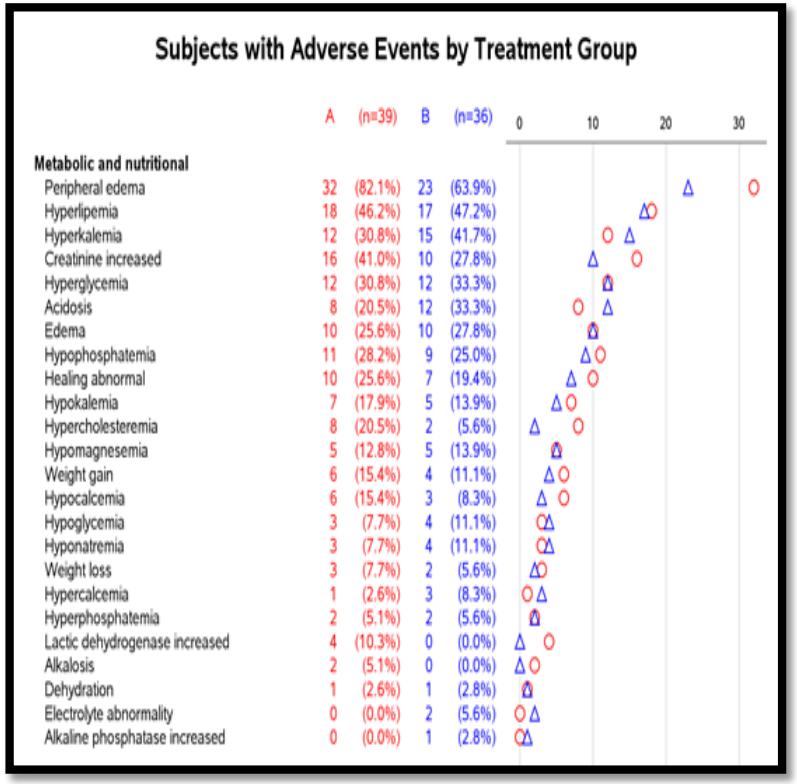








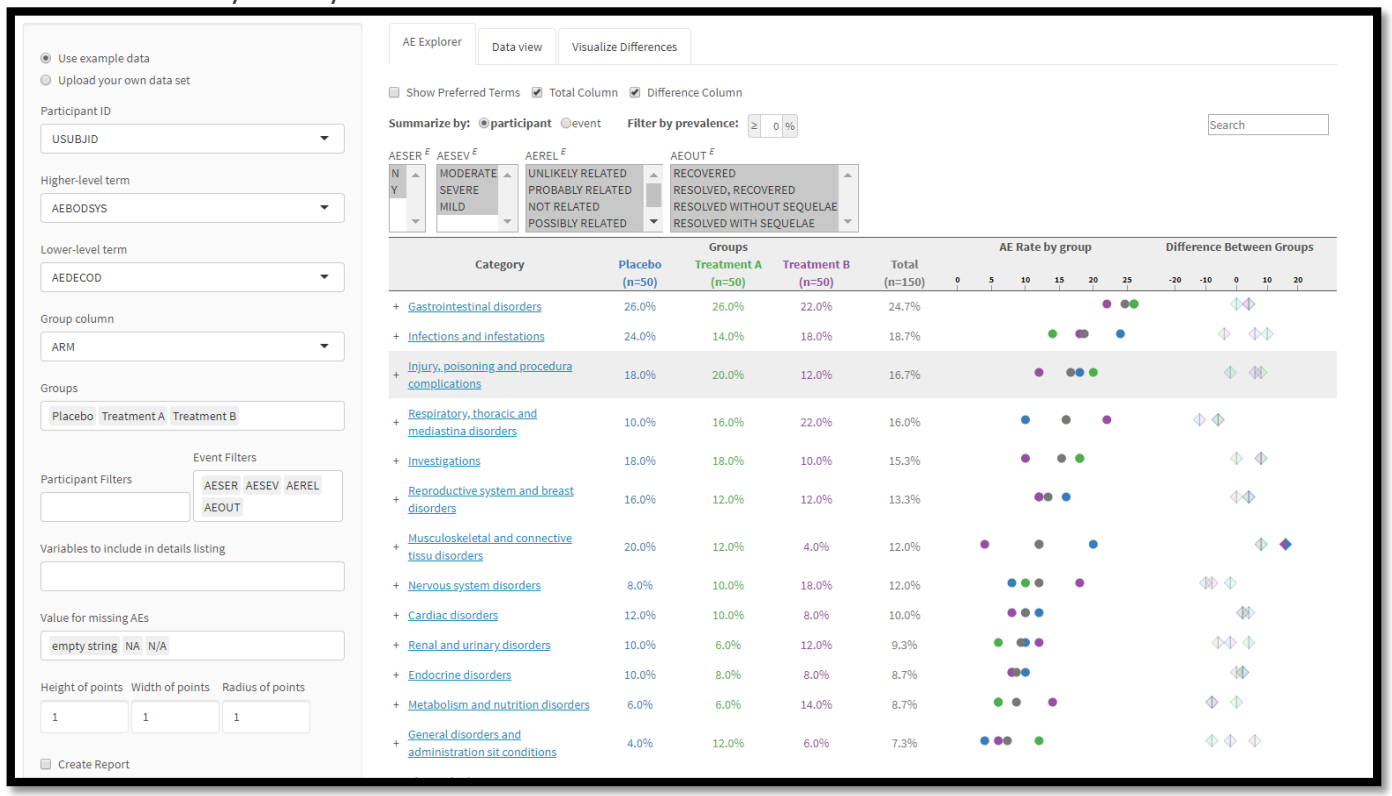
Dot plot



Source: https://pharmasug.org/proceedings/2017/DV/PharmaSUG-2017-DV03.pdf

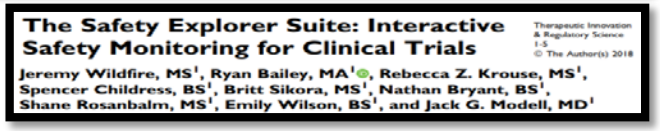
Source: https://github.com/RhoInc/aeplot

With Interactivity - Analytics



Source: https://becca-krouse.shinyapps.io/safetyapp/

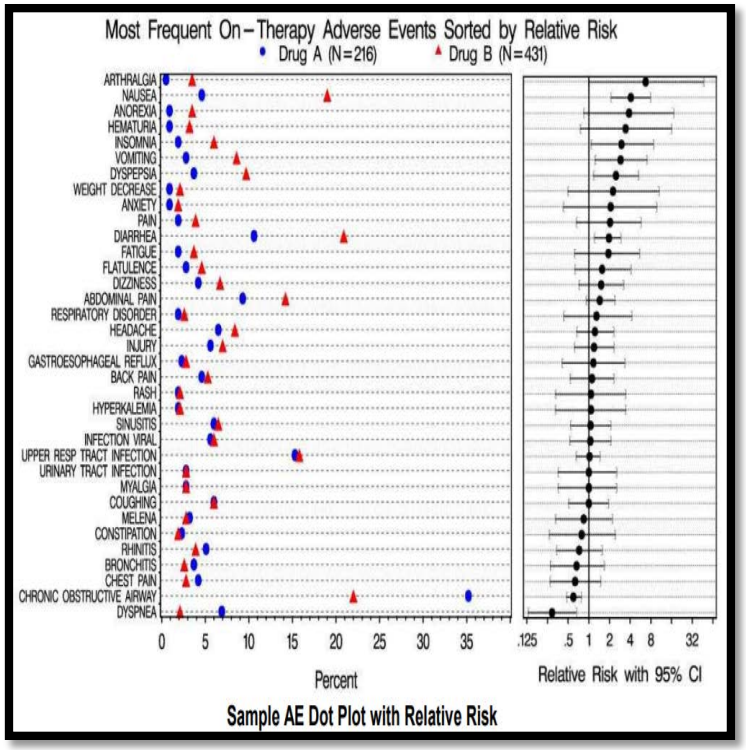
Source: https://github.com/RhoInc/safetyexploreR

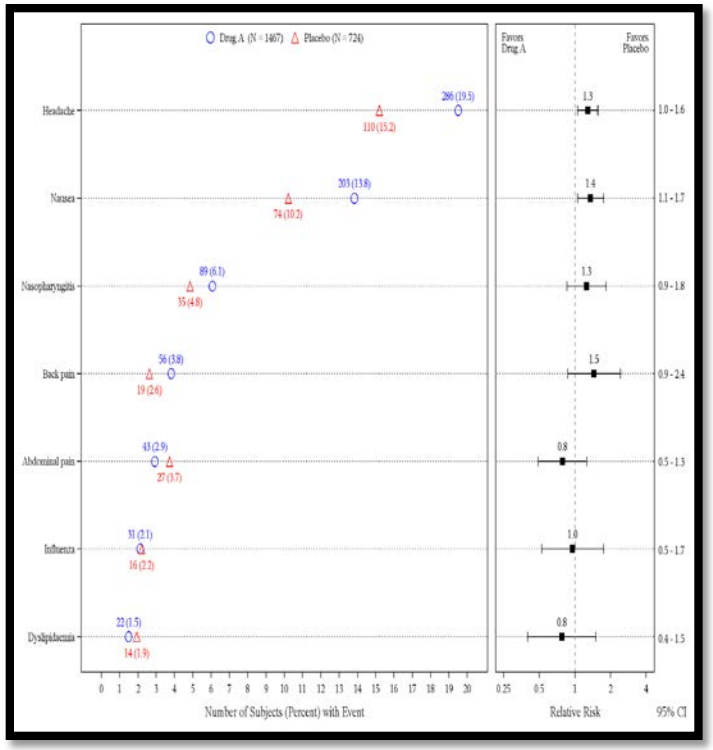

The Safety Explorer Suite: Interactive Safety Monitoring for Clinical Trials

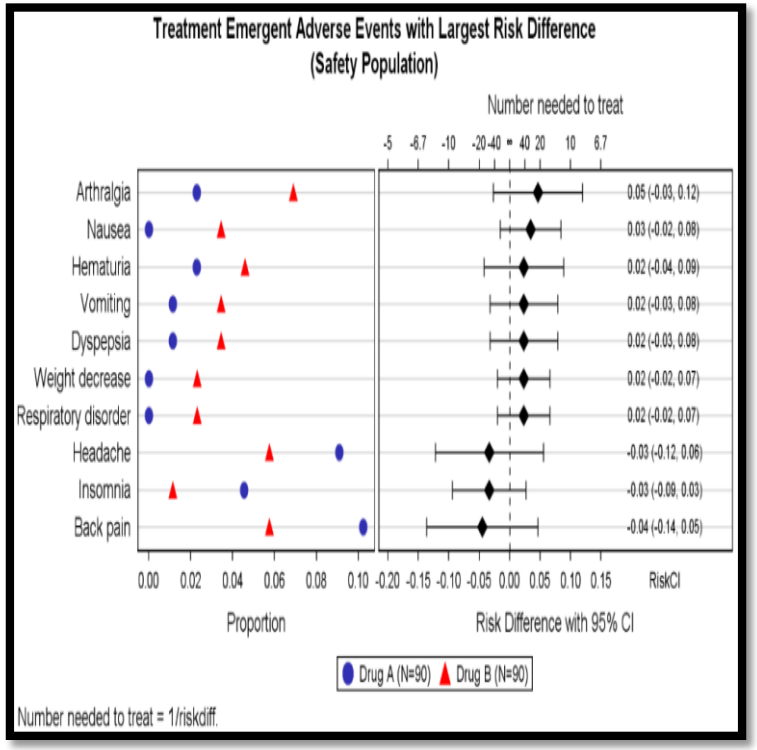
Therapeutic Innovation & Regulatory Science 1-5 © The Author(s) 2018

Jeremy Wildfire, MS[1], Ryan Bailey, MA[1], Rebecca Z. Krouse, MS[1], Spencer Childress, BS[1], Britt Sikora, MS[1], Nathan Bryant, BS[1], Shane Rosanbalm, MS[1], Emily Wilson, BS[1], and Jack G. Modell, MD[1]

Dot plot + RD and CIs - Analytics

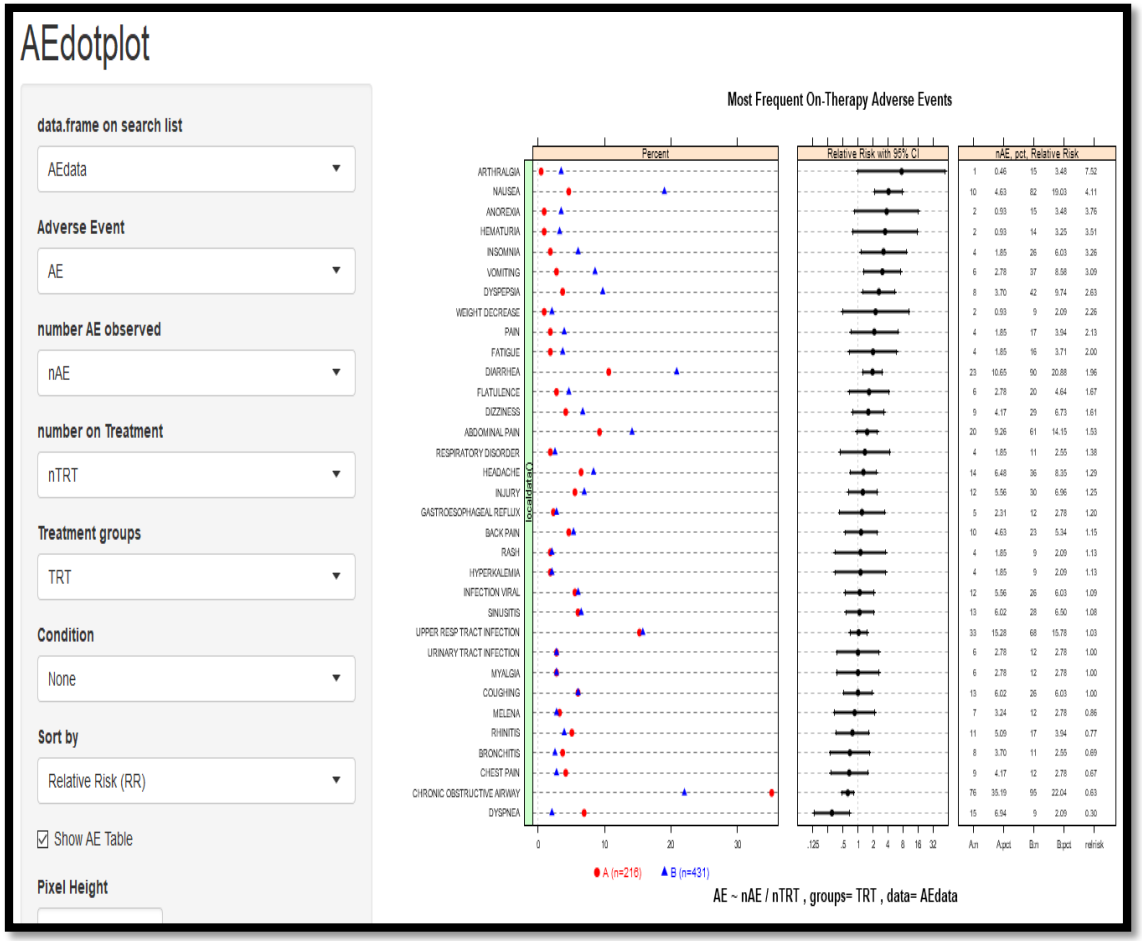






Source: https://blogs.sas.com/content/graphicallyspeaking/2015/10/31/adverse-events-graph-with-nnt/

Dot plot + RR and CIs and Shiny App - Analytics




```
library(HH)
data(AEdata)
head(AEdata)
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups = TRT, data = AEdata)
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata, sortbyVar="PCT")
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata, sortbyVar="PCT",
sortbyVarBegin=2)
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata,
sortbyRelativeRisk=FALSE)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups = TRT, data = AEdata,
sortbyVar="ase.logrelrisk")
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups = TRT,
        data = AEdata[c(AEdata$OrgSys %in% c("GI","Resp")),])
ABCD.12345 <- AEdata[1:12,]
head(ABCD.12345)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups=TRT, data=ABCD.12345)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups=TRT, data=ABCD.12345,
sort=FALSE)
tmp <- AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata)
print(tmp, AEtable=FALSE)
shiny::runApp(system.file("shiny/AEdotplot", package="HH"))
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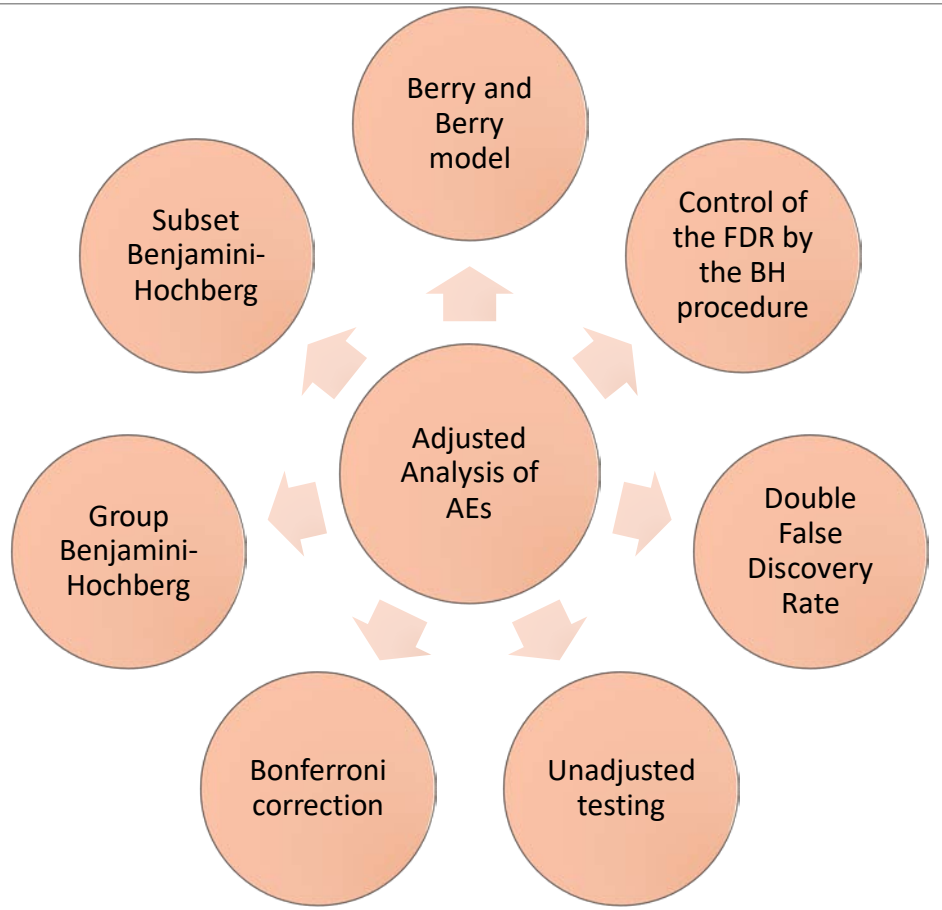
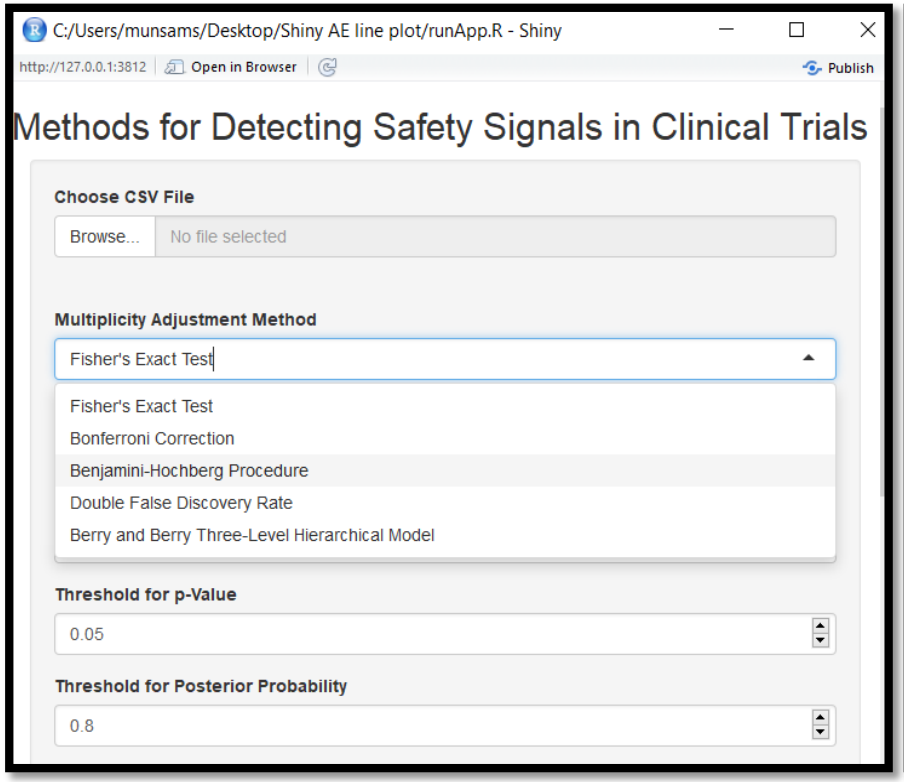
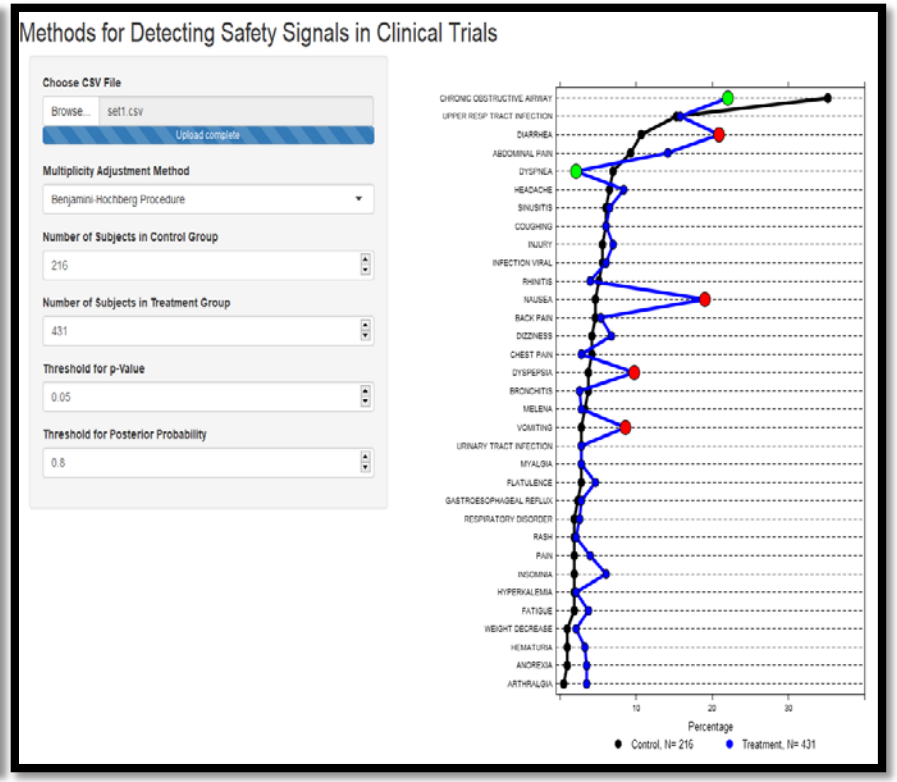
Dot plot + Adjusted Analysis - Analytics



Ref: http://www.sctweb.org/public/meetings/2015/slides/CPS%2013%20-%20Carragher.pdf

Dot plot + Adjusted Analysis – Analytics, R Shiny App





Misha R Programs (2013) + Raymond Carragher (2015) C212 R package

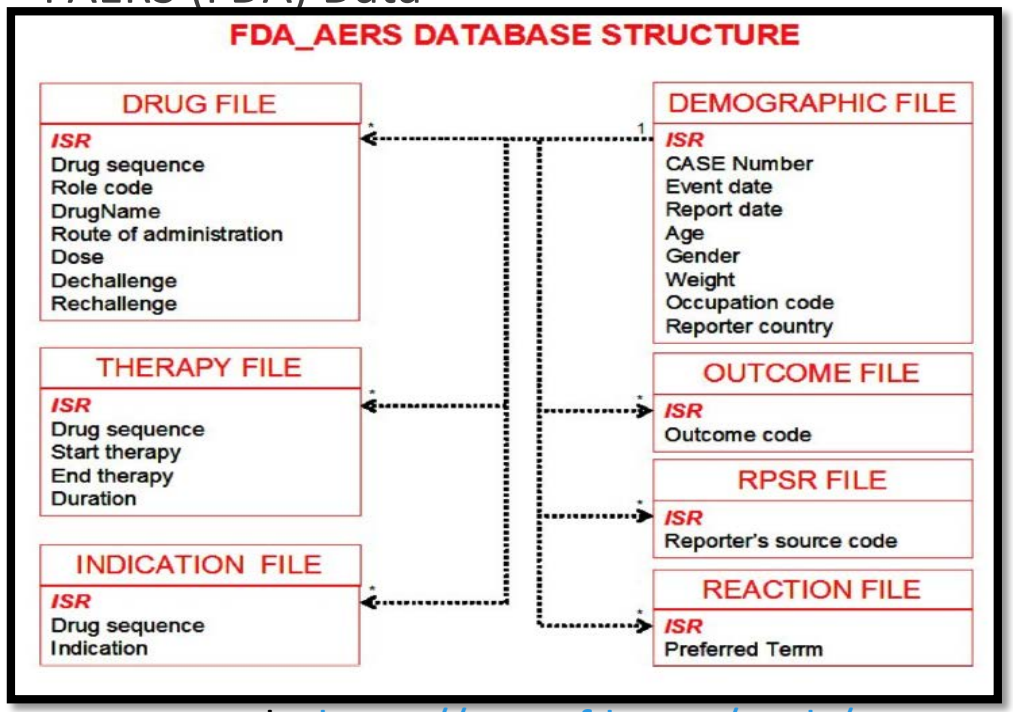
Source: https://ww2.amstat.org/meetings/fdaworkshop/index.cfm?fuseaction=AbstractDetails&AbstractID=302825.

Source: http://personal.strath.ac.uk/raymond.carragher/

Examples – Spontaneous Reports Systems (SRS)

Examples – Spontaneous Reports Systems (SRS)

FAERS (FDA) Data



JADER (PMDA) Data

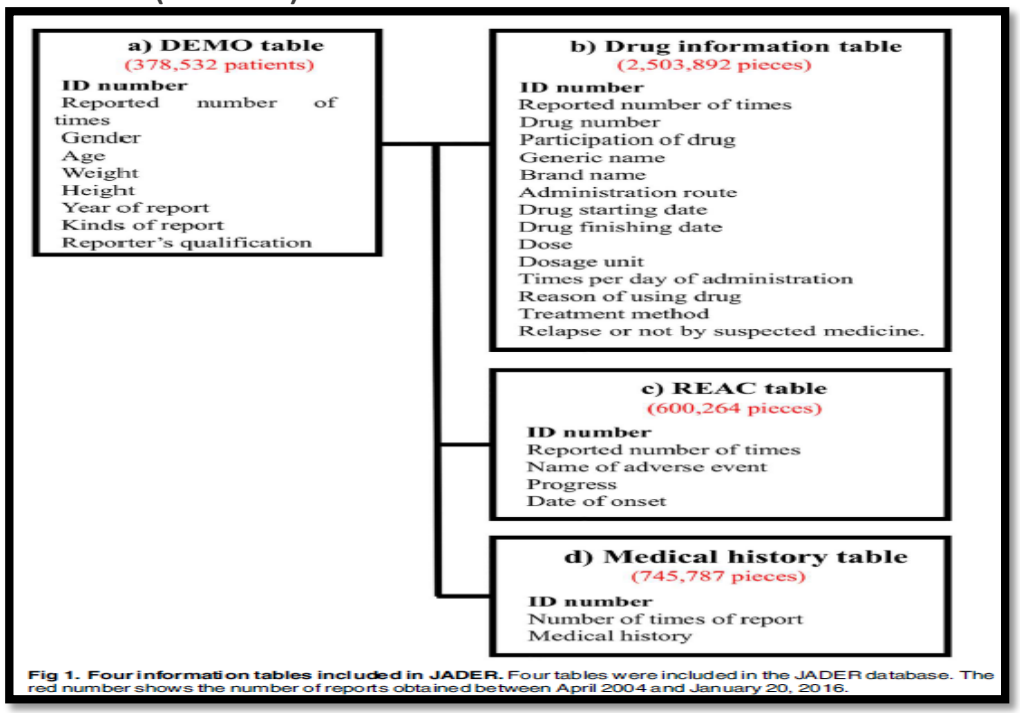
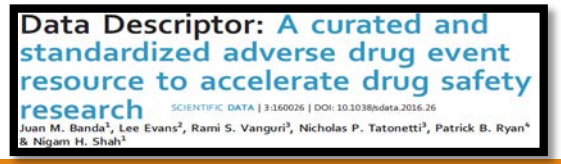


Fig 1. Four information tables included in JADER. Four tables were included in the JADER database. The red number shows the number of reports obtained between April 2004 and January 20, 2016.

openFDA Tools: https://open.fda.gov/tools/



Data Descriptor: A curated and standardized adverse drug event resource to accelerate drug safety research

SCIENTIFIC DATA | 3:160026 | DOI: 10.1038/sdata.2016.26

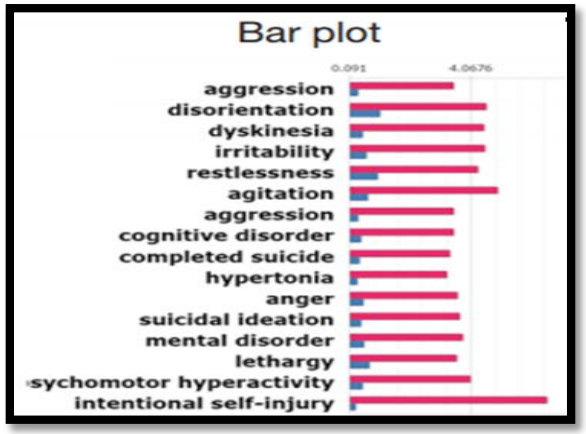
Juan M. Banda[1], Lee Evans[2], Rami S. Vanguri[3], Nicholas P. Tatonetti[3], Patrick B. Ryan[4] & Nigam H. Shah[1]

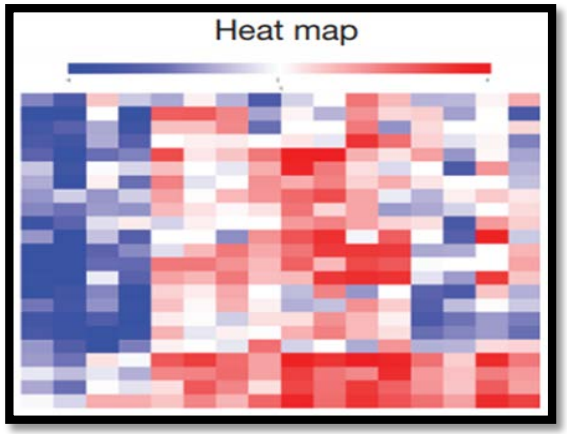
Others, CAERS (Canadian), Vigibase

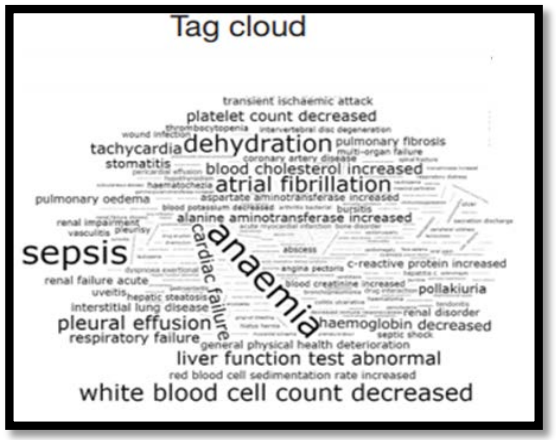
Some Questions to Ask on AEs

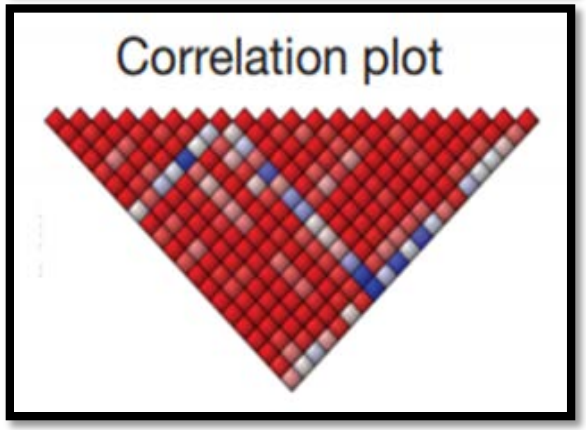
- What is the total number of AE reported to FAERS database? How is each AE occurrence compared with other AEs?
- Is there a relationship with other AEs? Is there a relationship with use of concomitant medications? Which AEs are occurring together in clusters or in a constellation?
- Is the potential reported AE of interest increasing over time?
- Which AEs could be a safety signal? Are there any surprises in the data?
- Which AEs are elevated in patient subgroups?
- AE patterns across multiple population subgroups

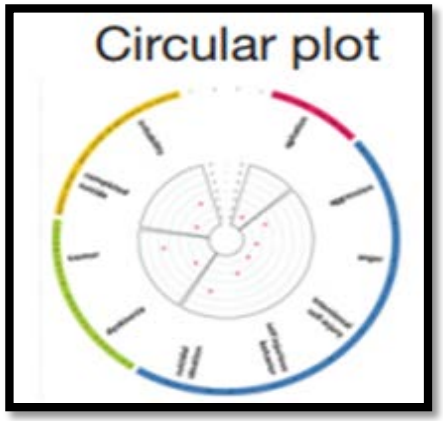
AE Plots – Many Available Charts to Graphically Present AEs

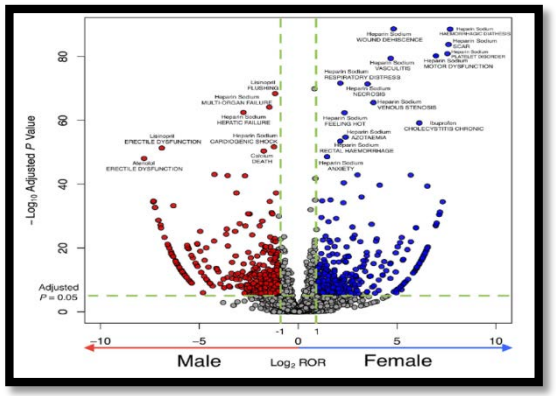






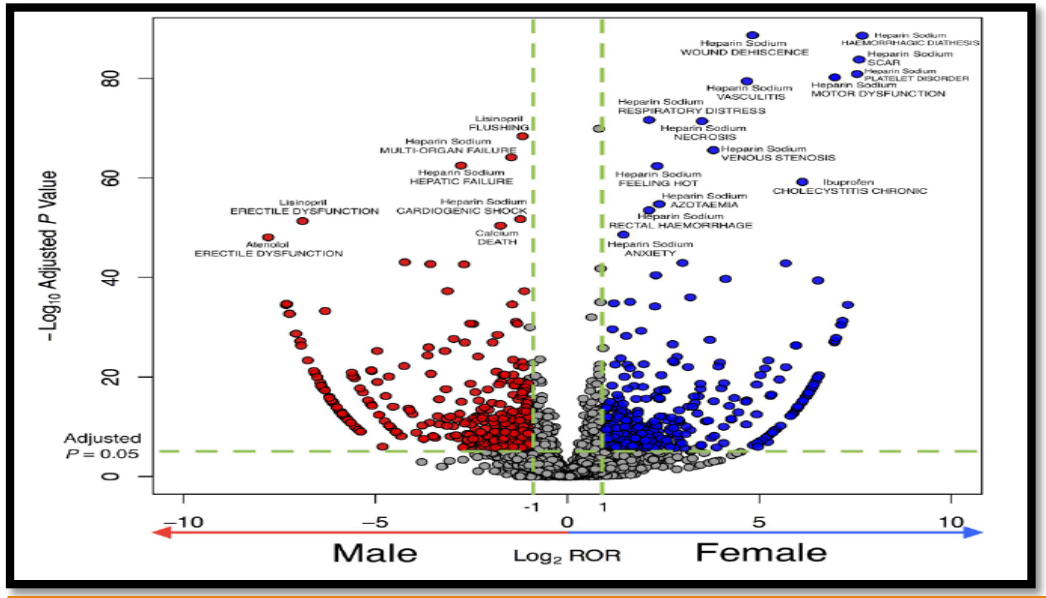


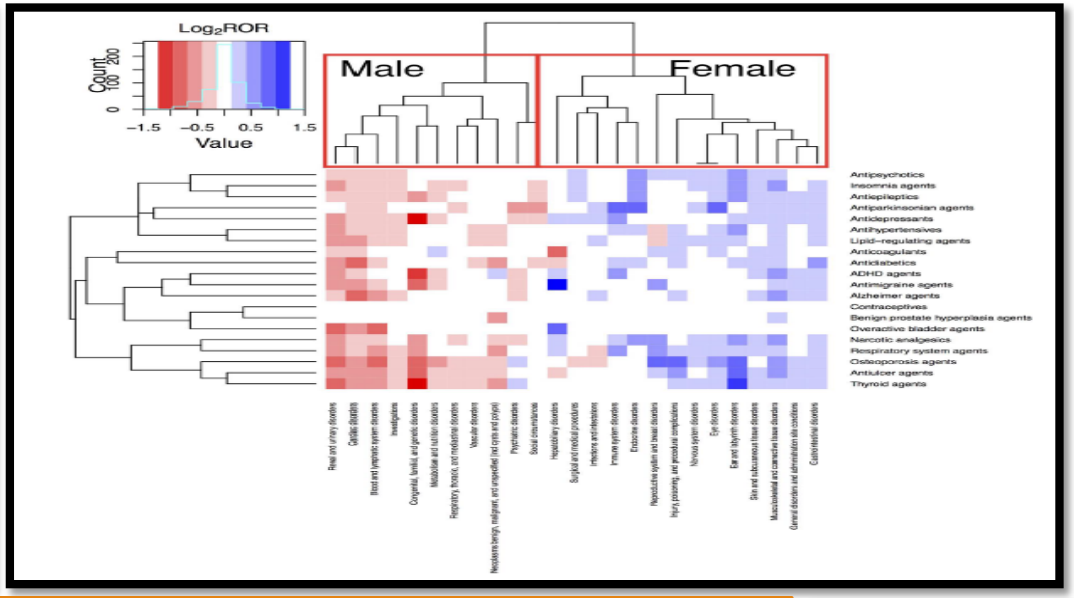




Source: https://research.cchmc.org/aers/home

Volcano Plot + Adjusted Analysis – Analytics





Volcano Plot of Significant Adverse Drug Event (ADE) Signals. In the volcano plot of ADE signals, the signal detection result shows the magnitude (log2 reporting odds ratio [ROR], x-axis) and significance (− log10 adjusted *P* value, y-axis) for sex- drug-event combinations associations of specific drugs. Each spot represents a specific drug- drug-event combination interaction. The dashed horizontal green line signals statistical significance threshold ($P \leq 0.05$ after adjustment with Bonferroni correction). Two vertical green lines show the threshold of ROR (log2 ROR > 1 or < − 1). The blue spots represent the drug-event combinations more frequently associated with female patients; the red spots, drug-event combinations more frequently associated with male patients.

Systematic Analysis of Adverse Event Reports for Sex Differences in Adverse Drug Events

Yue Yu[1,2], Jun Chen[3], Dingcheng Li[2], Liwei Wang[1], Wei Wang[3] & Hongfang Liu[2]

Examples - Social Media/Web Data

Examples - Social Media/Web Data

Natural Language Processing (NLP)

- Data from web sources/social medial outlets: Clinicatrial.gov, FDA website, EMA website, PubMed, Twitter, Facebook, Special Platforms, e.g., PatientsLikeMe, WebMD, etc
- Largely unstructured text data
- Safety data from social media should be part of a comprehensive safety assessment program
  - Patients are more likely to post drug-related AEs on Twitter than report them to the FDA (http://www.policymed.com/2014/10/mining-social-media-for-adverse-events.html)
- The new data landscape is complex and needs to be strategically looked at
- Being proactive is critical – good business sense
- Can discover valuable product and patient insights from monitoring social media, including:
  - Patient concerns and behaviors and potential product abuse and misuse
  - Tolerance and compliance and gain insights related to brand awareness and sentiment
  - Learn about product use patterns and preferences in the real world

Examples - Social Media/Web Data

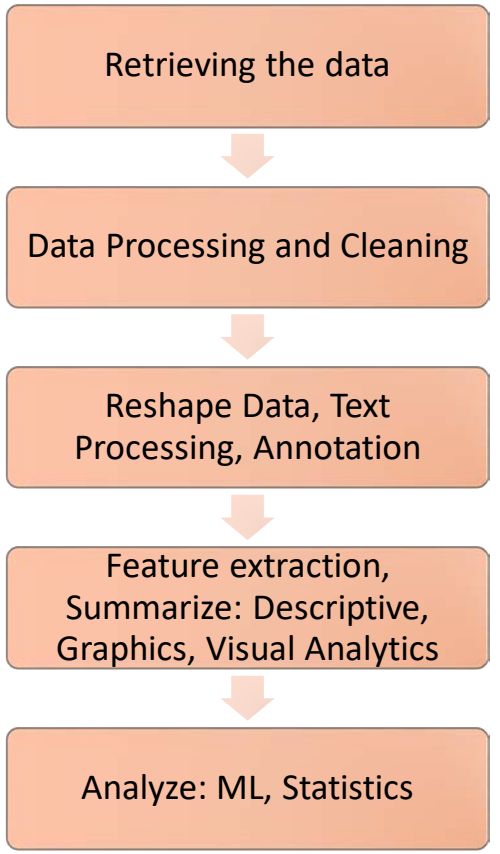
Key Potential benefit → Improve patient outcomes with detection

- If an error or AE is not detected, it cannot be managed
- Detection can help improve cognitive processes surrounding possible future events
- Help place resources in prevention efforts:
  - Nadarajah (2017): *Side effects were seen as a major reason for switchover based on social media conversations*
  - Gurulingappa, et al (2013): *Automatic detection of AEs to predict drug label changes using text and data mining techniques*
  - Jensen, et al (2017): *Analysis of free text in EHR for identification of cancer patient trajectories*
- Questions to ask – same as in SRS

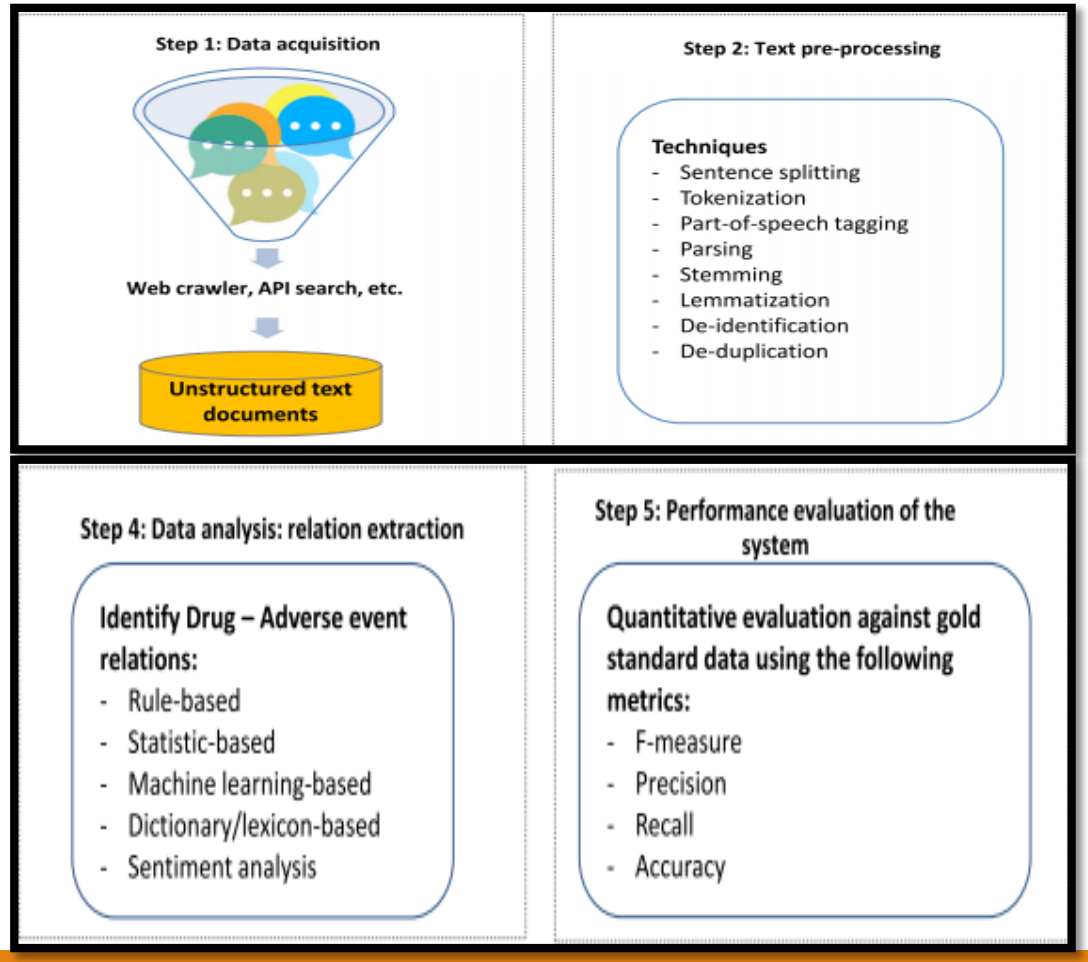
NLP - Typical Data Flow

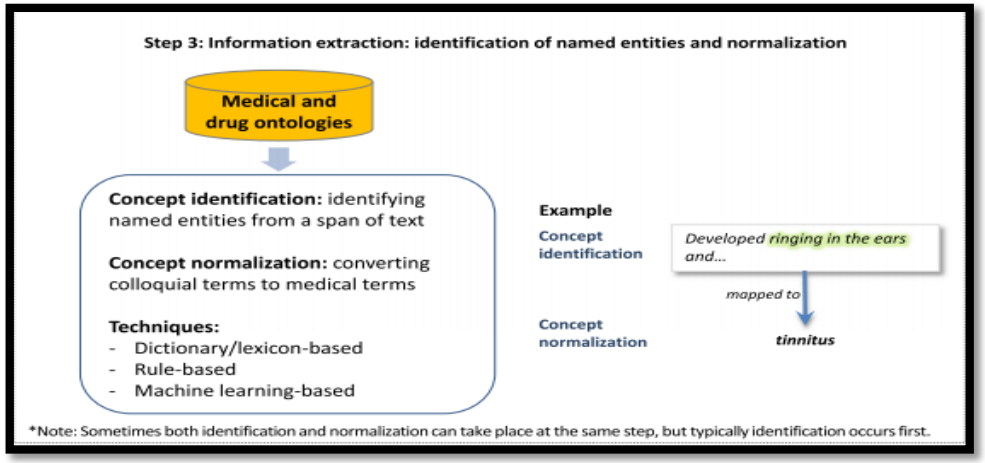
Key Concepts

- Information retrieval
- Tokenization
- Normalization
- Lemmatization
- Document
- Corpus
- Stop words
- Parts-of-Speech-Tagging
- N-grams
- Bag-of-words
- Polarity
- Term Frequency - Inverse Document Frequency (tf-idf)
- Document-Term Matrix/Term-Document Matrix
- Analysis



NLP - Typical Data Flow

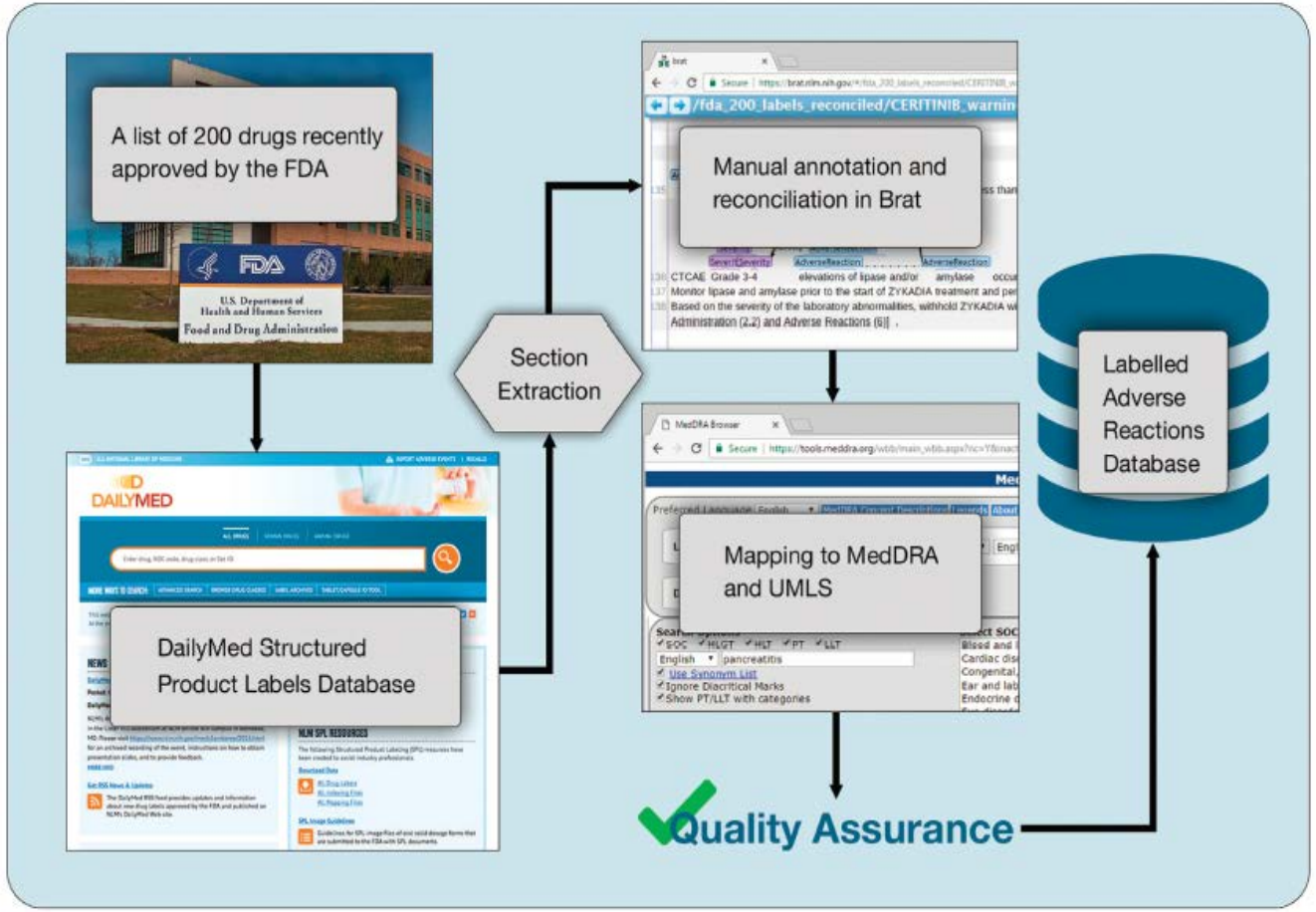




Utility of social media and crowd-intelligence data for pharmacovigilance: a scoping review

Andrea C. Tricco[1,2*], Wasifa Zarin[1], Erin Lillie[1], Serena Jeblee[3], Rachel Warren[1], Paul A. Khan[1], Reid Robson[1], Ba' Pham[1], Graeme Hirst[3] and Sharon E. Straus[1,4] *BMC Medical Informatics and Decision Making* (2018) 18:38

NLP - Typical Data Flow



Data Descriptor: A dataset of 200 structured product labels annotated for adverse drug reactions

SCIENTIFIC DATA | 5:180181 | DOI: 10.1038/sdata.2018.1

Dina Demner-Fushman[1], Sonya E. Shooshan[1], Laritza Rodriguez[1], Alan R. Aronson[1], Francois Lang[1], Willie Rogers[1], Kirk Roberts[2] & Joseph Tonning[3]

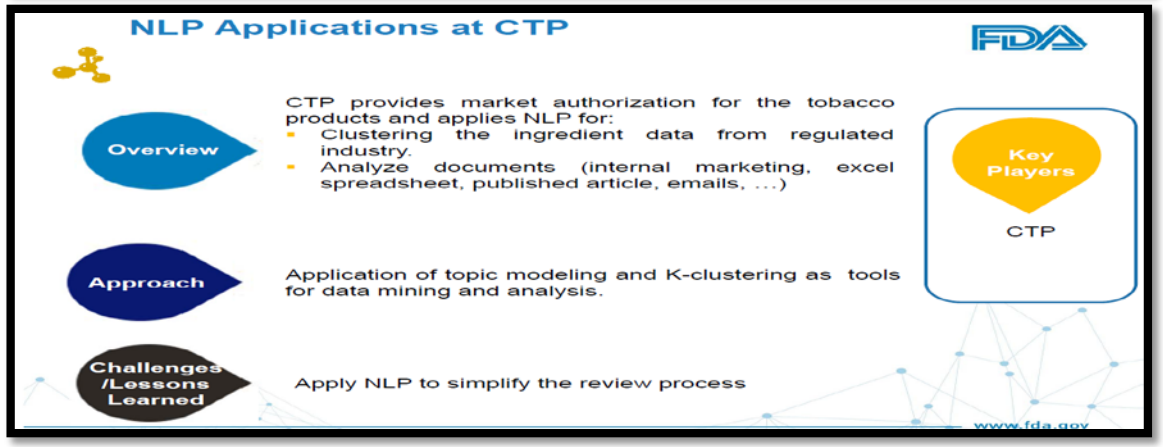
NLP in the Context of Safety Data

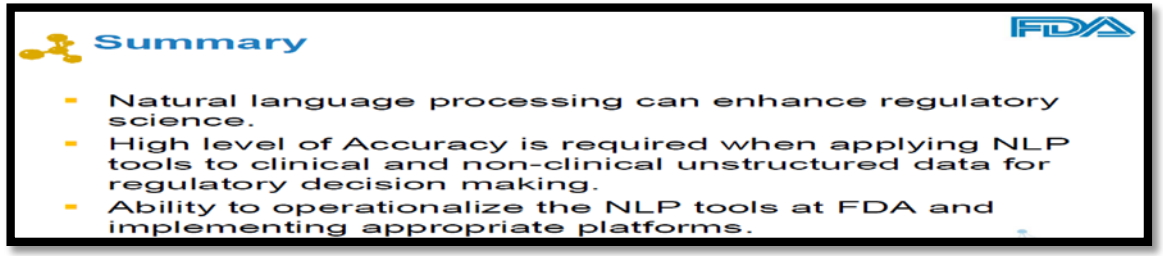
Example of patient text data

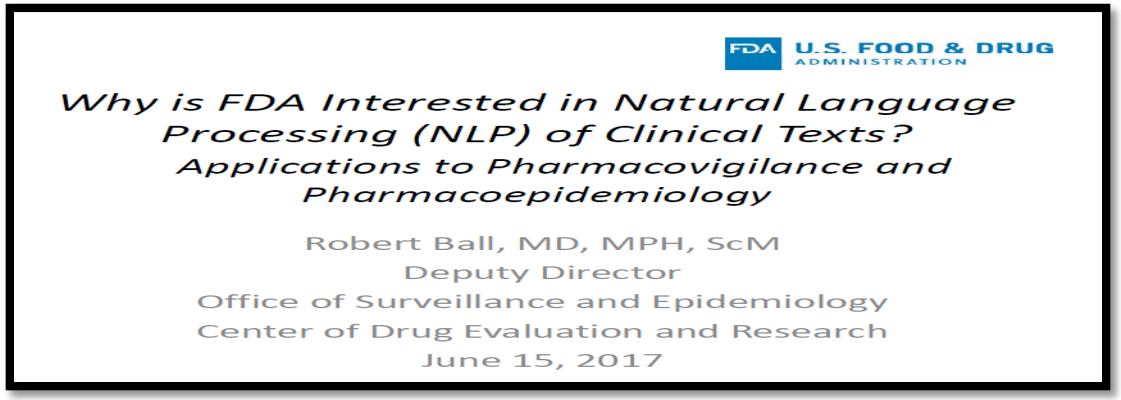
Sample Comments	Classification	Annotations
20s 8th day with #Effexor still experiencing some side effects (drowsiness,sleepiness,GI effects). Moderate improvement in mood #depression	*hasADR*	"drowsiness" - *drowsiness: adverse effect*, "sleepiness" - *sleepiness: adverse effect*, "GI effect" – *gastro intestinal reaction: adverse effect*, "depression" – *depression: indication*
Over-eaten AGAIN just before bed. Stuffed. Good chance I will choke on my own vomit during sleep. I blame #Olanzapine #timetochange #bipolar	*hasADR*	"over-eaten" – *increased appetite: adverse effect*, "bipolar" – *bipolar disorder: indication*
@brokenmind_ Quetiapine was horrific for me in relation to wait gain. Such a horror story. But the weight will come off one day at a time.	*hasADR*	"wait gain" – *weight gain: adverse effect*
Tomorrow, my second infusion of Tysabri! Good luck for me! #Godblessme #MSLife	*noADR*	"MS" *multiple sclerosis:indication*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4419871/

Regulators are also Interested







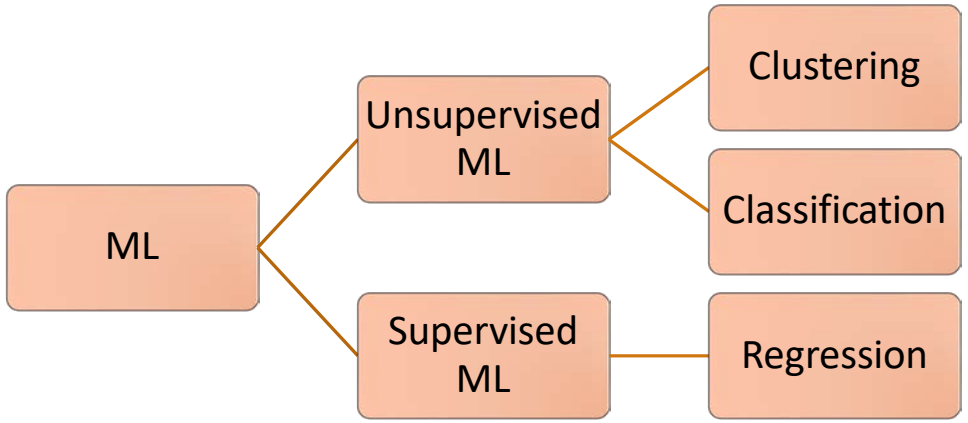
https://pink.pharmaintelligence.informa.com/PS055880/Adverse-Events-In-Social-Media-FDA-Expects-Signal-Detection-Revolution

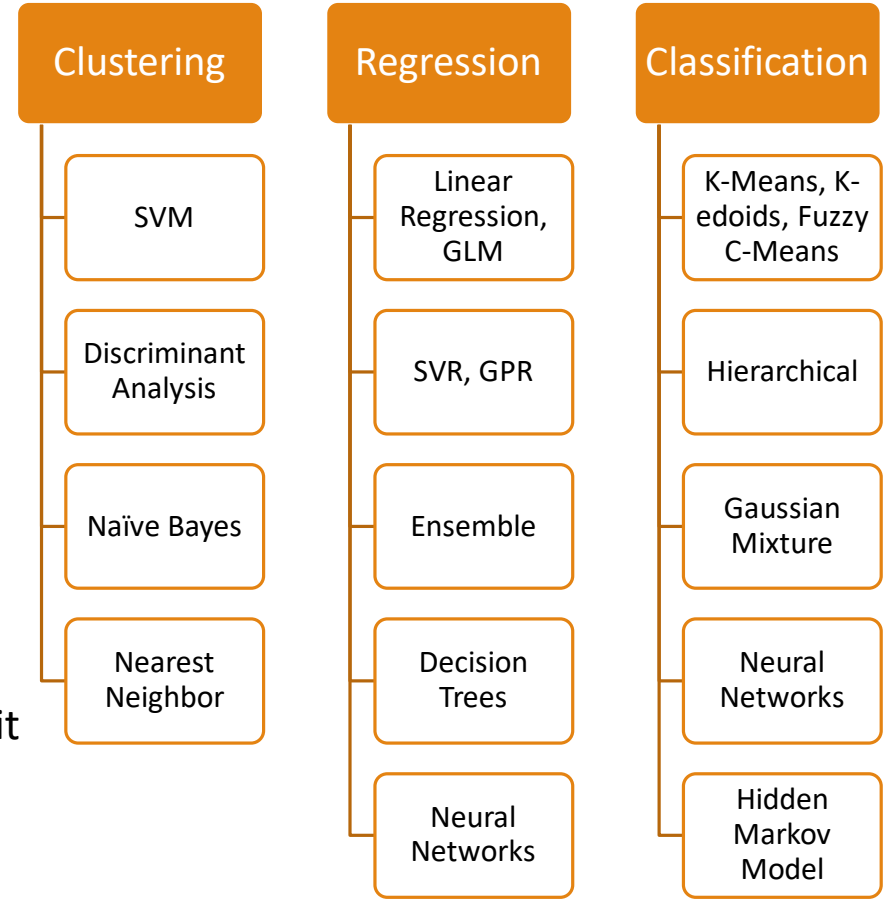
NLP in the Context of Safety Data

Some challenges

- Drugs may be described by their brand names, active ingredients, colloquialisms or generic drug terms
- AEs may be referred to using creative idiomatic expressions or terms not found within existing medical lexicons
- Informal nature of social media results in a prevalence of poor grammar, spelling mistakes, abbreviations and slang
- Existence of a side effect may be clear while the specific side effect experienced remains unclear
- Discussion of a drug could involve indications, beneficial effects or concerns of an adverse event
- Analysis methods, such as ML, while powerful, need training data which requires time-consuming and expensive generation of human-annotated data
- Transcription errors - spelling or grammar
- Synonymy, related/similar terms, abbreviations (often redundant), context-specific meanings
- Challenge for dealing with uncertainty, negation, and timing

Machine Learning (ML) Overview





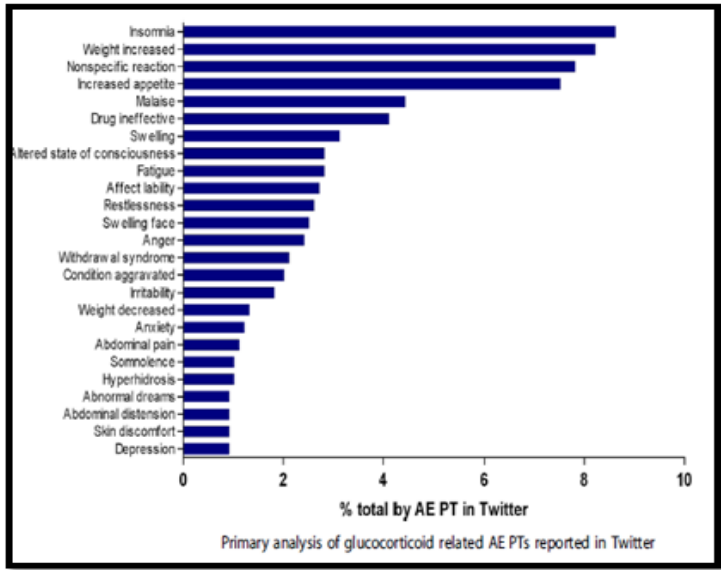
- Supervised learning
  - train a model on known input and output data so that it can predict future outputs
- Unsupervised learning
  - find hidden patterns or intrinsic structures in input data

Visualization of Text Data

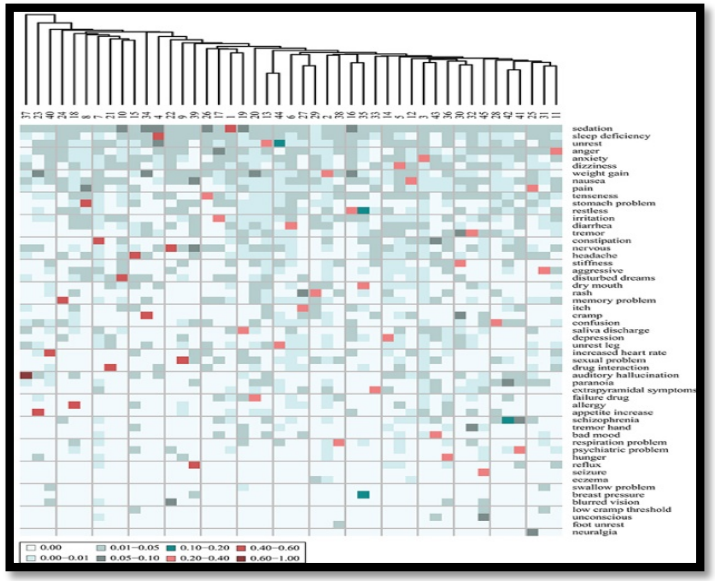
Can use different visualizations
Will depend on the research question at hand

Word Cloud

Bar Charts

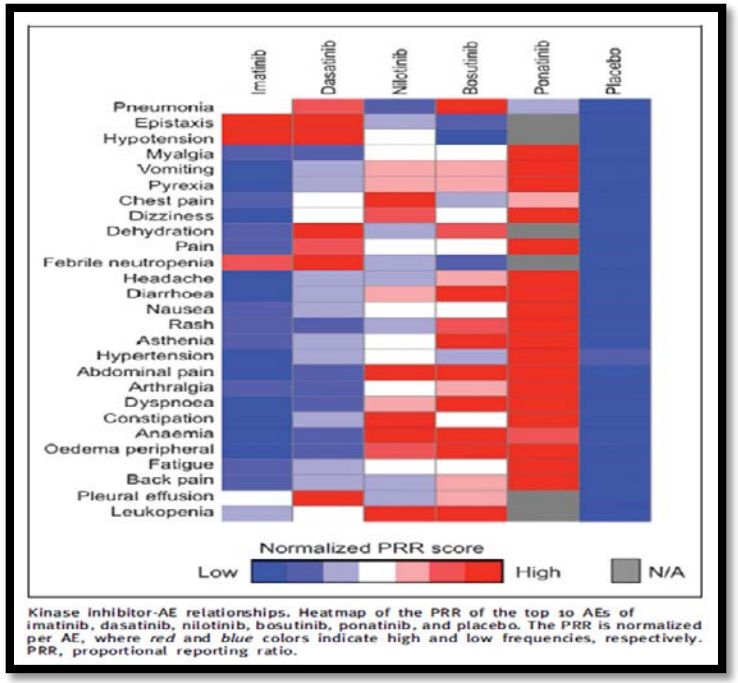


Heat Map



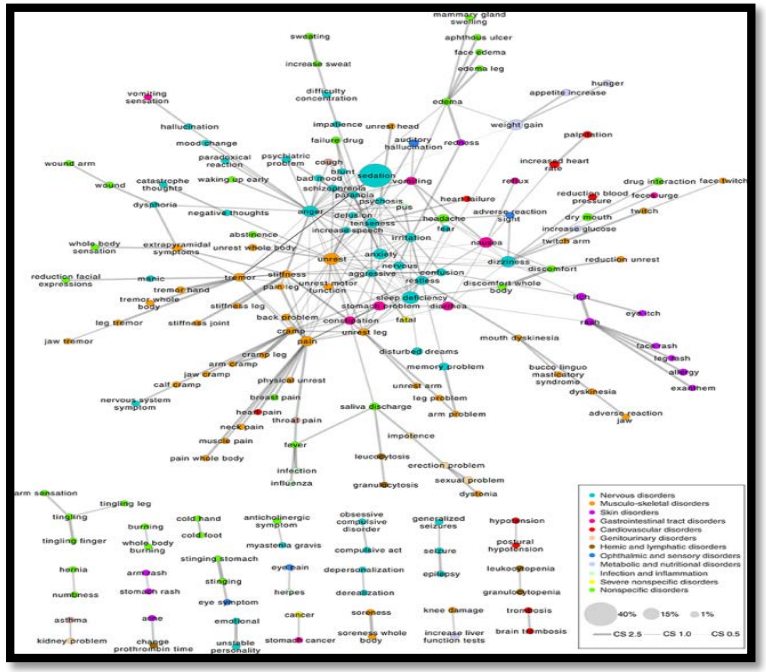
Visualization of Text Data

Heat Map

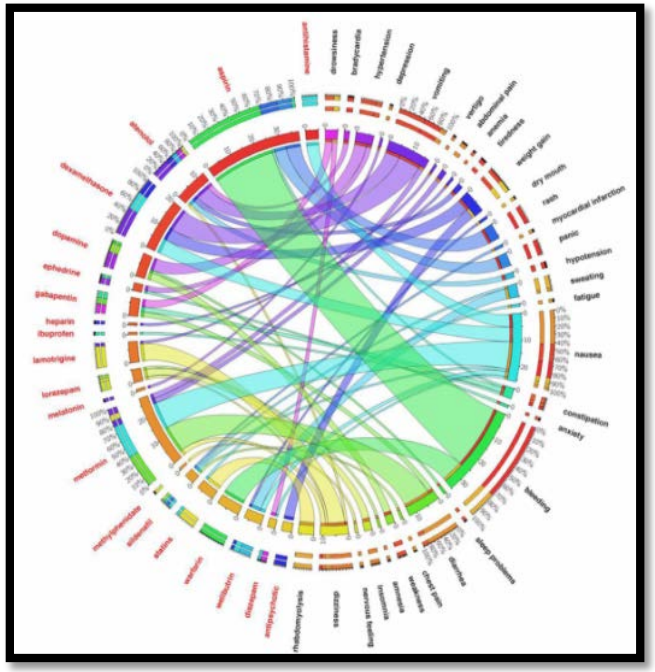


Kinase inhibitor-AE relationships. Heatmap of the PRR of the top 10 AEs of imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and placebo. The PRR is normalized per AE, where *red* and *blue* colors indicate high and low frequencies, respectively. PRR, proportional reporting ratio.

Network Plot



Chord/Radial Plot



Harnessing ML - Many Choices, example Naïve Bayes

Many ML algorithms, example Naïve Bayes

Task: Classify a new instance d based on a tuple of attribute values $d = \langle x_1, x_2, \ldots, x_n \rangle$ into one of the classes $c_j \in C$

$$c_{MAP} = \underset{c_j \in C}{\operatorname{argmax}} P(c_j \mid x_1, x_2, \ldots, x_n)$$

$$= \underset{c_j \in C}{\operatorname{argmax}} \frac{P(x_1, x_2, \ldots, x_n \mid c_j) P(c_j)}{P(x_1, x_2, \ldots, x_n)}$$

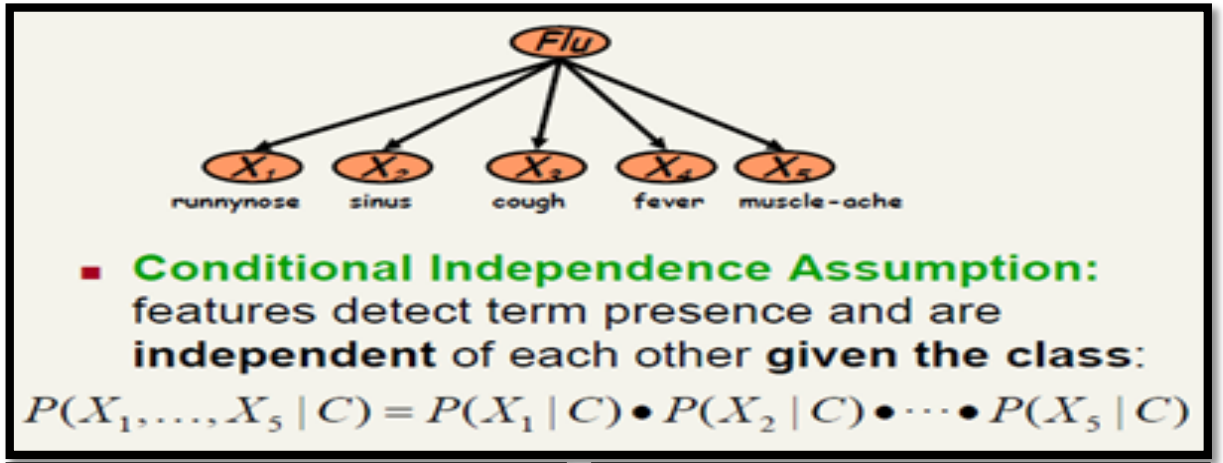
$$= \underset{c_j \in C}{\operatorname{argmax}} P(x_1, x_2, \ldots, x_n \mid c_j) P(c_j)$$

MAP is "maximum a posteriori" = most likely class

- $P(c_j)$
  - Can be estimated from the frequency of classes in the training examples.
- $P(x_1, x_2, \ldots, x_n \mid c_j)$
  - $O(|X|^n \cdot |C|)$ parameters
  - Could only be estimated if a very, very large number of training examples was available.

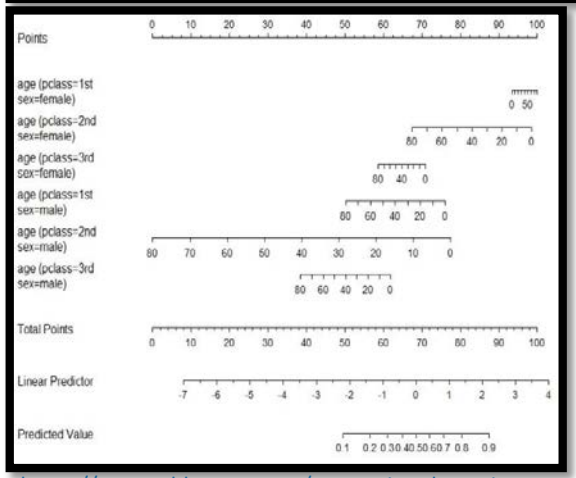
Naive Bayes Conditional Independence Assumption:

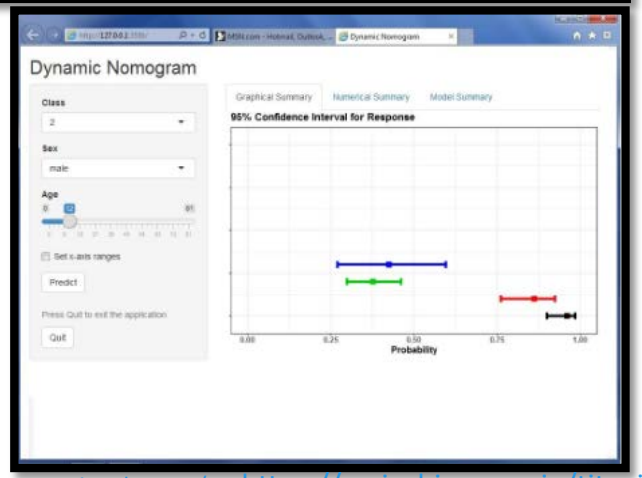
- Assume that the probability of observing the conjunction of attributes is equal to the product of the individual probabilities $P(x_i \mid c_j)$.



- **Conditional Independence Assumption:** features detect term presence and are **independent** of each other **given the class**:

$$P(X_1, \ldots, X_5 \mid C) = P(X_1 \mid C) \bullet P(X_2 \mid C) \bullet \cdots \bullet P(X_5 \mid C)$$





https://www.r-bloggers.com/generating-dynamic-nomograms-using-dynnom/ https://amir.shinyapps.io/titanic/

Some Tools

Free/Open Source

Some R Tools

- **Special packages**
  - Pubmed.mineR: https://zipfslaw.org/2015/10/19/pubmed-miner/
  - RISMed: https://amunategui.github.io/pubmed-query/
  - Rclinicaltrials: https://github.com/sachsmc/rclinicaltrials
  - MedlineR: https://github.com/akastrin/MedlineR
- R Shiny:
  - Interactive Text Mining Suite (ITMS): http://www.interactivetextminingsuite.com
  - Text Classification App: https://anishsingh.shinyapps.io/text_classification_app/

Some Python Tools

- NLTK: https://www.nltk.org/
- SpaCy: https://spacy.io/
- Pattern: https://github.com/clips/pattern
- TextBlob: http://textblob.readthedocs.org/en/dev/
- Gensim: https://github.com/piskvorky/gensim
- PyNLPl: https://pypi.python.org/pypi/polyglot

Some Open Source/Online Tools

Different degrees of functionality

- LimTox: http://limtox.bioinfo.cnio.es/
- NLPReViz: https://nlpreviz.github.io/
- ADRMine: http://diego.asu.edu/Publications/ADRMine.html
- cTakes: http://ctakes.apache.org/
- Stanford CoreNLP: https://stanfordnlp.github.io/CoreNLP/

Concluding Remarks

- Explosion of clinical health data has created a trove of information that can be leveraged to accelerate discovery and delivery of new drugs and therapy that ultimately improve the health of patients
- Need to harness all available data sources in characterizing drug safety profiles pre- and post-marketing, including unstructured text based data sources
- Visual analytics can help in safety monitoring and 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
- Software tools, commercial and open sources, are available that can help in analyzing text based data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FAERS: FDA Adverse Event Reporting System. https://open.fda.gov/data/faers/

FAERS: OpenFDA Powered Research Tools: https://open.fda.gov/tools/

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Back Up Slides

Enhancing Visual Analytics and Safety Monitoring

Examples

- Word Cloud

WordCloudStatic.html

WordCloudInteractive.html

Examples

– Collapsible Tree

8_Java_script.html

9_Java_script.html

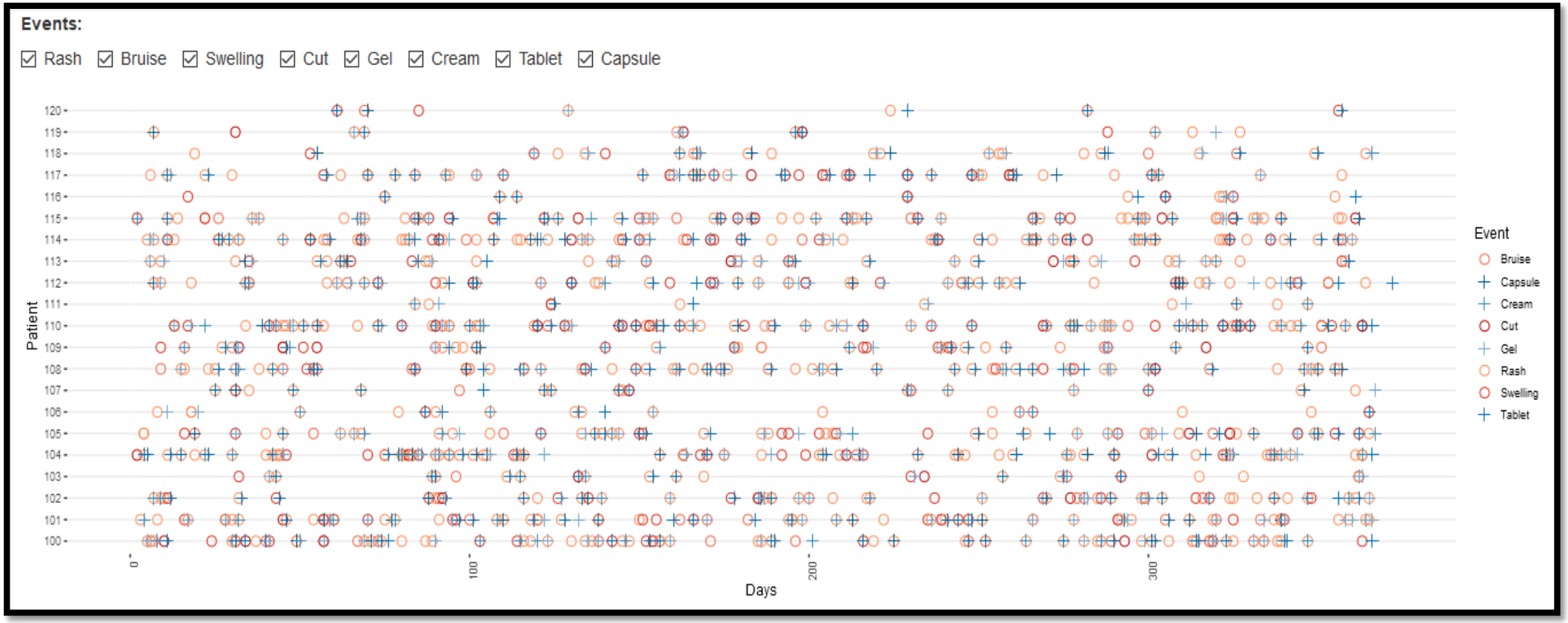
collapsible_tree.html

Examples

– Dynamic eDISH Plot

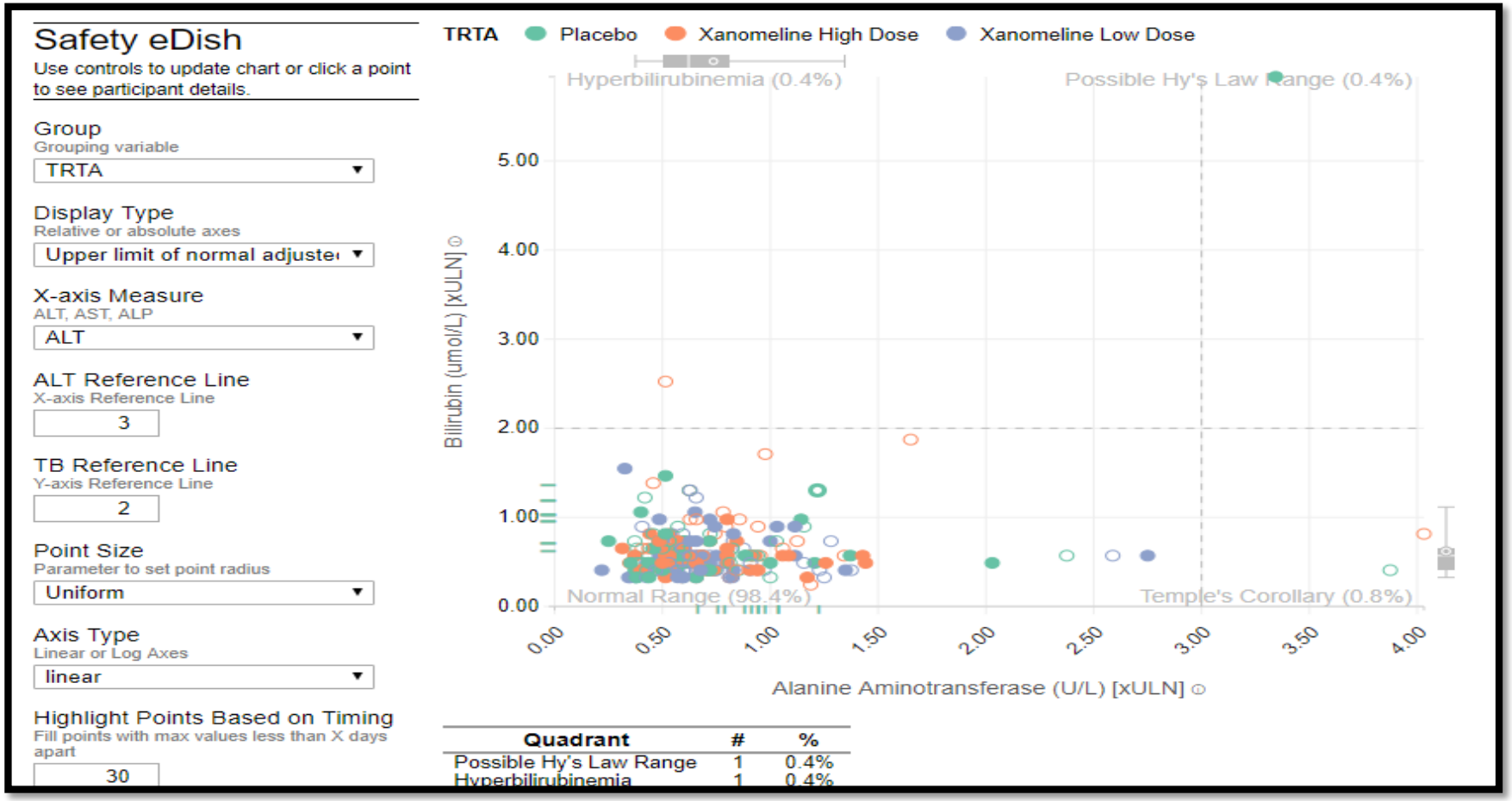
Chrome HTML Document

Subject Level Data – Estimand?



Mika Mäkinen, 2016 https://www.phusewiki.org/docs/Conference%202016%20DV%20Papers/DV02.pdf

ASA-DIA Collaboration




```
library(ReDish)
eDISH(data= adlbc)
```

Tool of Choice

Tool Functionality

- Integrated Development Environment (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

By Michael Grogan September 07, 2016

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

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! Plenty!
- Shared resources – github, Rpubs, etc
- Open source, flexibility, can use many tools, reproducibility, etc

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
- R Flexdashboard: http://rmarkdown.rstudio.com/flexdashboard/
- R Bookdown: https://bookdown.org/yihui/bookdown/
- R Shiny App: https://shiny.rstudio.com/
- R in Clinical Research and Evidence-Based Medicine: http://www.r-clinical-research.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